EMJ EUROPEAN MEDICAL JOURNAL

ONCOLOGY

ISSN 2054-619X — Vol 4.1 • November 2016 • emjreviews.com

INSIDE

Review of

ESMO 2016

Copenhagen, Denmark

CONTENTS

ONCOLOGY

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

AML is swarming with challenges

Strikingly heterogeneous at diagnosis, acute myeloid leukaemia (AML) is a complex disease that has a rapidly evolving and distinct pattern of molecular abnormalities. Many important kinases and proteins are involved, with up to two-thirds of AML patients having a FLT3 (ITD or TKD) and/or NPM1 mutation.[1,2]

Progress has been made in supportive treatment as well as in understanding the prognostic importance of oncogenic drivers underlying the onset of AML. Although there have been many incremental advances over several decades, challenges remain.[2]

Novartis Oncology is dedicated to the international research effort to find new options for AML patients worldwide.

For more information, please visit:
www.AMLchallenges.com

FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; NPM1, nucleophosmin 1; TKD, tyrosine kinase domain.

References: 1. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med.* 2012;366:1079-1089. **2.** Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet.* 2013;381:484-495.

October 2016 G-PKC-1149410

See how you can guide the path her cancer takes

At the advanced edge of oncology, rapid access to accurate data on disease state is vital. The fully automated Idylla™ system, in combination with the Idylla™ Assays, is the future of diagnosis and monitoring.

With first-time-right results you create the opportunity for disease interception - changing the course of your patients' cancer.

Current Idylla™ Assays:
KRAS and BRAF (CE IVD)
ctBRAF, EGFR S492R and NRAS (RUO)

To join the investigation visit www.biocartis.com

BIOCARTIS

Editorial Board

ONCOLOGY 4.1
NOVEMBER 2016

EUROPEAN UNION
Investing in Your Future
European Regional
Development Fund 2007-13

Published by the European Medical Group
The MedBIC, Anglia Ruskin University, Chelmsford, CM1 1SQ

Welcome

Welcome to the latest edition of *EMJ Oncology*, providing a selection of articles regarding research from across the field of oncology as well as news from the European Society for Medical Oncology (ESMO) Congress, which took place this year in the beautiful Nordic city of Copenhagen, Denmark.

This year's congress spanned 5 days, welcoming participants from across the globe. There is no doubt that this year's event had something for all healthcare professionals in the oncological sphere. Within this edition, we have included a broad range of abstract reviews from the congress as well as an analysis of the major highlights of the event in our congress review section.

Moving on to our carefully selected peer-reviewed articles, we provide a manuscript by Nielsen et al. who explore muscle dysfunction in childhood cancer. This fascinating piece suggests that skeletal muscle toxicities could be an integral part of the development of late effects in childhood cancer survivors. In terms of the future, the authors urge the importance of investigating the impact of such treatment which would improve the overall quality of childhood cancer survivorship.

Also included is Lipski et al. who discuss the safety and efficacy of endoscopic surgery. Within their article, the authors warn that despite some studies showing positive results, further research into newer technologies regarding endoscopic surgery are needed to improve the ability to manage pathologies endoscopically. Adil et al. provide a review on gastrointestinal stromal tumours, which are commonly known to occur in all parts of the gastrointestinal tract in patients in their 50s and 60s.

Kaggwa et al. look at the occurrence of bladder outlet obstruction in men with prostate cancer in a Sub-Saharan environment. This retrospective study was conducted in an urban teaching hospital, measured patients' ability to pass urine through the urethra, and set out to investigate the efficacy of certain therapies to relieve such symptoms. Blau et al. discuss recently discovered somatic mutations in the context of stem cell transplantation in myelodysplastic patients, and additionally, Körner et al. examine microRNAs that confer resistance to different treatments in breast cancer.

This edition is one not to be missed. We hope you find some fascinating insights into the ever-expanding world of oncological research which you can incorporate into your daily practice. We are confident that next year's edition will provide in-depth coverage of further developments in this exciting field of study, including features from ESMO 2017, taking place in Madrid, Spain.

Spencer Gore

Director, European Medical Journal

European Medical Journal Oncology is published once a year.
For subscription details please visit www.emjreviews.com

Front cover and contents photograph: Copenhagen, Denmark, home of ESMO 2016.


EMJ EUROPEAN MEDICAL JOURNAL
CALL
for
PAPERS
If you are interested in submitting a paper to EMJ, contact: editor@emjreviews.com
Follow us:
www.emjreviews.com
EUROPEAN UNION
Investing in Your Future
European Regional
Development Fund 2007-13

Foreword

Dr Ahmad Awada

Head of the Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium.

Dear Colleagues,

I would like to wish you a very warm welcome to *EMJ Oncology 4.1*, which puts all the latest news and progress across the field of oncology into the spotlight, including a comprehensive and engaging report on the European Society for Medical Oncology (ESMO) 2016 Congress, hosted in the spectacular city of Copenhagen, Denmark.

Record numbers were seen at this year's congress with a total of 20,522 participants in attendance as well as a large volume of impactful and top quality research. The congress review selection features a detailed collection of the most topical and insightful presentations made at the event, making it an informative read for all interested parties.

“The congress review selection features a detailed collection of the most topical and insightful presentations made at the event, making it an informative read for all interested parties.”

As always, *EMJ Oncology* is proud to showcase a selection of peer-reviewed articles spanning a number of important oncological topics. Our Editor's Pick for this publication is a riveting read by Nielsen et al., covering the physiological manifestations of treatment-induced muscular toxicities in paediatric oncology and moving on to assess the value of structured exercise as a focussed countermeasure. Furthermore, Adil et al. have penned a paper reviewing the genetics, pathology, risk stratification, clinical characteristics, investigation, and treatment of gastrointestinal stromal tumours; Körner et al. summarise the role microRNAs play in the carcinogenesis and treatment of breast cancer, one of the deadliest cancer types globally; Kaggwa et al. report on a study conducted at the Mulago National Referral Hospital, Kampala, Uganda, evaluating the utility of high-dose external beam radiation therapy combined with bilateral subcapsular orchidectomy in the relief of bladder outlet obstruction caused by prostate cancer. Additionally, Lipski et al. consider the latest indications for endoscopic endonasal surgery, as well as describing advantages of endoscopic surgery for aggressive benign tumours.

I took great pleasure in perusing this publication and trust that you will find it similarly absorbing and glean fresh insights into the immense progress being made in oncology.

Kind regards,

Ahmad Awada

Head of the Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium.

NOW APPROVED

CABOMETYX® Abbreviated prescribing information (Before prescribing please consult the full Summary of Product Characteristics (SmPC))

CABOMETYX® 20mg, 40mg and 60mg film-coated tablets

Pack size: one plastic bottle with 30 tablets

Active ingredient: Cabozantinib (*S*)-malate 20mg, 40mg and 60mg

Other components: Lactose

Indications: CABOMETYX® is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Dosage and Administration: The recommended dose of CABOMETYX® is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of CABOMETYX® therapy. For dose modification, please refer to full SmPC. CABOMETYX® is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX®.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

Special warnings and precautions for use: As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmarplantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting). Dose reductions and dose interruptions due to an AE occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 19.3% of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days.

Perforations and fistulas: Serious gastrointestinal perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.

Thromboembolic events: Events of venous thromboembolism, including pulmonary embolism, and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

Haemorrhage: Severe haemorrhage has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage.

Wound complications: Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention.

Hypertension: Hypertension has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. During treatment with cabozantinib, all patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Palmar-plantar erythrodysaesthesia syndrome: Palmar-plantar erythrodysaesthesia syndrome (PPES) has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.

CABOMETYX® ▼
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

"CABOMETYX® is indicated for the treatment of advanced RCC in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy".[1]

Proteinuria: Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.

Reversible posterior leukoencephalopathy syndrome: Reversible Posterior Leukoenceph-alopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with RPLS.

Prolongation of QT interval: Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

Interactions: CYP3A4 inducers and inhibitors: Cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore, chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided. P-glycoprotein substrates: Cabozantinib was an inhibitor but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate while receiving cabozantinib. MRP2 inhibitors: Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors should be approached with caution. Bile salt-sequestering agents: Bile salt-sequestering agents may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown. Excipient related warnings: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy and lactation: Avoid pregnancy, use effective methods of contraception and discontinue breast-feeding during treatment with cabozantinib, and for at least 4 months after completing therapy.

Drive and use machines: Caution is recommended

Undesirable effects: The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%), and nausea (2%). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar-plantar erythrodysaesthesia syndrome (PPES) (42%), hypertension (37%), vomiting (32%), weight decreased (31%), and constipation (25%). Other very common adverse reactions: anemia, hypophosphataemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyperbilirubinemia, dysgeusia, headache, dizziness, dysphonia, dyspnea, cough, stomatitis, abdominal pain, dyspepsia, rash, dry skin, muscle spasms, arthralgia, proteinuria, mucosal inflammation, serum ALT, AST, and ALP increased, creatinine increased, triglycerides increased, hyperglycaemia, hypoglycaemia, lymphopenia, neutropenia, thrombocytopenia, GGT increased, amylase increased, blood cholesterol increased, lipase increased.

For all common and uncommon adverse reactions, please refer to full SmPC.

Ipsen Pharma 65, Quai Georges Gorse, 92100 Boulogne-Billancourt, France

For more information, see the regularly updated registered product information on the European Medicine Agency www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Reference: 1. CABOMETYX® (cabozantinib) Summary of Product Characteristics 2016.

CBZ-ALL-000305

Scan the QR Code to access the full SmPC

IPSEN
Innovation for patient care

ESMO ANNUAL CONGRESS 2016

BELLA CENTER,
COPENHAGEN, DENMARK
7TH-11TH OCTOBER 2016

Welcome to the *European Medical Journal* review of the European Society for Medical Oncology Congress

This year, Copenhagen played host to the annual ESMO Congress which took place over 5 days and welcomed 20,522 participants. During the closing press conference, Prof Andrés Cervantes, Scientific Chair of the ESMO 2016 Congress, commented: "ESMO 2016 Congress has broken records, not only of attendance, but in terms of the quality science being presented that will impact the practice of oncology."

Over 1,640 studies were presented, including 47 late-breaking trials and over 1,500 posters. The leading countries contributing to this year's vast number of delegates were: the USA, France, the UK, Germany, Spain, Switzerland, Italy, China, Japan, and Denmark. Prof Cervantes noted the importance of such a popular and successful congress, stating: "This is certainly a record number, but what is most important is the good news for physicians and patients in many areas of unmet needs such as ovarian cancer, lung cancer, renal cell carcinoma, sarcomas, and other less common diseases."

Prof Solange Peters, ESMO 2016 Press Officer and member of the *EMJ Oncology* Editorial Board, reflected on the most prominent aspects of the congress: "The accent on immunotherapy, that has changed the oncology landscape, as well as targeted therapies and personalised medicine in general; the use of biomarkers for predicting response and outcomes is of huge benefit to patients. Beyond data, our pre-occupation is about patients; that is why a study on quality of life, beyond survival, was included in a Presidential Symposium. That is also why we have a hugely successful Patient Advocacy Track and we also publish guidelines for cancer patients."

During the Women for Oncology Session, Prof Sumitra Thongprasert was awarded the ESMO Women for Oncology Award for her career as a distinguished role model for women in oncology among countless other achievements. Three renowned oncologists were also presented with ESMO awards in the opening session of the congress: Prof Alberto Sobrero was presented with the ESMO Award for his remarkable original work and countless publications in the field of gastrointestinal cancers; Prof Carlos Caldas received the Hamilton Fairley Award for his

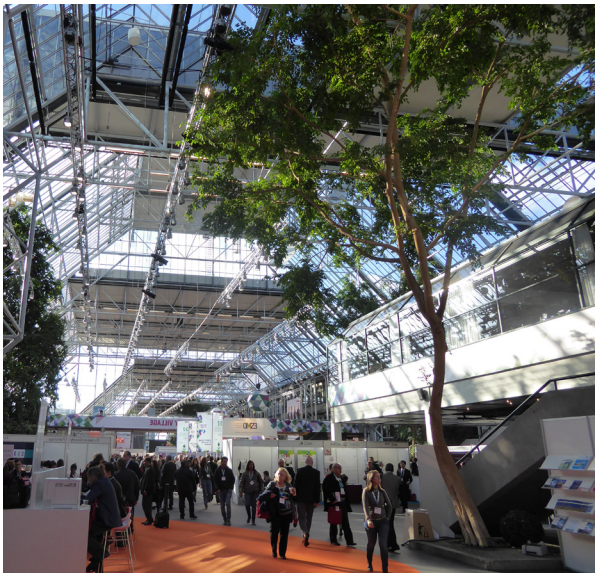
outstanding contributions to cancer science and clinical/translational research; and Prof Sir Richard Peto was awarded the ESMO Lifetime Achievement Award, recognising his extensive involvement in cancer research and education.

Prof Ulrik Lassen, ESMO National Representative for Denmark and Local Officer for the ESMO 2016 Congress, stated: "ESMO brought us a lot of information in terms of better practice and science, and we will be busy in the coming months finding ways to integrate this new knowledge into our oncology practice."

In the following congress review section, we bring you descriptions of some of the most impactful presentations that were made at the event. This includes a vast range of possible new treatments for conditions such as non-small cell lung cancer, breast cancer, and ovarian cancer. In addition, there is coverage of a study which looked at the issue of the lack of reporting on adverse events in targeted therapy and immunotherapy trials, and another which analysed the financial implications that face cancer patients around the world in regard to their treatment, amongst many others.

Following the clear success of this year's congress, we look forward to reviewing the next ESMO annual congress in Madrid, Spain, in 2017.

> "ESMO brought us a lot of information in terms of better practice and science, and we will be busy in the coming months finding ways to integrate this new knowledge into our oncology practice."



ESMO-MCBS: A Quantification Tool for the Treatment of Rare Cancers

THE FIRST practicality study to assess the potential application of the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) tool within clinical practice has shown promising results, as presented in a ESMO press release dated 10th October 2016.

Developed and first analysed in field testing by the Medical University of Vienna (MUV), Vienna, Austria, one of the largest cancer research centres in Europe, a second study of the ESMO-MCBS tool has reflected that its applications may extend even further to potentially become a global online implement for the assessment and treatment of rare cancers.

The ESMO-MCBS considers predefined drug trial endpoints, overall survival and progression-free rates, and corresponding quality of life or toxicity results. Developed as a three-step approach, this innovative study retrospectively acquired data on common treatments presently used throughout practice, before assessing these with the ESMO-MCBS and evaluating the overall grades to ascertain the feasibility of their use within a real-life clinical context. The study looked particularly at neuroendocrine tumours, glioblastoma, sarcomas, and thyroid, pancreatic, ovarian, head/neck, and urothelial cancers.

> “We found that the ESMO-MCBS is a helpful tool for clinical practice in rare tumours, as well as for common tumour entities, if randomised data is available.”

Of particular interest, the study obtained supporting data on the clinical benefit of CHECKMATE 141 checkpoint inhibitors, which scored an EMSO-MCBS value of 3, consistent with the results seen in practice. However, it was noted that the scale’s use for the treatment of rare cancers is limited by the volume and variety of published clinical trial data. Dr Barbara Kiessewetter, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria, explained, “We found that the ESMO-MCBS is a helpful tool for clinical practice in rare tumours, as well as for common tumour entities, if randomised data is available. It supports treatment decisions based on the expected clinical benefit. It is very simple to use and we feel that it is going to prove to be a very important tool for daily clinical practice based on our study results. Clinicians can go back to the data when considering new treatments and use the

ESMO-MCBS online to analyse what can be expected from a new approach."

Are Fibroblastic Growth Factor Receptor Inhibitors the Future for Rare Cancer Treatment?

THE FIRST dose escalation study in humans of pan-fibroblast growth factor receptor (FGFR) inhibitor BAY 1163877 has been investigated for its utility as a potential treatment of locally advanced or metastatic tumours, discussed in a ESMO press release dated 8th October 2016.

FGFR expression is often dysregulated via both epigenetic and genetic mechanisms in many types of cancer, particularly in bladder cancers. This potent, oral, novel anticancer therapy is designed to inhibit FGFRs 1–3, meaning the messenger RNA (mRNA) expression levels of FGFR in each individual patient may correlate with the potential benefit of BAY 1163877 therapy thus acting as a sensitive biomarker. Dr Markus Joerger, attending Medical Oncologist, St Gallen Cancer Centre, St Gallen, Switzerland, explained: "Most studies of FGFR inhibitors have looked at FGFR abnormalities in tumours with limited success. This study used an innovative biomarker approach for tumour FGFR mRNA expression."

Conducted across six countries, this multicentre Phase I trial enrolled a total of 80 patients; 23 for a dose-escalation phase and 57 for an expansion phase. The type of cancer exhibited by each individual was not limited within this study, and included but was not limited to, bladder cancer, head and neck cancer, and lung cancer.

Over 1,640 studies presented

Patients were divided into six dose cohorts, ranging from 50–800 mg twice daily. No dose-limiting toxicities were observed; the majority of patients developed slight hyperphosphataemia, however, this is seen with all FGFR inhibitors. As a result, it is recommended that the maximum concentration of 800 mg be used in further Phase III trials. Within the expansion cohort 3 out of 8 bladder cancer patients showed partial remission. Patients with squamous cell carcinoma of the head and neck, squamous cell lung cancer, and adenoid cystic carcinoma were also observed to exhibit partial remission.

> "FGFR inhibitors may provide a therapeutic opportunity to patients with rare tumours."

Prof Giuseppe Curigliano, Chair of the Division of Early Drug Development Therapeutics, European Institute of Oncology, Milan, Italy, commented: "FGFR inhibitors may provide a therapeutic opportunity to patients with rare tumours."

Optimism for the Future of Metastatic Bladder Cancer Treatment

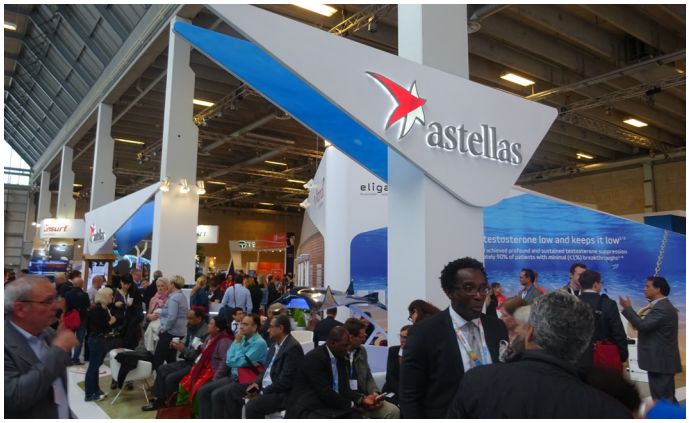
METASTATIC bladder cancer patients who are not eligible for current cisplatin-based chemotherapy could benefit from immunotherapy. A ESMO press release dated 8th October 2016 elucidated the promising results of two recent Phase II trials measuring the safety and efficacy of these classes of drugs in first and second line treatment of the disease.

Researchers presented data on the first 100 patients to be studied in the Phase II KEYNOTE-052 trial; this study tested a programmed cell death-1 (PD-1) blockade with pembrolizumab as first-line therapy in

patients suffering from metastatic or locally advanced bladder cancer, who were not eligible for cisplatin. The primary endpoint of an objective response rate of 24% was targeted. At the time of the presentation, the median duration of response had not yet been reached and treatment had been well-tolerated. The biomarker cut point identifying patients most likely to respond to treatment was set at ≥10% total PD-L1 expression in immune cells or tumour cells, and 30 patients achieved this. Eleven of these patients (37%) responded to treatment.

> “We expect even more dramatic changes in the coming years with the use of immunotherapy in other clinical stages and as combination therapy.”

The second Phase II study, CHECKMATE 275, evaluated 265 metastatic bladder cancer patients who had progressed following first line platinum-based chemotherapy. The team studied the PD-1 inhibitor nivolumab, assessing its safety and activity with the primary endpoint: an objective response rate of 19.6%. The median follow-up of the study was 7 months but median duration of response had not been reached. The objective response rate in the study was found to be higher than historically achieved with chemotherapy, for patients with tumours expressing either higher or lower levels of PD-L1.



Dr Maria De Santis, Associate Clinical Professor for Oncology, Cancer Research Centre, Warwick Medical School, University of Warwick, Coventry, UK, commented: “Immune checkpoint inhibitors have started to alter the therapeutic landscape for bladder cancer. We expect even more dramatic changes in the coming years with the use of immunotherapy in other clinical stages and as combination therapy.”

Poor Reporting of Adverse Events in Targeted Therapy and Immunotherapy Trials

REPORTING of adverse events in trials of targeted therapies and immunotherapies has been suboptimal in recent years, thereby withholding vital information about the safety of drugs, according to research presented in a ESMO press release dated 5th October 2016.

For this study, the publications of 81 trials for the treatment of solid malignancies in adult patients approved by the US Food and Drug Administration (FDA) were assessed. Over 90% of the trials scored poorly in reporting recurrent and late toxicities as well as the true duration of adverse events. Additionally, the time point of the adverse event occurrence was not adequately reported in 86% of the trials and only adverse events that occurred at a frequency above the fixed threshold were reported in 75% of published trials.

Limitations in the method for presenting adverse events, in the follow-up interval assessment, and in describing toxicities leading to therapy withdrawal, were found in over half of the publications assessed. Researchers also discovered that in one-third of the trials, dose reductions due to adverse events were not reported at all.

Copenhagen

"Toxicities of targeted agents and immunotherapy are obviously different from the toxicities we are used to observing and treating due to chemotherapy, and there are some aspects of the toxicities of these newer agents that we are not so well-informed about," stated the Principal Investigator of the study, Dr Paolo Bossi, Head and Neck Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, in a ESMO press release dated 5th October 2016.

Despite this, Dr Bossi expressed optimism with regards to novel methods that have become available in recent years to improve the quality of adverse event reporting: "The most important and innovative one is the PRO-CTCAE form, which is the patient-reported outcome version of the common toxicity criteria of adverse events, and which will allow physicians to collect the symptoms as reported by the patients, considering also the severity, intensity, and influence of the symptoms on their quality of life."

For the full interview with Dr Paolo Bossi, at ESMO click here.

> "Toxicities of targeted agents and immunotherapy are obviously different from the toxicities we are used to observing and treating due to chemotherapy, and there are some aspects of the toxicities of these newer agents that we are not so well-informed about."

Single-Arm Trials Grant Patients Rare Cancer Drugs Earlier

OPPORTUNITIES to accelerate the time of cancer drug development and approval are provided by single-arm trials (SATs), especially for drugs with dramatic activity and significant biological rationale, according to a ESMO press release dated 10th October 2016.

As regulatory guidance regarding the circumstances in which SATs are able to offer adequate evidence to achieve European Union (EU) authorisation is limited, the European Medicines Agency (EMA) and ESMO are currently working together to clarify evidence requirements for market access decision-makers, patients, and medical professionals as well as making innovative cancer drugs more widely available.

An analysis of the role SATs played in 263 applications for initial approval or indication extension for cancer drugs reviewed by EMA between 1995–2014 was recently carried out. It was discerned that approximately 20% of cancer drug approvals in the EU during this period were based on results from SATs, as well >50% of the initial authorisations for haematological malignancies. Dr Jorge Martinalbo, Scientific Advisor, EMA, reported that: "Altogether this reflects the flexibility of regulatory requirements for approval, supported by early access tools like conditional and exceptional circumstances authorisations used in almost half of the initial approvals based on SATs."

> Clinical researchers must develop new solutions that span from proof of concept to effectiveness, constantly taking the challenges to bring solid evidence to patients and not too easily compromising towards easier routes such as SATs which should be limited to situations where strong biological evidence emerges in absence of relevant existing therapeutic strategies and/or unmet needs.

Another obstacle facing patients who wish to have access to new cancer drugs is the financial cost which was a main discussion point in a recent workshop held jointly by EMA and ESMO. The meeting focussed on evidence requirements and challenges facing cancer drug approval and reimbursement decisions based on SATs.

Commenting on the study Dr Denis Lacombe, Director General, European Organisation for Research and Treatment of Cancer (EORTC), cautioned: "Clinical researchers must develop new solutions that span from proof of concept to effectiveness, constantly taking the challenges to bring solid evidence to patients and not too easily compromising towards easier routes such as SATs which should be limited to situations where strong biological evidence emerges in absence of relevant existing therapeutic strategies and/or unmet needs. Discussing SATs outside of a complete transformation of clinical research may jeopardise appropriate recognition of SATs where they may be useful and is certainly a disservice to patients."

Sharp Disparities in Cancer Treatment Availability Across Europe

DISCORDANCE in the availability of access and reimbursement of innovative treatments for metastatic melanoma patients across Europe has raised ethical questions regarding healthcare inequality, reports a ESMO press release dated 7th October 2016.

The web-based online survey, conducted in 34 oncology centres across 29 European countries, found that while 70% of western European patients received the latest first-line treatments as recommended by European Guidelines, <10% of eastern European patients had access to the same therapy. These numbers become all the more significant in light of the improvements to long-term survival for metastatic melanoma patients over the past 5 years with innovative medicines; durable responses of up to 10 years are now reported. Nonetheless, the majority of Eastern and South-Eastern European patients continue to receive palliative chemotherapy.

Commenting on the disparities, Dr Alexandru Eniu, Chair of the ESMO Global Policy Committee, said: "This study confirms what ESMO has highlighted in the past: access to the best treatment according to evidence-based clinical guidelines such as ESMO's, is not equal across Europe. ESMO advocates for equal access to treatment and care, which is the fundamental right of every patient. Despite the encouraging rate of new medicine development, there are still unacceptable inequalities in the availability and accessibility of new and effective cancer medications across Europe."

With melanoma rates in Europe at 1 in 100 people and rising, the findings of the study are projected to become more pronounced if stakeholders fail to act. The survey found that across Europe, 27% of all metastatic melanoma patients had not received access to the latest treatments. Moreover, registration and reimbursement estimations stood at 75% and 58% compared with 42% and 18% in Western and Eastern Europe, respectively, for the BRAFi+MEKi immunotherapy combination treatment.

> “Despite the encouraging rate of new medicine development, there are still unacceptable inequalities in the availability and accessibility of new and effective cancer medications across Europe.”

Universal access to healthcare has been called into question by the stark reality of both figures and similar findings in studies concerning other forms of cancer. Advocacy and data collection, along with reimbursement and access programmes were among the appeals by the authors to combat these continuing trends.

Positive Trial Results Set the Stage for New Paediatric Brain Cancer Treatment

THERAPY trialled for the treatment of paediatric brain cancer may completely change the way low-grade gliomas in children with the mutation are treated.

According to a ESMO press release dated 7th October 2016, the drug dabrafenib specifically targeting the cancer mutation, has shown a high response rate with a low toxicity rate in a Phase I/II trial, opening up the possibility of combining dabrafenib with a MEK inhibitor to treat these patients; previous studies have shown that combining a BRAF inhibitor with a MEK inhibitor produces more activity and reduce toxicity for a longer period of time in adult patients.

The first trial focussed on determining the correct dosage for the following trial and found no significant toxicity limitations. The Phase II trial went on to assess the toxicities associated with dabrafenib, a selective inhibitor of mutant protein, and whether it could cause tumours to shrink. Patients recruited for the study (N=32) with the BRAF V600-mutant low-grade glioma ranged from 1–16 years old; 15 participated in the Phase I trial, and 17 in Phase II. Of the patients treated, 23 out of 32 responded to the drug with 11 patients’ tumours reducing by more than half of their original size and 2 patients’ tumours disappearing completely. Currently, 13 patients have stable disease of a 6-month duration and 11 of them remain on therapy.

> “We want to make the response rate with dabrafenib even higher by combining it with a MEK inhibitor since that works in adults.”

Currently the side effects of radiation therapy can cause lifelong complications such as cognitive damage and secondary malignancies. This study provides hope that a combination therapy of dabrafenib and a MEK inhibitor could be utilised in the future, meaning low-grade gliomas can be treated by being targeted specifically, without such risks. A trial combining the two drugs is currently underway.

Lead author Dr Mark Kieran, Paediatric Medical Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA commented: "We want to make the response rate with dabrafenib even higher by combining it with a MEK inhibitor since that works in adults."

Intramuscular Injections as an Alternative Standard of Care

POSITIVE results of a new study investigating the effects of fulvestrant in women with breast cancer suggest a potential alternative therapy for those requiring a low toxicity approach, reports a ESMO press release dated 8th October 2016.

A hormonal therapy, fulvestrant is an oestrogen receptor degrader that works selectively, meaning it can target hormone receptor function without affecting oestrogen levels. With progression-free survival (PFS) as the primary endpoint, the Phase III, double-blind, multicentre study randomised patients (1:1) to 1 mg of anastrozole daily (n=232) or 500 mg intramuscular injections of fulvestrant at 0, 14, and 28 days and every 4 weeks thereafter (n=230). All patients were also administered one line of chemotherapy. Inclusion criteria enrolled patients with inoperable endocrine receptor and/or progesterone receptor-positive locally-advanced or metastatic breast cancer, who had received no previous hormonal therapy.

> "For patients with non-visceral disease whose life is not immediately threatened by breast cancer, a group for whom physicians would typically choose endocrine therapy as a first approach, it looks like fulvestrant could be a new standard of care compared to anastrozole."

The results were significant at both group and subgroup levels of analysis. The 21% improvement in PFS between the fulvestrant and anastrozole groups (16.6 months versus 13.8 months), noted after a median follow-up of 25 months, was found to be statistically significant at p=0.048. For those whose cancer had not metastasised to the lungs or liver at baseline, PFS was further extended in the fulvestrant arm (22.3 months versus 13.8 months).

Despite some adverse events such as arthralgia (16.7% versus 10.3%) and hot flushes (11.4% versus 10.3%), according to lead author Prof Matthew Ellis, Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, Texas, USA, fulvestrant was generally tolerated as well as anastrozole. "For patients with non-visceral disease whose life is not immediately threatened by breast cancer, a group for whom physicians would typically choose endocrine therapy as a first approach, it looks like fulvestrant could be a new standard of care compared to anastrozole," Prof Ellis commented.

Nonetheless, the strict inclusion criteria, combined with the advances in other CDK4/6 and aromatase inhibitor combination therapies, means that further investigations are paramount in defining the right therapy for the right patient.

Ribociclib Improves Progression-Free Survival in Advanced Breast Cancer

COMBINING letrozole therapy with the CDK4/6 inhibitor ribociclib was reported in a ESMO press release, dated 8th October 2016, to significantly improve progression-free survival in postmenopausal women with hormone receptor-positive advanced breast cancer.

> "The results of this trial represent a compelling proof of principle, and suggest a paradigm shift in metastatic HR+ breast cancer."

The randomised, double-blind MONALEESA2 study randomly assigned 668 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer, who had not undergone any systematic treatment previously, to two treatment groups. The first group was assigned ribociclib (600 mg/day, 3-weeks-on/1-week-off) and letrozole (2.5 mg/day, continuous), whilst the second was given letrozole plus a placebo.

It was discovered that the ribociclib group showed a 44% improvement in progression-free survival compared with the placebo group (hazard ratio: 0.556, p=0.00000329). Patients with measurable disease at baseline had a significantly greater objective response rate within the ribociclib group (53% versus 37%, p=0.00028), as well as an improved clinical benefit rate (80% versus 72%, p=0.02). While serious adverse events presented in <5% of patients, other adverse events were far more common in the ribociclib group compared with the placebo group. For instance, neutropenia occurred in 59% of ribociclib patients and 1% of patients within the placebo group; leukopenia occurred in 21% and 1%, respectively. Despite the increase in toxicity, it was felt that the magnitude of the associated clinical benefit outweighed this, and that the addition of ribociclib to letrozole therapy proved beneficial.

Commenting on these findings, principal investigator Prof Gabriel Hortobagyi, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, announced: "The results of this trial represent a compelling proof of principle, and suggest a paradigm shift in metastatic HR+ breast cancer. They also suggest that testing combinations of ribociclib with other inhibitors of various signalling pathways might lead to additional progress in the management of several subtypes of breast cancer."

Outcomes for Ovarian Cancer Patients Significantly Improved with the Drug Niraparib

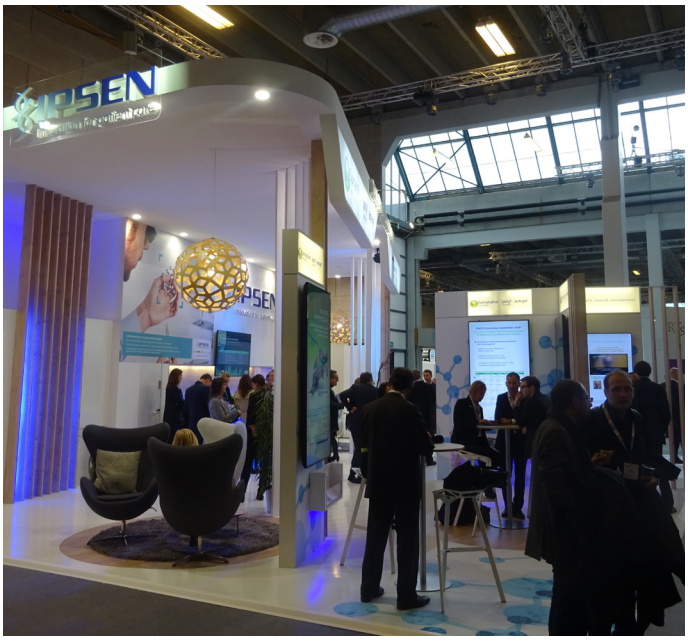
SURVIVAL outcomes of platinum-sensitive recurrent ovarian cancer patients are significantly improved following treatment with the PARP inhibitor niraparib, according to a ESMO press release dated 8th October 2016.

Treatment options are currently very limited for recurrent ovarian cancer. For example, the only options available for maintenance therapy within the European Union (EU) are bevacizumab, which can only be used once and improves progression-free survival by just a few months, and the PARP inhibitor olaparib, which can only be used by patients

with a germline *BRCA* mutation. Outside of the EU, no maintenance therapy is approved. The ENGOT-OV16/NOVA trial therefore sought to determine the safety and efficacy of the inhibitor, niraparib, as a maintenance therapy for this form of cancer.

> “Niraparib significantly improved all endpoints across a broad patient population representing 70% of all ovarian cancer patients. These landmark results could change the way we treat this disease.”

In the study, 553 recurrent ovarian cancer patients were divided into two cohorts: those with a germline *BRCA* mutation (n=203) and those without (n=350). The participants were randomised 2:1 to be treated with a 300 mg dose of niraparib or placebo once daily. The primary endpoint of progression-free survival was significantly higher in patients given niraparib than those who received the placebo in both the germline *BRCA* mutation group and the non-germline *BRCA* mutation group (median: 21.0 versus 5.5 months and 9.3 versus 3.8 months, respectively). The secondary endpoints of second progression-free survival, time to first subsequent treatment, and chemotherapy-free interval were also significantly improved in those who received niraparib compared to placebo in both cohorts.



1,500 posters

“This is a breakthrough for patients with ovarian cancer,” stated lead author Dr Mansoor Raza Mirza, Chief Oncologist, Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, in a ESMO press release dated 8th October 2016. “We have never seen such large benefits in progression-free survival in recurrent ovarian cancer. Niraparib significantly improved all endpoints across a broad patient population representing 70% of all ovarian cancer patients. These landmark results could change the way we treat this disease.”

Ceritinib Increases Progression-Free Survival in Lung Cancer

CERITINIB increases progression-free survival (PFS) compared with chemotherapy in crizotinib-pre-treated non-small cell lung cancer (NSCLC) patients harbouring an anaplastic lymphoma kinase (ALK) rearrangement, as disclosed in a study presented in a ESMO press release dated 9th October 2016.

In this study, 231 patients with NSCLC who had been treated with crizotinib were randomised 1:1 to receive either ceritinib or chemotherapy (pemetrexed or docetaxel). If a patient discontinued chemotherapy because of disease progression, they could cross over to ceritinib. The study’s primary endpoint was PFS. Results demonstrated that the median PFS was significantly improved in the ceritinib arm compared with the chemotherapy arm (5.4 versus 1.6 months, hazard ratio: 0.49, p<0.001). In addition, ceritinib improved the overall response rate to 39.1%, compared with 6.9% for chemotherapy. Toxicities in patients taking ceritinib were similar to those observed in previous Phase I and II studies, with the most common Grade 3/4 adverse events being nausea and vomiting (both 7.8%). There was also a significant improvement in patient reported outcomes, such as lung cancer-

specific symptoms and overall health status, with ceritinib as compared with a placebo ($p<0.05$). While there was no improvement in overall survival with ceritinib, it was suggested that this might be as a result of the patients who crossed over, diluting the potential improvement.

> “This study opens up a new treatment paradigm after crizotinib failure.”

Commenting on the implications of these findings for clinical practice, the lead author of the Phase III ASCEND-5 study Prof Giorgio Scagliotti, Full Professor of Respiratory Medicine, Department of Oncology, University of Torino, Torino, Italy, announced: “This study opens up a new treatment paradigm after crizotinib failure. It would be logical now to give a sequence of active drugs, starting with crizotinib in first line and moving to ceritinib in second line.”

Survival Benefits in New Drug to Treat Non-Small Cell Lung Cancer

THE FIRST Phase III study of atezolizumab, a programmed death ligand-1 (PD-L1) inhibitor, has shown significant improvements in survival compared to standard chemotherapy reported in a ESMO press release dated 9th October 2016. The OAK study registered 1,225 patients who had previously been treated for non-small cell lung cancer (NSCLC). The investigators began by stratifying patients into groups according to their PD-L1 status, number of chemotherapy regimens, and histology, then randomised the patients to receive either intravenous atezolizumab (1,200 mg) or docetaxel (75 mg/m^2), every 3 weeks.

Initial analysis during the trial of 850 of the patients exhibited a 27% improvement in overall survival (OS) in patients receiving atezolizumab compared to those treated with docetaxel. This was regardless of their PD-L1 expression levels and included patients with PD-L1 expression of <1%. When patients were organised into PD-L1 expression levels, the OS was 59% among patients in the highest tertile of PD-L1 expression who were treated with atezolizumab, compared with the group treated with docetaxel. In the groups where PD-L1 expression was non-existent there still remained a 25% improvement in OS in atezolizumab patients compared with docetaxel. Similar improvements were seen in patients with squamous and non-squamous histology.

Investigator Dr Fabrice Barlesi, Multidisciplinary Oncology and Therapeutic Innovations Department, Aix-Marseille University and the Assistance Publique Hôpitaux de Marseille, Marseille, France, confirmed the importance of the results stating: “Atezolizumab offers a new second-line therapeutic strategy for patients with NSCLC, regardless of the PD-L1 status of the tumour.” Prof Martin Reck, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, Germany, added: “This is a very important piece of information on the role of PD-L1/PD-1 antibodies in treatment of NSCLC, and confirms the OS benefits shown in the POPLAR and CHECKMATE trials.”

> “Atezolizumab offers a new second-line therapeutic strategy for patients with NSCLC, regardless of the PD-L1 status of the tumour.”

In response to next stages or possible future trials, Prof Reck explained: “My suggestion would be that PD-L1 is perhaps one imperfect surrogate marker to describe the activity; it is a good enrichment factor but we need additional markers for the characterisation of patients who might not benefit from this treatment or who might really benefit.”

Pembrolizumab with First-Line Chemotherapy Significantly Improves Outcomes

INCLUDING pembrolizumab, a programmed cell death-1 (PD-1) antibody, to standard first-line chemotherapy for treatment-naïve, non-squamous non-small cell lung cancer (NSCLC) patients was found to greatly improve response rates and progression-free survival, according to study results presented in a ESMO press release dated 9th October 2016.

In carrying out this Phase II study, 123 patients with Stage IIIB/IV, chemotherapy-naïve, non-squamous NSCLC were randomly selected and split into two groups. While both groups were treated with four cycles of carboplatin and pemetrexed (500 mg/m^2 every 3 weeks), Group 1 also received 24 months of treatment with pembrolizumab (200 mg every 3 weeks) while Group 2 did not. Researchers followed up patients after a median of 10.6 months.

A significantly larger objective response rate (55% versus 29%, p=0.016) in Group 1 compared with Group 2 was identified. Furthermore, Group 1 patients were found to have an improved progression-free survival rate (median of 13.0 months versus 8.9 months), though the 6-month survival rate remained similar for both groups at 92%. While it should be noted that there was a greater incidence of adverse events of Grade 3 or above in Group 1 patients (39% versus 26%) compared with Group 2 patients, ultimately this did not appear to have an effect on treatment discontinuation rates or treatment related deaths, with 10% of Group 1 patients and 13% of Group 2 patients discontinuing treatment.

> “If these benefits are confirmed in an ongoing Phase III trial, the results may radically alter the treatment paradigm in advanced NSCLC.”

This was the first randomised Phase II trial to evaluate the impact of adding a monoclonal antibody targeting PD-1 to standard chemotherapy in cases of treatment-naïve, non-squamous NSCLC. Speculating on the broader implications of these findings, the study’s principal investigator Dr Corey Langer, Director, Thoracic Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, commented: “If these benefits are confirmed in an ongoing Phase III trial, the results may radically alter the treatment paradigm in advanced NSCLC.”

Sunitinib: A Potential Adjuvant Therapy for High-Risk Renal Cell Carcinoma

A PHASE III, randomised, double-blind trial of the inhibitor sunitinib as a novel adjuvant treatment for renal cell carcinoma (RCC) development following nephrectomy has shown promising results, reports a press release from this year’s ESMO Congress dated 10th October 2016.

A distinguishable characteristic of kidney cancer is its extremely high recurrence rate of ≤50% in some patient subgroups, even following partial or total nephrectomy. Although positive therapies to control metastases are already available, no standard adjuvant treatments for kidney cancer have been specifically developed.

Within this trial, sunitinib, a receptor tyrosine kinase inhibitor, was used to establish a primary endpoint of disease-free survival among therapy-naïve, high-risk RCC patients following nephrectomy. Split into two separate groups, the results of sunitinib versus placebo over a 1-year period were monitored; 50 mg was administered daily following a 4-weeks-on, 2-weeks-off schedule. One patient was permitted to drop down to 37.5 mg.

Abdominal computed tomography (CT) scans of each patient were evaluated by

an independent central review committee of radiologists. Cancer still localised to the kidneys, found within lymph nodes of close proximity, metastases, or second malignancies, were noted as recurrences. Where disagreement between the panel and authors arose, biopsies of the respective tumour were sampled to detect the presence of cancerous cells.

> “Sunitinib is a potential new option for adjuvant therapy in RCC, given the increase in disease-free survival and the manageable safety profile.”

Following the collation of data, the disease-free survival rate of patients on sunitinib therapy versus placebo was significantly increased (6.8 years versus 5.6 years; hazard ratio 0.761, p=0.03). Although recurrence events categorised as ≥Grade 3 were more common in sunitinib-treated individuals (62.1% versus 21.2% on placebo), serious adverse events were comparable and no deaths were recorded as a result of drug toxicity.

Lead author Prof Alain Ravaud, Head of Medical Oncology, University Hospital of Bordeaux, Bordeaux, France, emphasised: “Sunitinib is a potential new option for adjuvant therapy in RCC, given the increase in disease-free survival and the manageable safety profile.” However, the adjuvant study ASSURE followed a very similar design and yet showed no difference in disease-free survival rates. To corroborate these new results, further meta-analyses would be needed.

Adjuvant Ipilimumab Improves Overall Survival in High-Risk Melanoma Patients

OVERALL SURVIVAL (OS) in patients with high-risk Stage III melanoma was significantly improved using ipilimumab as an adjuvant therapy, according to a ESMO press release dated the 8th October 2016 discussing the results of the EORTC 18071 Phase III trial. Summarising the trial’s findings, lead author Prof Alexander Eggermont, Director General, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, stated: “Ipilimumab adjuvant therapy brings a significant improvement of OS and has a favourable risk-benefit ratio. It clearly represents a serious option for patients with Stage III melanoma.”

> “Ipilimumab adjuvant therapy brings a significant improvement of OS and has a favourable risk-benefit ratio.”

This was the first effort to test a checkpoint blockade such as ipilimumab in adjuvant therapy for melanoma. The trial randomly assigned 951 patients to either ipilimumab or a placebo during 2008–2011. In 2015, after the study had met its primary endpoint, it was announced that ipilimumab had greatly improved recurrence-free survival after a median follow-up of 2.3 years. In 2016, with a median follow-up of 5.3 years, the authors reported the impact of ipilimumab on OS; it was found to reduce the relative risk of death by 28%. Furthermore, the OS rate after 5 years was 11% higher in those treated with ipilimumab (65%) compared with those given the placebo (54%). While ipilimumab has been shown to cause immune-related adverse events, there were no additional toxicities or deaths since the initial report at 2.3 years. The key Grade 3–4 adverse events were gastrointestinal (16%), hepatic (11%), and endocrine (18%).

The findings of this trial are expected to pave the way for other studies focussing on checkpoint blockade to attempt to improve cure rates in the adjuvant setting of melanoma and other types of disease.

47 late-breaking trials

Metastatic Renal Cell Carcinoma Patient Survival Aided by Cabozantinib

PROGRESSION-FREE SURVIVAL and response rate in patients is significantly improved by cabozantinib compared with sunitinib, according to a ESMO press release dated 10th October 2016.

While both sunitinib and cabozantinib target tyrosine kinases, cabozantinib also inhibits the activity of MET and AXL proteins. A recent Phase II multicentre trial included 157 patients who had untreated clear-cell metastatic renal cell carcinoma of poor or intermediate risk. Patients were randomised either to take oral cabozantinib (60 mg once daily), or to sunitinib (50 mg once daily, 4-weeks-on, 2-weeks-off).

> "Obviously, this study will raise a lot of questions, such as whether these results are expandable to all metastatic renal cell carcinoma patients, including the good prognosis group..."

A 31% reduction in the median rate of progression or death was observed in the cabozantinib patients compared with sunitinib patients (8.2 months versus 5.6 months; p=0.012), and the objective response rate in the cabozantinib arm was far greater than in the sunitinib arm (46% versus 18%, respectively). The incidence of Grade 3 or higher adverse events, including diarrhoea, fatigue, hypertension, palmar-plantar erythrodysesthesia, haematological events, and toxicity forced 16 patients to end their treatment earlier than anticipated. This was similar between the both arms of the study: 70.5% in the cabozantinib arm, and 72.2% in the sunitinib arm.

Although the study did not include good-risk patients, it is believed that cabozantinib will prove equally as successful in such patients according to the principal investigator Dr Toni Choueiri, Director of the Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Dr Bernard Escudier, Chairman of the Renal Cancer Unit, Institut Gustave-Roussy, Villejuif, France, commented: "Obviously, this study will raise a lot of questions, such as whether these results are expandable to all metastatic renal cell carcinoma patients, including the good prognosis group; whether cabozantinib should become a new standard of care in the first-line setting; and how we should interpret all the ongoing Phase III first-line studies which selected sunitinib as the control arm."

Nevertheless, these results are likely to provide new expectations for the treatment of this condition, according to Dr Escudier.

Neoadjuvant Chemotherapy and High-Risk Carcinoma Patients

IFOSFAMIDE in conjunction with an anthracycline as an adjuvant therapy has been trialled for the treatment of soft tissue sarcoma patients, explains a ESMO press release dated 10th October 2016. Patients with cancer isolated to the trunk or extremities and at high risk of relapsing showed a significant extension of survival on the therapy when compared with histologically-tailored regimes.

In this multicentre European randomised assessment, 287 patients were selected using a risk of relapse averaging 60–70%, and categorised into five histological subtypes representative of roughly 80% of soft tissue sarcoma cases detected within an extremity or trunk wall. Each subgroup was randomised 1:1 to determine their therapy regime; patients were trialled preoperatively on either epirubicin plus ifosfamide for three cycles (120 mg/sqm and 9 g/sqm, respectively) or a specific histologically-tailored therapy: gemcitabine plus docetaxel for patients with undifferentiated pleomorphic sarcoma; trabectedin for high-grade myxoid liposarcoma; high-dose prolonged infusion of ifosfamide for individuals with synovial sarcoma; etoposide plus ifosfamide in malignant peripheral nerve sheath tumours; or gemcitabine plus dacarbazine for leiomyosarcoma patients.

> In this 80% of patients who have a high-risk soft tissue sarcoma of the trunk or extremities, it is worthwhile considering chemotherapy with epirubicin plus ifosfamide because their prognosis is improved by 20%.

Patients given epirubicin plus ifosfamide reflected a higher relapse-free rate at 46 months compared to both those following a histology-driven regimen (0.62 versus 0.38, p=0.004) and the overall survival of the participants (0.89 versus 0.64, p=0.033). Principal investigator Dr Alessandro Gronchi, Chair of Sarcoma Surgery at the National Cancer Institute, Milan, Italy, emphasised, "In this 80% of patients who have a high-risk soft tissue sarcoma of the trunk or extremities, it is worthwhile considering chemotherapy with epirubicin plus ifosfamide because their prognosis is improved by 20%."

The aim of this study was to provide evidence of a one-third reduction in recurrence for high-risk patients; this primary target however was not met. Additionally, the study failed to provide evidence of any benefit from histologically-tailored regimens. Prof Thomas Brodowicz, Program Director of the Bone and Soft Tissue-Sarcoma Unit, Department of Medicine, Medical University Vienna, Vienna, Austria, commented, "What we can conclude out of this is that the neoadjuvant anthracycline plus ifosfamide is better than the histology-driven regimens, but the question still is, is it better in comparison to no treatment?

The Financial Burden for Cancer Patients

FINANCIAL burden experienced by cancer patients regarding their treatment was discussed at this year's ESMO Congress. According to a ESMO press release dated the 10th October 2016, researchers argued that such a burden not only impacts a patient's financial circumstances but also ameliorates quality of life and subsequently increases the risk of death.

It has been noted that even in countries where the national public health systems cover the majority of expenses, additional costs still negatively impact patients financially. For the purpose of this research, the study defined 'financial burden' as any financial difficulty reported at baseline. Investigators also defined 'financial toxicity' as a worsening of the financial score.

Lead investigator Dr Francesco Perrone, Director, Unità Sperimentazioni Cliniche, National Cancer Institute, Naples, Italy, and colleagues, gathered data from a pooled analysis of 16 prospective multicentre trials conducted within Italy, with a total of 3,670 patients with either lung, breast, or ovarian cancer. Included in the trial was The European Organisation for Research and Treatment of Cancer (EORTC) quality of life C30 questionnaire, which asked patients to assess their financial difficulties in relation to their disease or treatment on a scale from 'not at all' to 'very much'.

> ...oncologists should pay attention to the social and economic possibilities of our patients and try to advise them regarding their rights in terms of public support and respect due to their condition.

Results from the analysis identified a visible link between cancer treatment and financial burden, present in 26% of the patients at baseline, and was associated with a greater risk of a poorer global quality of life of 35% (p=0.009). In regards to financial toxicity, this was observed in 22.5% of the 2,735 who

completed the subsequent questionnaire and was associated with a 20% increase in the risk of death (p=0.007).

The results of this study, although moderate, still indicate that the financial risks of having cancer need to be better prioritised to lessen the burden. Dr Perrone commented: "Based on common sense, we oncologists should pay attention to the social and economic possibilities of our patients and try to advise them regarding their rights in terms of public support and respect due to their condition."

Patient Adherence to Oral Cancer Therapy Influenced by Cognitive Function

THE IMPACT of cognitive disorders upon patient adherence to oral anti-cancer therapies is believed to be wildly underestimated following a recent study, according to a ESMO press release dated 4th October 2016.

The development of oral anti-cancer drugs in recent years has exposed a surprisingly high frequency of patients not adhering to their prescriptions, something seen most commonly among elderly patients. Prof Florence Joly, Centre François Baclesse, Caen, France, explained: "The objective of this initial study was to assess the relationship between cognitive functions and oral medication adherence in order to identify the patient profiles who are more likely to be non-adherent."

Dr Joly stated: "This study included patients starting a new oral therapy and half were >70 years of age. Before starting treatment, a standardised neuropsychological test battery including an assessment of autonomy, depression, and anxiety were performed. Information on socio-demographic conditions was also collected."

Of the 126 patients included in the study, 111 (88%) completed the adherence questionnaires at 1 month, showing an adherence rate of 90%. The Montreal Cognitive Assessment (MoCA) showed that 50% suffered from global cognitive impairment, and that depression and working memory disorders were strongly linked with non-adherence (4.67, [1.11–19.59], p=0.0352 and 1.38, [1.03–1.85], p=0.0326, respectively).

In the study, depression and working memory dysfunctions proved to be indicators of non-adherence. It is therefore vital that physicians focus on cognitive functions before prescribing the oral anti-cancer therapy in order to distinguish patients who are most likely not to take the drugs, so the physician can make a more informed decision about patients' treatment.

> "So instead of enforcing adherence against patients' preferences, we need to first understand and then tackle the true reasons underlying non-adherence."

Dr Bettina Ryll, Chair of the ESMO Patient Advocacy Working Group, noted: "I believe the current concept of adherence is too narrow i.e. physicians expect patients to take their medication as prescribed, and non-adherence is considered a form of disobedience. Intentional non-adherence, the patient deciding not to take medication as indicated, is actually revealing patients' true preferences, and these might simply be very different from what physicians and other stakeholders consider relevant." She added: "So instead of enforcing adherence against patients' preferences, we need to first understand and then tackle the true reasons underlying non-adherence."

For the full interview with Prof Florence Joly, at ESMO click here.

22,522 participants

ESMO Calls for Improved Participation in Cancer Screening Programmes

A SELECTION of presentations at this year's ESMO congress have demonstrated the extremely low participation rates in cancer screening programmes across the globe. The studies, summarised in a ESMO press release dated 6th October 2016, looked at the possible reasons for the low numbers seen across screening programmes for a variety of the most common cancers.

> "In this particular period of extreme evaluation of cost/effectiveness ratio, screening is still the best investment for the health of our populations."

An Australian study used questionnaires to gather data from 1,562 participants on their views on cancer screening programmes, finding that time constraints and cost were the predominant reasons for non-participation. The proposal of a 'one stop cancer screening shop' received support from the vast majority of participants (85.3%; confidence interval 83.4–86.9).

The diagnoses made following emergency presentation of cancer symptoms were researched and presented within a second study. The team demonstrated the efficacy of nurse-led Acute Diagnostic Oncology Clinics (ADOCs) as an addition to current outpatient cancer diagnostic pathways. The clinics could help reduce the number of emergency presentations by supporting primary care physicians in urgent cases, thus allowing earlier diagnosis and improved patient outcomes.

A study in France has found that participation in mammography screening amongst non-breast cancer survivors is lower than that of the general population (78% versus 87%), demonstrating that awareness of a second cancer, distinct from the recurrence of a primary cancer, must be improved. The authors hope that by increasing awareness of the necessity of mammography screening, high-risk patients will be easier to identify and therapy can be initiated earlier.

Finally, a study into lung cancer screening amongst smokers has revealed that intention to take part in screening programmes amongst current smokers linked with an intention to stop smoking. However, barriers to participation amongst smokers in general were found to be complex. Further research is needed to establish significant data.

Prof Virgilio Sacchini, Weill Cornell Medical College, New York City, New York, USA, commented: "The studies being presented at the ESMO 2016 Congress should help encourage doctors and patients to respond to screening programmes proposed by national health services. [...] In this particular period of extreme evaluation of cost/effectiveness ratio, screening is still the best investment for the health of our populations."

Nivolumab Immunotherapy Superior for Cancer of The Head and Neck

IMMUNOTHERAPY is fast becoming the future of cancer therapy across the globe. Now, patient-reported outcomes from the CHECKPOINT 141 trial (NCT02105636) have reflected a statistically significant and clinically relevant benefit from nivolumab treatment, not only regarding overall survival rates, but also the maintenance of quality of life, as explained in a ESMO press release dated 9th October 2016.

Squamous cell carcinoma of the head and neck (SCCHN) patients can present with additional clinical complications compared with other cancers, for example, growths of the neck can impair eating, speaking, and lead to social isolation in some cases. Consequently, patient-completed questionnaires regarding cancer therapy often overlook important aspects negatively influencing quality of life when evaluating effectiveness.

To target this, Prof Kevin Harrington, Division of Radiotherapy and Imaging, Institute of Cancer Research, London, UK, and team utilised questionnaires encompassing functional capacity during everyday life in addition to the patients' social, cognitive, and emotional wellbeing for the completion of their randomised, open-label, Phase III trial. In total, 361 patients with recurrent or metastatic SCCHN were split into two treatment arms; those who received anti-PD-1 nivolumab and those who received their physician's choice of standard care. Of these, 129 patients completed questionnaires at baseline and during follow-up at 9 and 15 weeks. Collating the physical aspects and symptoms that were experienced, the researchers calculated an overall global health score for each participant.

nivolumab therapy was shown to maintain scores comparable to baseline more competently compared with standard treatment regimes. In some SCCHN patients, functionality even improved from baseline across the therapeutic period. Prof Harrington explained, "Nivolumab not only prolongs life but it does so while maintaining function and reducing symptoms compared to standard of care chemotherapy."

As nivolumab is only found to benefit roughly one-third of patients, the assessment of biomarkers for targeted therapy proves the next milestone pursued by researchers across cancer immunotherapy investigation. Prof Sandrine Faivre, Beaujon University Hospital, Clichy, France, commented, "This is the first study to show that an immunotherapy is superior to classical treatment options for improving quality of life and symptoms, on top of prolonging survival."

Click here to view the ESMO Awards

> "Nivolumab not only prolongs life but it does so while maintaining function and reducing symptoms compared to standard of care chemotherapy."

Paolo Bossi

Head and Neck Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

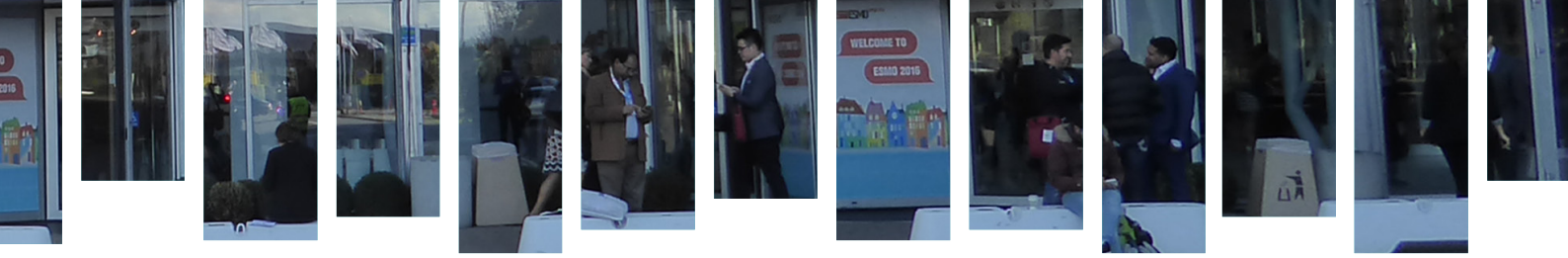
During the earlier congress review section, we included a review of an innovative presentation about the reporting of adverse events in clinical trials of targeted therapies and immunotherapies. The principal investigator of this study was Dr Paolo Bossi and the EMJ team was honoured to interview the distinguished Italian oncologist at the ESMO annual meeting. In our discussion we found out more about the study and its possible implications for medical practitioners and patients alike.

We began by asking Dr Bossi the reasons behind the review of trials that led to the approval of new drugs from 2000-2015. "A precise, clear, and unbiased way of reporting the adverse events is vital to ensure the safety of the drugs," he answered, "it is also important in order to have shared decision-making in engaging with discussion with a physician and the patient. In my original clinical practice, when I start a new treatment with a patient, I have to tell him or her what are the expected results of this drug which are the benefits the patient wants to have. But there is the other side of the coin, so the adverse event, if I am able to know, to explore, to analyse in a good way which of the toxicities I expect from this drug, I will be able to more clearly explain these to the patient and I will have more compliance and the patient will be more alert to the treatment itself."

As can be seen from our congress review story, the results of this study displayed a worrying lack of reporting of such events with many of the trials scoring poorly in reporting recurrent and late toxicities and the duration of adverse events. So what are the main factors behind these disappointing figures according to Dr Bossi? "I think that as an oncology community we are accustomed to dealing with the chemotherapy of adverse events; it is a 40-year-old story," he stated, "But we are somewhat new, inexperienced even, in toxicity of targeted therapies and immunotherapy. For example, there is a fast-track approval for new drugs and that is a very lucky thing because it means that the specific drugs are able to cover patient needs. But the other side of the coin is that sometimes we are not given the opportunity to catch the late toxicity of the drug if I have a fast-track approval and so my great concern is that we have to pay more attention also to the post-marketing reports of the adverse events of these new drugs."

The specialist in head and neck cancer then went on to describe an often under-recognised issue that is heavily related to this: the duration of adverse events from certain drugs. "I used to call the duration of the adverse event the third axis, because if you evaluate the frequency of an adverse event or the intensity, the duration of the adverse event is not usually reported in clinical trials. For example, you know that with chemotherapy we may expect higher grade adverse events but generally with a limited duration. With targeted agents or immunotherapy this is not so true: these kind of treatments are somewhat better-tolerated by the patient, but there is the cost of longer duration of adverse events, even if of a lower grade."

He then gave an example to better illustrate this point: "If you have a chemotherapy drug that causes mucositis, diarrhoea, nausea, and vomiting of a higher grade, for some Grade 3 and 4, it is typical that we expect this specific period of time from one cycle to another. Generally, by and large, it lasts 2 or 3 days, so the patient spends 2 or 3 days with a higher grade toxicity. On the other side, when you have targeted agents, it is difficult to reach such a high grade of the mucositis or nausea and vomiting and so on, but it is typical to have a longer duration of months in which the patient has got low grade diarrhoea or mucositis or fatigue and so on." Dr Bossi added: "So I do not know



which of the toxicities are more troublesome to the patient. I think we should be able to precisely describe to our patient what we expect upon this specific drug because in this way I think we will be able to prolong the treatment when it is effective and not to stop it because of some unexpected side effects."

As a prominent member of several major oncology societies and an author of a large number of important papers in his specialist areas, Dr Bossi certainly has a prominent voice within the oncology community. We asked him about his thoughts on the potential impact of this study on fellow medical professionals in the future. "As physicians we envision that it will push us to give more attention to these kind of events," he opined.

Dr Bossi had a thoughtful tone as he made his concluding remarks to us: "I think that this research will have the greatest impact on me because I will be more critical in reading and observing a new paper, and telling my next patient what he or she expects from this specific drug. In the future I would like to have more trials reporting the third axis, the duration of the adverse events. There is another key point in the future that will happen: more attention to the patient report on their health. This is not an alternative way in assessing an adverse event but is a complimentary one which will have the patient voice more listened to, and we will be able to capture, in a more sophisticated way, the adverse events of the specific trials."

> "A precise, clear, and unbiased way of reporting the adverse events is vital to ensure the safety of the drugs."

Florence Joly

Centre François Baclesse, Caen, France.

During the ESMO 2016 Congress we sat down with Prof Florence Joly to discuss her new research findings, which were presented as a part of the event. To examine the effect of relative cognitive function on oral treatment adherence, her team conducted a longitudinal study that evaluated >100 patients, with a median age of 70 years old, receiving targeted therapy or hormone therapy for metastatic disease. "For us it was a very important topic to assess the cognitive function of the patient before starting an oral therapy, because nowadays in oncology, we have more and more drugs taken orally," Prof Joly explained. At baseline, they found that 50% of the enrolled patients had moderate cognitive decline; of that 50%, only 10% demonstrated poor treatment adherence. "But among these patients, we identified that the two major parameters that may influence on the observance were depression (patients who had depression were at 4-times the risk) and also cognitive dysfunction and especially working memory." Outlining the importance of the latter, Prof Joly emphasised that: "It is particularly important because we know that working memory is one part of the memory that declines with age, and it is particularly important because this domain of memory is implicated in multi-tasking; for example, for the patients who have multiple pills to take, it could impact on the non-observance."

Highlighting that the median number of medications per patient in their study was six, Prof Joly drew our attention to the difficulty patients may experience in managing multiple treatments. "[And] we think it is a major point to improve for the future, and more particularly among the onco-geriatric domain, we have to improve the assessment of cognitive function of our patients … because this is a major issue if we want to be sure

that patients take correctly their pills ... because they could be exposed to some toxicity if we do not take this precaution." Another important point alluded to by the professor was the fact that oncologists are only recently becoming alert to the impact of cognitive function on adherence to treatment. In the past, most treatments have been administered through intravenous routes, "...but with the development of targeted therapy nowadays, we have some treatments that are taken at home by oral route, and we have to be sure that patients take the treatments correctly." To further illustrate this notion, Prof Joly drew a pertinent contrast with colleagues working in other fields, for example diabetes, who may follow-up with patients for a long period to observe and ensure treatment adherence.

Prof Joly noted that there were some unexpected findings from the study. They expected to observe a correlation between the degree of treatment adherence and patient living situations. For example, patients who lived in couples were expected to demonstrate better adherence than patients who lived alone. "We could think that the wife [for example] could help to take the pill, but we did not find that," she stated. "Really, our two major factors that could influence observance were depression and cognitive dysfunction." Furthermore, when asked about the impact of states of anxiety, the professor explained that: "We did not have a high proportion of patients with anxiety, we had a high proportion of patients who had some depression so maybe that is why we just found it among patients with depression and not with anxiety."

Most of the patients in Prof Joly's study were metastatic, thus the team found that there was no intentional non-adherence as most wanted active treatment. "Though we do not have the problem of intentional non-observance in this group of patients, it is not the case when you are in an adjuvant setting of patients taking their pills, for example breast cancer [patients] for 5 years," she elucidated. These patients may be more frustrated and demonstrate intentional non-adherence, however for the patients in her study, the non-adherence was a result of cognitive dysfunction. The other difficulty lies in identifying those patients with cognitive decline. "It is not so easy because it is not patients who have major cognitive decline, so the first time you meet them you do not realise they have cognitive decline so you have to do some more subtle tests instead of the tests we use in Alzheimer's disease," the professor explained.

Reflecting on the importance of the research, Prof Joly asserted that: "I think it is a major point we have to progress because imagine, [with] seven pills, eight pills, there are so many interactions, so for the efficacy of our drug, maybe we are not on the top of what we would like to do, [but] I think it is [nonetheless] particularly important and I insist among elderly patients before starting an oral treatment in oncology to check all the treatments they have and to see if we can decrease this list, and to be sure that there is no interaction on that [list]. Some new generations of oral treatment, for example PARP inhibitors, they are eight pills in the morning and in the evening, so imagine if you are already taking six pills; it is a very important issue, I think a major issue, we need to work on."

The professor also made some useful suggestions as to how this research could be expanded and applied in the future. "...my opinion is now we have to introduce geriatric oncology clinics in other parts of the world, because in France we have developed some specific clinics for elderly patients, and in this type of clinic we assess all comorbidities and factors linked to age to help the decision of the best oncological strategy. We should include the cognitive assessment better than we do today, and it could help the decision. For example, if you have two alternative possibilities for treatment, one i.v. and one oral, if the patient has cognitive decline maybe it is better to have i.v., or if you choose to do an oral treatment, maybe you have to organise nurse assistance at home to be sure the treatment is taken correctly."

> "...my opinion is now we have to introduce geriatric oncology clinics in other parts of the world..."

EMJ EUROPEAN MEDICAL JOURNAL

Exclusive Interviews from the European Society of Medical Oncology (ESMO) 2016 Congress

(Click on video clip to view)

An interview with Dr Simon Chowdhury at the 2016 ESMO Congress

An interview with Prof Florence Joly at the 2016 ESMO Congress

An interview with Dr Paolo Bossi at the 2016 ESMO Congress

Congress Review - ESMO 2016

SUBSCRIBE

FREE TO OUR YOUTUBE CHANNEL

www.youtube.com/EMJreviews

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

STATE-OF-THE-ART INTEGRATION OF MULTIPLE KINASE INHIBITORS IN THE TREATMENT OF GASTROINTESTINAL CANCERS

This satellite symposium took place on 4th September 2016 as a part of the European Society of Medical Oncology (ESMO) Congress in Copenhagen, Denmark

Chairperson

Axel Grothey[1]

Speakers

Marc Ychou,[2] Jean-Yves Blay,[3] Eric Van Cutsem,[4] Jordi Bruix[5]

1. Mayo Clinic, Rochester, Minnesota, USA
2. Montpellier Cancer Institute, Montpellier, France
3. Medical Oncology Department, Centre Léon Bérard, Lyon, France
4. University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium
5. BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain

Disclosure: Prof Grothey has received honoraria and grants, paid to the Mayo Foundation, from Amgen, Bayer, Boehringer Ingelheim, Boston Biomedicals, Genentech, and Taiho. Prof Ychou has received research support and honoraria from Bayer, Roche, Celgene, Baxalta, and Lilly. Prof Blay has received research support and honoraria from Bayer, Novartis, Pfizer, and Roche. Prof Van Cutsem has received a research grant from Bayer. Dr Bruix has received consultancy fees from AbbVie, Argule, Bayer, BMS, Boehringer Ingelheim, BTG, Eisai, Gilead, Kowa, Novartis, Onxeo, OSI, Roche, Sirtex, and Terumo, and has received research grants from Bayer.
Acknowledgements: Writing assistance was provided by Dr Blair Hesp, CMPP, ApotheCom, London, UK.
Support: The symposium was sponsored by Bayer. Authors received honoraria for preparation and delivery of their presentations. The views and opinions expressed are those of the authors and not necessarily of Bayer.
Citation: EMJ Oncol. 2016;4[1]:38-46.

MEETING SUMMARY

This symposium provided an overview of the efficacy and safety of multikinase inhibitors in colorectal cancer, including treatment sequencing, followed by an examination of the evidence in support of combination therapies and the use of regorafenib in gastrointestinal stromal tumours (GISTs) and other sarcomas. Prof Axel Grothey opened the symposium by introducing multikinase inhibitors and their role in treating malignancies. Prof Marc Ychou reviewed the Phase III studies supporting the use of regorafenib in later lines of therapy for patients with metastatic colorectal cancer (mCRC). Prof Grothey then discussed practical considerations when treating patients with regorafenib, including treatment sequencing and management of adverse events (AEs). Prof Jean-Yves Blay reviewed the efficacy and safety of regorafenib in treating GISTs and other sarcomas. Prof Eric Van Cutsem discussed potential future roles for regorafenib in treating difficult-to-treat malignancies such as advanced gastric and oesophagogastric cancer. Dr Jordi Bruix then demonstrated the possibility of using regorafenib as a second-line therapy in patients with hepatocellular carcinoma (HCC) who have progressed following sorafenib therapy.

Introduction

Professor Axel Grothey

Oral multikinase inhibitors have the potential to improve outcomes for patients with a variety of malignancies, such as colorectal cancer, gastric cancer, HCC, and sarcomas, including GISTs. However, many oncologists remain unfamiliar with multikinase inhibitors and their role in treating gastrointestinal tumours, despite >2 years of

real-world experience since regorafenib received marketing approval in Europe.

Maximising Patient Benefit with Third-line Treatment of Metastatic Colorectal Cancer

Professor Marc Ychou

Regorafenib is an oral multikinase inhibitor that targets multiple proteins which target kinases involved in angiogenesis (e.g. vascular endothelial growth factor receptors [VEGFR] 1–3 and TIE-2), tumour microenvironment (e.g. platelet-derived growth factor receptor [PDGFR]-β and fibroblast growth factor receptor), and oncogenesis (e.g. RAF, RET proto-oncogene, and stem cell growth factor receptor [KIT]).[1]

Regorafenib has demonstrated an overall survival (OS) and progression-free survival (PFS) benefit in patients with mCRC who have progressed after standard therapies in the randomised, placebo-controlled CORRECT and CONCUR (performed in Asian patients) trials (Figure 1).[2,3]

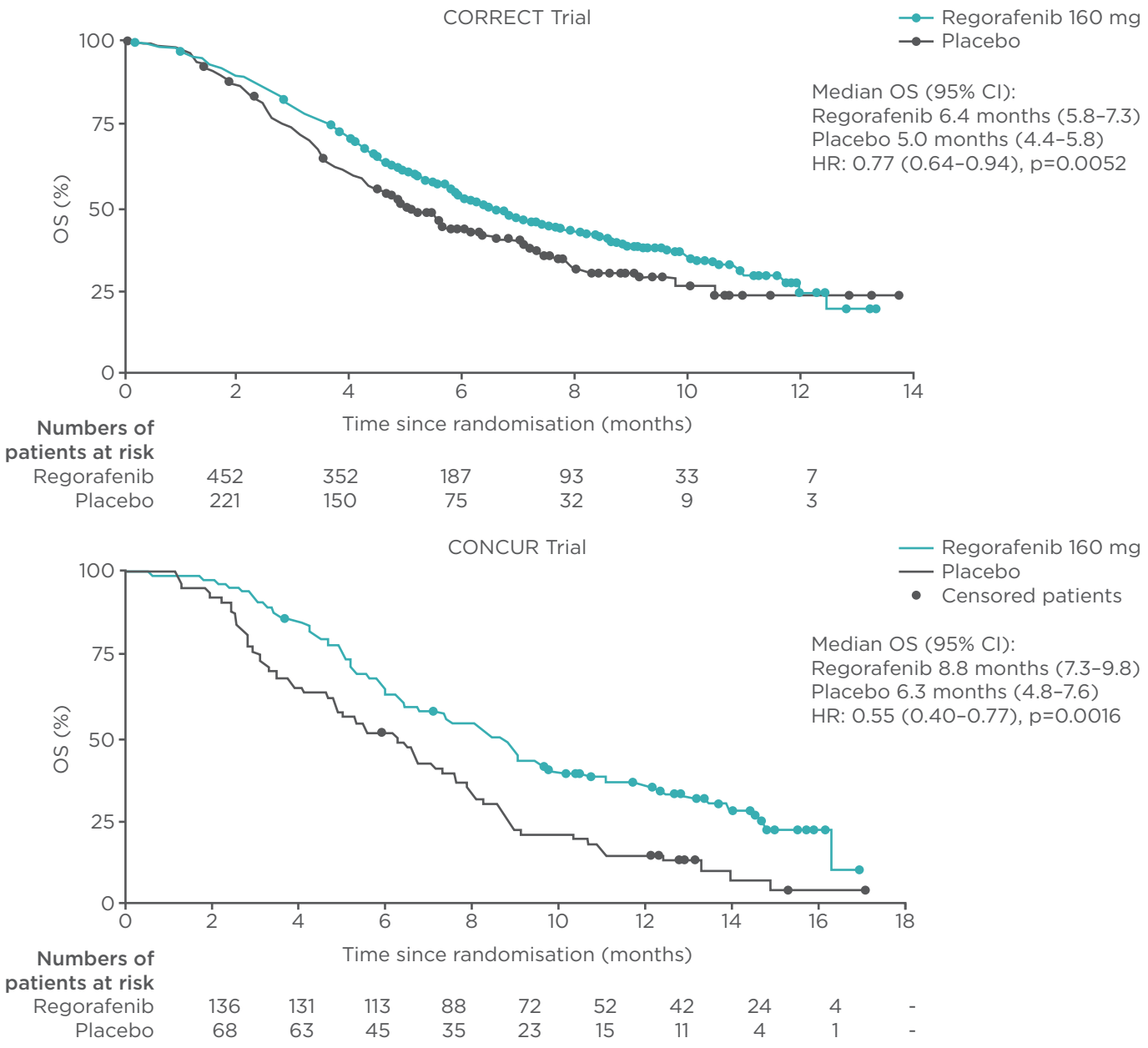


Figure 1: Overall survival benefit for patients with metastatic colorectal cancer who were administered regorafenib as a third or fourth-line treatment option.

CI: confidence interval; HR: hazard ratio; OS: overall survival.

Adapted from Grothey et al. 2013 and Li et al. 2015.[2,3]

Interestingly, the lower hazard ratios (HRs) for OS in the CONCUR trial are largely thought to relate to lower levels of pretreatment with targeted therapies in CONCUR compared with the CORRECT trial, in which all patients were pretreated with bevacizumab.[2,3] Comparable PFS outcomes have also been observed in the real-world setting in patients administered regorafenib in a third-line setting.[4]

A clinical benefit of regorafenib as a third or fourth-line therapy in patients with mCRC is the ability to achieve stable disease in a high percentage of patients. Tumour changes observed in patients with stable disease may provide early clinical markers for predicting therapeutic efficacy. One such marker is cavity formation within lesions, which is frequently observed in patients receiving anti-angiogenic therapy for primary lung tumours or pulmonary metastases.[5] A retrospective analysis of 108 patients enrolled in the CORRECT study (75 and 33 patients in the regorafenib and placebo arms, respectively) found that cavitation of lung metastases after 8 weeks of treatment was a feature observed exclusively in patients treated with regorafenib (38.7% versus 0.0% of patients treated with regorafenib or placebo, respectively; $p<0.01$).[6] Additionally, the presence of lung cavitation was associated with the absence of progressive disease at Week 8.[7]

Other potential markers have also been explored as indicators of drug efficacy. Some correlation was observed between several clinical characteristics (including Eastern Cooperative Oncology Group Performance Status [ECOG PS], the number of metastatic sites, and the time from diagnosis of metastatic disease) and extended PFS (>4 months) in the CORRECT study (representing 19% of patients in the regorafenib arm),[8] and a retrospective study in Japan (N=121), which also reported that patients administered regorafenib with a decrease in serum cancer antigen 19-9 (CA19-9) levels of >10% had a longer PFS than those whose CA19-9 levels did not decrease after one cycle of regorafenib treatment.[9] Additionally, the Colorectal Cancer Consortium Consensus for molecular subtypes has used a gene expression-based CRC classification to stratify patients with mCRC into four consensus molecular subtypes (CMS)1–4.[10] Preliminary data suggest that CMS can be used as a prognostic marker for regorafenib efficacy, with greater OS and longer PFS being observed in patients with CMS2 and CMS4.[11,12] However, this still needs to be validated in a large patient population.

In conclusion, regorafenib has demonstrated a benefit in improving survival in both Western and Asian populations.[2,3] Imaging and molecular markers, such as cavitation of lung metastases and serum CA19-9 levels, are potential indicators of regorafenib efficacy.[6,7,9] In the future, further research elucidating the molecular markers that predict drug efficacy will be beneficial for identifying patients who are most likely to benefit from regorafenib therapy.

Practical Treatment Sequencing in Third-Line Metastatic Colorectal Cancer

Professor Axel Grothey

Improved outcomes in patients with mCRC are being driven by the sequential use of multiple lines of treatment.[13] While guidelines provide direction on appropriate patient selection and treatment sequencing in first and second-line therapy, numerous options are now also available in the third and fourth lines, including regorafenib and TAS-102.[14,15]

Regorafenib has been shown to be efficacious in two large Phase III studies as a third or fourth-line treatment for patients with mCRC (52% of patients in CORRECT and 59% in CONCUR received ≤3 prior therapies for mCRC),[2,3] particularly in patients who have been less heavily pretreated with targeted therapies.[16] While oncologists can be wary of treatment-related AEs, regorafenib has a different mechanism of action and AE profile compared with chemotherapy, which may be beneficial, particularly for patients with myelosuppression.[2,3,17] Regorafenib treatment may also offer an opportunity for patients to have a break from chemotherapy, before being re-challenged, if appropriate.[2,18]

Patients selected for regorafenib therapy should generally be less heavily pretreated, have an ECOG PS of 0 or 1, and be capable of understanding and managing treatment-related AEs.[19] Fatigue and hand–foot skin reactions tend to appear early in patients treated with regorafenib, so patients should be educated on how to manage these AEs.[19] For example, patients may be advised to remove calluses, dead skin, make their skin smoother, and wear comfortable shoes.[19] Reminding patients that they may experience fatigue and voice changes also allows them to prepare for therapy.[19]

Regular and frequent monitoring (weekly during the first 2 months) of patients treated with

regorafenib is recommended so that therapy can be interrupted or reduced before any serious AEs occur.[19] The dose of regorafenib can also be titrated to meet the needs of individual patients.[1,19]

Patients whose disease progressed following regorafenib therapy can subsequently be treated with chemotherapy. In the CORRECT study, 26% of patients were treated with chemotherapy following regorafenib.[2] In the real-world experience (Mayo Clinic, MD Anderson Cancer Center, University of Southern California, California, USA; N=173), it was found that 37% of patients treated with regorafenib went on to receive subsequent therapy (either standard chemotherapy or an investigational therapy in a clinical trial), with disease control achieved in 61% of patients treated with chemotherapy after regorafenib.[20]

TAS-102 remains a treatment option for patients who have progressed on regorafenib. In the randomised, placebo-controlled Phase III RECOURSE study, the clinical benefit associated with TAS-102 was maintained irrespective of prior treatment with regorafenib.[17] Data from a small retrospective Japanese study (N=43) indicated that better outcomes are observed with TAS-102 treatment in regorafenib-pretreated versus regorafenib-naïve patients.[21] Furthermore, patients who were administered regorafenib before TAS-102 had increased OS.[21]

Further investigation is needed regarding the use of regorafenib in combination with other regimens, including chemotherapy and targeted therapies.[22-24] For example, second-line therapy with regorafenib (160 mg Days 4–10 and 18–24) in combination with FOLFIRI (Days 1–2 and 15–16) significantly increased PFS (primary endpoint), but not OS, compared with FOLFIRI alone in patients with mCRC who have progressed following first-line oxaliplatin-based chemotherapy, and was generally well-tolerated with little increase compared with the control chemotherapy regimen.[25] However, more prospective data are required in this realm before it is fully integrated into clinical practice. Furthermore, preclinical studies combining anti-VEGF therapy with immune checkpoint blockade suggest a favourable anti-tumour response, and preclinical data indicate that, in theory, regorafenib may enhance anti-tumour activity when combined with these therapies.[24]

Therefore, while regorafenib is recommended as a third or fourth-line treatment for patients with mCRC, treatment sequencing and the timing of later lines of treatment should be considered when attempting to achieve optimal survival outcomes. Future research will further clarify the role of regorafenib in treating patients with mCRC, including optimal dosing combination therapies.[24,25]

Targeting Kinase Pathways to Treat Progressive Gastrointestinal Stromal Tumours and Other Sarcomas

Professor Jean-Yves Blay

Sarcomas are a relatively rare form of cancer, accounting for approximately 1% of all tumours.[26] GISTs are the most common sarcomas, and are most frequently driven by gain-of-function mutations in *KIT* and *PDGFRA*.[27]

The tyrosine kinase inhibitor (TKI) imatinib is the standard first-line therapy for patients with metastatic and/or unresectable GISTs.[28,29] However, the impact of targeted treatment with imatinib depends on the nature of the underlying mutation. For example, imatinib 400 mg is effective when treating most GISTs, but patients with exon 9 mutations require 800 mg to achieve optimum PFS. In addition, certain gene mutations confer resistance to imatinib, particularly mutations involving *PDGFRA*, and these more difficult-to-treat GISTs require different treatment approaches.

Oral multikinase inhibitors, such as sunitinib and regorafenib, are second and third-line treatment options, respectively, for patients with GISTs who have progressed following imatinib treatment.[30] However, resistance to treatment with TKIs can emerge through the clonal selection of additional mutations, mostly in exon 17 and 18, or 13 and 14, of *KIT*. Therefore, the kinase inhibition profiles of multikinase inhibitors are clinically important.

The benefits of regorafenib in treating advanced GISTs have been well-documented. In a single-arm Phase II study, patients with unresectable or metastatic GISTs (N=33) that had progressed following imatinib and sunitinib treatment, and were treated with regorafenib, had a PFS of 13.2 months and an OS of 25.0 months.[31] The Phase III GRID study reported that regorafenib significantly improved PFS (HR: 0.27 [95% confidence interval (CI): 0.19–0.39]) compared with placebo in patients with advanced GISTs that progressed after failure of imatinib and sunitinib.[31] Of particular interest

was that the activity of regorafenib was similar in patients with *KIT* exon 9 and exon 11 mutations (HR: 0.21 [95% CI: 0.098–0.458] for exon 11 mutations versus HR: 0.24 [95% CI: 0.07–0.88] for exon 9 mutations; Figure 2).[32] Regorafenib was found to be efficacious in patients with previously treated GISTs, regardless of the presence of secondary *KIT* mutations.[31,32] Furthermore, the AE profile of regorafenib was consistent with that observed in other studies, but the rate of discontinuation due to AEs was similar to placebo.[31] Following on from these results, the efficacy and safety of alternating between imatinib and regorafenib therapy as a first-line therapy for patients with GISTs is being investigated in a Phase II trial.[33]

Regorafenib may also be effective in treating patients with soft-tissue, visceral, and bone sarcomas. The PALETTE study demonstrated improved median PFS in patients with a soft-tissue sarcoma and progressive disease following treatment with chemotherapy, administered the multikinase inhibitor pazopanib compared with placebo (4.6 versus 1.6 months; HR: 0.31 [95% CI: 0.24–0.40], p<0.0001).[34] Following this, the randomised Phase II REGO-SARC study explored regorafenib in doxorubicin-pretreated patients with a variety of soft-tissue sarcomas. There was no significant difference observed for the liposarcoma cohort but improvement in PFS compared with placebo was observed in:[35]

- Leiomyosarcoma (3.7 versus 1.8 months; HR: 0.46 [95% CI: 0.26–0.80], p=0.005)
- Synovial sarcoma (5.6 versus 1.0 months; HR: 0.10 [95% CI: 0.03–0.35], p<0.00001)
- Other sarcomas (2.9 versus 1.0 months; HR: 0.46 [95% CI: 0.25–0.82], p=0.006)

Overall, in a pooled analysis, regorafenib was found to increase PFS for non-adipocytic sarcoma (4.0 versus 1.0 months; HR: 0.36 [95% CI: 0.26–0.53], p<0.0001) and exhibited a trend towards increased OS (13.4 versus 9.0 months; HR: 0.67 [95% CI: 0.44–1.02], p=0.06). In this study, the AE profile was consistent with the known safety profile of regorafenib.[1,35]

Further investigations of the role of regorafenib in treating patients with metastatic bone sarcomas that cannot be cured by surgery or radiotherapy are also currently underway in the REGOBONE study.[36] Patients are currently being randomised to regorafenib or placebo and data from this study will be disseminated in due course.

Regorafenib therefore offers a potential treatment option for patients with GISTs who have progressed following prior TKI therapy or who present with secondary resistance mutations.[31,33]

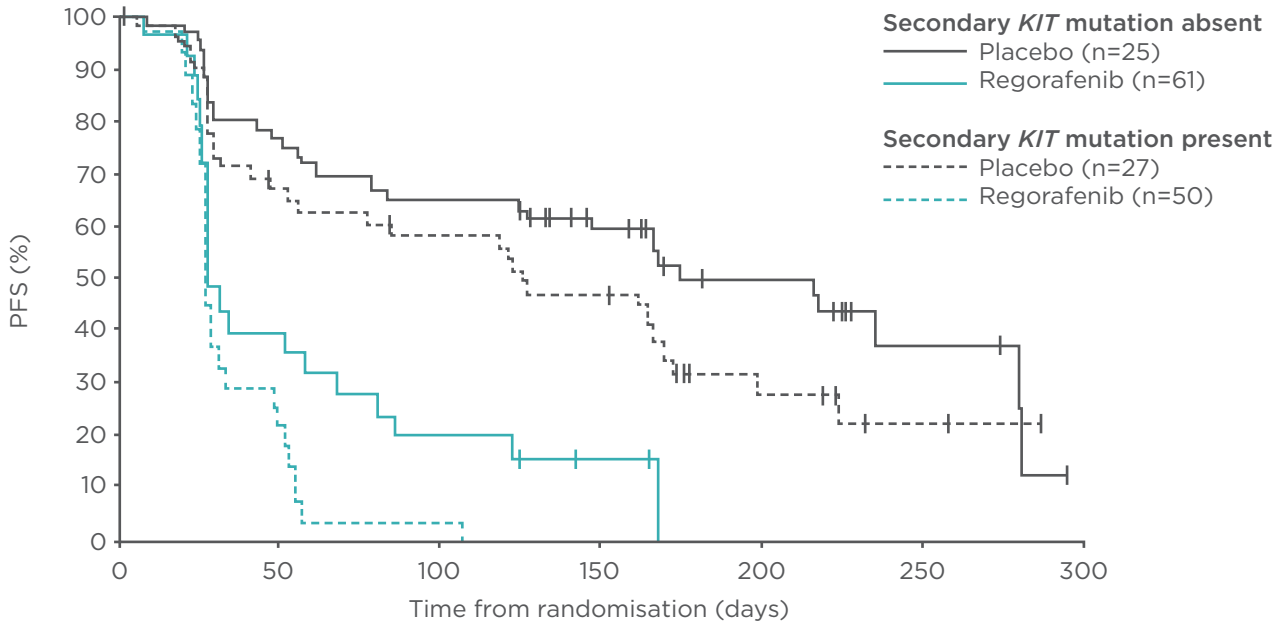


Figure 2: Progression-free survival in patients with a gastrointestinal stromal tumour with secondary *KIT* mutations.

PFS: progression-free survival.

Adapted from Demetri et al. 2013.[32]

Likewise, regorafenib may offer a potential treatment option for patients with other soft tissue sarcomas or bone sarcoma, and studies of the efficacy and safety of regorafenib in these patients are ongoing.[35,36]

The Emerging Role of Multikinase Inhibitors for Treatment of Refractory Advanced Oesophagogastric Cancer

Professor Eric Van Cutsem

Gastric and oesophageal cancers are common causes of cancer-related deaths worldwide[37] yet relatively few treatment options are available. Surgical resection offers the only potentially curative option, although many patients present with advanced disease or develop metastases post-resection.[38,39] Multikinase inhibitors, such as regorafenib, represent a potential therapeutic option for patients for whom curative resection is not an option.

Current treatment options for advanced oesophagogastric cancer either inhibit the human epidermal growth factor receptor 2 (HER2) or act by antagonising VEGFR2. The European Society of Medical Oncology (ESMO) guidelines recommend trastuzumab in combination with doublet chemotherapy as a first-line treatment option for patients with HER2-positive gastric cancer,[39] but for patients with HER2-negative tumours, ramucirumab, an anti-VEGFR2 monoclonal antibody, is the only approved targeted therapy.[40]

For patients with advanced gastric cancer, an extensively targeted approach aimed at selectively inhibiting VEGFR2 is an alternative treatment option. Apatinib, a TKI that targets endothelial migration and proliferation, is believed to be effective in combination with cytotoxic chemotherapy.[41] In a Chinese Phase III study, apatinib significantly increased OS by 1.8 months compared with patients administered a placebo to 6.5 months (HR: 0.71 [95% CI: 0.54–0.94], p=0.015), making apatinib a potentially attractive treatment option for patients with advanced gastric cancer.[42] The randomised, double-blind, placebo-controlled Phase II INTEGRATE study investigated regorafenib in patients with a metastatic or locally recurrent gastric or oesophagogastric junction adenocarcinoma that were refractory to first or second-line chemotherapy (N=152 [regorafenib, n=100; placebo, n=52]) as the molecular targets of regorafenib include kinases that act downstream from VEGFR2.[43] In this study, regorafenib treatment resulted in a significant increase in PFS versus placebo (2.6 versus 0.9 months; HR: 0.40 [95% CI: 0.28–0.59], p<0.001) and a non-significant longer trend in OS.[43] Additionally, regorafenib was generally well-tolerated, with an AE profile that was consistent with those previously reported in other studies.[2,3,43] Following this data, the Phase III INTEGRATE II study regorafenib is further investigating the efficacy and safety of regorafenib in patients with treatment-refractory advanced oesophagogastric cancer.[44]

Therefore, while treatment with first-line trastuzumab and second-line ramucirumab is possible for patients with HER2-positive gastric cancer,[39,40] oral multikinase inhibitors such as apatinib and regorafenib may offer an effective treatment option for patients with advanced oesophagogastric cancer who have limited treatment options.[41-43]

State-of-the-Art Treatment of Hepatocellular Carcinoma

Doctor Jordi Bruix

Most physicians consider HCC to be a disease that lacks effective treatment options, despite the availability of therapies that effectively improve patient survival and as such are recommended in evidence-based practice guidelines. Treatment is recommended based on an HCC-specific staging model that delineates HCC into different evolutionary stages.[45] Importantly, the pattern and location of disease in patients with HCC dictates whether surgical resection, transplantation, ablation, or transcatheter chemoembolisation is feasible, or whether the patient should be treated with systemic therapy.

Almost 10 years ago, a new era in the treatment of HCC was heralded when the first data indicating that sorafenib, a drug unsuitable for locoregional therapy, increased OS for both Western and Asian patients with HCC were disseminated.[46,47] Since then all Phase III trials of novel systemic therapies for HCC have failed to improve outcomes in first or second-line settings. Hence, sorafenib was the sole systemic agent providing survival benefit.[48-57] However, data from the Phase III placebo controlled trial demonstrated the efficacy of regorafenib as a second-line treatment in

patients with HCC who progressed following sorafenib therapy.[58] In addition, the study showed a manageable safety profile, with drug-related AEs causing treatment interruption in 10% of patients. Quality of life, measured by patient-reported outcomes, was not affected by treatment.

In the randomised (2:1), double-blind RESORCE study, patients with HCC (Barcelona Liver Cancer Clinic Stage B or C disease who could not benefit from resection, local ablation, or transcatheter chemoembolisation; Child–Pugh A liver function) and documented radiological progression following sorafenib treatment were randomised to receive 4-week cycles of regorafenib 160 mg daily (3 weeks on/1 week off; n=379) or placebo (n=194) within 10 weeks of their last sorafenib dose.[59] Importantly, patients enrolled in this study were required to have tolerated sorafenib therapy given that both treatments are TKIs.[59] OS in patients treated with regorafenib significantly increased to 10.6 months compared with 7.8 months in the placebo arm (HR: 0.63 [95% CI: 0.50–0.79], p<0.001).[59] All subgroup analyses also indicated a favourable outcome in patients treated with regorafenib.[59]

A PFS benefit was observed in patients treated with regorafenib compared with placebo (3.1 versus 1.5 months; HR: 0.46 [95% CI: 0.37–0.56], p<0.001).[59] A comparable result was also observed when assessing time to progression (TTP) in patients treated with regorafenib or placebo (3.2 versus 1.5 months; HR: 0.44 [95% CI: 0.36–0.55], p<0.001).[59] A consistent PFS and TTP benefit was also observed for all subgroups in the regorafenib treatment arm.[59] The ORR and disease control rate were also significantly increased in patients treated with regorafenib compared with placebo, when assessed using either modified or revised (version 1.1) Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[59] Notably, the disease control rate of 65% with regorafenib compared with 36% with placebo represented disease stabilisation in a greater proportion of patients (assessed using modified RECIST criteria; p<0.001), while the TTP was not different when using RECIST or mRECIST.[59]

Regorafenib treatment was well-tolerated, with 49% of regorafenib-treated patients maintaining the full dose of therapy throughout the study, and the AE profile was consistent with that observed in other studies.[2,3,59] The most common AEs were hand–foot skin reactions, fatigue, and hypertension.[59] Treatment-emergent and drug-related AEs led to treatment discontinuation in 25% and 10% of patients in the regorafenib arm, respectively, and regorafenib did not appear to affect liver function.[59]

Regorafenib is thus effective as a second-line treatment option for patients with HCC who have progressed following previous sorafenib treatment.[59] Regorafenib is generally well-tolerated in patients who have tolerated sorafenib therapy and stabilises the disease in a high proportion of patients, with a significant and clinically relevant increase in TTP, PFS, and OS.[59]

REFERENCES

1. European Medicines Agency. Stivarga® (regorafenib). Summary of product characteristics. May 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002573/WC500149164.pdf. Last accessed: 18 October 2016.

2. Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international multicentre randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

3. Li J et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16(6):619-29.

4. Van Cutsem E et al. CONSIGN: An open-label phase 3B study of regorafenib in patients with metastatic colorectal cancer (mCRC) who failed standard therapy. Abstract 2139. European Cancer Congress, 25-29 September 2015.

5. Crabb SJ et al. Tumor cavitation: impact on objective response evaluation in trials of angiogenesis inhibitors in non-small-cell lung cancer. J Clin Oncol. 2009;27(3):404-10.

6. Ricotta R et al. Cavitation of lung metastases induced by regorafenib in patients with colorectal carcinoma: Data from the phase III CORRECT study. Abstract 2015. European Cancer Congress, 25-29 September 2015.

7. Ricotta R et al. Regorafenib for metastatic colorectal cancer. Lancet. 2013;381(9877):1537.

8. Grothey A et al. Subgroup analysis of patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) in the CORRECT trial who had progression-free survival (PFS) longer than 4 months. Abstract 710. ASCO Gastrointestinal Cancers Symposium, 15-17 January 2015.

9. Komori A et al. Serum CA19-9 response is an early predictive marker for the efficacy of regorafenib in refractory metastatic colorectal cancer. Abstract 169P. ESMO Asia Congress, 18-21 December 2015.

10. Guinney J et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21(11):1350-6.

11. Teufel M et al. Molecular subtypes and outcomes in regorafenib-treated patients with metastatic colorectal cancer (mCRC) enrolled in the CORRECT trial. Abstract 3558. ASCO Gastrointestinal Cancers Symposium, 15-17 January 2015.

12. Dienstmann R et al. Colorectal

Cancer Subtyping Consortium (CRCSC) identification of a consensus of molecular subtypes. Abstract 3511. ASCO Annual Meeting, 30 May-3 June 2014.

13. Hanna N et al. Survival benefit associated with the number of chemotherapy/biologic treatment lines in 5,129 metastatic colon cancer patients. Abstract 559. ASCO Gastrointestinal Cancers Symposium, 16-18 January 2014.

14. Van Cutsem E et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386-422.

15. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Colon Cancer. Version 2. 2016. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Last accessed: 18 October 2016.

16. Li J et al. CONCUR: A randomized, double-blind, placebo-controlled phase 3 study of regorafenib monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC). Ann Oncol. 2016;27(Suppl 2):ii114-5.

17. Mayer RJ et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.

18. Van Cutsem E et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii1-9.

19. Grothey A. Regorafenib in metastatic colorectal cancer: optimal dosing and patient selection recommendations. Clin Adv Hematol Oncol. 2015;13(8):514-7.

20. Kidd MT et al. Efficacy of chemotherapy after treatment with regorafenib in metastatic colorectal cancer (mCRC). Abstract 678. ASCO Gastrointestinal Cancers Symposium, 15-17 January 2015.

21. Arita S et al. Efficacy and safety of TAS-102 in clinical practice of salvage chemotherapy for metastatic colorectal cancer. Anticancer Res. 2016;36(4):1959-66.

22. Napolitano S et al. Primary and acquired resistance of colorectal cancer to anti-EGFR monoclonal antibody can be overcome by combined treatment of regorafenib with cetuximab. Clin Cancer Res. 2015;21(13):2975-83.

23. Sanz-Garcia E et al. Current and advancing treatments for metastatic colorectal cancer. Expert Opin Biol Ther. 2016;16(1):93-110.

24. Ott PA et al. Inhibition of immune checkpoints and vascular endothelial growth factor as combination therapy for metastatic melanoma: An overview of rationale, preclinical evidence, and initial clinical data. Front Oncol. 2015;5:202.

25. O'Neil B et al. A multi-center, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo for patients with metastatic colorectal cancer who failed one prior line of oxaliplatin-containing therapy. Ann Oncol. 2016;27(Suppl. 6):vi154.

26. Mastrangelo G et al. Incidence of soft tissue sarcoma and beyond: a population-based prospective study in 3 European regions. Cancer. 2012;118(21):5339-48.

27. Corless CL et al. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011;11(12):865-78.

28. Gastrointestinal stromal tumor meta-analysis group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247-53.

29. Blay JY et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol. 2015;16(5):550-60.

30. Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.

31. Ben-Ami E et al. Long-term follow-up results of the multicentre phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol. 2016;27(9):1794-9.

32. Demetri GD et al. Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes. Abstract 10503. ASCO Gastrointestinal Cancers Symposium, 24-26 January 2013.

33. Clinicaltrials.gov. NCT02365441. A randomised trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (GIST) (ALT GIST). 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02365441. Last accessed: 8 November 2016.

34. van der Graaf WT et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.

35. Penel N et al. Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes. Abstract 11003. ASCO Gastrointestinal Cancers Symposium, 24-26 January, 2013.

36. Clinicaltrials.gov. A Phase II study evaluating efficacy and safety of regorafenib in patients with metastatic bone sarcomas (REGOBONE). 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02389244?term=regobone&rank=1. Last accessed: 19 October 2016.

37. Globocan. All cancers (excluding non-melanoma skin cancer) Estimated Incidence, Mortality and Prevalence Worldwide in 2012. 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Last accessed: 17 October 2016.

38. Kofoed SC et al. Intrathoracic anastomotic leakage after gastroesophageal cancer resection is associated with increased risk of recurrence. J Thorac Cardiovasc Surg. 2015;150(1):42-8.

39. Smyth EC et al.; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl. 5):v38-v49.

40. Van Cutsem E et al. Gastric cancer. Lancet. 2016. [Epub ahead of print].

41. Mi YJ et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res. 2010;70(20):7981-91.

42. Li J et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016;34(13):1448-54.

43. Pavlakis N et al. Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial. J Clin Oncol. 2016;34(23):2728-35.

44. Clinicaltrials.gov. NCT02773524. A Study of Regorafenib in Refractory Advanced Gastro-Oesophageal Cancer (INTEGRATEII). 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02773524. Last accessed: 31 October 2016.

45. Bruix J et al. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;150(4):835-53.

46. Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.

47. Cheng AL et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised,

double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34.

48. Cheng AL et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol. 2013;31(32):4067-75.

49. Cainap C et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol. 2015;33(2):172-9.

50. Qin S et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol. 2013;31(28): 3501-8.

51. Johnson PJ et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol. 2013;31(28):3517-24.

52. Zhu AX et al. Biomarker Analyses of Clinical Outcomes in Patients with Advanced Hepatocellular Carcinoma Treated with Sorafenib with or without Erlotinib in the SEARCH Trial. Clin Cancer Res. 2016;22(19):4870-9.

53. Leniconi R et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64(5):1090-8.

54. Llovet JM et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013;31(28):3509-16.

55. Zhu AX et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA. 2014;312(1):57-67.

56. Zhu AX et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859-70.

57. Abou-Alfa GK et al. Phase III randomized study of second line ADI-peg 20 (A) plus best supportive care versus placebo (P) plus best supportive care in patients (pts) with advanced hepatocellular carcinoma (HCC). Abstract 4017. ASCO Gastrointestinal Cancers Symposium, 21-23 January 2016.

58. Bruix J et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer. 2013;49(16):3412-9.

59. Bruix J et al. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial. Ann Oncol. 2016;27:140-1.

OPTIMISING SALVAGE THERAPY IN AGGRESSIVE B CELL NON-HODGKIN LYMPHOMA

This symposium took place on 7th October 2016 as a part of the European Society for Medical Oncology (ESMO) 2016 Congress in Copenhagen, Denmark

Chairpersons

Francesco D'Amore,[1] Ruth Pettengell[2]

Speakers

Pieternella Lugtenburg,[3] Ruth Pettengell,[2] Pier Luigi Zinzani,[4] Raul Cordoba[5]

1. Aarhus University Hospital, Aarhus, Denmark
2. St George's, University of London, London, UK
3. Erasmus MC Cancer Institute, Rotterdam, Netherlands
4. Institute of Hematology "Lorenzo e Ariosto Seràgnoli", University of Bologna, Bologna, Italy
5. University Hospital Fundacion Jimenez Diaz, Madrid, Spain

Disclosure: Prof Francesco D'Amore has received speaker's honoraria, advisory boards, and research support from Servier/CTI; speaker's honoraria and research support from Takeda; fees for advisory boards from Nanovector; and research support from Sanofi/Genzyme and Roche. Dr Ruth Pettengell has acted as a speaker for CTI, Gilead, Pfizer, Servier, Takeda, and TEVA. Dr Pieternella Lugtenburg has received research funding from Takeda, Servier, and Roche; has acted as an advisor for Roche, Servier, Takeda, Celgene, Genmab, and BMS; and has acted as a speaker for Servier. Prof Raul Cordoba has acted as an advisor or speaker for Pfizer, Janssen, Gilead, Roche, and Servier. Prof Pier Luigi Zinzani has acted as an advisor or speaker for Roche, Celgene, Servier, Gilead, Janssen, Takeda, Pfizer, Astellas, and TG Pharmaceuticals.
Acknowledgements: Writing assistance was provided by Karen Yee, PhD, of ApotheCom.
Support: The symposium and publication of this article was funded by Servier. The views and opinions expressed are those of the authors and not necessarily of Servier.
Citation: EMJ Oncol. 2016;4[1]:47-55.

MEETING SUMMARY

Prof D'Amore opened the symposium by highlighting that management of patients with relapsed or refractory aggressive B cell non-Hodgkin lymphoma (NHL) remains an unmet clinical need because of its poor prognosis and the lack of effective therapeutic options. He proceeded to introduce pixantrone, the first approved single-agent treatment for the management of aggressive NHL in the third or fourth lines. Dr Lugtenburg then outlined the current treatment landscape for diffuse large B cell lymphoma (DLBCL). Dr Pettengell presented clinical evidence from the PIX301 study, explaining the clinical evidence behind the regulatory approvals for the use of pixantrone in relapsed or refractory aggressive NHL as well as discussing the mechanism of action of pixantrone. Prof Zinzani discussed the use of pixantrone as a new therapeutic option in clinical practice, and was followed by Prof Cordoba, who presented two clinical cases of patients treated with pixantrone. The symposium concluded with a panel discussion.

Introduction

Professor Francesco D'Amore

Pixantrone is the first single-agent treatment for the management of aggressive NHL in the third or fourth lines approved by the European Medicines Agency (EMA)[1] on the basis of data from the PIX301 study. It is indicated for the treatment of adult patients with multiple relapsed or refractory aggressive NHL and this recommendation is reflected in national/international treatment

guidelines such as the European Society of Medical Oncology (ESMO)[2] and National Institute for Health and Care Excellence (NICE) guidance in the UK.[3] The use of this new treatment option in clinical practice is currently being established.

Current Treatment Landscape of Diffuse Large B Cell Lymphoma

Doctor Pieternella Lugtenburg

Epidemiology and Prognosis

The majority (about 85%) of NHLs arise from B-lymphocytes; with DLBCL being the most common subtype (37%).[4] DLBCL can present *de novo*, or as a transformation from a more indolent form of lymphoma.[5] The incidence of DLBCL varies across the world, ranging from 3.8 per 100,000 inhabitants in Europe[6] to 7 per 100,000 in the USA. It is mainly a disease of the middle-aged and elderly, with a median age at presentation of 64 years. Known risk factors for DLBCL include a family history of haematological malignancies, autoimmune diseases (such as Sjögren's syndrome), and certain viral infections like HIV.[7] Immunosuppression is also a well-known risk factor for the development of DLBCL.

DLBCL is a curable disease; data from the French Cancer Registry Population have shown a favourable prognosis for DLBCL. Even though elderly patients have a poorer prognosis than young patients, the prognosis for all age groups over the last decade has improved significantly,[8] primarily due to the introduction of rituximab, a monoclonal antibody that targets the CD20 antigen expressed on almost all B cell lymphomas.[9]

DLBCL is a heterogeneous disease and, as such, not all patients have the same prognosis; in the clinic, the International Prognostic Index (IPI) score is used to determine the prognosis. The IPI score is determined by five different negative prognostic factors related to the patient and disease (age, performance status, lactate dehydrogenase levels, stage of disease, and extranodal lesions).[10] Gene-expression profile studies have also revealed two important molecular subtypes of DLBCL according to the cell-of-origin: germinal-centre B cell-like (GCB) DLBCL and activated B cell-like (ABC) DLBCL. Patients with the ABC subtype have been shown to have a worse outcome compared with those with the GCB subtype,[11] and therefore, there is a high unmet medical need in this subgroup of patients.

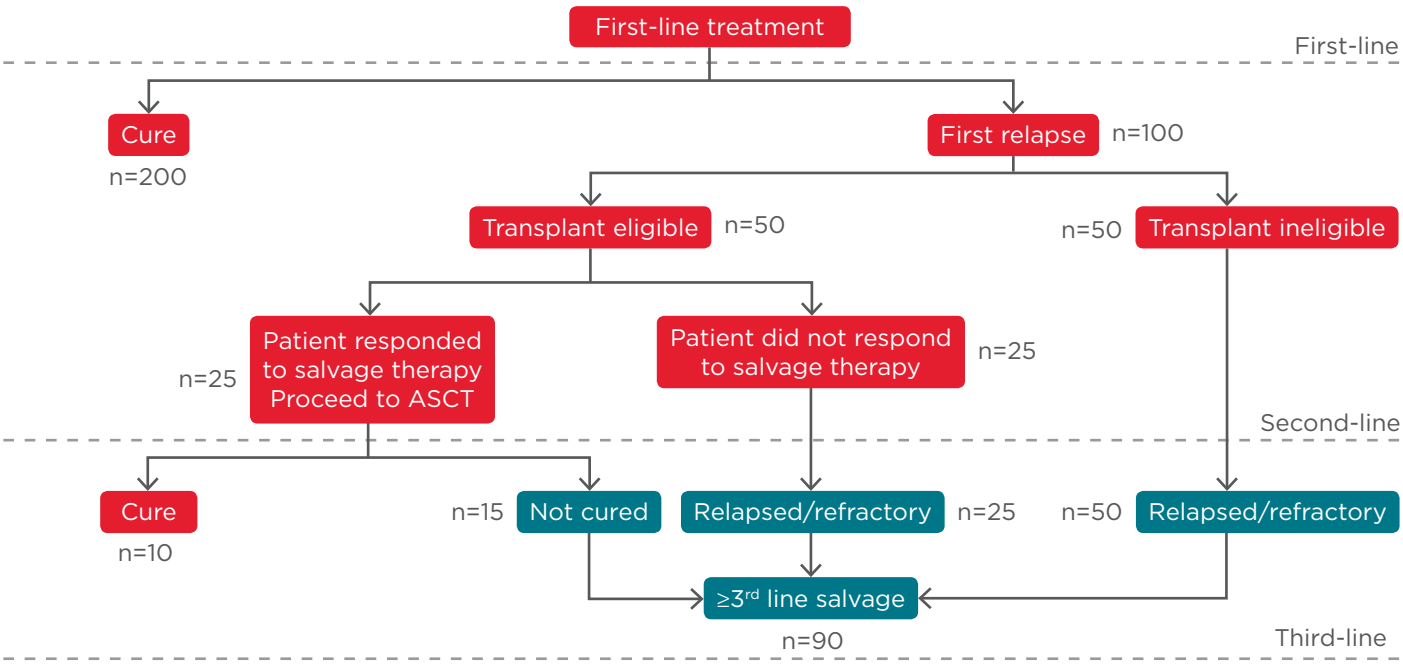


Figure 1: A treatment algorithm for aggressive B cell non-Hodgkin lymphoma.*
*Based on 300 patients diagnosed with diffuse large B cell lymphoma.
ASCT: autologous stem cell transplantation.
Adapted from Friedberg 2011.[12]

Treatment Algorithm for Aggressive Non-Hodgkin Lymphoma

Figure 1 depicts a treatment algorithm for treatment of aggressive NHL.[12] According to the ESMO guidelines, R-CHOP (rituximab with cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine, and prednisolone) or R-CHOP-like therapy are recommended for first-line treatment of aggressive NHL for both young and elderly fit patients.[12] Patients with a high IPI score who are at a high risk of relapse could be given a more intensive regimen, such as initial high-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (ASCT). Doxorubicin can be substituted with other drugs (e.g. gemcitabine, etoposide, or liposomal doxorubicin) in patients who are unfit or frail. With R-CHOP treatment, between 50% and 60% of patients are cured, 30–40% relapse, and 10% have refractory disease.[13] Most relapses occur within the first 2 years of initiation of therapy, and are usually symptomatic;[14] this patient population with relapsed/refractory (RR)-DLCBL disease is very heterogeneous and has a poor life expectancy.

Following relapse, the eligibility of patients with RR-DLBCL for HDCT followed by ASCT can be assessed using criteria from various organisations, such as the American Society for Blood and Marrow Transplantation (ASBMT)[15] and Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GEL-TAMO) experience.[16] Additional considerations include performance status of the patient and organ (cardiac, pulmonary, liver, and kidney) function.

Transplant-eligible patients should be treated with salvage chemotherapy regimens (i.e. rituximab, cisplatin, cytarabine, dexamethasone [R-DHAP]; rituximab, ifosfamide, carboplatin, etoposide [R-ICE]; rituximab, cisplatin, gemcitabine, dexamethasone [R-GDP]); if patients are responsive, this will be followed by HDCT and subsequent ASCT.[2] Allogeneic stem-cell transplantation should be considered if patients relapse after rituximab-HDCT with ASCT. The role of ASCT following HDCT in relapsed DLBCL has previously been established as standard-of-care in the PARMA trial.[5,17]

To date, only two randomised controlled trials in RR-DLBCL have been carried out: the CORAL study evaluating R-DHAP versus R-ICE; and another comparing R-DHAP and R-GDP. There was no difference in efficacy; however, differences in toxicity profiles were observed among the various treatment regimens. Although the best therapy for second-line treatment has not been established, it was suggested that clinicians should prescribe the treatment that they are most familiar with, while evaluating the comorbidities of the patient balanced against the toxicity of the chosen regimen. In the CORAL study, subanalyses of event-free survival showed that patients with early relapse (<12 months after diagnosis) had a significantly better survival rate if they had not received prior rituximab;[18] these results indicate that patients treated with rituximab in the first line cannot be salvaged with the current salvage therapies and therefore have a high unmet clinical need. In the Bio-CORAL study, which evaluated R-DHAP versus R-ICE, patients with GCB DLBCL responded significantly better to R-DHAP compared to patients with non-GCB subtypes.[19] Thus, cell-of-origin remains a major and independent factor in RR-DLBCL.

Transplant-ineligible patients generally receive palliative treatment with platinum and/or gemcitabine-based regimens or are treated with novel drugs in clinical trials.[2] R-DHAP or R-ICE regimens are generally not considered because they are too toxic. The most frequently used combination regimens are those that contain gemcitabine, oxaliplatin, lenalidomide, and/or bendamustine. Rituximab is frequently added to salvage regimens to improve outcomes.[20] In the Netherlands, the PECC (prednisone, etoposide, chlorambucil, and lomustine) regimen is utilised; particularly for elderly patients. The regimen has a low toxicity profile and results in an overall response rate (ORR) in >50% of the patients and complete remission (duration <12 months) in half of these patients.[21]

With regards to third-line treatment following relapse/progress of disease (Figure 1), the ESMO guidelines recommend allogeneic stem cell transplantation (SCT) as an option (for transplant-eligible patients).[2] The eligibility/feasibility for allogeneic SCT has improved in the last decade, mainly due to the use of the reduced intensity conditioning regimen. Encouraging cure rates (40%) have been observed, though few patients are eligible for a second transplant.[22] Apart from allogeneic SCT, other treatment options include palliative care and drugs from clinical trials. A number of single-agent therapies are also available for third- or fourth-line treatment, of which pixantrone seems promising. In conclusion, 40% of patients with DLBCL who fail first-line R-CHOP treatment have a dismal outlook, and novel therapies are warranted for this patient population.

Relapsed/Refractory Aggressive B Cell Non-Hodgkin Lymphoma: What Can We Expect in Third- and Fourth-line Treatments?

Doctor Ruth Pettengell

Depending on IPI risk factor at presentation, between 5% and 50% of patients with DLBCL will relapse, with the majority (96%) relapsing within the first year. Of the 30% of patients eligible for intensive salvage therapy, only 50% actually receive a transplant, with 40% subsequently progressing within the first year. These patients, together with those who fail/respond poorly to salvage induction and those who are on palliative care, are the main target patients for pixantrone, which is approved by the EMA and mentioned in the ESMO guidelines (in heavily treated patients)[2] and by NICE (in patients receiving third- or fourth-line treatment who have previously received rituximab),[3] primarily on the basis of the results from the PIX301 study.

PIX301 was a multicentre, randomised, active-controlled study evaluating the efficacy and safety of pixantrone as a single-agent therapy in the management of patients with aggressive RR-NHL who had received at least two prior therapies (one of which had to have contained an anthracycline); patients had to have had a 3-month response to that anthracycline to be eligible.[23] Patients were randomly assigned to treatment with pixantrone dimaleate or to a comparator (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, or gemcitabine) given at standard single-agent therapeutic doses and schedules. The results of the study showed a significant improvement in responses (complete response/unconfirmed complete response [CR/CRu] and ORR) and a trend to longer duration of response with pixantrone versus active comparator agents. Pixantrone was also effective in patients who had received a significant lifetime dose of prior anthracyclines. Importantly, from a clinical point of view, it was observed that most patients who were going to respond had experienced some response by two cycles, thereby avoiding treatment and toxicity for patients who would not derive benefit from the treatment. A *post hoc* analysis of the PIX301 study showed that the efficacy of pixantrone (improvement in ORR and progression-free survival) versus a comparator was independent of previous rituximab therapy.[24] In terms of toxicity, pixantrone has a predictable and manageable safety profile, with the main toxicity being neutropenia. Patients on pixantrone stayed in the study longer than those in the comparator arm, with no significant cardiac toxicity (a common toxicity with anthracyclines). This was thought to be due to the distinct mechanism of action of pixantrone compared with other anthracyclines; rather than acting through topoisomerase II to induce apoptosis, pixantrone appears to induce cell death through accumulation of aberrant cell divisions.[25]

In summary, pixantrone has been demonstrated to have efficacy as a single agent for the third- or fourth-line treatment of multiple RR-aggressive B cell NHL, with a predictable safety profile. The benefit of pixantrone has not been formally established for fifth-line or greater chemotherapy in patients who are refractory to last therapy. The structure and mechanism of action of pixantrone is distinct from anthracyclines, with a promising cardiac toxicity profile. It is the first and only EMA-approved therapy in this setting, and studies of combination therapy are ongoing.

Implementing a New Therapeutic Option

Professor Pier Luigi Zinzani

Although aggressive B cell NHL has a cure rate of approximately 50–60%, relapse within the first 2 years following initial therapy is common. There is no approved treatment or standard of care for patients who fail first- and second-line treatment. Market research among clinicians in the European Union (EU) demonstrated that nine or more different regimens may be used in the third- and fourth-line setting. The life expectancy of the multiple relapsed population is poor; as such, there is a significant unmet medical need in multiple RR patients.[26] Indeed, according to the algorithm for aggressive NHL in the EU (Figure 1), there is a large population of patients who would be suitable for treatment with pixantrone; in particular, heavily pretreated patients from the third-line or patients who are ineligible for autologous transplantation.

A large number of targeted agents are being evaluated for the treatment of DLBCL (Table 1),[23,27-34] including phosphoinositide 3-kinase (PI3K) and Bruton's tyrosine kinase (BTK) inhibitors such as idelalisib, copanlisib, and ibrutinib. There are some interesting preliminary data on the potential

role of ibrutinib as a single agent, particularly in ABC DLBCL, and the final data of the Phase III randomised PHOENIX trial (NCT01855750) are awaited. On the other hand, the data for the new humanised anti-CD20 monoclonal antibodies (obinutuzumab and ofatumumab) and for the antibody-drug conjugates (polatuzumab or brentuximab vedotin) are not very encouraging. Finally, preliminary data from the Phase I/II trials on checkpoint inhibitors like nivolumab or pembrolizumab demonstrate an ORR of <20% to 25% in RR-DLBCL.

In terms of single-agent therapy in RR-NHL or RR-DLBCL, pixantrone has been shown to be very active with a comparable or better CR/CRu rate than other agents (Table 1), with a manageable toxicity profile and the potential for use in patients who are close to reaching their threshold for maximal anthracycline cumulative dose. Comparisons of studies showed that the CR observed for pixantrone as a single agent or in combination regimens (e.g. R-CPOP [rituximab with cyclophosphamide, pixantrone, vincristine, and prednisone] and PSHAP [pixantrone, methylprednisolone, cisplatin, and cytosine arabinoside]) were encouraging compared with other immune-polychemotherapy regimens (Table 2).[18,24,35-37] In particular, in the trial evaluating the PSHAP regimen, 6 out of 11 responding patients were able to proceed to ASCT.[36]

Thus, pixantrone monotherapy can be a treatment option in RR-aggressive B cell NHL, and the combination with other chemotherapy drugs appears to be safe and effective. A pixantrone-based regimen may represent a new bridge to transplant in selected elderly patients.

A multicentre UK-wide retrospective study evaluating the efficacy of pixantrone in RR-DLBCL in clinical practice reported a lower response rate than PIX301 (18% versus 24% CR/CRu, respectively), but these real-world patients had a much higher proportion of primary refractory tumours compared with the pivotal study (85% versus 57%, respectively, p<0.001) and fewer patients with an anthracycline response duration >24 weeks (71% versus 100%, respectively, p<0.001).[38]

Table 1: Single-agent therapy in relapsed/refractory-non-Hodgkin lymphoma or relapsed/refractory-diffuse large B cell lymphoma.[23,27-34]

Regimen	Type of lymphoma	No. of patients	Median number of previous lines	PFS (months)	CR/CRu (%)	ORR (%)
Gemcitabine	RR-a-NHL	30	2	TTP=6 for responders	0	20
Rituximab	RR-a-NHL	21	2	EFS=3.8	5	38
Lenalidomide	RR-a-NHL	217	3	PFS=3.7	13	35
	RR-a-DLBCL	108	3	PFS=2.7	7	28
Lenalidomide	RR-a-NHL	49	4	PFS=4.0	12	35
Bendamustine	RR-a-NHL	18	2	PFS=3.5	17	44
Ibrutinib (ABC)	DLBCL	80	3	PFS=1.6	10	25
	ABC DLBCL	38	3	PFS=2.0	16	37
Bortezomib	RR-NHL (excluding MCL)	21	4	PFS=36% at 6 months	5	19
Oxaliplatin	RR-NHL	30	2	Median time from last treatment=3	7	27
	RR-a-NHL	22	2	FFS=2.1	9	32
Pixantrone Active comparator*	RR-a-NHL	70 70	3 3	PFS=5.3 PFS=2.6	20 7	37 14

*Oxaliplatin, ifosfamide, vinorelbine, etoposide, mitoxantrone, gemcitabine.
ABC: activated B cell-like; a-NHL: aggressive non-Hodgkin lymphoma; a-DLBCL: aggressive diffuse large B cell lymphoma; CR: complete response; CRu: unconfirmed complete response; EFS: event-free survival; FFS: failure-free survival; MCL: mantle cell lymphoma; ORR: overall response rate; PFS: progression-free survival; RR: relapsed/refractory; TTP: time to progression.

Table 2: Response rates of relapsed or refractory lymphoma to salvage regimens.[18,24,35-37]

Regimen	Number of prior treatments	ORR (%)	CR (%)
R-CPOP	1	73	CR/CRu: 47
R-ICE	1	52	27
R-ICE vs. R-DHAP	1 vs. 1	64 vs. 64	CR/CRu: 37
R-EPOCH	Median of 4	68	28
Pixantrone	2 or 3	48	CR/CRu: 28

CR: complete response; CRu: unconfirmed complete response; ORR: overall response rate; R-CPOP: rituximab, cyclophosphamide, pixantrone, vincristine, prednisone; R-DHAP: rituximab, cisplatin, cytarabine, dexamethasone; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide.

Even in this subset of patients with poor prognosis, an ORR of 24% and CR rate of 10% was achieved with single agent pixantrone without rituximab.

In conclusion, the patients with DLBCL who would benefit most from pixantrone monotherapy within its current indication are the following:

- Patients relapsing after ASCT in second-line treatment
- Patients not eligible for transplantation and relapsing after second-line treatment
- Patients eligible for a bridging strategy to allogeneic SCT

Pixantrone in Daily Practice

Professor Raul Cordoba

Prof Cordoba presented two case studies of patients with B cell NHL (who had received two prior treatments) treated with pixantrone monotherapy. The case studies illustrated that complete remissions can be achieved with pixantrone in heavily pretreated adult patients with multiple RR-aggressive B cell NHL. As myelosuppression is common, blood counts should be monitored and use of recombinant haematopoietic growth factors may be considered.

Panel Discussion

Q: How do you determine the role of pixantrone in comparison with the cell-cycle checkpoint inhibitor immunotherapies such as nivolumab and pembrolizumab?

Dr Pettengell replied that as only data from early phase studies are available, there is still little evidence for how to use and combine these drugs. It is evident that, even in the era of checkpoint inhibitors and small molecules, there will still be a need for chemotherapy to reduce tumour bulk as well as to maintain remission. *In vitro* studies of pixantrone with ibrutinib and idelalisib have demonstrated synergy as opposed to simple additive effects, and so combinations may be feasible and safe, though currently off-label. *In vitro* studies with checkpoint inhibitors show enhanced activity. Ongoing trials, such as an 'umbrella' trial in Germany, are investigating the safety and efficacy of multiple drug combinations.

Q: Where do you see pixantrone fitting into your clinical practice, particularly in the frail elderly population?

Prof Cordoba replied that in his institution, a geriatrician in the lymphoma unit generally performs a comprehensive assessment on patients >70 years old and classifies them as a robust, frail, or palliative patient. A strategy will be put in place to achieve a response and to prolong survival in robust and frail patients. These assessments may also be necessary to identify patients that will benefit most from pixantrone.

Dr Lugtenburg replied that the available data show that pixantrone could be used in this very difficult patient population with advanced disease, who have relapsed after second- or third-line therapies, have comorbidities, and are unable to receive ASCT or allogeneic SCT.

Q: How important is it to know cell-of-origin when using pixantrone in relapse?

Prof Zinzani replied that there were no data so far to determine if pixantrone is more active in ABC or GCB DLBCL subtypes, or in both. There are several case reports concerning the activity of pixantrone as a single agent without rituximab in ABC DLBCL. He stated that pixantrone should be considered as a new chemotherapy agent due to its unique mechanism of action and should be used because of its specific clinical activity rather than just because it is less toxic than anthracyclines.

Q: If you had to choose between bendamustine-rituximab and pixantrone-rituximab, what would you choose?

Prof Zinzani replied that according to published data, the ORR for bendamustine-rituxumab in RR-DLBCL ranged from 30–50%, and at least 20% obtain a CR, with median duration of response <4 months. However, he preferred to use pixantrone in these selected patients, as the results (in terms of median duration of response) were better with pixantrone monotherapy (without rituximab). The final data concerning the role of pixantrone plus rituximab in an ongoing Phase III study are eagerly awaited due to potentially more beneficial clinical responses.[39]

Dr Pettengell replied that in terms of evidence-based medicine, pixantrone was the only drug with a licence in this setting and has been evaluated in a randomised Phase III trial. She agreed with Prof Zinzani that the evidence was better for pixantrone compared with bendamustine-rituxumab.

Prof D'Amore took this opportunity to briefly describe an ongoing open-label Phase I/II trial that is testing a new combination regimen using pixantrone, etoposide, bendamustine, and rituximab (in CD20-positive tumours only): P[R]EBEN. This programme has been set up on the basis of encouraging preliminary clinical experience with the pixantrone-containing regimen,[40] and will assess the safety and efficacy of this combination in patients with relapsed aggressive NHL (EudraCT number: 2015-0007).

Q: Can pixantrone be used in primary refractory patients, or should it be used only in selected patients?

Dr Pettengell said that patients had to have had a 3-month response to an anthracycline to see the results obtained in the PIX301 study. Therefore, patients who are anthracycline-refractory and have progressed through every line of therapy, or patients not fit for chemotherapy, may not do well with pixantrone (or with any novel agents being evaluated in this setting). Due to the predictable toxicity profile, it can be considered for fit elderly patients. Nonetheless, it may be worth trying pixantrone as any response will be detectable by two cycles of treatment; in the absence of an early signal, the drug can be discontinued thereby avoiding unnecessary toxicity without benefit.

Q: Is there any subset analysis information from the PIX301 study to indicate whether early responders are the ones doing best?

Dr Pettengell replied no, as the patient subsets are too small to give any meaningful answer.

Q: Are there any data on the role of pixantrone on the response rates in mantle cell lymphoma?

Dr Lugtenburg and Prof Zinzani were not aware of data regarding the role of pixantrone in mantle cell lymphoma.

Dr Pettengell mentioned some anecdotal single cases. Anthracyclines are active in mantle cell lymphoma, but only have a role in second-line given the availability of ibrutinib and idelalisib. However, pixantrone or gemcitabine may be added to the regimen in patients who progress on those drugs to prevent the rapid progression that occurs when BTK or PI3K inhibitors are stopped.

Conclusion

Despite the increased knowledge of disease biology and the development of new drugs within the last 10 years, there have not been any significant improvements in outcome for patients with RR-DLBCL. Pixantrone has emerged as an effective treatment, even as single-agent therapy, and has significant promise in combination studies. It is effective in treating patients who are older or with comorbidities, and also as a bridging therapy to consolidate autograft and allograft transplants (and perhaps radiotherapy), with the possibility of maintenance treatment following with other drugs.

REFERENCES

1. European Medicines Agency. EPAR summary for the public: pixuvri. 2012. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002055/human_med_001549.jsp&mid=WC0b01ac058001d124. Last accessed: 10 November 2016.

2. Tilly H et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116-25.

3. National Institute for Health and Care Excellence. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014. Available at: https://www.nice.org.uk/Guidance/ta306. Last accessed: 10 November 2016.

4. Lymphoma Research Foundation, Understanding Non-Hodgkin Lymphoma: A Guide For Patients, Survivors, and Loved Ones 2012, 4th edition, New York: Lymphoma Research Foundation.

5. Raut LS, Chakrabarti PP. Management of relapsed-refractory diffuse large B cell lymphoma. South Asian J Cancer. 2014;3(1):66-70.

6. Sant M et al.; HAEMACARE Working Group. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.

7. Morton LM et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):130-44.

8. Monnereau A et al. Lymphome diffus à grandes cellules B. Available at: http://invs.santepubliquefrance.fr/content/download/121772/429928/version/1/file/Cancer_Survie_lymphome-diffus-B.pdf. Last accessed: 10 November 2016.

9. Jaglowski SM et al. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood. 2010;116(19):3705-14.

10. Shipp MA et al. A predicitve model for aggressive non-Hodgkin's lymphoma. N Eng J Med. 1993;329(14):987-94.

11. Lenz G et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med. 2008;359(22):2313-23.

12. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:498-505.

13. Perry AR, Goldstone AH. High-dose therapy for diffuse large-cell lymphoma in first remission. Ann Oncol. 1998;9 Suppl 1:S9-14.

14. Pfreundschuh M et al.; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7(5):379-91.

15. Majhail NS et al.; American Society for Blood and Marrow Transplantation. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015;21(11):1863-9.

16. Rodriguez J et al. Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience. Ann Oncol. 2004;15(10):1504-9.

17. Philip T et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med. 1987;316(24):1493-8.

18. Gisselbrecht C et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.

19. Thieblemont C et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. 2011;29(31):4079-87.

20. Gisselbrecht C. Use of rituximab in diffuse large B-cell lymphoma in the salvage setting. Br J Haematol. 2008;143(5):607-21.

21. Lennard AL et al. An effective oral combination in advanced relapsed Hodgkin's disease prednisolone, etoposide, chlorambucil and CCNU. Cancer Chemother Pharmacol. 1990;26(4):301-5.

22. van Kampen RJ et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol. 2011;29(10):1342-8.

23. Pettengell R et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. Lancet Oncol. 2012;13(7):696-706.

24. Pettengell R et al. Monotherapy with pixantrone in histologically confirmed relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: post-hoc analyses from a phase III trial. Br J Haematol. 2016;174(5):692-9.

25. Beeharry N et al. Pixantrone induces cell death through mitotic perturbations and subsequent aberrant cell divisions. Cancer Biol Ther. 2015;16(9):1397-406.

26. Cabanillas F et al. Results of recent salvage chemotherapy regimens for lymphoma and Hodgkin's disease. Semin Hematol. 1988;25(2 Suppl 2):47-50.

27. Fosså A et al. Gemcitabine as a single agent in the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 1999;17(12):3786-92.

28. Rothe A et al. Rituximab monotherapy is effective in patients with poor risk refractory aggressive non-Hodgkin's lymphoma. Haematologica. 2004;89(7):875-6.

29. Witzig TE et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22(7):1622-7.

30. Wiernik PH et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(30):4952-7.

31. Weidmann E et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2002;13(8):1285-9.

32. Wilson WH et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922-6.

33. Goy A et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2005;23(4):667-75.

34. Oki Y et al. Phase II study of oxaliplatin in patients with recurrent or refractory non-Hodgkin lymphoma. Cancer. 2005;104(4):781-7.

35. Herbrecht R et al. Comparison of pixantrone-based regimen (CPOP-R) with doxorubicin-based therapy (CHOP-R) for treatment of diffuse large B-cell lymphoma. Ann Oncol. 2013;24(10):2618-23.

36. Lim ST et al. A phase I/II trial of pixantrone (BBR2778), methylprednisolone, cisplatin, and cytosine arabinoside

(PSHAP) in relapsed/refractory aggressive non-Hodgkin's lymphoma. Leuk Lymphoma. 2007;48(2):374-80.

37. Jermann M et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. Ann Oncol. 2004;15(3):511-6.

38. Eyre TA et al. Results of a multicentre UK-wide retrospective study evaluating the efficacy of pixantrone in relapsed, refractory diffuse large B cell lymphoma. Br J Haematol. 2016;173(6):896-904.

39. Belada D et al. Pixantrone-rituximab versus gemcitabine-rituximab in relapsed/refractory aggressive non-Hodgkin lymphoma. Future Oncol. 2016; 12(15):1759-68.

40. d'Amore F et al. Preliminary Clinical Experience on the Efficacy and Feasibility of a New Combination Regimen Consisting of Pixantrone, Etoposide, and Bendamustine with or without the Addition of Rituximab in Patients with Relapsed/Refractory Aggressive Non-Hodgkin Lymphomas. Blood. 2014; 124:5435.

CABOZANTINIB AS FIRST-LINE THERAPY FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA WITH POOR OR INTERMEDIATE-RISK CHARACTERISTICS

This Presidential Symposium took place on 10th October 2016 as a part of the European Society for Medical Oncology (ESMO) Congress in Copenhagen, Denmark

Speaker

Toni K. Choueiri

Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Disclosure: Associate Prof Choueiri has received honoraria for advisory board membership and consultancy from Pfizer, Exelixis, Novartis, Merck, BMS, Bayer, Roche, Prometheus, Calithera, Peloton, and Foundation Medicine. His institution has received research funding from Exelixis, Pfizer, Novartis, BMS, Merck, Roche, Tracon, and Peloton.
Acknowledgements: Writing assistance was provided by Dr Blair Hesp, CMPP, of ApotheCom.
Support: The author has received a research grant from Exelixis to support this review. The views and opinions expressed are those of the authors and not necessarily of Exelixis.
Citation: EMJ Oncol. 2016;4[1]:56-59.

MEETING SUMMARY

The oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) sunitinib is a standard first-line therapy for patients with metastatic renal cell carcinoma (mRCC).[1] Survival outcomes for patients with mRCC treated with sunitinib vary between prognostic risk groups, defined by the International mRCC Database Consortium (IMDC) criteria.[2,3] For example, median progression-free survival (PFS) is expected to be lower in patients with poor or intermediate-risk characteristics compared with the overall patient population, with one study reporting PFS of 5.6 months following first-line targeted therapy in patients with poor or immediate-risk characteristics compared with 7.2 months for the overall population.[4] Furthermore, the presence of bone metastases is also associated with less favourable outcomes in patients with mRCC.[5]

Cabozantinib Versus Sunitinib (CABOSUN) as Initial Targeted Therapy for Patients with Metastatic Renal Cell Carcinoma in Poor and Intermediate-Risk Groups

One of the major challenges in treating patients with mRCC is resistance to VEGF pathway-targeted therapy. An example of such resistance occurs as a consequence of inactivation of the von Hippel-Lindau tumour suppressor gene leading to upregulation of the AXL and MET tyrosine kinases as well as VEGF. This upregulation is associated with poor prognosis and resistance to VEGFR inhibitor therapy.[6-8]

In an effort to overcome this challenge cabozantinib was developed and has recently been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a treatment option for patients with advanced RCC who have received prior anti-angiogenic therapy (FDA) or have received prior VEGF-targeted therapy (EMA). Cabozantinib is an oral TKI whose targets include VEGFR2, MET, and AXL.[9] In the Phase III METEOR study, cabozantinib met all three efficacy endpoints of improved PFS, overall survival (OS), and objective response rate (ORR) compared with everolimus in patients who had been previously treated with VEGFR TKI therapy.[10,11]

The cabozantinib versus sunitinib (CABOSUN) study (clinicaltrials.gov identifier: NCT01835158; sponsored by the National Cancer Institute [NCI]) is an important addition to the body of clinical knowledge regarding methods of treating mRCC

because, unlike previous studies, the trial was designed to evaluate the efficacy and safety of cabozantinib versus sunitinib in patients with previously untreated mRCC, who were categorised as having poor or intermediate-risk characteristics, according to the IMDC criteria.[2]

CABOSUN was a randomised, multicentre, open-label, Phase II study that aimed to enrol 150 patients with advanced RCC, with an 85% power to detect a hazard ratio (HR) of 0.67 for the primary endpoint of PFS (123 events assessed by the investigators according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1).[12] Patients were randomly allocated to one of two treatment groups and received either cabozantinib (60 mg daily, 6-week cycles) or sunitinib (50 mg daily, 4 weeks on/2 weeks off).[12] Secondary endpoints included OS and ORR, which were assessed by RECIST, and safety.[12] Treatment with either cabozantinib or sunitinib was continued until disease progression or intolerable toxicity resulted in treatment discontinuation.[12] The efficacy analyses were performed on the intention-to-treat population, and the safety analyses undertaken only in patients who received the study drug (Figure 1).[12]

Baseline patient characteristics were well balanced across both treatment groups.[12] As shown in Figure 2, patients treated with cabozantinib had a significantly higher PFS compared with patients treated with sunitinib (median PFS of 8.2 months for cabozantinib versus 5.6 months for sunitinib; HR adjusted for bone metastases and IMDC risk group was 0.69 [95% confidence interval (CI): 0.48–0.99]; one-sided p=0.012; data cut-off date: 15th April 2016).[12] Furthermore, the significant improvement in median PFS with cabozantinib treatment was observed consistently, both in patients with poor-risk (6.3 versus 2.8 months for sunitinib; HR: 0.75, 95% CI: 0.34–1.66) and intermediate-risk (8.4 versus 6.2 months for sunitinib; HR: 0.68, 95% CI: 0.45–1.01) characteristics.[12] Notably, the HR of 0.51 (95% CI: 0.29–0.90) for PFS was lower in patients with bone metastases compared with that in patients without bone metastases (HR: 0.80, 95% CI: 0.51–1.26).[12] However the study was not sufficiently powered to perform statistical analyses between patient subgroups.[12]

After adjusting for bone metastases and IMDC risk group, cabozantinib was associated with a non-significant OS benefit compared with sunitinib after a median follow-up of 22.8 months (median OS of 30.3 months for cabozantinib versus 21.8 months for sunitinib; HR: 0.80, 95% CI: 0.50–1.26; Figure 3).[12] Patients treated with cabozantinib also had a higher investigator-assessed ORR of 46%, compared with 18% for patients treated with sunitinib. Progressive disease was reported as the best response for 18% and 26% of patients treated with cabozantinib and sunitinib, respectively.[12] Reduction in tumour target lesions was also seen in a greater proportion of patients with cabozantinib than with sunitinib (69/79 patients [87.3%] versus 34/78 patients [43.6%], respectively).[12]

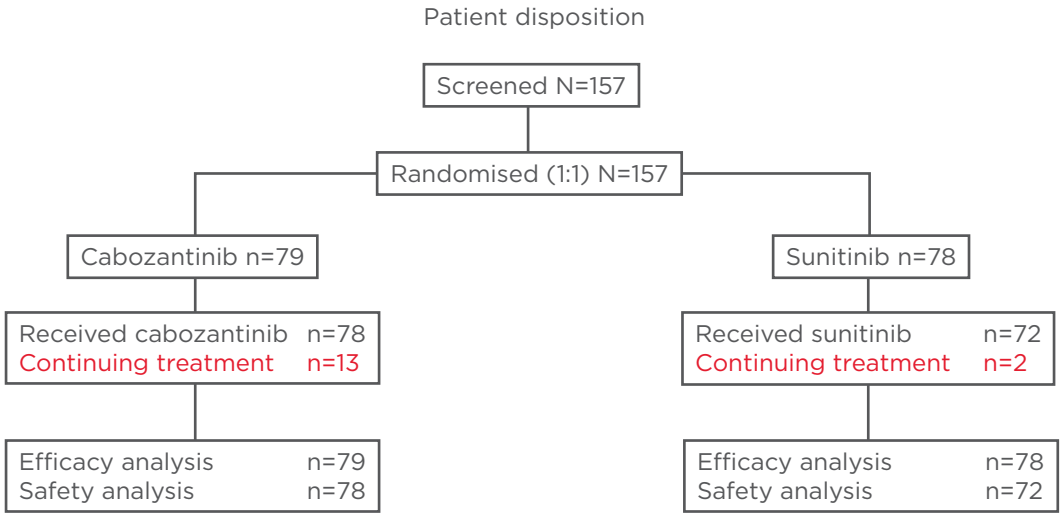


Figure 1: Patient disposition in the CABOSUN study.
Adapted from Choueiri et al. 2016.[12]

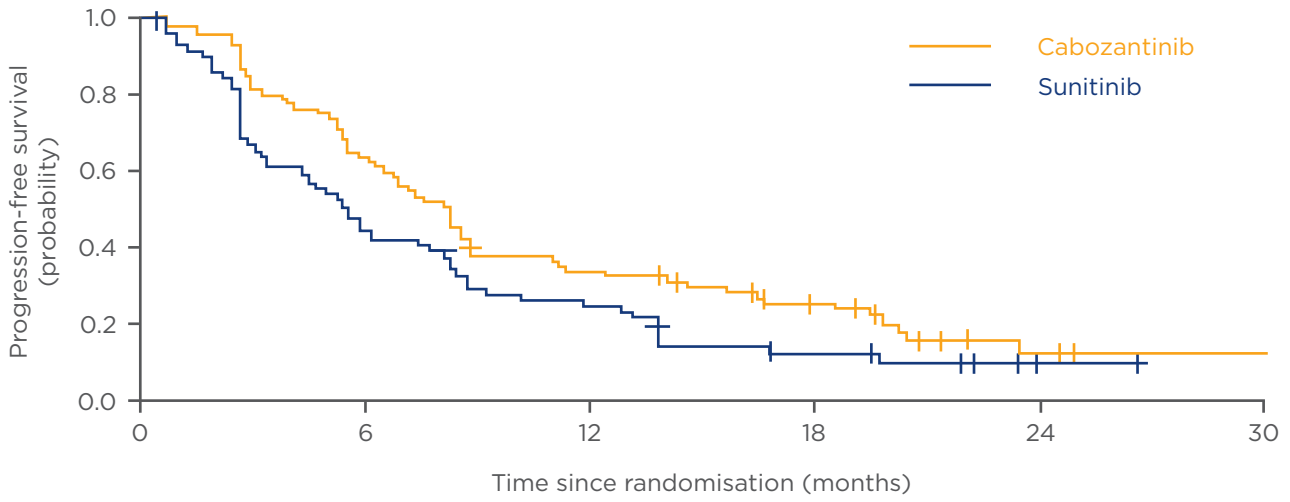


Figure 2: Progression-free survival in patients treated with cabozantinib versus sunitinib.
Adapted from Choueiri et al. 2016.[12]

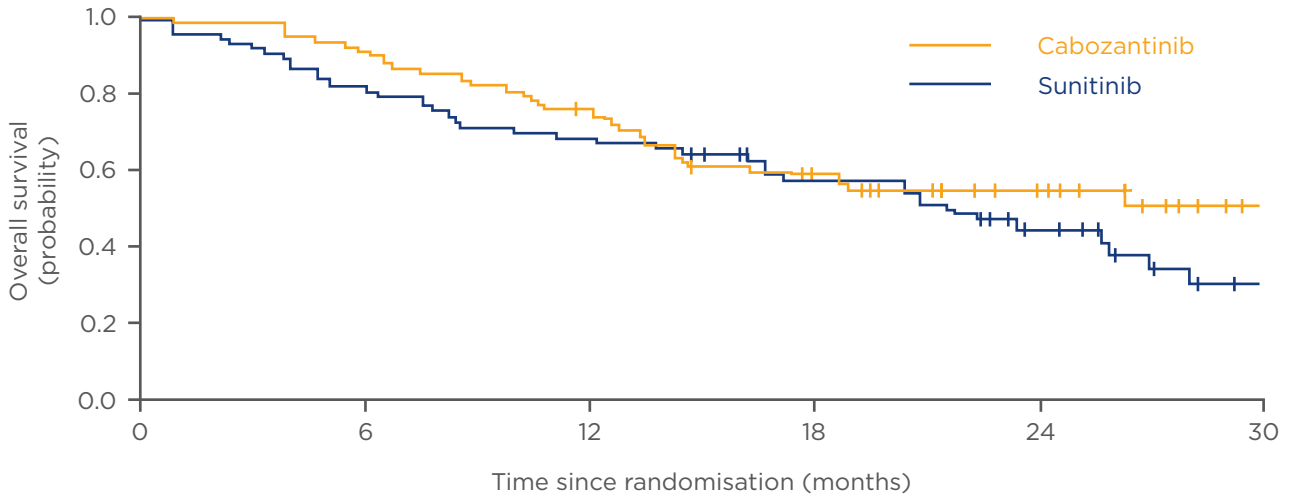


Figure 3: Overall survival in patients treated with cabozantinib versus sunitinib.
Adapted from Choueiri et al. 2016.[12]

The overall prevalence of all-cause adverse events (AEs), including Grade 3–4 AEs, was comparable between the two treatment arms (65% and 68% of patients for cabozantinib and sunitinib, respectively), and the safety profiles of both treatments were similar to those previously reported in patients with advanced RCC administered VEGFR inhibitors.[12] The most common Grade 3–4 AEs included hypertension (28%), diarrhoea (10%), palmar plantar erythrodysesthesia (8%), fatigue (6%), increased alanine aminotransferase (5%), oral mucositis (5%), and anorexia (5%) for patients treated with cabozantinib, and hypertension (22%), fatigue (15%), diarrhoea (11%), thrombocytopenia (11%), oral mucositis (6%), neutropenia (4%), and leukopenia (3%) for patients treated with sunitinib.[12]

The rate of treatment discontinuation due to AEs was similar in both study arms (20% versus 21% for cabozantinib and sunitinib, respectively); although, a higher rate of dose reduction due to AEs was reported in patients treated with cabozantinib (58%) compared with patients treated with sunitinib (49%).[12]

Conclusion

The CABOSUN study demonstrated that cabozantinib significantly improves PFS compared with sunitinib in previously untreated patients with mRCC with poor or intermediate-risk characteristics, according to the IMDC criteria.[12]

Additionally, cabozantinib treatment improves ORR, with an emerging trend towards improved OS, and has a similar safety profile to that of sunitinib.[12] Overall, data from the CABOSUN study indicate that cabozantinib should be a treatment option for previously untreated patients with mRCC.[12]

REFERENCES

1. Bedke J et al. Systemic therapy in metastatic renal cell carcinoma. World J Urol. 2016. [Epub ahead of print].

2. Heng DYC et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794-9.

3. Motzer RJ et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584-90.

4. Ko JJ et al. First-, second-, third-line therapy for mRCC: benchmarks for trial design from the IMDC. Br J Cancer. 2014;110(8):1917-22.

5. McKay RR et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol. 2014;65(3):577-84.

6. Zhou L et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016; 35(21):2687-97.

7. Ciamporcero E et al. Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. Mol Cancer Ther. 2015;14(1):101-10.

8. Harshman LC, Choueiri TK. Targeting the hepatocyte growth factor/c-Met signalling pathway in renal cell carcinoma. Cancer J. 2013;19(4):316-23.

9. Yakes FM et al. Cabozantinib (XL184), a Novel MET and VEGFR2 Inhibitor, simultaneously Suppresses Metastasis, Angiogenesis, and Tumor Growth. Mol Cancer Ther. 2011;10(12):2298-308.

10. Choueiri TK et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015; 373(19):1814-23.

11. Choueiri TK et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-27.

12. Choueiri TK et al. CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups. Abstract LBA30-PR. ESMO Congress, 7-11 October 2016.

REGORAFENIB IN METASTATIC COLORECTAL CANCER AND ADVANCED SOFT TISSUE SARCOMAS

Summary of Presentations from the 2016 Meeting of The American Society of Clinical Oncology (ASCO) held in Chicago, Illinois, USA, from 3rd–7th June 2016

Speakers

Eric Van Cutsem,[1] Yuji Miaymoto,[2] Tanios Bekaii-Saab,[3] Nicolas Penel[4]

1. University Hospitals Leuven, Leuven, Belgium
2. Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, California, USA
3. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA
4. Centre Oscar Lambret, Lille, France

Disclosure: Prof Eric Van Cutsem has received research funding from Amgen, Bayer, Boehringer Ingelheim, Lilly, Merck Serono, Novartis, Rochem, and Sanofi. Dr Yuji Miyamoto has declared no conflicts of interest. Dr Tanios Bekaii-Saab has served as an advisor or consultant for Celgene, Genentech, and Merrimack Pharmaceuticals. Dr Nicolas Penel has served as an advisor/consultant for PharmaMar and received research funding from Bayer, PharmaMar, and Roche/Genentech.
Acknowledgements: Medical writing was provided by Ewen Legg, PhD, of Halcyon Medical Writing.
Support: The publication of this article was funded by Bayer. The views and opinions expressed are those of the authors and not necessarily those of Bayer.
Received: 20.07.16 **Accepted:** 11.08.16
Citation: EMJ Oncol. 2016;4[1]:60-65.

MEETING SUMMARY

Oncologists face multiple challenges when treating patients with cancer, especially if patients are elderly or if they experience adverse events (AEs). Several presentations at the American Society of Clinical Oncology (ASCO) 2016 meeting focussed on overcoming these challenges with regorafenib, an oral multikinase inhibitor approved for treating refractory metastatic colorectal cancer (mCRC), and gastrointestinal stromal tumours (GIST).

A retrospective analysis of the Phase IIIb CONSIGN study in patients with mCRC reported while most AEs were similar between age groups, when compared to the younger subgroup, the patients in the older subgroups had a higher incidence of Grade ≥3 fatigue and a lower incidence Grade ≥3 hand-foot syndrome (HFS), while other AEs were similar between age groups. Thus, patient age should not be considered a barrier to regorafenib use. This age analysis also highlighted the key role of dose modification in the management of regorafenib-related AEs.

Another tactic for AE management is to utilise specific treatments targeted to the AE of interest. Interim analysis of a Phase II study demonstrated that prophylactic dexamethasone had promising effects in reducing regorafenib-related fatigue and HFS in patients with mCRC. In an ongoing Phase II study, ReDOS, both regorafenib dose-escalation and use of clobetasol propionate to actively manage regorafenib-induced HFS are under investigation.

Finally, the success of regorafenib in treating GIST, the most common soft tissue sarcoma (STS), has been extended to patients with other STS. In REGOSARC, a Phase II study, regorafenib significantly prolonged progression-free survival (PFS) in patients with non-adipocytic STS, with an AE profile similar to that seen in mCRC and GIST. These presentations offer insights into the practical management of patients treated with regorafenib.

Introduction

Regorafenib is an oral multikinase inhibitor that targets several protein kinases involved in angiogenesis (vascular endothelial growth factors 1–3 and TIE2), regulation of the tumour microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptors), and oncogenesis (*KIT*, *RET*, *RAF-1*, and *B-RAF*).[1] Regorafenib significantly improved overall survival (OS) in patients with previously treated mCRC compared with placebo in the CORRECT Phase III trial.[2] A significant increase in PFS in patients with advanced GIST, a type of STS, was also reported for regorafenib versus placebo in the GRID Phase III trial.[3] Based on these trials, regorafenib received approval for use in adult patients with mCRC (either previously treated with or who are not considered for available therapies), and those with unresectable or metastatic GIST (who have progressed on or are intolerant to prior treatment with imatinib and sunitinib). Regorafenib is also being evaluated in a wide range of solid tumours, including renal cell carcinoma, hepatobiliary, and upper gastrointestinal cancers.[4,5]

Safety and Efficacy of Regorafenib in Metastatic Colorectal Cancer by Age in the Consign Trial

Professor Eric Van Cutsem

mCRC is a leading cause of cancer deaths, particularly in elderly patients. Moreover, 60% of patients diagnosed with mCRC are aged ≥65 years. This patient population may be under-treated in clinical practice and under-represented in clinical trials, as they are more susceptible to treatment-induced toxicities due to a range of comorbidities and reduced organ function. However, with appropriate management, certain elderly patients with mCRC can gain significant benefits from a range of cancer treatments, including biological therapies.[6,7]

To gain further insight in to the management of elderly patients, a retrospective analysis of outcomes by patient age was carried out in CONSIGN (NCT01538680), a large, open-label, single-arm, Phase IIIb study conducted in 186 centres in 25 countries.[8,9] Patients (N=2,872) recruited into CONSIGN had mCRC with disease progression disease progression following standard therapies and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤1. They received regorafenib at 160 mg/day for Weeks 1–3 of each 4-week cycle until unacceptable toxicity, disease progression, or death. The primary endpoint was safety, and the only efficacy measurement was investigator-assessed PFS.[8]

This latest analysis was presented at ASCO 2016 by Dr Eric Van Cutsem from the University Hospitals Leuven, Leuven, Belgium. Patients were categorised into two sets of different age groups: <65 years (n=1,720) compared to ≥65 years (n=1,152), and <70 years (n=2,245), compared to ≥70 years old (n=627).[9] Baseline characteristics were generally well-balanced across the age subgroups. At least 50% of patients in each age subgroup had a mutated *KRAS* gene, which is slightly higher than typically seen in mCRC (35–45%).[10] The results of this analysis indicate that patient age does not appear to impact treatment duration, impact treatment duration (2.2-2.5 months across age groups). No age effects were seen for the median number of median number of cycles (3.0 in all groups). Across the age groups, almost 90% of patients required treatment modification (defined as reductions, interruptions/delays or re-escalation of re-escalation of treatment). Treatment interruptions occurred in up to 84% of patients in each subgroup and almost half of the patients required dose reductions.

Most patients (≥91%) in each age subgroup had a regorafenib-related, treatment-emergent AE (TEAE) of any grade. A low number of patients (≤13%) in each age category discontinued regorafenib as a result of regorafenib-related TEAEs. The proportion of patients with some Grade ≥3 regorafenib-related TEAEs (i.e hypophosphataemia and diarrhoea) was also generally similar across the age subgroups.[9] However, the incidence of ≥3 regorafenib-related HFS tended to be lower and hypertension and fatigue appeared to be higher in the older subgroups compared with the younger subgroups. The incidence of Grade ≥3 TEAEs seen in CONSIGN were typical of those reported in other regorafenib studies.[2] Treatment-emergent Grade ≥3 hepatic laboratory toxicities were also similar across age groups.

The estimated median PFS was comparable between the age subgroups. The median (PFS 95% confidence interval [CI]) was 2.7 (2.6–2.8) and 2.6 (2.5–2.7) months for patients aged <65 years and ≥65 years, respectively. Similarly, for patients aged

<70 years and ≥70 years, median (95% CI) PFS was 2.7 (2.6–2.8) and 2.5 (2.3–2.7) months, respectively.

In conclusion, this subgroup analysis of CONSIGN demonstrated that the safety and dosing profiles, as well as efficacy (based on PFS), were generally similar in older versus younger mCRC patients. The overall high rate of dose interruptions and reductions in all age subgroups highlights the importance of this tactic in managing TEAEs.

Impact of Dexamethasone on Regorafenib-Related Fatigue and Malaise in Metastatic Colorectal Cancer

Doctor Yuji Miyamoto

Fatigue is a well-recognised symptom of many cancers,[11] and can also be caused by cancer treatments, including multikinase inhibitors.[12] With regorafenib, fatigue is a common drug-related AE that has been observed across a range of clinical trials.[5] In common with other regorafenib-related AEs, fatigue occurred mainly in the first few cycles of treatment in the Phase III CORRECT study, with a lower incidence in later cycles.[13] Oral corticosteroids have been used to treat cancer-related fatigue, although the evidence for their effectiveness is limited.[14,15]

A Phase II, multicentre, randomised, double-blind, placebo-controlled study (KSCC1402/HGCSG1402) prospectively evaluated the prophylactic effects of oral dexamethasone on regorafenib-related fatigue and malaise in patients with unresectable mCRC. Interim results[16] were presented for 74 patients aged ≥20 years with histologically confirmed mCRC that failed to respond to standard therapy, had adequate organ function, and had an ECOG PS ≤1. They were randomised 1:1 to receive either regorafenib 160 mg/day for Weeks 1–3 of a 4-week cycle and dexamethasone 2 mg/day for 4 weeks, or regorafenib and placebo. Patients with Grade ≤1 fatigue or malaise were allowed to enrol in this study.

The primary endpoint was the incidence of all-grade fatigue or malaise as assessed by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 during the first 4 weeks. Secondary endpoints included patient-reported outcome (PRO; assessed by the Brief Fatigue Inventory), AEs, and the relative dose intensity of regorafenib.

Baseline characteristics were generally well-balanced between the arms. There were more patients with an ECOG PS of 0 in the dexamethasone arm (61% versus 47% in the placebo arm), and correspondingly more patients with an ECOG PS of 1 in the placebo arm (53% versus 39% in the dexamethasone arm). More patients in the placebo arm had hypertension (64%) as a comorbidity versus the dexamethasone group (33%).

The study highlighted that the incidence of all-grade fatigue and/or malaise by both the NCI-CTCAE v4.0 (regorafenib plus dexamethasone arm: 55.6% versus regorafenib plus placebo arm: 58.3%, p=0.8119) and PRO (regorafenib plus dexamethasone arm: 47.2% versus regorafenib plus placebo arm: 58.3%, p=0.3450) were numerically lower with the co-administration of dexamethasone with regorafenib compared with placebo, although these results were not statistically significant.[16] The incidence of fatigue and/or malaise Grade ≥2 by PRO was significantly lower in the regorafenib plus dexamethasone arm versus the regorafenib plus placebo arm (27.8% versus 52.8%, p=0.0306). Using the PROs, reduction in the incidence of Grade ≥2 fatigue and/or malaise with dexamethasone versus placebo was seen from Week 1.

Dexamethasone was well-tolerated in this study. Compared to placebo, dexamethasone reduced the incidence of certain AEs (all grades), including including alopecia (11.1% versus 27.8%), anorexia (30.6% versus 47.2%), and neutropenia (2.8% versus 19.4%). Dexamethasone compared with placebo also reduced the incidence of Grade ≥3 HFS (8.3% versus 13.9%) and Grade ≥3 sensory neuropathy (0% versus 5.6%). It was suggested that these effects of dexamethasone warrant further investigation to clarify if this oral steroid could help to limit the side effects of regorafenib in patients with mCRC.

In summary, although this study did not meet its primary endpoint, the PRO results indicated that dexamethasone might have a role to play in reducing the incidence of regorafenib-induced Grade ≥2 fatigue and/or malaise. Furthermore, certain other treatment-related AEs, such as HFS, were apparently reduced by dexamethasone co-administration. Patient follow-up is continuing and the longer-term outcomes in this study will be analysed in due course.

Regorafenib Dose Optimisation Study in Refractory Metastatic Colorectal Cancer

Doctor Tanios S. Bekaii-Saab

The most common AEs with regorafenib include palmar-plantar erythrodysesthesia syndrome (PPES, also known as hand-foot syndrome [HFS]),[2,17,18] and fatigue.[2] HFS is a common side effect of multikinase drugs, and can have a profound effect on quality of life. Generally, HFS is seen in the first few weeks of regorafenib treatment.[13] Thus, there is a need for effective management of regorafenib-associated toxicities.

In clinical practice, the approaches used to minimise regorafenib toxicities include dose reduction and/or revision of the interval schedule.[19,20] However, there is a lack of high-quality evidence to support these strategies. A Phase II regorafenib dose optimisation study (ReDOS; NCT02368886)[21] is being led by the Academic and Community Cancer Research Unit (ACCRU) network in the USA and aims to compare the effects of the standard regorafenib dose with a lower dose strategy.

ReDOS is a four-arm study during which approximately 120 patients will be randomised to either the escalating regorafenib dosing group (during which patients receive 80 mg/day in Week 1, 120 mg/day in Week 2, and 160 mg/day in Week 3, followed by 1 week off then cycle 2 will commence) or the stable regorafenib dosing group (patients receive daily regorafenib 160 mg for 21 days, then 1 week off followed by cycle 2). Within the two treatment arms, patients will then be assigned to either a pre-emptive strategy for palmar-plantar erythrodysesthesia syndrome (PPES) where clobetasol cream is prophylactically applied to hands and soles for the first 12 weeks or a reactive PPES treatment strategy where treatment is initiated at investigator discretion.[21]

Key inclusion criteria include: men and women (non-pregnant and using adequate contraception, surgically sterilised, or post-menopausal) aged >18 years; histologically confirmed mCRC; ECOG PS ≤1; acceptable bone marrow and organ function; and no prior regorafenib use. Patients are required to have failed all standard treatments for mCRC, including biological agents.

The primary endpoint of ReDOS is the 8-week planned continuation rate. This endpoint is defined as the proportion of patients that have completed two treatment cycles, and, if there is no disease progression, intend to initiate a third cycle. Secondary endpoints include PFS, OS, and time-to-progression. Other assessments will be, the cumulative regorafenib dose, and the proportion of patients with Grade 3 or 4 HFS and/or fatigue. Patients will also self-report outcomes using the HFS-14 questionnaire, and these results will be compared between arms and between pre-emptive and reactive HFS strategies.

In order to calculate the required sample size, the assumed 8-week planned continuation rate is 75% in the control arm and the target continuation rate is 90% in the dose-escalation group. Thus, a one-side test with α=0.20 and 80% power will require a total of 110 patients in this study. The aim is to enrol a total of 120 patients to allow for patient withdrawals. The accrual and follow-up of patients in ReDOS is expected to take approximately 2 years.

Efficacy and Safety of Regorafenib in Advanced Soft Tissue Sarcomas

Doctor Nicolas Penel

STS are a very heterogeneous group of rare solid tumours, with more than 100 types accounting for <1% of all adult tumours.[22,23] Treatment of metastatic STS is challenging, and the median OS is only 12–18 months.[24,25] The current mainstay of treatment for metastatic STS is chemotherapy, the choice of which depends upon the type of STS.[23] As angiogenesis plays a key role in STS biology,[26] targeted therapies are under investigation for STS management,[23,27] including regorafenib.[26,27] First-line treatment is generally doxorubicin, but there is no consensus on second-line treatment of STS, and the different options include: ifosfamide, trabectedin, pazopanib, dacarbazine, and eribulin.

The stratified, double-blind, placebo-controlled, randomised, Phase II trial REGOSARC (NCT01900743)[27] had four parallel cohorts of patients with advanced, refractory STS, mainly doxorubicin pre-treated.[28] Patients with liposarcomas (n=43), leiomyosarcomas (n=56), synovial sarcomas (n=27), or other sarcomas (n=56) were randomised 1:1 to receive either regorafenib at 160 mg/day for 3 weeks of each 4-week cycle or placebo, both with best supportive care. This study had a 95% statistical power to detect a 3-month longer PFS with regorafenib versus placebo.

In the final analysis, baseline characteristics were generally balanced between both arms within each STS cohort regarding proportion of women, age, metastases, and prior treatments. However, 50% of patients with leiomyosarcomas in the regorafenib group had ECOG PS Grade 3 versus 25% in the placebo group. Other sarcomas included in the trial were undifferentiated pleomorphic sarcoma (n=24), solitary fibrous tumours (n=7), angiosarcoma (n=6), and fibrosarcoma (n=4). Only a small number of patients had received prior pazopanib.

The primary endpoint was PFS assessed by the Response Evaluation Criteria in Solid Tumours in a blinded central radiological review. Regorafenib significantly prolonged PFS versus placebo in all sarcoma groups with the exception of liposarcomas, which may not be surprising due to the heterogeneity of angiogenesis in liposarcomas[29] A pooled analysis of non-adipocytic sarcomas also showed significantly prolonged PFS with regorafenib versus placebo.[27] OS was not statistically significantly different between the regorafenib and placebo groups for any STS type,[27] which is most likely because 82% of patients in the placebo group crossed-over to the regorafenib group after disease progression.

No patients in REGOSARC had a complete tumour response. Five patients had a partial tumour response: one in the placebo arm (leiomyosarcoma, lasting 6 months), and four in the regorafenib arm (synovial sarcoma, 2.8 months; other sarcomas: 2, 7, and 13 months). Overall, the most frequent drug-related AEs (all grades) in the regorafenib group were asthenia (63%), diarrhoea (44%), mucositis (44%), HFS (44%), anorexia (38%), and arterial hypertension (36%). These AEs were all Grade 1–3 in severity. There was one toxic death due to hepatitis in the regorafenib group, which was considered to be drug-related.

Regorafenib met the primary objective of prolonging PFS in patients with pre-treated, non-adipocytic sarcoma versus placebo, and showed superiority to placebo with regards to PFS. However, REGOSARC was not powered to demonstrate a statistically significant improvement in OS, due to the cross-over option for patients in the placebo group, and the small sample sizes. The AE profile was as expected for regorafenib.

The challenges in sarcoma treatment should be emphasised, particularly as there are numerous receptor tyrosine kinases, which are all potential targets for inhibition.[30] Of note, the PFS results with regorafenib[27] were similar to those with pazopanib, which is approved for refractory non-adipocytic STS with a significant 3-month PFS benefit,[31] but is not active in liposarcomas.[32]

Conclusions

Continued interest in regorafenib is clearly evident from these studies reported at ASCO 2016. As with other treatments for cancer, the use of regorafenib in elderly patients as well as management of TEAEs are key aspects of using the drug in clinical practice. These studies demonstrated that regorafenib not only has a similar efficacy and safety profile in elderly patients with mCRC compared with their younger counterparts, but that dose modifications are important in managing TEAEs regardless of age. Dexamethasone may also be an option to reduce regorafenib-related fatigue and other regorafenib related AEs, including HFS, although further investigation is warranted. Moreover, results from an ongoing study on dose-escalation and active use of clobetasol propionate will help to further refine the management of regorafenib-related HFS. The significant effects of regorafenib in extending PFS in non-adipocytic STS (leiomyosarcomas, synovial sarcomas, or other sarcomas) follows on from the success of regorafenib in the treatment of GIST, the most common type of STS, and may provide a much needed additional option in treating these challenging range of cancers.

REFERENCES

1. Wilhelm SM et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245-55.

2. Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

3. Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.

4. Chan SL, Ma BB. An update on the safety and efficacy of regorafenib in the treatment of solid tumors. Expert Opin Drug Metab Toxicol. 2014;10(11):1607-14.

5. Grothey A et al. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. Oncologist. 2014;19(6): 669-80.

6. Kurniali PC et al. Management of locally advanced and metastatic colon cancer in elderly patients. World J Gastroenterol. 2014;20(8):1910-22.

7. Kim JH. Chemotherapy for colorectal cancer in the elderly. World J Gastroenterol. 2015;21(17):5158-66.

8. Van Cutsem E et al. Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer. Ann Oncol. 2015;26(Suppl 4):iv118.

9. Van Cutsem E et al. Regorafenib in previously treated metastatic colorectal cancer (mCRC): analysis of age subgroups in the open-label phase IIIb CONSIGN trial. J Clin Oncol. 2016;34(Suppl 15):3524.

10. Tan C, Du X. KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol. 2012;18(37):5171-80.

11. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597-609.

12. Crean S et al. Safety of multi-targeted kinase inhibitors as monotherapy treatment of cancer: a systematic review of the literature. Curr Drug Saf. 2009; 4(2):143-54.

13. Grothey A et al. Time profile of adverse events (AEs) from regorafenib (REG) treatment for metastatic colorectal cancer (mCRC) in the phase III CORRECT study. J Clin Oncol. 2013;31(15):3637.

14. Yennurajalingam S et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013;31(25):3076-82.

15. Begley S et al. The use of corticosteroids in reducing cancer-related fatigue: assessing the evidence for clinical practice. Int J Palliat Nurs. 2016;22(1):5-9.

16. Miyamoto Y et al. A randomized, double-blind, placebo-controlled phase II study of prophylactic dexamethasone (dex) therapy for fatigue and malaise due to regorafenib in patients (pts) with metastatic colorectal cancer (mCRC): (KSCC1402/HGCSG1402). J Clin Oncol. 2016;34(15):10127.

17. Belum VR et al. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. Invest New Drugs. 2013;31(4):1078-86.

18. Llamas-Velasco M et al. Regorafenib-induced hand-foot skin reaction with striking epidermal dysmaturation - a new histopathological pattern associated with the use of multi-kinase inhibitors. Br J Dermatol. 2016;175(1):216-7.

19. McLellan B et al. Regorafenib-associated hand-foot skin reaction: practical advice on diagnosis, prevention, and management. Ann Oncol. 2015; 26(10):2017-26.

20. Sastre J et al. Clinical management of regorafenib in the treatment of patients with advanced colorectal cancer. Clin Transl Oncol. 2014;16(11):942-53.

21. Bekaii-Saab TS et al. Regorafenib dose optimization study (ReDOS): a phase II randomized study of lower starting dose regorafenib compared to standard dose regorafenib in patients with refractory metastatic colorectal cancer. J Clin Oncol. 2016;34(15):TPS3630.

22. Schöffski P et al. Soft tissue sarcoma: an update on systemic treatment options for patients with advanced disease. Oncol Res Treat. 2014;37(6):355-62.

23. Arifi S et al. Treatment of adult soft tissue sarcomas: an overview. Rare Cancers Ther. 2015;3:69-87.

24. Italiano A et al. Trends in survival for patients with metastatic soft-tissue sarcoma. Cancer. 2011;117(5):1049-54.

25. Judson I et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15(4):415-23.

26. Rocchi L et al. The angiogenic asset of soft tissue sarcomas: a new tool to discover new therapeutic agents. Biosci Rep. 2014;34(6):e00147.

27. Penel N et al. Regorafenib (RE) in liposarcomas (LIPO), leiomyosarcomas (LMS), synovial sarcomas (SYN), and other types of soft-tissue sarcomas (OTS): results of an international, double-blind, randomized, placebo (PL) controlled phase II trial. J Clin Oncol. 2016;34(15):11003.

28. Brodowicz T et al. Study protocol of the REGOSARC trial: activity and safety of regorafenib in advanced soft tissue sarcoma: a multinational, randomized, placebo-controlled, phase II trial. BMC Cancer. 2015;15:127.

29. Almog N et al. Prolonged dormancy of human liposarcoma is associated with impaired tumor angiogenesis. FASEB J. 2006;20(7):947-9.

30. Patwardhan PP et al. Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. Oncotarget. 2016;7(4): 4093-109.

31. van der Graaf WT et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.

32. Sleijfer S et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19):3126-32.

PROGRESSING G1-G2 WELL-DIFFERENTIATED NEUROENDOCRINE TUMOURS IN TREATMENT WITH CAPECITABINE PLUS SOMATOSTATIN ANALOGUE: A SINGLE-CENTRE EXPERIENCE

***Riccardo Marconcini**

Oncology Department,
University Hospital of Pisa, Pisa, Italy
**Correspondence to*
marconcini.riccardo@gmail.com

The role of chemotherapy in neuroendocrine tumours (NETs) has evolved in recent years. In particular, temozolomide has become a treatment option and has been used as both a single agent and in combinations, especially with capecitabine (CAPTEM) in several studies, with heterogeneous populations and outcomes. The CAPTEM regimen has been shown to have significant activity in pancreatic NETs. A retrospective analysis of 30 pancreatic NET patients demonstrated a 70% response rate and a median progression-free survival (PFS) of 18 months. A similar retrospective analysis that included both pancreatic and non-pancreatic NETs with PFS of the entire cohort reported at 4.7 months, pancreatic NETs having a PFS of 4.9 versus 2.8 months for non-pancreatic NETs. In a Phase II study looking at CAPTEM in both pancreatic and non-pancreatic NETs, an interim analysis of 28 patients has shown an overall response rate of 43% and rate of stable disease of 54%.

Results from Phase II and non-randomised trials with fluoropyrimidine (without temozolomide) in combination with somatostatine analogues (SSA) in well-differentiated (WD)NET are limited, and are considered investigational. Fluoropyrimidine monotherapy has a more favourable toxicity profile, and more data regarding its efficacy are needed to understand its role in NET treatment.

We reviewed our experience in metastatic WDNET patients treated with capecitabine and SSA, to identify eventual subgroups that may benefit from this treatment in terms of efficacy and tolerability, adding new data in favour of the delay of temozolomide administration.

From October 2005, 40 WDNET patients with progressive disease after failure of SSA and/or everolimus, peptide receptor radionuclide therapy, or other chemotherapy were treated with capecitabine and SSA. The primary tumour site was the pancreas in 17 patients, the intestine in 13 patients, the lung in 6 patients, and unknown in 4 patients. Patients received in media capecitabine 1,000 mg/mq/b.i.d Days 1–14, and SSA (octreotide long acting release [LAR] 30 mg, 1 fl i.m. q28; or lanreotide LAR 120 mg, 1 fl i.m. q28). Treatment efficacy was evaluated by response rate according to RECIST criteria and in terms of PFS. Safety and tolerability were evaluated following Common Terminology Criteria for Adverse Events (CTCAE) v4 criteria.

Seven patients (17.5%) had a partial response, 17 patients (42.5%) showed stable disease, and 16 patients (40%) showed progressive disease; median PFS was 6.1 (1–72.2) months, and 3 patients are still on treatment. In intestinal NET, median PFS was 25.3 (2.2–70.8) months; in particular G1 intestinal NET and G2 intestinal NET median PFS was 46.2 (13.5–70.8) months and 4.3 (2.2–5.5) months, respectively. In pancreatic NET, the median PFS was 7.3 (2.0–72.2) months; G1 pancreatic NET and G2 pancreatic NET median PFS was 7.5 (2.0–72.2) months and 6.1 (2.5–34.0) months, respectively. In lung NET the median PFS was 5.4 (1.4–6.6) months, and in unknown NET it was 2.3 (1.0–11.6) months. At a median follow-up at 40 months, median OS was 48.7 (2.43–85.7) months. Reported G1-G2 toxicities were diarrhoea, nausea, and asthenia; G3-G4 toxicities were not reported.

Capecitabine plus SSA showed interesting activity and efficacy in pretreated patients, with

progressive WDNET with acceptable toxicity. In particular, intestinal NET showed prolonged median PFS, and in this group capecitabine plus SSA seems a valid therapeutic option. Our retrospective analysis raises the question of whether monochemotherapy treatment with capecitabine associated to SSA could be considered as an alternative treatment, particularly in G1 intestinal NET. This subtype of NET is known for its better prognosis; our data confirm that this subgroup is the one that benefits mostly from capecitabine plus SSA, with a PFS remarkably higher than the other groups. Capecitabine plus SSA showed a particularly low toxicity profile that seems more feasible than the capecitabine plus temozolomide toxicity profile. If efficacy advantage is provided, capecitabine could be proposed as an option especially for G1 intestinal NET, and the association with temozolomide could be considered in a sequential strategy, to enrich the treatment options of NET patients.

PROGNOSTIC IMPACT OF THE CUMULATIVE DOSE AND DOSE INTENSITY OF EVEROLIMUS IN PATIENTS WITH PANCREATIC NEUROENDOCRINE TUMOURS

***Rossana Berardi, Mariangela Torniai**

Clinica Oncologica, Università Politecnica delle Marche, Ospedali Riuniti di Ancona, Ancona, Italy
**Correspondence to r.berardi@univpm.it*

The aim of the present study was to analyse clinical factors potentially influencing the global outcome of advanced pancreatic neuroendocrine tumour (PNET) patients receiving everolimus in clinical practice in order to help clinicians in the decision-making process for the identification of a treatment strategy within this setting.

PNETs are still considered a rare disease, accounting for approximately 10% of all cases of pancreatic cancer. Nevertheless, the increasing incidence and prevalence of PNETs observed in the last four decades, together with the frequent delay in diagnosis, have led to increasing interest in PNETs, with major progress being made in their treatment and management.

Among these advances, the elucidation of the high expression and activity of mammalian target of rapamycin (mTOR) in PNETs has led to the recognition of mTOR as an important therapeutic target. On this basis, everolimus has been shown to be an effective therapeutic agent in these tumours since Yao et al.[1] reported a significant improvement in progression-free survival in patients treated with the mTOR compared with placebo; thus everolimus has become an established recommended standard therapy for patients with advanced PNETs.

Although everolimus exerts a very selective action on a specific molecular target, this drug may be associated with a number of adverse effects including: stomatitis, rash, fatigue, pneumonitis, and metabolic alterations mainly represented by hyperlipidaemia. Other common events include: abdominal pain, nausea and/or vomiting, anaemia, increased serum creatinine level, liver function test abnormalities, dizziness, headache, and epistaxis. These adverse effects frequently lead to modification of the dosage by drug delay and/or reduction of dose, with a significant impact on cumulative dose (CD) and dose intensity (DI) and potential negative effects on patient outcome.

The safety profile of everolimus has been proven to be generally acceptable in PNET patients, with severe toxicities occurring only in a tiny minority of subjects. The onset of adverse events seems to be not correlated with the presence of liver metastasis, while previous treatment might affect the tolerability of this drug. Furthermore, the onset of toxicities, especially mucositis, appear to be

correlated with a major disease control rate and a longer progression-free survival, as already known for other targeted agents used in the management of PNETs.

To the best of our knowledge, the present study is the first to investigate the prognostic significance of CD and DI of everolimus in advanced PNETs. The present study includes all consecutive patients with advanced (unresectable or metastatic) PNETs treated with everolimus in 14 Italian institutions between December 2009 and December 2015. CD patients were stratified into two groups with one group containing patients treated with an everolimus CD ≤3,000 mg and the other with those who had received a CD >3,000 mg. Multivariate analysis demonstrated that everolimus CD >3,000 mg was an independent prognostic factor both for overall survival (OS) (hazard ratio: 0.16; 95% confidence interval: 0.06–0.41, p<0.0001) and for progression-free survival (hazard ratio: 0.56; 95% confidence interval: 0.34–0.92, p<0.047).

Although the prolonged OS observed in patients with higher CD may be because patients who maintain a higher dose are usually more responsive to therapy, our results showed a significant correlation between the CD and DI of everolimus and OS in a large series of patients with PNET; namely better prognosis in patients maintaining both a high CD and DI. The difference in OS in patients treated with everolimus seemed strictly dependent upon the CD taken by sensitive patients thus suggesting that efforts should be made to manage toxicity without interrupting the treatment.

Although selection bias and the retrospective nature of the study may have influenced our findings, the present overall data seem to suggest that CD and DI potentially play a prognostic role for patients with advanced PNETs treated with everolimus. This should prompt efforts to continue everolimus administration in responsive patients up to at least 3,000 mg despite delays or temporary interruptions.

REFERENCES

1. Yao JC et al.; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic Neuroendocrine Tumors. N Engl J Med. 2011;364(6):514-23.

FIRST EVIDENCE OF SIGNIFICANT CLINICAL ACTIVITY OF PROGRAMMED CELL DEATH-1 INHIBITORS IN METASTATIC, CASTRATION-RESISTANT PROSTATE CANCER

***Julie N. Graff**

Knight Cancer Institute, Oregon Health & Science University; VA Portland Health Care System, Portland, Oregon, USA
**Correspondence to graffj@ohsu.edu*

Until recently, most researchers and clinicians did not believe programmed cell death (PD)-1 inhibition could clinically benefit men with metastatic castration-resistant prostate cancer (mCRPC). We designed a Phase II study of pembrolizumab (200 mg intravenously every 3 weeks for 4 doses) and enzalutamide in men with mCRPC, progressing on enzalutamide alone, based on evidence that enzalutamide failure is associated with upregulation of PD-L1 on dendritic cells.

Participants had not received prior checkpoint inhibiting immunotherapy (PD-1, PD-L1, or CTLA-4 inhibitors) or chemotherapy for mCRPC. However, they may have received prior abiraterone or sipuleucel-T. We chose a prostate specific antigen (PSA) response rate (defined as ≥50% decrease in PSA) of 25% in men as worthy of further examination, and this required a sample size of 28 men. From April 2015–August 2016, we enrolled 28 patients at the Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, USA. The median age was 72 years, with a median PSA of 26.6 ng/mL. As expected, most men had

bone and/or lymph node metastases (n=25). Two patients had liver metastases, and one patient had pulmonary metastases. All men had progressive disease on enzalutamide, as required by this protocol, with a median time on enzalutamide prior to study entry of 52 weeks. Most had a response to enzalutamide prior to failure (n=23). Prior therapies also included chemotherapy for castration-sensitive disease (n=4), sipuleucel-T (n=5), and abiraterone (n=10). A baseline biopsy was required for all participants with a metastatic deposit deemed amenable to biopsy, and 16 participants fell into this group.

The median progression-free survival on this study was 34 weeks. There were 27 participants who were evaluable for the primary endpoint at the time of this analysis, and 5 of them (19%) had a PSA response. There were 19 patients followed for >6 months, and 4 of them had stable disease lasting at least 6 months on study (21%). In the five responders, the PSA responses were >99%. To date, none of these responders have experienced disease relapse (range 4–18 months). Three of them had measurable disease at baseline and achieved a partial response by Response Evaluation Criteria in Solid Tumours (RECIST). Three of the responders also had a baseline biopsy; the genetic analysis was complete on two of them, and one of them had microsatellite instability. Both patients with liver metastatic disease had a disease response on pembrolizumab.

This study demonstrates that the combination of pembrolizumab plus enzalutamide in men with mCRPC failing enzalutamide has potential. The number of responders is relatively small but the extent of their response is dramatic. It is premature to use PD-1 inhibitors for mCRPC outside of a clinical trial, and there is a clear need to design clinical trials to determine the true level of activity and clinical characteristics of patients whose cancers do respond to PD-1 inhibition.

NON-METASTATIC NON-SMALL CELL LUNG CANCER AND OTHER THORACIC MALIGNANCIES

***Dirk De Ruysscher**

Department of Radiation Oncology (Maastro Clinic), GROW School Maastricht, Maastricht University Medical Centre, Maastricht, Netherlands

**Correspondence to dirk.deruysscher@maastro.nl*

Many interesting contributions were submitted to this year's European Society for Medical Oncology (ESMO) Congress. The three highlights I selected were all oral presentations, however I would like to stress that many high-quality abstracts were also presented. I selected three topics: immune treatment for early stage non-small cell lung cancer (NSCLC), neo-adjuvant versus adjuvant chemotherapy for resectable early stage NSCLC, and new drugs for metastatic small cell lung cancer.

Immune therapy for Stage IV NSCLC has received great attention because checkpoint inhibitors targeting programmed cell death-1 (PD-1) and one of its ligands, PD-L1, leads to progression-free survival (PFS) rates of 15–20% at 18 months, which is better than those that can be achieved with chemotherapy. The toxicity of these agents is manageable with an improved quality of life compared to chemotherapy.

However, in resectable early stage NSCLC there is ample room for improvement of the long-term overall survival (OS) rate, as even with neoadjuvant or adjuvant chemotherapy the 5-year OS rate is only about 60%. The study presented by Dr Forde investigated the effect of nivolumab, a PD-1 inhibitor, in resectable early stage NSCLC.[1] The primary endpoint was feasibility. Toxicity was as expected with nivolumab and importantly did not lead to increased surgical morbidity, mortality, or delay of resection. An exciting pathological downstaging rate of 38% in this small series of 17 patients was observed. As expected, individuals without tumour shrinkage on a computed tomography (CT) scan could have a major

pathological response. The response correlated with expansion of the T cell repertoire. It is clear that this approach opens the door for window of opportunity trials aimed at improving the immune response further, e.g. by combining immune checkpoint inhibitors with radiation and immunocytokines, or vaccination while dissecting the immune mechanisms and identifying biomarkers.

A Chinese randomised trial aimed to identify the optimal strategy to deliver chemotherapy in operable early stage NSCLC, comparing adjuvant with neoadjuvant chemotherapy.[2] Although a significantly better PFS rate was observed in adjuvant chemotherapy compared with neoadjuvant chemotherapy, the PFS and OS rates were in line with earlier trials. Innovative strategies are needed to obtain higher OS rates.

The prognosis of patients with Stage IV small-cell lung cancer remains dismal; even responders to chemotherapy have a 1-year OS rate of about 30% and <10% at 2 years. In chemo-refractory patients, the prognosis is even more bleak. In a randomised Phase II trial, the aurora kinase A inhibitor alisertib with paclitaxel resulted in a gain in PFS of about 1 month compared to paclitaxel alone.[3] Importantly, a gain was also observed in refractory patients. C-MYC expression may be related to PFS. Although these are early results and no big improvement was observed, the fact that a detectable change in prognosis was observed opens the door to further research to find more effective treatments for this devastating disease.

REFERENCES

1. Forde PM et al. Neoadjuvant anti-PD1, Nivolumab, in early stage resectable NSCLC. Abstract LBA41_PR. ESMO Congress, 7-11 October, 2016.

2. Wu Y et al. Multi-centre randomized controlled study comparing adjuvant versus neo-adjuvant chemotherapy with docetaxel plus carboplatin in resectable stage IB to IIIA Non-small cell lung cancer: final results of CSLC0501 (NCT00321334). Abstract 1178O. ESMO Congress, 7-11 October, 2016.

3. Owonikoko TK et al. Randomized Phase 2 Study of the Investigational Aurora A Kinase (AAK) Inhibitor Alisertib (MLN8237) + Paclitaxel versus Placebo + Paclitaxel as Second-Line Therapy for Small Cell Lung Cancer (SCLC). Abstract 14230. ESMO Congress, 7-11 October, 2016.

BROAD DETECTION OF ALTERATIONS PREDICTED TO CONFER LACK OF BENEFIT FROM EPIDERMAL GROWTH FACTOR RECEPTOR ANTIBODIES OR SENSITIVITY TO TARGETED THERAPY IN ADVANCED COLORECTAL CANCER

***Samuel J. Klempner**

Angeles Clinic and Research Institute, Los Angeles, California, USA
**Correspondence to sklempner@theangelesclinic.org*

Advanced colorectal cancer is increasingly being defined by molecular features that impact both overall prognosis and therapeutic choices. Expanded RAS testing is now the standard of care in defining patients that are appropriate for the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab. However, despite RAS wild-type biomarker selection, nearly 40% of patients do not respond to anti-EGFR mAbs. Comprehensive genomic profiling looking beyond canonical RAS pathway alterations may provide insight into pre-existing mechanisms that may confer EGFR mAb resistance or lessen clinical response. In the associated presentation we examined 4,422 advanced colorectal cancers using a next-generation sequencing assay to simultaneously interrogate putative EGFR-mAb resistance mechanisms and investigate other actionable genomic alterations.

By going beyond expanded RAS testing we identified 62% of samples with RAS/RAF pathway

alterations that would predict a lack of benefit from EGFR mAb therapy. Importantly, >50% of cases that were negative for *KRAS G12/G13* and *BRAF V600* mutations by standard of care testing harboured a genomic alteration associated with resistance to EGFR mAb therapy. In addition, we identified oncogenic alterations including *ERBB2* amplification and mutation, MET amplification, and rare rearrangements in *ALK*, *RET*, *FGFR1-3*, and *NTRK1* which may offer alternate therapeutic options for colorectal cancers. Microsatellite instability (4% in our series) was negatively associated with *KRAS* mutation status.

This study received significant attention at the European Society for Medical Oncology (ESMO) Congress 2016 with discussion centred on the therapeutic implications and need for prospective validation and associated clinical outcomes. To our knowledge this represents the largest study comprehensively characterising the molecular landscape of advanced colorectal cancer. Although descriptive in nature, the study provides insight into the biologic underpinnings of the clinical observation of the lack of benefit from anti-EGFR mAbs in a significant portion of patients who are *KRAS* wild-type by standard testing. Whether or not we should be more restrictive in selecting advanced colorectal cancer patients appropriate for anti-EGFR mAbs requires prospective study. Overall, this work supports a role for more comprehensive genomic profiling in advanced colorectal cancer and suggests which subgroups are unlikely to benefit from anti-EGFR therapies, and additional small subsets who may be considered for immunotherapies and targeted therapies.

RISK OF SERIOUS ADVERSE EVENTS AND FATAL ADVERSE EVENTS WITH SORAFENIB USE IN PATIENTS WITH SOLID CANCER: A META-ANALYSIS OF PHASE III RANDOMISED CONTROLLED TRIALS

***Bishal Gyawali, Tomoya Shimokata, Kazunori Honda, Yuichi Ando**

Department of Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, Nagoya, Japan

**Correspondence to bg.bishalgyawali@gmail.com*

Sorafenib is a commonly used vascular endothelial growth factor-tyrosine kinase inhibitor in a variety of cancers. It has been approved for use in renal cell cancer, hepatocellular cancer, and thyroid cancer in the advanced/metastatic setting. However, the benefit of using sorafenib in these cancers must be weighed against the adverse events (AEs). Although common AEs contribute to significant morbidity and are frequently discussed with patients at the clinic, serious and fatal AEs are not usually discussed. We however believe that, although infrequent, any data on serious AEs (SAEs) and fatal AEs (FAEs) carry information of high significance for patients because of their gravity. We do not have any information on the incidence and risk of sorafenib-induced SAEs and FAEs. Thus we performed an up-to-date meta-analysis of all Phase III randomised controlled trials (RCTs) of sorafenib to quantify the increased risk of SAEs and FAEs.

We carried out a systematic search for all the RCTs of sorafenib. In our meta-analysis we included only Phase III RCTs of solid tumours comparing sorafenib either alone or in combination with non-targeted chemotherapy versus placebo or non-targeted chemotherapy. We then extracted data on SAEs and FAEs for both the arms from each study and pooled the data to determine the overall incidence, risk ratios (RRs), and 95% confidence intervals (CIs).

We found a total of 12 Phase III RCTs involving 6,797 solid cancer patients comparing sorafenib

with a control. The RCTs involved hepatocellular carcinoma (n=5), melanoma (n=2), non-small cell lung cancer (n=2), pancreatic cancer, renal cell carcinoma, and thyroid cancer (n=1 each). The overall incidence of SAEs and FAEs with sorafenib were 24.5% (95% CI: 16.0–35.5%) and 1.6% (95% CI: 0.7–3.3%), respectively. We found that sorafenib significantly increased the risk of both SAEs (RR: 1.51, 95% CI: 1.20–1.92, p<0.001) and FAEs (RR: 1.84, 95% CI: 1.29–2.64, p=0.001) versus control. This association varied significantly with cancer types (p=0.001) and approval status (p=0.018) for SAEs but no evidence for heterogeneity was found for FAEs. The risk for SAEs was significantly higher for hepatocellular carcinoma (RR: 2.20, 95% CI: 1.18–4.10, p=0.013) and non-approved use of sorafenib (RR: 1.68, 95% CI: 1.24–2.29, p=0.001).

This meta-analysis of Phase III RCTs demonstrated an increased risk of SAEs and FAEs with sorafenib use in patients with solid cancers. Special vigilance is recommended while using sorafenib in non-approved settings.

For the full study click here.

LIVER DISEASE AETIOLOGY FOR PROGNOSIS, EFFICACY, AND SAFETY OF SECOND-LINE RAMUCIRUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

***Takuji Okusaka,[1] Jean-Frédéric Blanc,[2] Ian Chau,[3] Paolo Abada,[4] Andrew X. Zhu[5]**

1. Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan
2. Hôpital Saint-André, Bordeaux, France
3. Royal Marsden NHS Foundation Trust, London and Surrey, UK
4. Eli Lilly and Company, Indianapolis, Indiana, USA
5. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA
**Correspondence to tokusaka@ncc.go.jp*

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer death globally.[1] Cirrhosis is the most important risk factor and is present in about 80% of patients with HCC.[2] Risk factors for cirrhosis and subsequent development of HCC are heterogeneous and include chronic viral hepatitis (Types B and C), alcohol use, inherited metabolic diseases (haemochromatosis and alpha-1 antitrypsin deficiency), and non-alcoholic fatty liver disease.[3]

Ramucirumab is a recombinant human monoclonal antibody that specifically binds to VEGF receptor-2 (VEGFR-2), inhibiting ligand-stimulated activation of VEGFR-2 and downstream signalling.[4] REACH was a global, randomised Phase III study evaluating the safety and efficacy of single agent ramucirumab in patients with advanced HCC following first-line therapy with sorafenib (Figure 1).[5] While a significant median overall survival (OS) benefit was not observed in the intention-to-treat population ([ITT], N=565), a survival benefit was observed in patients with elevated baseline alpha-fetoprotein ([AFP] ≥400 ng/mL); the median OS for ramucirumab was 7.8 months (n=119) versus 4.2 months for the placebo group (n=131; hazard ratio: 0.67, p=0.006).[5]

Ad hoc analyses of REACH by liver disease aetiology were performed to assess potential differences in outcomes associated with specific HCC aetiologies. The ITT population was subgrouped by disease aetiology (hepatitis B: n=209, 37%; hepatitis C: n=154, 27%; or other: n=202, 36%).[6] Baseline patient characteristics were generally balanced between treatment arms in each subgroup. Patients with hepatitis B were

more likely to be Asian, Eastern Cooperative Oncology Group (ECOG) Performance Status 1, have extra-hepatic spread, and elevated baseline AFP (≥400 ng/mL).

Patients with the disease aetiology of hepatitis B had shorter survival rates compared to patients with hepatitis C or other, suggesting hepatitis B to be a poor prognostic factor for survival. However, exploratory multivariable Cox analysis did not confirm disease aetiology to be a significant prognostic factor for OS after adjusting for other potentially prognostic or baseline imbalanced covariates (p=0.3). A potentially greater OS benefit was seen in all aetiology subgroups with an elevated baseline AFP, with similar improvements in median OS observed in all aetiology subgroups (Table 1).

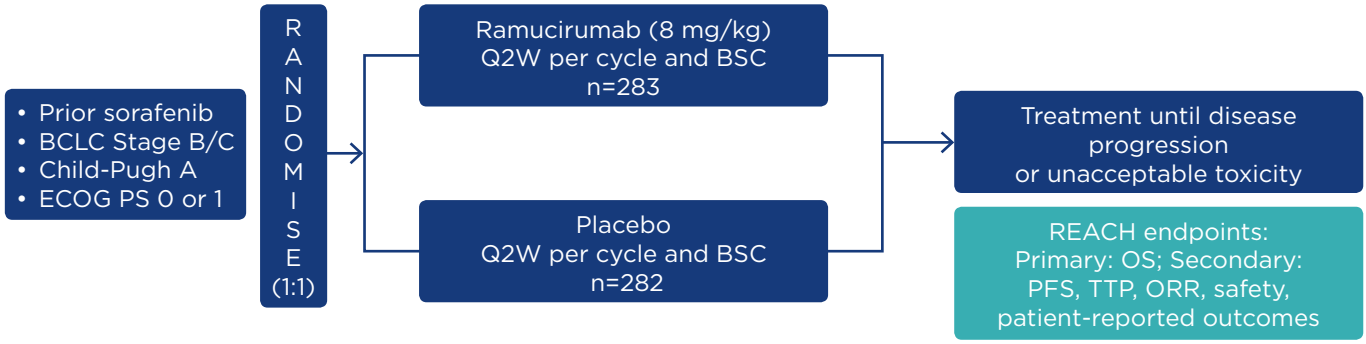


Figure 1: REACH study design (NCT01140347).
BCLC: Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Q2W: every 2 weeks; BSC: best supportive care; OS: overall survival; PFS: progression-free survival; TTP: time-to-progression; ORR: objective response rate.

Table 1: Overall survival[a] and overall response rate[b] by disease aetiology.

	Hepatitis B		Hepatitis C		Other aetiology	
Intent-to-treat population	RAM n=106	PBO n=103	RAM n=78	PBO n=76	RAM n=99	PBO n=103
OS, median	8.2	5.4	9.2	8.8	11.1	8.5
HR (95% CI)	0.785 (0.582–1.060)		0.951 (0.664–1.362)		0.853 (0.620–1.174)	
p-value	0.114		0.786		0.332	
ORR (%)	2.8	0.0	10.3	2.6	9.1	0.0
Baseline AFP ≥400 ng/mL	RAM n=53	PBO n=65	RAM n=33	PBO n=27	RAM n=33	PBO n=39
OS, median	6.6	4.0	8.2	4.8	8.5	4.3
HR (95% CI)	0.672 (0.456–0.990)		0.887 (0.501–1.568)		0.446 (0.259–0.768)	
p-value	0.043		0.682		0.003	

OS: overall survival; HR: hazard ratio; ORR: overall response rate; AFP: alpha-fetoprotein; RAM: ramucirumab; PBO: placebo.
[a]OS was evaluated by the Kaplan–Meier method and compared using an unstratified log-rank test. HR was generated using an unstratified Cox regression model.
[b]ORR was defined as the proportion of patients with the best overall response of a complete or partial response, and compared using a Cochran-Mantel-Haenszel test.

No trend to survival benefit was observed in all subgroups with baseline AFP <400 ng/mL. In all three aetiology subgroups, the most common treatment-emergent adverse events of any grade included peripheral oedema, fatigue, pyrexia, and ascites. Incidences of specific Grade ≥3 adverse events were generally low and similar among aetiology subgroups.

Analyses of the sorafenib registration studies and other studies also reported that the presence of hepatitis B is associated with worse survival in patients with advanced HCC compared with other aetiologies, supporting the hypothesis that aetiology is an important prognostic factor in HCC.[7,8] Analyses of the REACH study suggested that disease aetiology alone was not a strong prognostic factor and that other baseline characteristics or regional patterns of care may be more important drivers of prognosis than aetiology.

The prognosis of patients with elevated baseline AFP was similar among aetiology subgroups, confirming the strength of baseline AFP as a prognostic factor. A similar potential improvement in median OS was observed in patients with an elevated baseline AFP from all aetiology subgroups after treatment with ramucirumab compared with placebo, suggesting there is no differential ramucirumab effect by aetiology. Ramucirumab was also well-tolerated with a similar safety profile in patients from all aetiology subgroups.

In conclusion, this ad hoc REACH analysis shows that while aetiology appears prognostic in HCC, it is not significant once other characteristics are considered. Across all aetiologies, patients with an elevated baseline AFP had a similar prognosis, derived a similar survival benefit, and reported a similar safety profile from ramucirumab treatment. The potential benefit of ramucirumab treatment in patients with baseline ≥400 ng/mL is being assessed in an ongoing trial, REACH-2 (NCT02435433).

REFERENCES

1. World Health Organization. Cancer fact sheet No. 297. 2015. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/. Last accessed: 20 October 2016.

2. Nordenstedt H et al. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liv Dis. 2010;42(Suppl3):S206-14.

3. Davis GL et al. Hepatocellular carcinoma: management of an increasingly common problem. Proc (Bayl Univ Med Cent). 2008;21(3):266-80.

4. Spratlin JL et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol. 2010;28(5):780-7.

5. Zhu AX et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859-70.

6. Okusaka T et al. Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Prognosis, efficacy, and safety by liver disease etiology. Abstract 617PD. ESMO Congress, 7-11 October 2016.

7. Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.

8. Bruix J et al. Efficacy and safety of sorafenib in patients with advanced cellular carcinoma: subanalyses of a phase III trial. J Hepatol. 2012;57(4):821-9.

PULSE, A PHASE II STUDY OF MODIFIED FOLFOX6-PANITUMUMAB WITH BIOMARKER STRATIFICATION AS FIRST-LINE THERAPY, IN PATIENTS WITH *KRAS* (EXON 2) METASTATIC COLORECTAL CANCER: A GEMCAD 09-03 STUDY

*Joan Maurel,[1] Carlos Fernández-Martos,[2] Marta Martín-Richard,[3] Vicente Alonso,[4] Jose Carlos Méndez,[5] Antonieta Salud,[6] Carles Pericay,[7] Jorge Aparicio,[8] Javier Gallego,[9] Alberto Carmona,[10] Enrique Casado,[11]

Hermini Manzano,[12] Carlos Horndler,[13] Michele Rubini,[14] Miriam Cuatrecasas,[15] Xabier García-Albéniz,[16] Jaime Feliu[17]

1. Medical Oncology Department, Hospital Clínic, Translational Genomics and Targeted Therapeutics in Solid Tumors Group, IDIBAPS, University of Barcelona, Barcelona, Spain
2. Department of Oncology, Instituto Valenciano de Oncologia, Valencia, Spain
3. Department of Oncology, Hospital Sant Pau, Barcelona, Spain
4. Department of Oncology, Hospital Miguel Servet, Zaragoza, Spain
5. Department of Oncology, Centro Oncológico de Galicia, Coruña, Spain
6. Department of Oncology, Hospital de Lleida, Lleida, Spain
7. Department of Oncology, Hospital Parc Taulí, Sabadell, Spain
8. Department of Oncology, Hospital La Fe, Valencia, Spain
9. Department of Oncology, Hospital de Elche, Elche; Hospital Parc Taulí, Sabadell, Spain
10. Department of Oncology, Hospital Morales Messeguer, Murcia, Spain
11. Department of Oncology, Hospital Infanta Sofia, Madrid, Spain
12. Department of Oncology, Hospital Son Espases, Mallorca, Spain
13. Pathology Department, Hospital Miguel Servet, Zaragoza, Spain
14. Department of Experimental and Diagnostic Medicine, University of Ferrara, Emilia-Romagna, Italy
15. Pathology Department, Centro de Diagnóstico Biomédico, Tumour Bank-Biobank, IDIBAPS, University of Barcelona, Barcelona, Spain
16. Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
17. Department of Oncology, Hospital La Paz, Madrid, Spain
**Correspondence to jmaurel@clinic.ub.es*

BACKGROUND

Matrilysin (MMP7) can activate phosphorylated insulin growth factor receptor 1 (pIGF-1R) through IGF binding protein 3 degradation, releasing IGF-1. IGF-1R blockade is also involved in the suppression of cancer cell invasion through downregulation of MMP7. Co-expression of MMP7 and pIGF-1R (double positivity [DP]) correlates with poor prognosis in wild-type (WT) *KRAS* patients treated with anti-epidermal growth factor receptor (EGFR) in second and third-line therapy. We performed a prospective clinical trial in WT *KRAS* (exon 2) patients, treated with FOLFOX6 and panitumumab in first-line chemotherapy to validate those findings.

METHODS

Positive cases were defined by immunohistochemistry as those with moderate or strong intensity and >70% expression for both MMP7 and pIGF-1R (antibody: anti-pY1316). The primary endpoint was progression-free survival (PFS). Seventy-eight patients and 56 events were required to have an 80% power to detect a difference in median PFS at 6 months (two-sided $p<0.05$).

RESULTS

We screened 196 metastatic colorectal cancer (mCRC) patients in 24 centres between November 2010 and April 2013 and 78 patients were included (42 non-DP and 36 DP). Median follow-up was 23 months. There were no differences in baseline characteristics (age, sex, liver metastases, lactate dehydrogenase levels, and performance status between both groups). There were no differences in the number of chemotherapy cycles received and second-line therapies between both groups. Response rate was 80.2% in non-DP and 72.2% in DP patients (p=0.37). Median PFS was 7.4 months (95% confidence interval [CI]: 5.2–13.3) in non-DP and 9.6 months (95% CI: 6.7–17.5, p=0.15) in DP patients. Median overall survival was 19.8 months (11.5–26.3) in non-DP patients and 39.1 months (26–not estimatable, p=0.071) in DP patients. Adjusted hazard ratio for PFS was 0.68

(95% CI: 0.41–1.12). Adjusted hazard ratio for overall survival was 0.50 (95% CI: 0.29–0.97).

DISCUSSION

This study suggests that there is a potential correlation of survival benefit in the subset of DP WT *KRAS* mCRC patients treated with an upfront FOLFOX-panitumumab schedule. This benefit was shown irrespective of basal patient characteristics, secondary surgery of metastases, or second-line therapies, establishing that the DP group lived 2-times longer than the non-DP group of *KRAS* WT mCRC patients. Only the prognostic factors in mCRC, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and BRAF status remained in the multivariate analysis, supporting the consistency of our findings.

Despite no major differences existing in PFS between both groups (non-DP versus DP) in the whole population (7.4 versus 9.6 months) and in the *KRAS* WT analysis (9.2 versus 10.5 months), major differences were found after progressive disease (12.4 versus 29.5 months) and in the all *KRAS* WT analysis (9.0 versus 28.6 months). These results emphasise the potential importance of currently unknown biomarkers, in order to adequately interpret contradictory results in prospective Phase III clinical trials (FIRE-3 and CALGB/SWOG 80405) comparing face-to-face upfront anti-EGFR and anti-vascular endothelial growth factor therapy in *KRAS* WT mCRC patients.

Although performed with a prospective design and with a pre-specified cut-off biomarker, we are aware that our study has some limitations. First of all, the primary endpoint, PFS, was not met. Secondly, due to the absence of a control arm (treated with chemotherapy alone or plus bevacizumab) we could not establish if DP is a potential prognostic or predictive biomarker. Finally, patients were entered after central biomarker determination (*KRAS* and DP status) and results were given after a median of 12 days (standard deviation: 5 days), therefore we cannot rule out that patients with aggressive behaviour were excluded from the study.

CONCLUSION

Our study suggests that, unexpectedly, co-expression of MMP7 and pIGF-1R could be a novel strong prognostic biomarker of survival benefit in mCRC WT *KRAS* (exon 2) patients treated in first-line with FOLFOX6-panitumumab.

EMJ EUROPEAN MEDICAL JOURNAL

Click here to view the

AWARD WINNERS

at the European Society of Medical Oncology 2016 Congress

The ESMO Awards celebrate outstanding individuals in the field who have contributed extraordinary research findings and ensured the continued progress in our understanding of, and treatments for, medical oncology.

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

EDITOR'S PICK

Paediatric oncology therapy has advanced significantly; this improvement is in large part due to experimental treatments and therapies. Nielsen et al. deliver a fascinating piece for this year's *EMJ Oncology* eJournal, providing an in-depth review of some of the implications of paediatric cancer treatments in terms of complications in later life. Muscle toxicities are only one of the wide-ranging, short and long-term physiological manifestations that can occur. The authors go on to assess the value of exercise-oncology in helping to reduce such complications.

MUSCLE DYSFUNCTION IN CHILDHOOD CANCER: BIOLOGICAL MECHANISMS AND IMPLICATIONS FOR LONG-TERM SURVIVORSHIP

Martin K.F. Nielsen,[1] Hanne B. Larsen,[1] Kjeld Schmiegelow,[1,2] *Jesper F. Christensen[3]

1. Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
2. Institute of Clinical Medicine, Faculty of Medicine, University of Copenhagen, Copenhagen, Denmark
3. Centre of Inflammation and Metabolism/Centre for Physical Activity Research (CIM/CFAS), Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
**Correspondence to jesper.frank.christensen@regionh.dk*

Disclosure: The authors have declared no conflicts of interest.
Received: 11.08.16 **Accepted:** 18.10.16
Citation: EMJ Oncol. 2016;4[1]:78-85.

ABSTRACT

Paediatric cancer treatment has advanced significantly over the last half century to a point where >80% of all childhood cancer cases survive >5 years from diagnosis. However, childhood cancer treatments cause a wide range of long-term adverse effects including endocrine dysfunctions, impaired physical function, and a markedly increased risk of developing metabolic and cardiovascular complications. Emerging evidence suggests that treatment-related muscle toxicities may play a key role in the development of such late effects, but limited research has been performed towards elucidating this phenomenon and therapeutic countermeasures are scarcely available in clinical practice. Here, we review the current literature describing the physiological manifestations of treatment-induced muscular toxicities in paediatric oncology and discuss the use of structured exercise as a targeted countermeasure.

Keywords: Childhood cancer, exercise-oncology, muscle dysfunction, treatment toxicities.

INTRODUCTION

Paediatric oncology therapy is a major medical success story largely owing to progressive, co-ordinated development and experimental testing of risk-based therapies,[1] leading to impressive improvements in 5-year relative survival rate which is currently >80%.[2] However, curative childhood cancer treatment is associated with a wide range of short and long-term complications constituting a major health concern in post-treatment survivors, including endocrine dysfunction,[3] functional

capacity deficits,[4-8] and a markedly increased risk of metabolic and cardiovascular diseases.[3,9-13]

Accordingly, substantial attention within childhood cancer survivorship is directed towards elucidating the clinical implications and underlying biological mechanisms responsible for serious late effects following curative treatments. Strong evidence has outlined the negative consequences of treatment-related endocrine deficiencies, cardiomyopathy, and endothelial dysfunction,[3,11,12,14-18] whereas limited attention has been directed towards the potential role of treatment toxicities in skeletal muscle, a known regulator of overall physical capacity and the foundation for functional independence. Reports in long-term survivors of childhood cancer indicate that patients are subjected to muscle toxicities which may manifest as poor physical function many years after cessation of treatment.[4-7] However, there is limited evidence available describing muscular toxicities from childhood anti-cancer therapy, including the role of treatment-induced muscle dysfunction in the aetiology of late-occurring metabolic disorders and their mechanisms of action.

Against this background, we present a conceptual outline of childhood cancer treatment with regard to skeletal muscular toxicities and their potential long-term implications for metabolic deficiencies and complications. We review the most common treatment modalities in modern paediatric oncology with a specific view towards their possible adverse impact on muscular biology and regulation, and discuss the emerging application of exercise training in paediatric oncology as a pleotropic strategy to minimise and/or reverse the treatment-induced muscular dysfunction.

CHILDHOOD CANCER MANAGEMENT

Multi-modality treatment approaches using multi-agent chemotherapy in combination with surgery and radiotherapy have led to improved survival rates and subsequently increased focus on treatment-related adverse late effects. Studies have demonstrated that ≤90% of childhood cancer survivors suffer from a chronic health condition by the age of 45.[19-20] Thus, while improvement in overall survival has been marginal over the last decade, progress in paediatric oncology has largely involved the adoption of a risk-adapted therapeutic approach. Specifically, the identification of clinical and biological prognostic factors has provided the ability to stratify patients and modify treatments accordingly, allowing treatment to be intensified in the high-risk patients, while therapy for low-risk patients can be decreased to minimise toxicities and the risk of adverse late effects without compromising survival. The concept of improved childhood cancer outcomes is no longer confined to better overall survival, but also focussed on minimisation of the prevalence and severity of short and long-term treatment-related complications.

Several cross-sectional studies have shown that survivors of childhood cancer present with low muscle strength many years after treatment,[4-7] which can translate into limitations in physical performance[4-6] and low quality of life.[21] While late-occurring muscle dysfunction has long been recognised as a clinical challenge in paediatric oncology, it has only recently been suggested that this may constitute an intrinsic feature associated with early onset and/or high incidence of metabolic complications in childhood cancer survivors.

Muscle Toxicities in Childhood Cancer Treatment

Different intramuscular deficiencies have been proposed to mediate the sequelae of post-treatment complications in childhood cancer survivors, including impairment in myofibre progenitor cells (satellite cells), neuromuscular deficiencies and loss of motor units, and mitochondrial dysfunction.[22] These various adverse effects are likely caused by specific treatment regimens consisting of one or more components, including multi-agent chemotherapy, radiotherapy, and glucocorticoid treatment.

Chemotherapy

In most childhood cancers, multi-agent chemotherapy constitutes a key component of standard treatment, with numerous agents capable of inducing toxic effects on skeletal muscle. Vincristine is commonly used in the treatment of many malignancies including acute lymphoblastic leukaemia and solid tumours, and is accompanied by severe side effects, including neuropathy and chronic pain.[23] The presence of vincristine-induced neuropathy is well-established and observed in both the central nervous system (CNS) and peripheral nervous system (PNS), and is characterised by acute and long-term deficits in both sensory and motor functions lasting several years after cessation of cancer treatment.[4,24-34] Vincristine-induced neuropathy occurs as a result of its high binding affinity to β-tubulin, leading to aborted cell division

and cell death. The disruption of the β-tubulin assembly and disassembly leads to serious changes in axonal microtubules, causing axonal swelling in myelinated and in unmyelinated fibres, and nerve damage.[23] The consequence of these changes has been thoroughly examined through electrophysical examination and studies have reported decreased compound muscle action potential (CMAP),[28,34] along with decreased and prolonged latency of motor evoked potentials (MEPs) along the entire motor nervous pathway[25] in children receiving treatment. Furthermore, these impairments persist in survivors of childhood cancer, and studies have demonstrated CMAP amplitude less than two standard deviations below normal values[27,32] and prolonged latencies of MEP.[31] These results strongly indicate that vincristine causes demyelination of motor axons, evidenced by prolonged latencies, and causes damage to motor units leading to denervation of muscle fibres and subsequent muscle atrophy. Collectively, these adverse effects explain in part the acute and prolonged deficits of motor function seen in patients and survivors of childhood cancer,[30] whom have received vincristine, even at low doses.[4,35]

While numerous studies have thoroughly described the neurotoxic impact of vincristine, to our knowledge no studies have evaluated the molecular effects on muscle morphology and intramuscular regulation. Thus, it remains unknown whether vincristine-induced muscle dysfunction is driven exclusively by the impact of impaired neural innervation, or whether vincristine is additionally associated with direct adverse effects on skeletal muscle regulation and metabolism.

Anthracyclines are frequently used in the treatment of childhood cancers and are known to cause cardiovascular complications including cardiomyopathy and endothelial dysfunction.[36] While these adverse reactions are considered to be the main drivers of the increased risk of cardiovascular disease in cancer survivors, studies have further outlined a direct anthracycline-related increase in oxidative stress within skeletal muscles contributing to poor physical function, impaired metabolic control, and elevated levels of fatigue.[37-38] Muscle biopsies taken before and after a 50-day period of chemotherapy with doxorubicin or melphalan in adults diagnosed with melanoma or sarcoma showed severe reductions in myofibre size, neurogenic alterations, and mitochondria-related damages.[39,40]

Methotrexate is given intrathecally in childhood cancer cases with CNS involvement, and thus has access to the PNS and CNS. It is generally accepted that methotrexate causes neuropathy, and autopsy studies have reported damage to the myelinated long tracts of the spinal cord, swelling, and loss of axons,[41] hypothetically inducing damage and/or loss of motor units, resulting in denervation and subsequently atrophy of muscle fibres.

L-asparaginase is especially used in the treatment of acute lymphoblastic leukaemia as the enzyme reduces the availability of L-asparagine, which is essential for the survival of leukaemic cells. L-asparaginase may inhibit muscle protein synthesis,[42] and studies have shown that L-asparaginase treatment is associated with muscle weakness in adolescent and young adult survivors,[5] lasting years after cessation of treatment.

Radiotherapy

The risk of adverse events, especially secondary cancer, caused by radiation has hampered the use of radiotherapy in modern paediatric oncology, which applies a risk-adapted approach with the overall intent of minimising or avoiding this modality as much as possible. However, in certain diagnostic groups (e.g. patients with sarcoma) and/or patients who are not responding to chemotherapy,[1] radiotherapy remains a treatment option, and is associated with high risk of toxic reaction in the targeted anatomical area. Specifically, radiotherapy may inhibit mitosis of progenitor cells[43] and disrupt cell membrane permeability and lipid fluidity, possibly resulting in Na^+/K^+ pump failure at the neuromuscular junction.[44] Furthermore, post-radiation inflammation facilitated by alteration of the growth factor-β family may inhibit muscle growth, and radiation-induced vascular and parenchymal damage may inhibit the supply of nutrients and metabolites.[45]

Glucocorticoids

Concurrent medication includes glucocorticoids (e.g. prednisolone) as an antiemetic treatment. A supra-physiological concentration of glucocorticoids displays strong immunosuppressive and anti-inflammatory actions, and is essential in the treatment of acute lymphoblastic leukaemia. The use of these agents has traditionally been hampered by considerable metabolic side effects. The adverse reactions to prolonged use of prednisolone in cancer patients is poorly investigated, but it has been demonstrated to cause

significant insulin resistance, increased protein breakdown, blunted protein synthesis, and inhibition of insulin signalling in healthy subjects.[46]

Behavioural factors

Cancer treatment is accompanied by side effects that indirectly affect the skeletal muscle, including: side effects, i.e. nausea (and subsequent malnutrition), pain, reduced pulmonary function, as well as prolonged hospitalisation associated with sedentary behaviour and limited contact with peers. The cumulative effects of the treatment-induced muscle toxicities and physical inactivity augments the level of muscle dysfunction, creating a negative spiral further reducing physical function; in the worst case to the point where patients are no longer functionally independent (Figure 1). Thus, the importance of breaking this vicious cycle is becoming readily apparent.

In summary, significant anti-cancer treatment-related muscle toxicities may include myopathies, neuropathy, and intramuscular dysregulation of protein turnover and metabolic properties induced by various therapy components (Table 1). These reactions can lead to decrements in physical function, and subsequent development of metabolic complications which affect cancer survivors long after cessation of treatment; emerging clinical interest is thus directed towards exploring and implementing effective therapeutic countermeasures.

EXERCISE TRAINING IN PAEDIATRIC ONCOLOGY

Exercise training is currently emerging as a promising strategy in the oncology setting, and a growing body of evidence has outlined the beneficial potential of exercise to improve a broad range of physiological endpoints, including muscle-specific outcomes, i.e. muscle strength, lean mass, and mean fibre area. In adults, a plethora of studies have been published showing that cancer patients are capable of performing physical exercise and adapting much to the same extent as non-cancer populations.[47,48]

While the body of evidence in paediatric oncology is less comprehensive, a number of exercise trials have been performed predominantly in acute lymphoblastic leukaemia patients in the later stages of treatment, demonstrating that exercise is safe and feasible even during intense treatment phases.[49] The majority of studies have investigated the effects of exercise interventions on physical function utilising different measures, including timed up and go,[50-53] timed up and down stairs,[50-54] gait speed test,[53,54] and various motor performance batteries.[55-57]

With emerging safety and feasibility data supporting exercise application, an important next generation of research constitutes mechanistic explorations of exercise-induced improvements with the purpose of developing targeted exercise therapies to reverse treatment-specific muscle toxicities, thus most efficiently ameliorating the level of long-term muscle dysfunction.

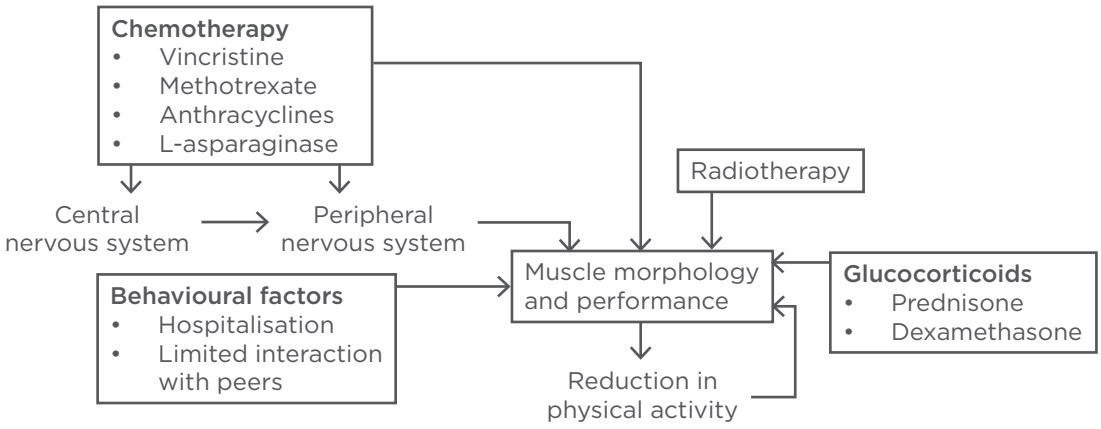


Figure 1: Schematic representation of childhood cancer treatment-related adverse effects on muscle morphology through direct actions or via neurotoxic impairments in the central or peripheral neural system, with a negative impact on muscle morphology and performance, potentially reducing activity level, which in turn reinforces muscular deterioration.

Table 1: Childhood cancer treatments, mechanisms of action, and skeletal muscle complications.

Cancer treatment	Mechanism of action	Muscle complications
Antimetabolites (e.g. methotrexate)	Disrupts DNA replication or RNA synthesis, resulting in cell death	Causes damage and loss of axon, thus denervation of muscle fibres;[41] potentially results in muscle atrophy
Anti-tumour antibiotics (e.g. anthracyclines)	Interferes with enzymes involved in DNA replication, resulting in prevention of replication	Increases oxidative stress within skeletal muscle, contributing to poor physical function, impaired metabolic control, mitochondrial damage, and muscle atrophy[37-40]
Mitotic inhibitors (e.g. vincristine)	Interferes with mitosis in the M stage of the cell cycle	Causes demyelination and damage to motor axons, resulting in denervation of muscle fibres.[23,25,28,34] Potentially results in muscle atrophy
L-asparaginase	Reduces the availability of L-asparagine which is essential for the survival of leukaemic cells	Inhibits muscle protein synthesis[42]
Radiotherapy	Double-stranded DNA breaks are unresponsive to repair, resulting in direct apoptosis	Inhibits mitosis of progenitor myosatellite cells, disrupts cell membrane permeability affecting neuromuscular junctions, increases inflammation inhibiting muscle growth, and inhibits supply of nutrients and metabolites[43-45]
Glucocorticoids	Long-term use results in multiple suppressive effects on the immune system	Increases insulin resistance, increases protein breakdown, and inhibits protein synthesis[46]
Side effects	Several factors indirectly affecting muscle dysfunction, including other side effects (nausea, pain, pulmonary function), hospitalisation, and limited contact with peers	Reduces physical activity and malnutrition, resulting in muscle atrophy

Mechanistic Rationale for Structured Exercise Training in Childhood Cancer

Voluntary physical exercise is a pleiotropic strategy inducing homeostatic perturbations in multiple organ systems including skeletal muscle. While the body of mechanistic data is from childhood cancer exercise studies, different plausible candidate mechanisms exist through which exercise may target and counteract treatment specific muscle toxicities.

Resistance exercise to reverse neuromuscular deficits

Treatment-induced neuromuscular deficits are evident through reduced and prolonged latencies of CMAP and MEP observed in childhood cancer patients and survivors.[25,27,28,32,34] These alterations may be a result of a demyelination of motor axons, evidenced by the prolonged latencies and/or reduced firing frequencies of motor units and/or damage to motor units. Structured resistance training, as characterised by 'high load, low volume' muscle contractions, is known to be highly effective for improving neuromuscular function in different populations.[58,59] Resistance training induces neural plasticity and includes alterations of motor unit recruitment, firing frequency, and synchronisation of motor unit activation,[58] all of which theoretically would counteract the cancer treatment-induced neuromuscular deficits. Improved firing frequency particularly represents a highly beneficial adaptation to counteract the decline in muscle fibre activation. In addition, increases in firing frequency will improve the ability to produce muscle force at a faster rate, which is of great importance in children suffering from severe neuropathy combined with low thrombocytes and/or porous bones (e.g. some solid tumours), thus lowering the risk of a fall in fragile populations. Furthermore, resistance training can improve markers of metabolic syndrome in healthy children through a combined effect improving insulin sensitivity, blood pressure, lipid profile, and body composition.[60]

Aerobic exercise to reverse mitochondrial dysfunction

Treatment-induced mitochondrial dysfunction or damage is a result of increased reactive oxygen species (ROS) production, which can lead to muscle atrophy and subsequent weakness.[61] Aerobic exercise training, characterised by 'low load, high volume' contractions, may counteract this development by stimulating mitochondrial biogenesis and anti-oxidant defences. A key regulator of mitochondrial biogenesis is PGC-1α which is upregulated through prolonged aerobic exercise, increasing the number and size of mitochondria in skeletal muscle[62,63] and thus potentially increasing the repair/replacement of damaged mitochondria. Although an increased number of mitochondria in the skeletal muscle would cause the mitochondria to produce more ROS, a parallel regulation of respiratory chain proteins and mitochondrial anti-oxidant enzymes would be an advantage. PGC-1α regulates the expression of anti-oxidant proteins upregulating ROS-removing enzymes, thus improving the anti-oxidant defence.[63]

In summary, the emergence of exercise-oncology research has led to progressive advances in the application of physical exercise training for patients with cancer, however in the paediatric field a paucity of research initiatives exists. There is a lack of investigations exploring exercise interventions during prolonged hospital stays to break the negative reinforcing spiral of sedentary behaviour and poor physical function, for which there is promising therapeutic potential.

FUTURE DIRECTIONS

Skeletal muscle toxicities may comprise an integrated part of the aetiology related to treatment-induced late effects in childhood cancer survivors. Notably, these impairments may not manifest into clinical symptoms until many years after cessation of treatment, and thus it may be difficult to separate treatment-related from non-treatment-related causes and other derived morbid conditions. To improve the current understanding of the prognostic role of muscle dysfunction in childhood cancer survivors, it is important to investigate the direct molecular impact of common therapeutic modalities in childhood cancer treatment on skeletal muscle biology and regulation. Specific attention should be given to the treatment-induced denervation of muscle fibres and mitochondria dysfunction through muscle biopsy sampling to evaluate fibre type distribution, mean fibre size, satellite cell count, capillary density, and mitochondria content and function.

Furthermore, introducing research initiatives into exercise interventions in paediatric cancer settings is warranted. Specifically, studies investigating the pathophysiological profile of children with cancer undergoing active therapies that may affect exercise adaptations are needed, as well as investigations of the structural and motivational barriers precluding daily activity and exercise for children during prolonged hospitalisation.

In conclusion, a strong clinical rationale is emerging for improving the current understanding of skeletal muscle toxicities in paediatric oncology to advance the evidence base from which therapeutic countermeasures can be developed and implemented in standard childhood cancer care. Maintaining physical capacity through reversal of muscle dysfunction in childhood cancer patients may translate into reduced risk of late-occurring metabolic complications, thus improving the overall quality of childhood cancer survivorship.

REFERENCES

1. Saletta F et al. Advances in paediatric cancer treatment. Transl Pediatr. 2014; 3(2):156-82.

2. Gatta G et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer. 2009; 45(6):992-1005.

3. Rose SR et al. Late endocrine effects of childhood cancer. Nat Rev Endocrinol. 2016;12(6):319-36.

4. Hartman A et al. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. Pediatr Blood Cancer. 2008;50(4):833-7.

5. Hovi L et al. Impaired muscle strength in female adolescents and young adults surviving leukemia in childhood. Cancer. 1993;72(1):276-81.

6. Ness KK et al. Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. Cancer. 2012; 118(3):828-38.

7. Talvensaari KK et al. Decreased isokinetic trunk muscle strength and performance in long-term survivors of childhood malignancies: correlation with hormonal defects. Arch Phys Med Rehabil. 1995;76(11):983-8.

8. Ness KK et al. Physical performance limitations in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009; 27(14):2382-9.

9. Meacham LR et al. Cardiovascular risk

factors in adult survivors of pediatric cancer--a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 2010;19(1):170-81.

10. Meacham LR et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med. 2009;169(15):1381-8.

11. Oeffinger KC et al. Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol. 2009;27(22):3698-704.

12. Oeffinger KC et al. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2001;23(7): 424-30.

13. Diller L et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. J Clin Oncol. 2009;27(14):2339-55.

14. Yamaguchi N et al. Comparison of cardiac events associated with liposomal doxorubicin, epirubicin and doxorubicin in breast cancer: a Bayesian network meta-analysis. Eur J Cancer. 2015;51(16): 2314-20.

15. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf. 2000; 22(4):263-302.

16. van Dalen EC et al. Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer. Cochrane Database Syst Rev. 2014; (9):CD006647.

17. de Fine Licht S et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. Lancet. 2014;383(9933):1981-9.

18. Abu-Ouf NM, Jan MM. Metabolic syndrome in the survivors of childhood acute lymphoblastic leukaemia. Obes Res Clin Pract. 2015;9(2):114-24.

19. Hudson MM et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA. 2013; 309(22):2371-81.

20. Bhatia S. Cancer survivorship--pediatric issues. Hematology Am Soc Hematol Educ Program. 2005;507-15.

21. Ness KK et al. The impact of limitations in physical, executive, and emotional function on health-related quality of life among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Arch Phys Med Rehabil. 2008;89(1):128-36.

22. Scheede-Bergdahl C, Jagoe RT. After the chemotherapy: potential mechanisms for chemotherapy-induced delayed skeletal muscle dysfunction in survivors of acute lymphoblastic leukaemia in childhood. Front Pharmacol. 2013;4:49.

23. Carozzi VA et al. Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms? Neurosci Lett. 2015;596:90-107.

24. Postma TJ et al. Long-term effects of vincristine on the peripheral nervous system. J Neurooncol. 1993;15(1):23-7.

25. Harila-Saari AH et al. Motor nervous pathway function is impaired after treatment of childhood acute lymphoblastic leukemia: a study with motor evoked potentials. Med Pediatr Oncol. 2001;36(3):345-51.

26. Vainionpaa L et al. Vincristine therapy for children with acute lymphoblastic leukemia impairs conduction in the entire peripheral nerve. Pediatr Neurol. 1995;13(4):314-8.

27. Jain P et al. Vincristine-induced neuropathy in childhood ALL (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. J Child Neurol. 2014;29(7): 932-7.

28. Courtemanche H et al. Vincristine-induced neuropathy: Atypical electrophysiological patterns in children. Muscle Nerve. 2015;52(6):981-5.

29. Lavoie Smith EM et al. Patterns and severity of vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. J Peripher Nerv Syst. 2015;20(1):37-46.

30. Gilchrist L, Tanner L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. Pediatr Phys Ther. 2016; 28(1):16-22.

31. Lehtinen SS et al. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. Cancer. 2002;94(9):2466-73.

32. Ramchandren S et al. Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. J Peripher Nerv Syst. 2009;14(3):184-9.

33. Harila-Saari AH et al. Nerve lesions after therapy for childhood acute lymphoblastic leukemia. Cancer. 1998; 82(1):200-7.

34. Yildiz FG, Temucin CM. Vincristine-induced neurotoxicity: electrophysiological features in children. Neurol Res. 2016;38(2):124-9.

35. Hartman A et al. Decrease in motor performance in children with cancer is independent of the cumulative dose of vincristine. Cancer. 2006;106(6):1395-401.

36. Scott JM et al. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. Circulation. 2011;124(5):642-50.

37. Gilliam LA, St Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. Antioxid Redox Signal. 2011;15(9): 2543-63.

38. Gilliam LA et al. The anticancer agent doxorubicin disrupts mitochondrial energy metabolism and redox balance in skeletal muscle. Free Radic Biol Med. 2013;65:988-96.

39. Bonifati DM et al. Neuromuscular damage after hyperthermic isolated limb perfusion in patients with melanoma or sarcoma treated with chemotherapeutic agents. Cancer Chemother Pharmacol. 2000;46(6):517-22.

40. Saiki JH et al. Paraplegia following intrathecal chemotherapy. Cancer. 1972; 29(2):370-4.

41. Clark AW et al. Paraplegia following intrathecal chemotherapy: neuropathologic findings and elevation of myelin basic protein. Cancer. 1982; 50(1):42-7.

42. Villa P et al. L-asparaginase effects on inhibition of protein synthesis and lowering of the glutamine content in cultured rat hepatocytes. Toxicol Lett. 1986;32(3):235-41.

43. Caiozzo VJ et al. The radiosensitivity of satellite cells: cell cycle regulation, apoptosis and oxidative stress. Radiat Res. 2010;174(5):582-9.

44. Leyko W, Bartosz G. Membrane effects of ionizing radiation and hyperthermia. Int J Radiat Biol Relat Stud Phys Chem Med. 1986;49(5):743-70.

45. Powers BE et al. Muscle injury following experimental intraoperative irradiation. Int J Radiat Oncol Biol Phys. 1991;20(3):463-71.

46. van Raalte DH et al. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest. 2009;39(2): 81-93.

47. Buffart LM et al. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev. 2014;40(2):327-40.

48. Schmitz KH et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.

49. Grimshaw SL et al. The Feasibility of Physical Activity Interventions During the Intense Treatment Phase for Children and Adolescents with Cancer: A Systematic Review. Pediatr Blood Cancer. 2016;63(9):1586-93.

50. San Juan AF et al. Benefits of intrahospital exercise training after pediatric bone marrow transplantation. Int J Sports Med. 2008;29(5):439-46.

51. San Juan AF et al. Early-phase adaptations to intrahospital training in strength and functional mobility of

children with leukemia. J Strength Cond Res. 2007;21(1):173-7.

52. San Juan AF et al. Effects of an intrahospital exercise program intervention for children with leukemia. Med Sci Sports Exerc. 2007;39(1):13-21.

53. Tanir MK, Kuguoglu S. Impact of exercise on lower activity levels in children with acute lymphoblastic leukemia: a randomized controlled trial from Turkey. Rehabil Nurs. 2013;38(1):48-59.

54. Marchese VG et al. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2004;42(2):127-33.

55. Hartman A et al. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009;53(1):64-71.

56. Esbenshade AJ et al. Feasibility and initial effectiveness of home exercise during maintenance therapy for childhood acute lymphoblastic leukemia. Pediatr Phys Ther. 2014;26(3):301-7.

57. Gohar SF et al. Feasibility and parent satisfaction of a physical therapy intervention program for children with acute lymphoblastic leukemia in the first 6 months of medical treatment. Pediatr Blood Cancer. 2011;56(5):799-804.

58. Aagaard P. Training-induced changes in neural function. Exerc Sport Sci Rev. 2003;31(2):61-7.

59. Ozmun JC et al. Neuromuscular adaptations following prepubescent strength training. Med Sci Sports Exerc. 1994;26(4):510-4.

60. Faigenbaum AD et al. Youth resistance training: updated position statement paper from the national strength and conditioning association. J Strength Cond Res. 2009;23(Suppl 5):S60-79.

61. Sorensen JC et al. Mitochondria: Inadvertent targets in chemotherapy-induced skeletal muscle toxicity and wasting? Cancer Chemother Pharmacol. 2016. [Epub ahead of print].

62. Little JP et al. Skeletal muscle and beyond: the role of exercise as a mediator of systemic mitochondrial biogenesis. Appl Physiol Nutr Metab. 2011;36(5): 598-607.

63. Olesen J et al. PGC-1alpha-mediated adaptations in skeletal muscle. Pflugers Arch. 2010;460(1):153-62.

THE IMPORTANCE OF MUTATIONAL ANALYSIS IN CHRONIC MYELOID LEUKAEMIA FOR TREATMENT CHOICE

***Hugues de Lavallade,[1,3] Aytug Kizilors[2,3]**

1. Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, UK
2. Laboratory for Molecular Haemato-Oncology, King's College Hospital NHS Foundation Trust/King's College London, London, UK
3. Haematology Department, King's College London, London, UK
**Correspondence to h.delavallade@nhs.net*

Disclosure: Hugues de Lavallade received research funding from Ariad Pharma and consultancy fees from Novartis. Aytug Kizilors has received research funding from Ariad Pharma.
Support: The publication of this article was funded by Incyte Biosciences. The views and opinions expressed are those of the authors and not necessarily of Incyte Biosciences.
Received: 03.03.16 **Accepted:** 16.06.16
Citation: EMJ Oncol. 2016;4[1]:86-95.

ABSTRACT

Since their introduction in 2001, tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have become the standard therapy for chronic myeloid leukaemia (CML). While allogeneic hematopoietic stem cell transplant is a recognised curative treatment for CML, TKIs prevent progression to advanced phase in most patients, and spectacularly improve the disease burden (in deep molecular responders) and the overall survival of CML patients.

However, mutations in the *BCR-ABL* kinase domain affect a significant proportion of CML patients and have been associated with primary or secondary (refractory disease following an initial response) resistance to imatinib. Such resistance may emerge at any time during TKI therapy and are a major mechanism of treatment failure, in addition to BCR-ABL-independent treatment resistance and treatment intolerance mechanisms. In the context of the above-described clinical settings, the management of CML patients remains challenging. The detection of mutations following imatinib resistance is therefore crucial to ensure appropriate second or third-line drug selection.

Keywords: Chronic myeloid leukaemia (CML), BCR-ABL, ponatinib, T315I, mutational analysis, tyrosine kinase inhibitors (TKIs).

INTRODUCTION

Chronic myeloid leukaemia (CML) is a Philadelphia chromosome positive (Ph+) clonal bone marrow stem cell disorder classified into the group of myeloproliferative neoplasms, along with polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis.[1,2] CML originates from a single pluripotent haematopoietic stem cell, in which cells of the myeloid lineage undergo inappropriate clonal expansion caused by a molecular lesion.[1,2]

CML is characterised by the occurrence of the Philadelphia chromosome, which results from the fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 and the Abelson murine leukaemia (*ABL*) gene on chromosome 9. This generates the *BCR-ABL* oncogene that encodes for a chimeric but active oncoprotein, the BCR-ABL tyrosine kinase; its deregulated activity is necessary and sufficient for malignant transformation.[1,2] The disease typically progresses through three distinct phases: chronic phase, accelerated phase, and blast crisis, during which the leukaemic clone progressively loses its ability to differentiate.

Since their introduction in 2001, tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have become the standard therapy for CML. While allogeneic hematopoietic stem cell transplant (Allo-HSCT) is a recognised curative treatment for CML, TKIs prevent progression to advanced phase in most patients,

and spectacularly improve the disease burden (in deep molecular responders) and the overall survival of CML patients.[3] At present, five TKIs are approved for the treatment of CML: imatinib (a first-generation TKI), nilotinib, dasatinib, bosutinib (second-generation TKIs), and ponatinib (a third-generation TKI). The first three compounds are approved for the treatment of newly-diagnosed patients who are treatment-naïve, while bosutinib and ponatinib are indicated in patients with resistant or intolerant CML.[4-6]

However, mutations in the *BCR-ABL* kinase domain (KD) affect a significant proportion of CML patients and have been associated with primary or acquired (refractory disease following an initial response) resistances to imatinib.[6-9] Such resistance may emerge at any time during TKI therapy and are a major mechanism of treatment failure, in addition to BCR-ABL-independent treatment resistances and treatment intolerance mechanisms.

In the context of the above-described clinical settings, the management of CML patients remains challenging. Indeed, while nilotinib and dasatinib are active against most imatinib-resistance mutations, other mutations also confer resistance (thus a poor response) to second-generation TKIs. Conversely, some imatinib-resistant mutations are insensitive to dasatinib and/or nilotinib.[10-14] The detection of such mutations following imatinib resistance is therefore crucial to ensure appropriate second or third-line drug selection.[15] Therefore, this article will review the available techniques to perform mutational analyses in CML patients, and how physicians can refine treatment selection pathways and rationales to select the appropriate therapy and tailor the management for each CML patient.

BCR-ABL KD MUTATIONS AND TREATMENT FAILURES

Mutations occur in cancerous cells where the genetic instability is high, leading to the accumulation of further abnormalities and evolution to advanced disease.[16,17] In newly-diagnosed chronic phase (CP)-CML patients, 15–30% who start first-line TKI therapy will not reach an optimal response, and a *BCR-ABL* KD mutation will be detectable in 25–50% of patients with treatment failure.[4,5,8,16,18-20] Furthermore, up to 80% of patients with blast phase (BP)-CML can carry mutations.[21]

Among *BCR-ABL* KD mutations, the *T315I* multiresistant mutant is found in 11-20% of cases.[11,20,22-24] Small cell populations in which mutations occur may have a survival advantage during TKI therapy and emerge later as the dominant clone, speeding up the progression to AP-CML.[16,17]

Although resistance to therapy can occur at any time point, it has been established that the sequential use of TKIs as the CML disease progresses increases the probability of mutations.[13,16,22,25] Relapsed patients usually display a greater genetic instability and have a higher likelihood to develop further mutations. As an example, a study showed that 83% of imatinib-resistant patients who relapsed while on a second or third-line TKI experienced an emergence of newly acquired KD mutations.[13] Moreover, the order of the TKI sequence may influence the emerging mutation type.[25]

SINGLE MUTATION AND COMPOUND MUTATIONS

Over 80 *BCR-ABL* KD single mutations that affect TKI sensitivity in CML have been identified with data collated from 27 studies, from patients resistant to first-generation TKI therapy.[16,26] Compound mutations, defined as ≥2 mutations in the same BCR-ABL molecule (as opposed to polyclonal mutations, multiple *BCR-ABL* mutant clones) can confer high-level resistance to TKIs and are associated with suboptimal response and poorer outcomes, due to a very low TKI sensitivity.[12,27-33] It has been suggested that sequential therapy with multiple TKIs may select for compound mutations that confer resistance to multiple TKIs.[12,18,28]

According to the type of mutation, corresponding TKI sensitivity can be observed, and *in vitro* potency of each TKI (IC_{50}, corresponding to the concentration at which 50% of the BCR-ABL tyrosine kinase is inhibited) can be useful to predict which TKI could be more effective than others.[34,35] As an example, Zabriskie et al.[32] developed a heat map of IC_{50} values for single and compound mutants (Figure 1).

TYPES OF MUTATIONAL ANALYSES

The presence of mutations is an important factor when making treatment decisions. Indeed, if an inappropriate TKI is chosen, there is a high-risk of subsequent treatment failure with clonal expansion of the resistant mutant, and a greater likelihood to

select for a compound mutant: the initial mutated clone is not eradicated, thus has the possibility to acquire additional mutations.[36] Several types of mutational assays have been developed to explore these mutational profiles in real-life clinical settings (absence/presence of mutations and mutation type) and their advantages and disadvantages are summarised in Table 1.[9,37-40]

The most common techniques for mutation screening of the entire KD are direct (Sanger) sequencing (SS) and ultra-deep sequencing (UDS) using next-generation sequencing (NGS). Assays for detection of given mutations include allele-specific oligonucleotide quantitative reverse transcription polymerase chain reaction (ASO-Rt-qPCR) and Sequenom mass spectrometry. Highly sensitive assays can be useful in predicting the best course of treatment for TKI-resistant patients and for monitoring resistant mutations in subsequent treatment settings.[41]

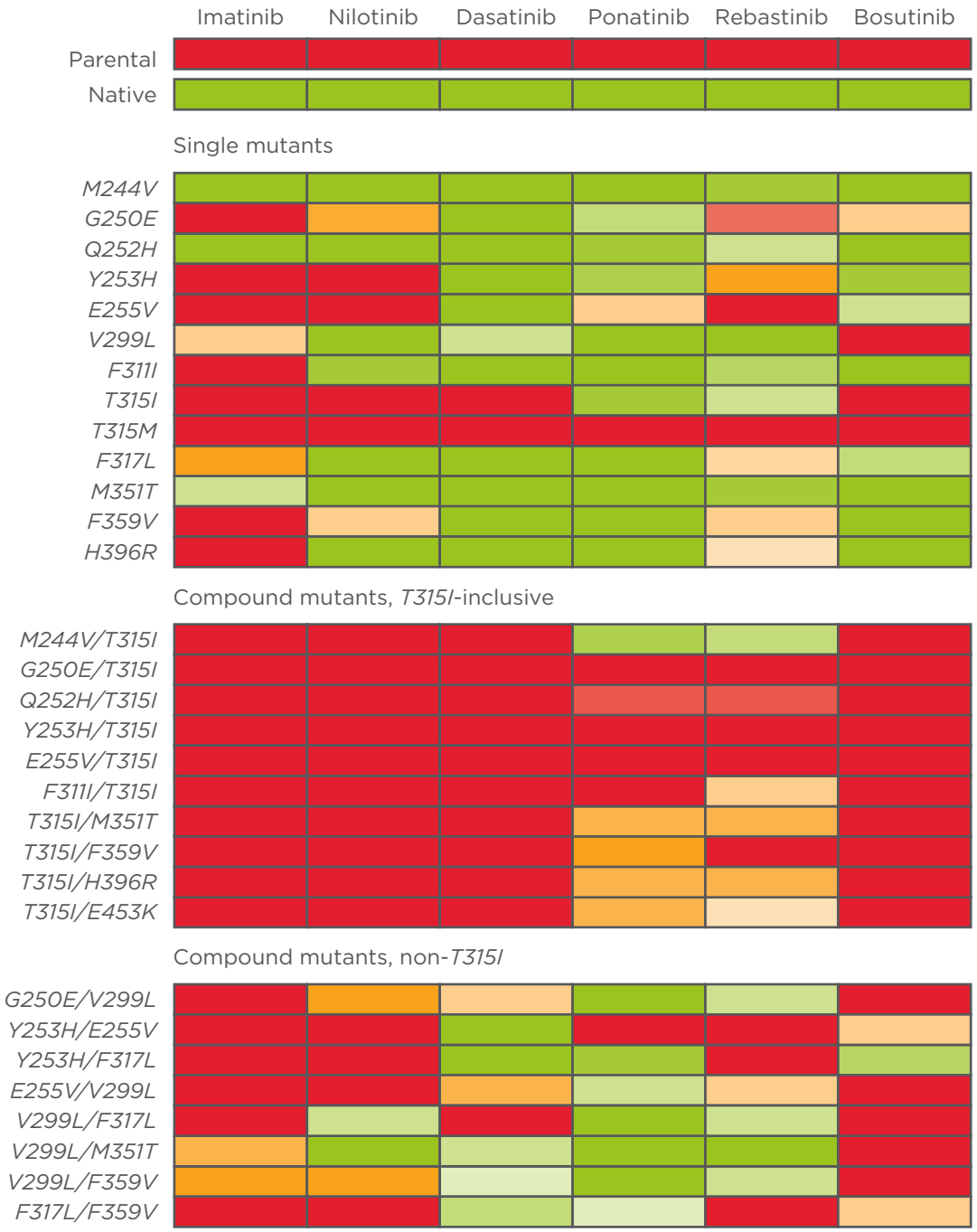


Figure 1: Heat map of TKI IC_{50} for single and compound mutants. A colour gradient from green (sensitive) to yellow (moderately resistant) to red (highly resistant) denotes the IC_{50} sensitivity to each TKI.[32]
TKI: tyrosine kinase inhibitor; IC_{50}: concentration when inhibitor response is 50%.

Table 1: Most common techniques for mutational analyses of *BCR-ABL* kinase domain mutations.[9,36-41,58]

	Method	Sensitivity	Advantages	Disadvantages
Sensitivity ↓	Direct sequencing (Sanger sequencing)	15–25%	• Universal technology • Fast turnaround • Low cost • Bidirectional conformation • Semi-quantitative	• Least sensitive (but sensitive enough for general use) • Can be time consuming and labour intensive, especially if a subcloning step is included • Does not detect compound mutations • Highly-dependent on RNA sample quality
	Denaturing high-performance liquid chromatography	0.1–10%	• More sensitive than direct sequencing • Can be used to screen a large number of samples for the need to do direct sequencing • Can detect sequence variation	• Not as widely available as direct sequencing • False-negative results possible if mutant subclone is abundant
	Next-generation sequencing/ ultra-deep sequencing	0.5–1.0%	• High sensitivity and specificity • Quantitative • Able to detect complex mutational profiles dynamically • Some platforms amendable to compound mutation detection	• Expensive • Limited availability • Slow turnaround • Unclear clinical significance of low-level mutation detection • Highly-dependent on RNA sample quality
	Allele-specific oligonucleotide quantitative reverse transcription polymerase chain reaction	0.001–0.01%	• High sensitivity and specificity • Quantitative • Easy to perform, no special equipment needed	• Specific for single mutation detection (i.e. requires prior knowledge of mutation) • Does not detect compound mutations • Low throughput • Can be insensitive to closely spaced compound mutations
	Mass spectrometry	0.05–0.5%	• High sensitivity • Detects low-level mutations	• Requires mass spectrometry instrumentation

Sanger Sequencing

SS (direct sequencing) is the most common technique to detect *BCR-ABL* KD mutations associated with TKI resistance, as currently recommended by international guidelines and consensus panel.[16,38,42] While being the least sensitive method available and associated to technical limitations, it has been deemed sufficient for general use by the haematological community, since it is widely available in laboratories worldwide.[42] However, SS may not detect all mutations present, namely compound mutations and mutations present in less than 20% of cells (low-level mutations), below the detection limit. Mutations detectable by SS may just be the 'tip of the iceberg'.[38,40,41,43]

Denaturing High-Performance Liquid Chromatography

Denaturing high-performance liquid chromatography is more sensitive (but not as widely available) than direct sequencing (0.1–10%), can detect sequence variation, and can be used to screen a large number of samples without the need to do direct sequencing.[37] However, false-negative results can be generated if mutant subclone is abundant.

Next-Generation Sequencing and Ultra-Deep Sequencing

Deep-sequencing boasts a higher level of sensitivity (≥1%) to detect clinically relevant *BCR-ABL* emergent mutant clones that are not detected by SS, including compound mutations and the *T351* mutation.[43,44] Of note, NGS is the technology, while UDS is the application of NGS for sensitive (deep) mutation screening of target genes (or gene panels). The increased sensitivity allows deep sequencing to qualitatively and quantitatively assess the clonal texture of the mutated *BCR-ABL*-positive subpopulations, giving the possibility to fully characterise the spectrum of mutants in a patient.[40,45,46]

In a cohort of 121 CP-CML patients presented at the 2015 American Society of Hematology (ASH) congress, we reported that NGS can reliably detect low-level KD mutations otherwise not detectable by SS. In particular, we found that NGS can detect low-level KD mutations in patients who achieve complete cytogenetic response (CCyR) but not major molecular response (MMR), thus allowing potential early clinical intervention.[47] Finally, NGS could also detect the appearance of KD mutations as early as 3 months post TKI initiation in patients who failed to respond.

Soverini et al.[48] recently reported the use of NGS to retrospectively screen a cohort of 60 imatinib-resistant patients (CML, n=45; Ph+ acute lymphoblastic leukaemia [ALL], n=15) who had failed second-line second-generation TKI therapy and acquired KD mutations (Group 1) compared to 25 imatinib-resistant patients (CML, n=21; Ph+ ALL, n=4) who had responded to second-line second-generation TKI therapy (Group 2).

The authors demonstrated that NGS was effective at detecting clinically-relevant mutations at the time of imatinib failure. In 43% of patients from Group 1, second-generation TKI-resistant mutations generating relapse were already detectable at low levels with NGS. When patients subsequently received a second-generation TKI therapy to which they were insensitive, mutations underwent clonal expansion in all cases. Conversely, no low-level mutation that was resistant to the second-generation TKI the patients subsequently received was detected in Group 2. This demonstrates that NGS at the time of imatinib failure could be efficient for more effective therapeutic tailoring and second-generation TKI therapy choice.

Allele-Specific Oligonucleotide Reverse Transcription Quantitative Polymerase Chain Reaction

ASO-Rt-qPCR boasts high sensitivity and specificity (the former at rates of 0.001–0.01%), and can be used for single mutation detection but not compound mutations. Its main drawbacks are a low throughput, restricted availability, and low sensitivity for closely-spaced compound mutations.[20,49]

A

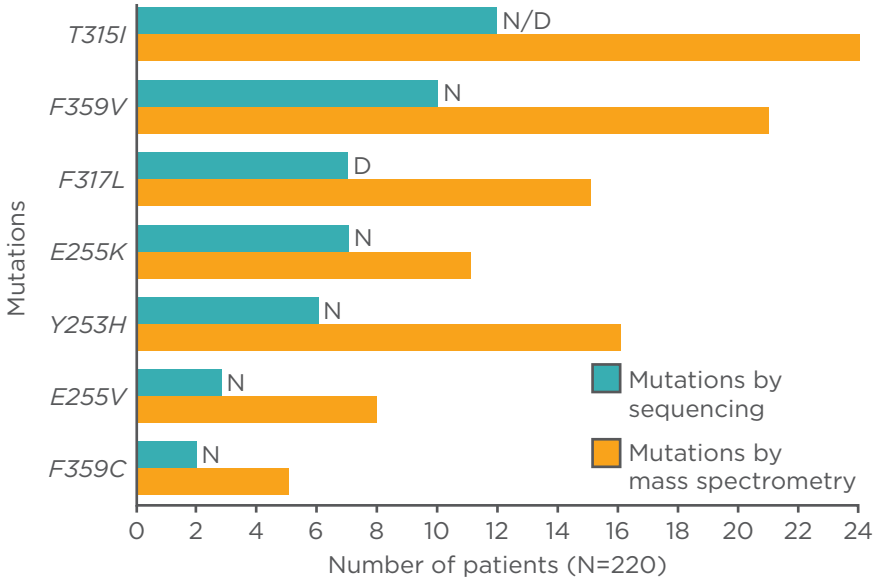


Figure 2A: Type of mutations detected by SS and mass spectrometry (only mutations that would influence therapeutic decisions after imatinib are presented).[36]

SS: direct (Sanger) sequencing; N: nilotinib; D: dasatinib.

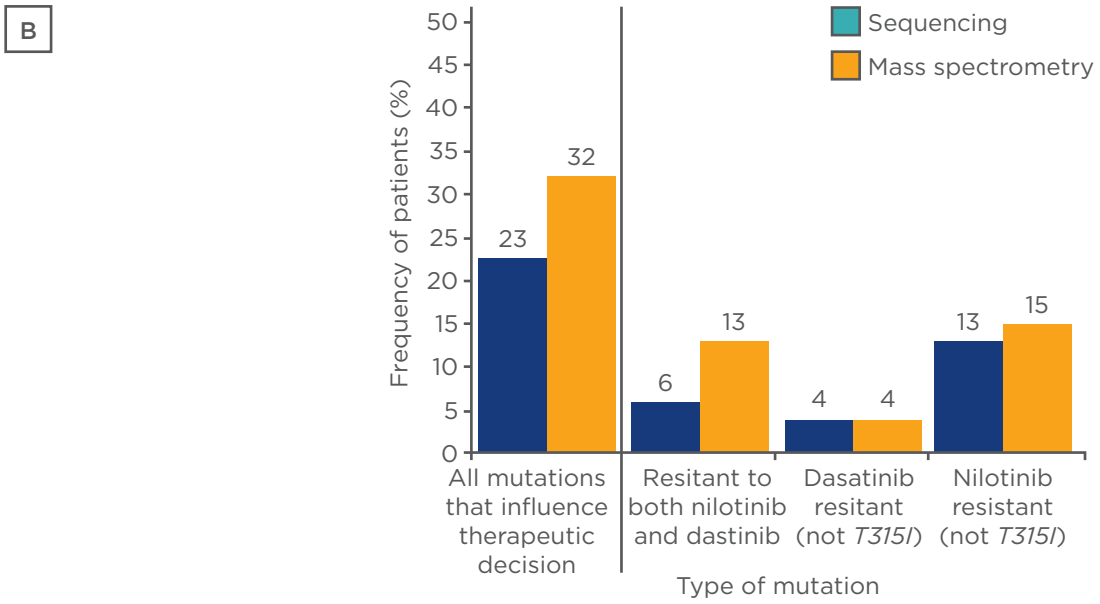


Figure 2B: Frequency of patients in whom one or more of their mutations detected at switchover would influence therapeutic decisions after treatment with imatinib failed.[36]

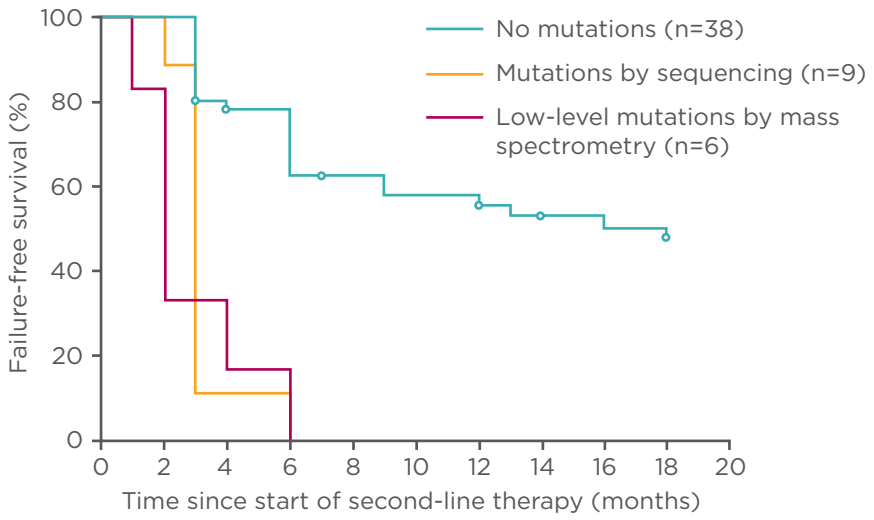


Figure 3: Failure-free survival by 18 months of nilotinib or dasatinib therapy for the 100 chronic phase patients according to mutation status at switchover.[36]

Mass Spectrometry

Mass spectrometry is a more sensitive (detection limit of 0.05–0.5%) technique and was demonstrated to detect low-level mutations versus SS in patients following imatinib failure. Indeed, some mutations have been associated to resistances to nilotinib and/or dasatinib, and low-level mutations can influence failure-free survival (FFS), as demonstrated in a large study evaluating CP-CML patients treated with nilotinib or dasatinib after imatinib failure.[36] In 220 CML patients with failure to imatinib, mutations that would influence therapeutic decisions and FFS were found in 71 patients with mass spectrometry compared to only 50 with SS (32% versus 23%; p=0.03; Figures 2 and 3).[36]

RECOMMENDATIONS IN PERFORMING MUTATIONAL ANALYSIS

European LeukemiaNet Recommendations

In a European LeukemiaNet (ELN) consensus meeting and article in 2011, experts stated that while mutations studies can help make treatment decisions in the context of patients presenting with AP/BP-CML at diagnosis, cytogenetic/haematologic

relapse, or suboptimal response to first-line therapy, loss of MMR, there is currently no role for mutation analysis at diagnosis or in patients with adequate response to therapy.[15,16,50]

The 2013 ELN recommendations for the management of CML suggest mutational analysis should be performed with SS in case of treatment failure or progression to AP or BP-CML (Table 2).[42] The 2013 ELN recommendations confirmed and replaced the term 'suboptimal response' with 'warning', so mutation analysis was recommended at diagnosis in patients presenting AP/BP, and in the case of failure or 'warning'. Patients with a 'warning' response status require more careful and frequent monitoring, that is to say a molecular and a cytogenetic test within <3 months, along with a mutational analysis.

National Comprehensive Cancer Network Guidelines

The 2016 National Comprehensive Cancer Network (NCCN) Guidelines ascertain that routine monitoring of *BCR-ABL* transcripts, in conjunction with cytogenetic evaluation, provides important information about long-term disease control in patients with CML.[51] These guidelines state that mutational analysis should be conducted in patients who fail to achieve first-line TKI treatment targets, who lose response, or who progress to AP-CML or BP-CML (Table 2).[51] Of note, NCCN guidelines do not recommend a specific technique, while the ELN guidelines recommend SS.[42,51]

Some authors have suggested the importance of conducting mutational analysis in patients with resistances either while maintaining the patient on TKI therapy or just before stopping/switching TKI therapy. Indeed, should TKI therapy be discontinued, the results of the mutational analysis (and detection of underlying mutant copies) could be biased by the proliferation of non-mutated *BCR-ABL* cells without kinase inhibition.[18] One of the suggested cut-offs for mutation analysis in the literature, including NCCN guidelines,[38,51] is a 5 to 10-fold increase in KD transcript levels and loss of MMR, which can be put in perspective with the findings of a study conducted in 150 patients receiving imatinib as first-line therapy.[52] The investigators observed that a 2.6-fold rise in BCR-ABL transcript levels was associated to the emergence of KD mutations. Moreover, transcript rise cut-offs of 5-fold or greater had poor diagnostic sensitivity and no significant association with mutations, which could suggest that such thresholds are insensitive and not universally applicable.

THE IMPORTANCE OF MUTATIONAL ANALYSIS FOR TREATMENT OUTCOMES

Despite being recommended in current treatment guidelines, mutational analysis is not always performed in patients with suspected TKI resistance and a repeated screening is rarely done in patients proven to be previously negative for *BCR-ABL* KD mutations. Physicians do not always test for mutations when appropriate, or for economic reasons, and many do not appreciate the role of mutation analysis in the overall management of CML.[18] In a prospective, non-interventional, cross-sectional study conducted in December 2010 through an online survey of 507 physicians treating patients with CML,[53] nearly half of physicians did not test for KD mutations in patients not achieving a MMR 2 years after the initiation of TKI therapy. Also, 9% indicated that they were unfamiliar with or had never ordered a test for KD mutations.

This could be explained by the fact that both ELN and NCCN recommendations/guidelines provide only general recommendations to evaluate patients with resistance to TKI therapy. While patients being resistant to first-line therapies clearly require a closer evaluation of their mutation profile, ELN and NCCN guidelines do not specify the most appropriate testing technique according to the clinical context. This lack of precise, harmonised guidance could partially explain why a substantial proportion of physicians do not use mutational analysis to guide their decisions.

CHOOSING THE RIGHT TYROSINE KINASE INHIBITOR FOR THE DETECTED MUTATION

As stated above, the type of mutation present can help determine appropriate subsequent therapy. The results of mutational analysis are one of many factors (e.g. efficacy, safety, patient comorbidities, cost) in making treatment decisions.[18] For patients with TKI-resistant CML, potential treatment options include an alternative TKI, protein synthesis inhibitors (omacetaxine, not approved in Europe) or ASCT.[42] Following first-line failure, the NCCN have elaborated treatment recommendations based on *BCR-ABL* KD mutations (Table 3).[51] The *T315I* mutant has shown resistance to all currently

available TKIs, with the exception of ponatinib.[16,32,42] Ponatinib is a third-generation TKI29 that has demonstrated clinical activity in the PACE Phase II trial, conducted on heavily pre-treated CML patients with or without KD mutation, and including the *T315I* mutant.[54,55] Current data seem to indicate that secondary resistance to ponatinib is scarce, only occurring in patients with advanced CML.[32,55]

Ponatinib could also be of importance in patients with multiple mutations (and without the *T315I* mutation) following TKI resistance, as compared with nilotinib or dasatinib as second-line treatment modalities, which generate inferior responses. In a subset analysis conducted on 267 heavily pre-treated CP-CML patients from the PACE Phase II trial, NGS was performed to define baseline KD mutation status.[43] SS was also conducted to identify clonally dominant mutants that may have developed on ponatinib therapy (30.1-month median follow-up). Robust and durable cytogenetic and molecular responses were observed regardless of the technique (NGS or SS) and irrespectively of baseline mutation status. No single or compound mutation was identified as consistently conferring resistance to ponatinib in this cohort, which included patients with low-level *T315I* and compound mutations.

These results indicate that ponatinib could be effective in CP-CML irrespective of baseline mutation status, including the *T35I* variant and compound mutations. In such clinical settings, NGS may have a role in patient selection, namely those with low-level *T315I* and susceptible to benefit from salvage ponatinib therapy following second-generation TKI failure.[43] To date, ponatinib is the most potent TKI and clinical data indicates rapid, deep, and durable clinical and molecular responses. However, considerable cardiovascular adverse events that could be dose-dependent should be taken into account to maximise the benefit-to-risk ratio.[56,57]

Table 2: Recommendations on when to perform mutational analysis.[16,42,51]

ELN Recommendations (2013)	NCCN Guidelines (2016)
At diagnosis • Only in AP-CML/BC-CML patients	Inadequate response • BCR-ABL >10% or if no PCyR at 3 and 6 months • BCR-ABL >1% or if no CCyR at 12 months Loss of response • Haematologic or cytogenetic relapse • 1-log increase in *BCR-ABL* transcript levels and loss of MMR Disease progression to AP-CML or BP-CML

AP-CML: accelerated phase chronic myeloid leukaemia; CCyR: complete cytogenetic response; CP-CML: chronic phase chronic myeloid leukaemia; ELN: European LeukemiaNet; MMR: major molecular response; NCCN: National Comprehensive Cancer Network; PCyR: partial cytogenetic response; BP-CML: blast phase chronic myeloid leukaemia.

Table 3: National Comprehensive Cancer Network treatment recommendations based on *BCR-ABL* mutations.[51]

Mutation present	Second-line and subsequent therapy options
Y253H	dasatinib, bosutinib
E255K/V	dasatinib, bosutinib
F359V/C/I	dasatinib, bosutinib
F317L/V/I/C	nilotinib, bosutinib
V299L	nilotinib
T315A	nilotinib, bosutinib
T315I	ponatinib

CONCLUSIONS

BCR-ABL KD mutations may emerge at any time during TKI therapy and confer treatment resistance, thus warranting the need for proper detection and selection for appropriate subsequent therapy. Mutational analysis is not always performed in patients with suspected TKI resistance, but should be considered a standard part of monitoring CML patients treated with TKIs. Moreover, mutational analysis should also be considered a standard adjunct evaluation tool in clinical research, especially in the context of the advent of promising new agents, such as ponatinib, to address multiresistance.

REFERENCES

1. Faderl S et al. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 1999;131(3):207-19.

2. Hehlmann R et al. Chronic myeloid leukaemia. Lancet. 2007;370(9584): 342-50.

3. Druker BJ. Circumventing resistance to kinase-inhibitor therapy. N Engl J Med. 2006;354(24):2594-6.

4. Kantarjian H et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70.

5. Saglio G et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Medicine. 2010; 362(24):2251-9.

6. Druker BJ et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355(23):2408-17.

7. Hughes TP et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-32.

8. de Lavallade H et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol. 2008;26(20):3358-63.

9. Branford S et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood. 2003;102(1):276-83.

10. Hughes T et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol. 2009;27(25):4204-10.

11. Soverini S et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica. 2007;92(3):401-4.

12. Shah NP et al. Sequential ABL kinase inhibitor therapy selects for compound drug-resistant BCR-ABL mutations with altered oncogenic potency. J Clin Invest. 2007;117(9):2562-9.

13. Soverini S et al. Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. Blood. 2009;114(10):2168-71.

14. Muller MC et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009;114(24):4944-53.

15. Baccarani M et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-51.

16. Soverini S et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011;118(5):1208-15.

17. Sierra JR et al. Molecular mechanisms of acquired resistance to tyrosine kinase targeted therapy. Mol cancer. 2010;9:75.

18. Ai J, Tiu RV. Practical management of patients with chronic myeloid leukemia who develop tyrosine kinase inhibitor-resistant BCR-ABL1 mutations. Therap Advanc Hematol. 2014;5(4):107-20.

19. Kang HY et al. Comparison of allele specific oligonucleotide-polymerase chain reaction and direct sequencing for high throughput screening of ABL kinase domain mutations in chronic myeloid leukemia resistant to imatinib. Haematologica. May 2006;91(5):659-62.

20. O'Brien SG et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348(11):994-1004.

21. Johansson B et al. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta haematologica. 2002;107(2):76-94.

22. Cortes J et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood. 2007;110(12):4005-11.

23. Jones D et al. Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. J Mol Diagn. 2009;11(1):4-11.

24. Jabbour E et al. Characteristics and outcome of chronic myeloid leukemia patients with F317L BCR-ABL kinase domain mutation after therapy with tyrosine kinase inhibitors. Blood. 2008; 112(13):4839-42.

25. Bauer RC et al. Sequential inhibitor therapy in CML: in vitro simulation elucidates the pattern of resistance mutations after second- and third-line treatment. Clin Cancer Res. 2013;19(11): 2962-72.

26. Soverini S et al. Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia. Leuk Res. 2014;38(1):10-20.

27. Jabbour E et al. Use of second- and third-generation tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia: an evolving treatment paradigm. Clin Lymphoma Myeloma Leuk. 2015;15(6):323-34.

28. Khorashad JS et al. BCR-ABL1 compound mutations in tyrosine kinase inhibitor-resistant CML: frequency and clonal relationships. Blood. 2013;121(3): 489-98.

29. O'Hare T et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer cell. 2009;16(5):401-12.

30. Eide CA et al. Resistance profiling of BCR-ABL compound mutations linked to tyrosine kinase inhibitor therapy failure in chronic myeloid leukemia. Abstract 1416, ASH Annual Meeting, San Diego, California, USA, 10-13 December 2011.

31. O'Hare T et al. Pushing the limits of targeted therapy in chronic myeloid leukaemia. Nat Rev. Cancer. 2012;12(8): 513-26.

32. Zabriskie MS et al. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer cell. 2014;26(3):428-42.

33. Parker WT et al. Poor response to second-line kinase inhibitors in chronic myeloid leukemia patients with multiple low-level mutations, irrespective of their resistance profile. Blood. 2012;119(10): 2234-8.

34. Redaelli S et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-71.

35. Rivera VM et al. A Multi-Institutional Retrospective Analysis of Tyrosine Kinase Inhibitor (TKI) Clinical and Preclinical Efficacy According to BCR-ABL Mutation Status in CP-CML Patients. Abstract 2790. American Society of Hematology, 57th Annual Meeting, Orlando, Florida, USA. 5-8 December 2015.

36. Parker WT et al. Sensitive detection of BCR-ABL1 mutations in patients with chronic myeloid leukemia after imatinib resistance is predictive of outcome during subsequent therapy. J Clin Oncol. 2011;29(32):4250-9.

37. Deininger MW et al. Detection of ABL kinase domain mutations with denaturing high-performance liquid chromatography. Leukemia. 2004;18(4):864-71.

38. Hughes T et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood. 2006;108(1):28-37.

39. Shah NP et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer cell. 2002;2(2):117-25.

40. Soverini S et al. Unraveling the complexity of tyrosine kinase inhibitor-resistant populations by ultra-deep sequencing of the BCR-ABL kinase domain. Blood. 2013;122(9):1634-48.

41. Alikian M et al. BCR-ABL1 kinase domain mutations: methodology and clinical evaluation. Am J Hematol. 2012; 87(3):298-304.

42. Baccarani M et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84.

43. Deininger MW et al. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. Blood. 2016;127(6):703-12.

44. Soverini S et al. BCR-ABL Mutations in Chronic Myeloid Leukemia (CML) Patients (pts) with Failure and Warning to First- and Second-Line Tyrosine Kinase Inhibitor (TKI) Therapy: What Is the Advantage of Next-Generation Sequencing (NGS) over Conventional Sequencing? American Society of Hematology 57th Annual Meeting and Exposition, Orlando, Florida, USA. 5-8 December 2015.

45. Shuen A, Foulkes WD. Clinical implications of next-generation sequencing for cancer medicine. Curr Oncol. 2010;17(5):39-42.

46. Baccarani M et al. Molecular monitoring and mutations in chronic myeloid leukemia: how to get the most out of your tyrosine kinase inhibitor. Am Soc Clin Oncol Educ Book. 2014:167-75.

47. Kizilors A et al. Impact of Finding of Low Level Kinase Domain Mutations Using Ultra Deep Next Generation Sequencing in Patients with Chronic Phase CML. American Society of Hematology 57th Annual Meeting and Exposition, Orlando, Florida, USA. 5-8 December 2015.

48. Soverini S et al. Next-generation sequencing for sensitive detection of BCR-ABL1 mutations relevant to tyrosine kinase inhibitor choice in imatinib-resistant patients. Oncotarget. 2016. [Epub ahead of print].

49. Wongboonma W et al. BCR-ABL kinase domain mutations in tyrosine kinase inhibitors-naive and -exposed Southeast Asian chronic myeloid leukemia patients. Exp Mol Pathol. 2012;92(2):259-65.

50. Kantarjian H et al. Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine kinase inhibitors: practical advice on the use and interpretation of monitoring methods. Blood. 2008;111(4):1774-80.

51. NCCN. NCCN Guidelines, Chronic Myelogenous Leukemia, v1. 2016. Available at: http://www.nccn.org. Last accessed: 14 July 2016.

52. Press RD et al. Determining the rise in BCR-ABL RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. Blood. 2009;114(13):2598-605.

53. Kantarjian HM et al. Current practices in the management of chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2013;13(1):48-54.

54. Cortes JE et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012; 367(22):2075-88.

55. Cortes JE et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013; 369(19):1783-96.

56. Hochhaus A et al. Clinical impact of dose modification and dose intensity on response to ponatinib in patients with Philadelphia chromosome-positive leukemias. Abstract 7084. ASCO Annual Meeting, Chicago, Illinois, USA. 30 May-3 June 2014.

57. Cortes JE et al. Long-term follow-up of ponatinib efficacy and safety in the phase 2 PACE Trial. Abstract 3135. 56th American society of Hematology Annual Meeting, San Francisco, California, USA. 6-9 December 2014.

58. Brouckova A et al. Ultradeep-amplicon pyrosequencing for mutation detection in the kinase domain of BCR-ABL revealed artificial low-level variants that need to be avoided for relevant mutational data interpretation. Abstract 1396, 2012 ASH Annual Meeting, Atlanta, Georgia, USA, 8-11 December 2012.

MODERN INDICATIONS FOR ENDOSCOPIC ENDONASAL SURGERY

***Samuel M. Lipski,[1,2] Antoine Digonnet,[1] Pierre Dolhen[2]**

1. Head and Neck Department, Jules Bordet Institute, Free University of Brussels, Brussels, Belgium
2. Ear Nose Throat Department, Tivoli University Hospital, Free University of Brussels, Brussels, Belgium
**Correspondence to sam@lipski.be*

Disclosure: The authors have declared no conflicts of interest.
Received: 01.03.16 **Accepted:** 21.07.16
Citation: EMJ Oncol. 2016;4[1]:96-102.

ABSTRACT

Endoscopic endonasal surgery has become a standard procedure for functional treatment of benign pathologies. Materials and improved surgeon skills have allowed the number of indications for this approach to increase. We describe some of the main pathologies, including malignancies, that can be treated endoscopically, focussing on the orbital and skull base pathologies. The orbital indications discussed here are dacryocystorhinostomy, orbital decompression, and optic nerve decompression. Advantages of endoscopic surgery for aggressive benign tumours such as inverted papilloma and juvenile nasopharyngeal angiofibroma are described. The skull base pathologies detailed are ethmoid adenocarcinoma and esthesioneuroblastoma for the anterior skull base surgery and endoscopic transsphenoidal approach to the sella for pituitary tumour surgery. Evidence of the safety and efficacy of endoscopic surgery is increasing but there is a lack of randomised long-term studies.

Keywords: Endoscopic sinus surgery, skull base surgery, orbital surgery.

INTRODUCTION

Over the last two decades, important progress has been made in endoscopic endonasal surgery. Functional endoscopic treatment of benign pathologies such as chronic sinusitis, nasal polyposis, and mucoceles have become standard procedures that are widely performed. Indications for endoscopic procedures are constantly increasing. This progress was made possible thanks to the development of surgeons' skills and dedicated instrumentation. This instrumentation includes, among others, long and small calibre cold instruments, powered instruments such as microdebriders and drills, navigation systems, endoscope-fitted irrigation systems, and haemostasis systems. Acquisition of video was also a key issue in the development of endoscopic endonasal surgery. Modern high-definition cameras offer good visualisation and magnification of the lesions and the anatomical landmarks. Ultra-high-definition (4K) cameras, screens, and three-dimensional endoscopic sinus surgery have recently become available and are very promising. This paper gives an overview of the new indications of this surgery, which are mainly related to orbital and skull base pathologies.

ADVANTAGES AND LIMITS OF ENDOSCOPIC ENDONASAL SURGERY

In comparison with open surgery, the endoscopic approach offers several advantages. Firstly, it is valuable for the education of residents and staff as they can follow the procedures in real-time on screens. Secondly, endoscopic surgery causes no facial incision, scars, or facial swelling. Additionally, the patient's hospitalisation is generally shorter and the postoperative pain is reduced,[1] and complication rates are notably lower. The most common complications of endoscopic nasal surgeries are: cerebrospinal fluid (CSF) leak, orbital injury (blindness, haematoma, diplopia, epiphora), prolonged crusting, infections, synechiae,

and bleeding. The complication rate naturally depends on the extent of the surgery. The major complication rate for primary functional endoscopic surgery is <1%. In the review published by Krings et al.[2] for example, the major complication rate was 0.36% including 0.13% skull base complications, 0.23% orbital complications, and 0.0001% major haemorrhagic complications. The major complication rate was higher during expanded endonasal surgery (involving skull base) with 0.9% vascular complications and 2% neural complications reported.[1] The most common complication of expanded endonasal surgery is CSF leak. This complication rate has however dramatically decreased with the evolution of reconstructive techniques and is now around 5% when the proper reconstruction technique is performed.[3] It can be managed with a lumbar spinal drainage or additional endoscopic surgery in 95% of the cases. Infectious complications are surprisingly rare with an incidence of 1–2%.[1,4] In light of this evidence, expanded endoscopic procedures can be considered safe.

The endoscopic approach, in comparison with the traditional open surgeries, reduces the need for soft tissue dissection, skeletal disassembly, and brain retraction for lesion access and resection.[5] The rate of complications following open craniofacial resection for malignancies of the skull base is around 36%, with 16% relating to central nervous system-related complications, 20% wound complications, 4.7% mortality, 2% orbital complications, and 5% systemic complications.[6] Concerning expanded endonasal surgery, procedural quality relies on experienced, multidisciplinary surgical teams. Patient selection is also very important. For instance, previous endoscopic sinus surgery is a bad prognostic factor. Finally, pathology topography is one of the main issues in endoscopic nose surgery. Indeed, the location and proximity to important neural and vascular structures will determine the feasibility of the procedure. The endonasal corridor provides the best access with the least manipulation of neural and vascular structures to many nasosinusal tumours. The endonasal corridor provides a direct pathway to an olfactory groove meningioma without the need for brain retraction, for example. Conversely, a tumour lateral to the optic nerve is best treated using another approach. Large tumours may require a combination of external and endonasal approaches.[4] The invasion of the following structures is a limit to endoscopic resection: anterior wall or floor of the maxillary sinus, external part of the orbit, skin, lateral part of frontal sinus, or dura above the orbits.

ORBITAL INDICATIONS

Dacryocystorhinostomy

Until recently, surgery of nasolacrimal duct obstruction was performed using the external approach with very good outcomes. The endonasal endoscopic approach was first described in 1989 by McDonogh and Meiring.[7] The outcomes of this procedure improved over time through the development of techniques and instrumentation. It has now become a standard procedure routinely performed by many teams with excellent results, comparable to those achieved using an external approach.[8-11] Among the benefits of the endoscopic approach are: absence of skin incisions and facial scars, palpebral ligaments as well as angular facial vessels, orbicularis oculi muscle and lacrimal pump preservation, and direct access to lacrimal sac through the lacrimal bone thus avoiding double-side dissection.[12] The indications of this procedure are now expanding beyond primary acquired nasolacrimal duct obstruction to include dacryocystorhinostomy revisions, acute lacrimal sac abscesses, and nasolacrimal duct obstructions in patients who have received chemotherapy or radiation.[12,13]

Orbital Decompression

Described in 1990 by Kennedy et al.,[14] endoscopic endonasal orbital decompression has been demonstrated to be a safe and effective technique for the treatment of Graves' orbitopathy.[15] Indeed, endoscopy provides the surgeon with an enhanced visualisation and a good access to the medial orbital wall and to the medial part of the floor. The main complication after this procedure is new-onset diplopia or worsening pre-existing diplopia. Strabismus surgery is sometimes needed and the patient should always be informed about this complication. A lacrimal duct wound is also a possible complication. CSF leak and blindness are uncommon but have been reported.

Optic Nerve Decompression

The main indication for this procedure is optic neuropathy. This neuropathy is often traumatic but can also result from compression caused by a tumour (such as meningioma, neuroma, fibrous dysplasia) or an infection.[16] Optic nerve

decompression remains controversial in whether it should be mandatory in the treatment of traumatic optic neuropathy.[17] For this procedure, the endoscopic approach offers very good access to the inferior medial part of the optic canal. When the roof of the optic canal has to be decompressed, an open approach is preferred. Endoscopic surgery should be performed when possible. Indeed, it offers a very good visualisation of orbital apex and the bony structures covering the neurovascular complex. It avoids brain retraction and therefore preserves olfaction. It also avoids external scars.[18,19]

Orbital Tumour Surgery

Many different kinds of tumours such as cavernous haemangioma, schwannomas, haemangiopericytomas, lymphomas, etc. can occur in the orbit. It can also be invaded secondarily by tumours of brain, skin, bone, and sinus origin. Endoscopic endonasal surgery offers a minimally invasive approach for tumours located inferomedially in the orbit. The window between the medial and inferior rectus muscle represents an ideal corridor to access the inferomedial orbital spaces, from the eyeball to the orbital apex.[20] Crossing of the optic nerve should be avoided during surgery.[21,22] Tumours located superiorly and laterally are thus not good candidates for endonasal approach. Cavernous haemangiomas, which are the most common intraorbital primary tumours in adults, are easily manipulated with low-risk of rupture and can thus be ideally assessed endoscopically if located medially.[23,24] Some series have now been published demonstrating the safety and feasibility of this approach in properly selected cases.[25] Direct transorbital endoscopic approaches have recently been described and appear to be a very promising alternative for posterolateral orbital tumours.

TUMOURAL INDICATIONS AND SKULL BASE SURGERY

Benign Tumours

There is a wide variety of sinonasal benign tumours. These include: epithelial tumours (keratotic papilloma, inverted papilloma, etc.), mesenchymal tumours (osteoma, chondroma, fibroma, etc.), neural tumours (schwannoma, neurofibroma, meningioma), fibro-osseous tumours (fibrous dysplasia, ossifying fibroma, giant cell tumours, etc.), and vascular tumours (haemangioma, etc.).[13] Endoscopy and radiology can sometimes lead to the correct diagnosis but biopsy and histology are often needed for confirmation. The surgical management of those tumours has been dramatically improved by using endoscopic surgery. We will here describe two examples of benign tumours whose management was challenging before the introduction of endoscopic techniques.

Inverted Papilloma

Sinonasal inverted papilloma is the most common benign lesion that occurs in the nasal cavity and paranasal sinuses. It is characterised by a high recurrence rate and malignant transformation potential.[26,27] Although its aetiology is unknown, there seems to be a link with the human papilloma virus.[28] The management of inverted papilloma can be challenging because despite its benign histology it can be aggressive, causing bone erosion, remodelling, or destruction. It may also lead to squamous cell carcinoma in 5–15% of the cases.[29] In a meta-analysis published by Busquets and Hwang,[30] a total cohort of 1,060 patients was analysed and showed that patients treated endoscopically had a lower recurrence rate (12%) than patients treated non-endoscopically (20%). The study indicates that endoscopic surgery is a favourable treatment option for most cases of sinonasal inverted papilloma. Attention should be paid to extracting all of the tumoural tissue. The bone underlying the origin of the papilloma can be burred to microscopic remnants. A medial maxillectomy is performed endoscopically when needed.

Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma is a benign vascular tumour which affects young males, especially teenagers. It accounts for 0.05% of all head and neck tumours[1] and its prevalence is higher in India and the Middle East. It arises from the sphenopalatine foramen and it is the most common tumour involving the pterygopalatine and infratemporal fossa. It is highly vascularised, mainly by the internal maxillary artery. This tumour is characterised by typical radiological findings (computed tomography [CT] and magnetic resonance imaging [MRI]). Biopsy is not recommended in this scenario due to the bleeding risk. Preoperative identification of tumour vascularisation is essential to choose the best treatment option. Preoperative embolisation

24–48 hours before surgery is recommended by most authors as a standard procedure to reduce blood loss during surgical resection.[31] Surgery is the treatment of choice where feasible. Increasing experience in endoscopic surgery together with better understanding of complex sinonasal anatomy, the possibility to safely reach adjacent sites through the nose such as the orbit, infratemporal fossa, masticatory space, parasellar region, the availability of navigation systems, and the well-known morbidity associated with external procedures have made an endoscopic approach a viable alternative.[31] Lesions with large skull base infiltration, extensive vascular supply from internal carotid artery (ICA), or encasement of the artery itself should be treated with an external or combined approach. Radiation therapy is sometimes recommended in unresectable tumours. Endoscopic surgery is also contraindicated for residual tumours involving critical areas (ICA, optic nerve, cavernous sinus, dura). However, Nicolai et al.[32] suggested that it may be used in the management of residual lesions in critical areas that have been shown to increase in size.

Cerebrospinal Fluid Leak Repair

CSF leak can occur spontaneously or it can occur after head trauma, surgery, neoplastic invasion, inflammatory erosion of the skull base, or malformation. In most cases, surgical repair of the leak is needed. The classical intracranial approach is associated with high morbidity and mortality. Endoscopic management of CSF leak, first mentioned by Wigand[33] in 1981, has now become a standard procedure. Large series have been published showing minimal morbidity and recalibrating the risk-benefit ratio of early leak closure versus watchful waiting.[34] CSF leak from the sphenoid sinus used to be especially challenging due to the anatomical relationships and the variable shape of the sinus. It is now commonly treated endoscopically with lower morbidity and better outcome.[35] One of the main challenges concerning CSF leak repair is to identify precisely the leak location. High-resolution CT scan is the best option for the identification of skull base defects while MRI can help in differentiating mucosal oedema from meningoencephalocoele. Intrathecal fluorescein is sometimes administered preoperatively to help to localise the leak using blue light endoscope. Various materials can be used to close the skull base defect: fat, fascia, collagenous matrix, pericranium, mucoperichondrial (nasal septum), or mucoperiosteal (middle turbinate) graft, etc., the use of pedicled septal flap relying on the sphenopalatine artery, and the multilayer reconstruction are some of the latest advances.[36] For example, collagenous matrix can be inserted intradurally (underlay) and mucoperichondrial, mucoperiosteal, or pedicled flap can be used extradurally (overlay). All layers are then fixed with fibrin glue and nasal packing is generally recommended.[35]

ONCOLOGIC AND SKULL BASE SURGERY PRINCIPLES

Endoscopic surgery has definitely improved the management of endonasal benign tumours by offering an effective local tumour control and decreasing morbidity compared with open approaches. One of the main issues concerning endoscopic resection in malignant lesions is *en bloc* resection.

It is often impossible to resect the tumour *en bloc* endoscopically. There is actually no evidence that debulking the tumour first increases the risk of local recurrence. Even with open techniques, *en bloc* excision is often not possible because of fragmentation of the specimen and proximity to vital structures. An endonasal approach may actually decrease the risk of tumour seeding compared with an open approach since there is less transgression of uninvolved tissues and visualisation of margins is improved. Ultimately it is the final resection margin that is important, not the method of tumour removal.[37]

Another important issue in skull base surgery is the reconstruction of the dural defect caused by the surgery. Endoscopic treatment of CSF leaks has become a standard procedure but the reconstruction of the defect caused by a skull base tumour removal can be much more challenging. This reconstruction is even more critical if radiotherapy is scheduled or has been previously performed. There are several benefits of proper closure techniques: to avoid CSF leakage that is a common complication of those procedures, to protect the uncovered carotid artery, to speed up healing, and to avoid radionecrosis and meningitis. Different materials can be used: cartilage, free mucosal flaps, pediculate flaps (nasoseptal, temporalis fascia, pericranial) fascia lata, fat, human thrombin and fibrinogen, dural substitute, etc. The dura is generally closed using several layers (known as the sandwich technique). The development of closure techniques was an essential part of

endoscopic skull base surgery development. A lumbar drainage is rarely needed. Reconstruction is not necessary in the absence of meningeal tear and CSF leak, particularly following pituitary surgery.[38]

ETHMOID ADENOCARCINOMA AND OLFACTORY NEUROBLASTOMA: ANTERIOR SKULL BASE SURGERY

Sinonasal malignancies are rare, accounting for only 1% of all malignancies.[39] Their management however, is often challenging due to their late presentation, histologic diversity, poor prognosis, and proximity to important structures such as orbit and skull base. We chose to emphasise the contribution of endoscopic surgery in the management of ethmoid tumours. In Europe, adenocarcinoma (AC) is the most common epithelium-derived neoplasm of the ethmoid. Wood dust and leather dust have been shown to be associated with the development of this tumour in several countries with a considerable delay between exposure and presentation, of up to 40 years.[40] Olfactory neuroblastoma (ON), also known as esthesioneuroblastoma, classically arises from olfactory epithelium in the upper nasal cavity and therefore spreads intracranially at an early stage to involve the olfactory bulb and tracts.[13] Skull base involvement occurs in 38% of ACs and 50–75% of ONs.[41] The management of these tumours is surgery followed by radiotherapy. The surgery is difficult and classically requires craniofacial resection using transfacial and sometimes transcranial approaches. However, these procedures entail significant morbidity such as pneumatocele, cerebral oedema, cerebral abscess, CSF leakage, meningitis, stroke, and even death in up to 4.5% of cases.[6] ACs and ONs are midline tumours; they are then easily accessible by an endoscopic approach. Successful endoscopic resection of those tumours has been described by several teams with excellent results.[42-45] An exclusively endoscopic approach has anatomic limitations such as invasion of lateral frontal sinus above the orbit or significant intradural invasion.[43] The main steps of the endoscopic anterior skull base approach are: biopsies made at the beginning of the surgery to ensure tumour-free margins; debulking of the tumour sometimes needed to ensure a wide field of vision; DRAF III procedure and removal of the anterior wall of the sphenoid sinus; exposition of the dura by drilling the roof of the ethmoid; resection of the crista galli; section of the falx cerebri; and resection of the dura. The skull base specimen can then be taken out and duraplasty is performed generally using layers of fascia latae.[43]

ENDOSCOPIC TRANSSPHENOIDAL APPROACH TO THE SELLA FOR PITUITARY TUMOUR SURGERY

First described by Jankowski et al.[46] in 1992, the endoscopic approach for pituitary surgery has become a standard procedure. The traditional transseptal/translabial microscopic approach is still performed by many teams with good surgical outcomes and little morbidity. Several reviews have compared the two techniques in the treatment of pituitary adenomas. The meta-analysis of Gao et al.[47] for example, concluded that endoscopic transsphenoidalpituitary adenoma surgery is associated with a higher rate of gross tumour removal, decreased hospital stay, and reduced observed postoperative complication (septal perforation). The meta-analysis of DeKlotz et al.[48] concluded that recent literature demonstrated superior outcomes and decreased postoperative complications with the endoscopic approach, potentially justifying a shift toward endoscopic pituitary surgery. The review of Ammirati et al.[49] concluded that the endoscopic technique is associated with a higher incidence of vascular complications compared with microscopic transsphenoidal removal of pituitary adenomas. That review was commented on by Laws,[50] who concluded that in the future there might be identical benefits between the two techniques, but it is too soon to be certain and keeping an open mind is still a very good strategy for now.

OTHER INDICATIONS

Some indications of endoscopic endonasal surgery were not detailed in this report. For example, septoplasty, probably the most common surgical indication for rhinologists, has quite recently started being performed endoscopically. The comparison between the classical and endoscopic approach is a recent concern. Some reports show that endoscopy offers a better approach to posterior deformation, fewer complications, and quicker patient recovery.[51-54] Transplanum, transclival, and transodontoid approaches are new applications. Their indications are mainly central nervous system benign tumours such as craniopharyngioma, chordoma, meningiomas, schwannomas, etc. The petrous apex can also be

reached to treat cholesterol granuloma. Those indications respect the same principles described above. Special attention should be paid to the noble structures located close to the pathology, such as the ICA and cranial nerves.

CONCLUSIONS

New indications of endoscopic nasal surgery involving orbital and skull base pathologies are expanding. Studies show a superiority of this technique in many indications including some malignant diseases. These studies however, have to be interpreted cautiously, as their follow-up is limited and their design does not include randomisation. Further studies will allow us to have a better view of the long-term outcomes, the precise indications, and limitations of this procedure. Development of new technologies as well as surgical training methods are likely to improve our ability to manage more pathologies endoscopically.

REFERENCES

1. Lund VJ et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl. 2010;(22):1-143.

2. Krings JG et al. Complications of primary and revision functional endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2014;124(4):838-45.

3. Kassam A et al. Evolution of reconstructive techniques following endoscopic expanded endonasal approaches. Neurosurg Focus. 2005; 19(1):E8.

4. Snyderman CH et al. What are the limits of endoscopic sinus surgery?: the expanded endonasal approach to the skull base. Keio J. Med. 2009;58(3):152-60.

5. Hanna E et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. Arch Otolaryngol Head Neck Surg. 2009; 135(12):1219-24.

6. Ganly I et al. Complications of craniofacial resection for malignant tumors of the skull base: report of an International Collaborative Study. Head Neck. 2005;27(6):445-51.

7. McDonogh M, Meiring JH. Endoscopic transnasal dacryocystorhinostomy. J Laryngol Otol. 1989;103(6):585-7.

8. Tsirbas A et al. Mechanical endonasal dacryocystorhinostomy versus external dacryocystorhinostomy. Ophthal Plast Reconstr Surg. 2004;20(1):50-6.

9. Cokkeser Y et al. Comparative external versus endoscopic dacryocystorhinostomy: results in 115 patients (130 eyes). Otolaryngol Head Neck Surg. 2000;123(4):488-91.

10. Ben Simon GJ et al. External versus endoscopic dacryocystorhinostomy for acquired nasolacrimal duct obstruction in a tertiary referral center. Ophthalmology. 2005;112(8):1463-8.

11. Ramakrishnan VR et al. Outcomes after endoscopic dacryocystorhinostomy without mucosal flap preservation. Am J Rhinol. 2007;21(6):753-7.

12. Eloy P et al. Endonasal dacryocystorhinostomy: indications, technique and results. Rhinology. 1995; 33(4):229-33.

13. Kennedy D, Huang PH (eds.), Rhinology: Diseases of the Nose, Sinuses, and Skull Base (2012), New York: Thieme Medical Publishers, Inc.

14. Kennedy DW et al. Endoscopic transnasal orbital decompression. Arch Otolaryngol Head Neck Surg. 1990;116(3): 275-82.

15. Platt MP et al. Endoscopic orbital decompression. Oper Tech Otolaryngol Head Neck Surg. 2008;19(3):162-6.

16. Berhouma M et al. Endoscopic endonasal optic nerve and orbital apex decompression for nontraumatic optic neuropathy: surgical nuances and review of the literature. Neurosurg Focus. 2014; 37(4):E19.

17. Kong DS et al. Endoscopic optic canal decompression for compressive optic neuropathy. J Clin Neurosci. 2011; 18(11):1541-5.

18. Metson R, Pletcher SD. Endoscopic orbital and optic nerve decompression. Otolaryngol Clin North Am. 2006;39(3): 551-61.

19. Pletcher SD, Metson R. Endoscopic optic nerve decompression for nontraumatic optic neuropathy. Arch Otolaryngol Head Neck Surg. 2007;133(8):780-3.

20. Dallan I et al. Transnasal approach to the medial intraconal space: anatomic study and clinical considerations. Minim Invasive Neurosurg. 2010;53(4):164-8.

21. McKinney KA et al. Seeing the light: endoscopic endonasal intraconal orbital tumor surgery. Otolaryngol Head Neck Surg. 2010;143(5):699-701.

22. Stippler M et al. Endoscopic endonasal approach for clival chordomas. Neurosurgery. 2009;64(2):268-77; discussion 277-8.

23. Boari N et al. Surgical treatment of orbital cavernomas: clinical and functional outcome in a series of 20 patients. Acta Neurochir (Wien). 2011;153(3):491-8.

24. Muscatello L et al. Transnasal endoscopic surgery for selected orbital cavernous hemangiomas: our preliminary experience. Head Neck. 2013;35(7): E218-20.

25. Castelnuovo P et al. Endoscopic transnasal intraorbital surgery: our experience with 16 cases. Eur Arch Otorhinolaryngol. 2012;269(8):1929-35.

26. Outzen KE et al. Inverted papilloma: incidence and late results of surgical treatment. Rhinology. 1996;34(2):114-8.

27. Baruah P, Deka RC. Endoscopic management of inverted papillomas of the nose and paranasal sinuses. Ear Nose Throat J. 2003;82(4):317-20.

28. Kraft M et al. Significance of human papillomavirus in sinonasal papillomas. J Laryngol Otol. 2001;115(9):709-14.

29. Lesperance MM, Esclamado RM. Squamous cell carcinoma arising in inverted papilloma. Laryngoscope. 1995;105(2): 178-83.

30. Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134(3):476-82.

31. Nicolai P et al. Juvenile angiofibroma: evolution of management. Int J Pediatr. 2012;2012: 412545.

32. Nicolai P et al. Endoscopic surgery for juvenile angiofibroma: a critical review of indications after 46 cases. Am J Rhinol Allergy. 2010;24(2):e67-72.

33. Wigand ME. Transnasal ethmoidectomy under endoscopical control. Rhinology. 1981;19(1):7-15.

34. Banks CA et al. Endoscopic closure of CSF rhinorrhea: 193 cases over 21 years. Otolaryngol Head Neck Surg. 2009; 140(6):826-33.

35. Muscatello L et al. Endoscopic transnasal management of cerebrospinal fluid leaks of the sphenoid sinus. J Craniomaxillofac Surg. 2010;38(5): 396-402.

36. Hadad G et al. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. Laryngoscope. 2006; 116(10):1882-6.

37. Snyderman CH et al. Endoscopic skull base surgery: principles of endonasal oncological surgery. J Surg Oncol. 2008; 97(8):658-64.

38. Verillaud B. Endoscopic endonasal skull base surgery. Eur Ann Otorhinolaryngol Head Neck Dis. 2012;129(4):190-6.

39. Tufano RP et al. Malignant tumors of the nose and paranasal sinuses: hospital of the University of Pennsylvania experience 1990-1997. Am J Rhinol. 1999;13(2):117-23.

40. Macbeth R. Malignant Disease Of The Paranasal Sinuses. J Laryngol Otol. 1965;79:592-612.

41. Suarez C et al. Prognostic factors in sinonasal tumors involving the anterior skull base. Head Neck. 2004;26(2): 136-44.

42. Nicolai P et al. Ethmoid adenocarcinoma--from craniofacial to endoscopic resections: a single-institution experience over 25 years. Otolaryngol Head Neck Surg. 2011;145(2):330-7.

43. Carta F et al. Endoscopy skull-base resection for ethmoid adenocarcinoma and olfactory neuroblastoma. Rhinology. 2011;49(1):74-9.

44. Camp S et al. Long-term follow-up of 123 patients with adenocarcinoma of the sinonasal tract treated with endoscopic resection and postoperative radiation therapy. Head Neck. 2016;38(2):294-300.

45. Vergez S et al. Multicenter study to assess endoscopic resection of 159 sinonasal adenocarcinomas. Ann Surg Oncol. 2014;21(4):1384-90.

46. Jankowski R et al. How I do it: Head and neck and plastic surgery: Endoscopic pituitary tumor surgery. Laryngoscope. 1992;102(2):198-202.

47. Gao Y et al. Endoscopic versus microscopic transsphenoidal pituitary adenoma surgery: a meta-analysis. World J Surg Oncol. 2014;12:94.

48. DeKlotz TR et al. Meta-analysis of endoscopic versus sublabial pituitary surgery. Laryngoscope. 2012;122(3):511-8.

49. Ammirati M et al. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2013;84(8):843-9.

50. Laws ER. Complications of transsphenoidal surgery: the shortcomings of meta-analysis. J Neurol Neurosurg Psychiatry. 2013;84(8):829.

51. Gupta M, Motwani G. Comparative study of endoscopic aided septoplasty and traditional septoplasty in posterior nasal septal deviations. Indian J Otolaryngol Head Neck Surg. 2005;57(4):309-11.

52. Gulati SP et al. Comparative evaluation of endoscopic with conventional septoplasty. Indian J Otolaryngol Head Neck Surg. 2009;61(1):27-9.

53. Getz AE, Hwang PH. Endoscopic septoplasty. Curr Opin Otolaryngol Head Neck Surg. 2008;16(1):26-31.

54. Sathyaki DC et al. A comparative study of endoscopic septoplasty versus conventional septoplasty. Indian J Otolaryngol Head Neck Surg. 2014;66(2): 155-61.

microRNAS IN THERAPY RESISTANCE OF BREAST CANCER

Janine Jung, Vinona Wagner, *Cindy Körner

Division of Molecular Genome Analysis, German Cancer Research Center (DKFZ) Heidelberg, Heidelberg, Germany
**Correspondence to c.koerner@dkfz-heidelberg.de*

Disclosure: The authors have declared no conflicts of interests.
Received: 29.09.16 **Accepted:** 07.11.16
Citation: EMJ Oncol. 2016;4[1]:103-112.

ABSTRACT

Breast cancer is one of the deadliest cancer types worldwide and consists of several subtypes differing in their molecular characteristics; each subtype requires various effective treatment strategies. Development of resistance to radiation or therapeutic agents is one of the main factors leading to the death of about 450,000 breast cancer patients each year. Since microRNAs (miRNAs) have been shown to be key players in health and disease, it is not surprising that they influence the development of resistance to treatment and thereby affect the fate of patients suffering from different types of cancer. miRNAs typically modulate the expression of hundreds of targets, forming a complex regulatory layer which we have only begun to understand. This review summarises miRNAs that confer resistance to different treatment options or sensitise breast cancer cells to a particular treatment. Moreover, this review addresses the high clinical value of miRNAs as biomarkers that allow prediction or monitoring therapy response. The focus of the review is to illustrate how much we know already but also to emphasise that a vast part of the miRNome and its implications for breast cancer therapy resistance remains in the dark and requires further investigation.

Keywords: Breast cancer, resistance, microRNAs (miRNAs), targeted therapy, chemotherapy, radiotherapy.

BACKGROUND

Breast cancer is one of the most prevalent cancer types worldwide with approximately 1.3 million cases and 450,000 deaths each year.[1] In spite of its apparent clinical and biological heterogeneity, it can be grouped into six clinical subtypes based on gene expression profiling of a 50-gene signature (PAM50) or immunohistochemical markers.[2] The subtypes include: Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, claudin-low, basal-like, and normal breast-like.[3,4] The Luminal subtypes are characterised by expression of the oestrogen receptor (ER) and can thus potentially be targeted by endocrine therapy.[3] Here, the Luminal A subtype has a far better prognosis and reduced relapse rate, mostly due to its higher ER expression, compared with the Luminal B subtype which is characterised by higher Ki67 staining and often additional overexpression of HER2, also named ERBB2.[3,5] The HER2-enriched subtype is defined by amplification in the locus of the *HER2* gene. Though it has been known to be quite aggressive and metastasis-prone, patients suffering from HER2-positive ($HER2^+$) breast cancer largely benefited from the clinical success of the trastuzumab monoclonal antibody which targets the HER2 receptor overexpressed or amplified in this subtype.[3] Basal-like breast cancer is known for its poor prognosis and limited therapy options.[6] It largely resembles the immunohistochemically defined subtype of triple-negative breast cancer (TNBC). The two subtypes, claudin-low and normal breast-like, are currently rather poorly characterised and due to the lack of targeted therapies, their treatment is mainly limited to chemotherapeutics and radiation, similar to the basal-like subtype.[3,7]

The occurrence of resistance to the targeted treatments of these subtypes has been well documented. As endocrine treatment is used for the ER-positive (ER^+) patients, the resistance to this approach is mainly mediated by the downregulation of ER or its corresponding signalling pathway. Similarly, as trastuzumab treatment in

HER2-enriched patients depends on expression of the receptor, the resistance is facilitated by downregulation of HER2, upregulation of other members of the ErbB-family, or mutations in downstream signalling molecules leading to constitutive activation of survival and proliferation pathways.[8] In contrast, resistance to conventional chemotherapy is often mediated by mechanisms that affect the metabolism of the drugs or their concentration within the cells, e.g. by the upregulation of efflux pumps. General resistance mechanisms usually involve desensitisation of cells to apoptosis or cell cycle arrest in response to genotoxic stress or pathway inhibition.

The primary microRNA (miRNA) is the product transcribed from the miRNA locus and is commonly produced by Pol II.[9] It is characterised by a hairpin structure and gets further processed by the *RNAse Drosha*, creating the precursor miRNA, which is then exported from the nucleus via Exportin 5.[10] In the cytoplasm, Dicer further cleaves the transcript, creating the mature miRNAs of 21–25 nt in length with 5' phosphate groups and a 3' overhang of two nucleotides. Mature miRNAs then associate with Argonaute proteins, forming the RNA-induced silencing complex.[11] In recent years, it has been shown that the miRNA processing machinery does not only produce two miRNA species from one precursor, namely the miRNA-3p and 5p, but can also give rise to so-called isomiRs. These are shifted forms of the canonical miRNAs derived from alternative processing displaying either altered stability (3'isomiRs) or altered seed sequences (5'isomiRs).[12] A miRNA usually exerts its function on its target RNAs by inducing Argonaute-dependent degradation or translational repression and subsequent Argonaute-independent degradation via perfect or mismatch complementarity, respectively.[9] For target recognition, only the so-called seed sequence, comprising nucleotides 2–8 of the miRNA, is essential.[13] While the miRNA usually binds in the 3' untranslated region of its target RNA, there are reports showing that it is also able to bind the 5' untranslated region or open reading frame and induce translational activation.[9]

This review article will summarise current literature on the impact of miRNAs on therapy resistance in breast cancer by dissecting the role of individual miRNAs and their identified targets in the underlying cellular processes. The gathered information is based exclusively on data obtained from cell culture or mouse experiments. Moreover, the review highlights the main miRNAs involved in therapy resistance by impairing pluripotency, cancer stem cell properties, or epithelial–mesenchymal transition (EMT) of breast cancer cells. Furthermore, it will also demonstrate the pleiotropic nature of miRNAs using miR-200c as an example which has been shown to affect at the same time the cellular response to conventional chemotherapy, radiotherapy, and targeted treatment of HER2 or ER.

MECHANISMS OF microRNAS IN CHEMOTHERAPY AND RADIOTHERAPY RESISTANCE

Several miRNAs have been shown to mediate resistance to various chemotherapeutic drugs or to radiotherapy by targeting general cellular mechanisms induced by the drugs, such as cell cycle arrest, apoptosis, and impairment of DNA repair. Their targets and modes of action are summarised in Figure 1. Among those miRNAs targeting components of the DNA repair machinery, which are implicated in chemotherapy resistance or sensitivity, are miR-28, miR-181, miR-182, and miR-146, all four targeting *BRCA1*. Others, such as miR-155, miR-96, miR-107, and miR-221/222, target RAD51, while miR-203 and miR-181 repress expression of ATM. Further targets include H2AX (miR-138), WEE1 (miR-15), TP53 (miR-125b), and BCL2 (miR-34a).[14] Moreover, various miRNAs with a role in chemotherapy resistance have been shown to enhance tumour progression by activating signalling pathways important for proliferation, cell cycle progression, and survival of the cancer cell. In addition, alterations in the methylation or histone modification pattern of the DNA can also be caused by miRNAs and thereby contribute to resistance. Further general mechanisms exploited by oncogenic miRNAs may also affect the availability of the drug. Transporters and metabolic enzymes, for instance, often play a role in decreasing the abundance of the drug. However, all these mechanisms can also be targeted by tumour-suppressive miRNAs enhancing sensitivity to chemo/radiotherapy and thus increasing the effectiveness of the treatment.[15,16]

microRNAs as Sensitisers to Chemotherapy

Chemotherapeutic drugs mainly target cell proliferation (anthracyclines) or induce severe DNA damage to cause cell cycle arrest or apoptosis (taxanes and platinum compounds).[17]

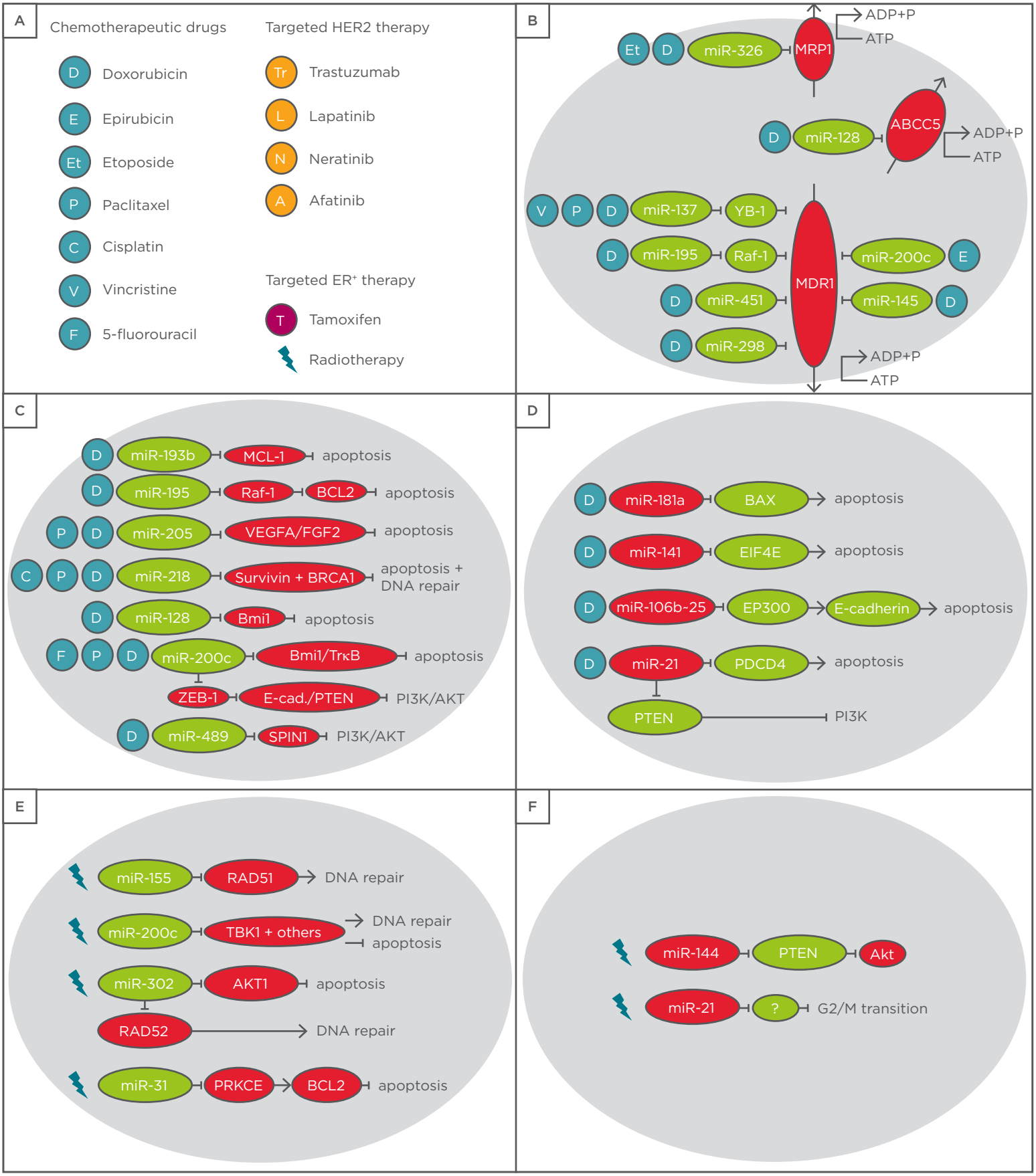


Figure 1: Overview of microRNAs with an impact on chemotherapy and radiotherapy in breast cancer patients.
A) These microRNAs can affect either B) efflux pumps, C) and D) apoptosis and DNA repair in response to chemotherapeutic agents, or E) and F) irradiation.
HER2: human epidermal growth factor receptor 2; ER+: oestrogen receptor positive.

Combinations of anthracyclines, such as doxorubicin, daunomycin, and epirubicin; and taxanes, such as paclitaxel and docetaxel, are among the most common treatment strategies for advanced breast cancer.[18] Among the most commonly used neoadjuvant regimens, which are administered before surgery or radiotherapy, are combinations of paclitaxel, docetaxel, doxorubicin, epirubicin, cyclophosphamide, and fluorouracil.[19]

One of the most efficient mechanisms by which cancer cells develop resistance towards chemotherapy is a high abundance of efflux transporters, which remove the chemotherapeutic drug from the cells. Multidrug resistance-associated protein 1 and multidrug resistance protein 1 (MDR1), for instance, belong to this group of transporters. Several miRNAs, including miR-451, miR-145, miR-298, miR-200c, and miR-326, have been shown to reduce expression of MDR1 and thereby sensitise breast cancer cells to anthracyclines.[20-23] miR-326, however, also increases the vulnerability of breast cancer cells to etoposide treatment by targeting MDR1.[24] Furthermore, high levels of miR-195 enhance the sensitivity of breast cancer cells to doxorubicin by reducing Raf-1 levels, which induces apoptosis via downregulation of BCL2 and also represses MDR1 levels.[25] miR-137 was also shown to render breast cancer cells more susceptible to various chemotherapeutic drugs (doxorubicin, vincristine, and paclitaxel) by targeting YB-1, which suppresses MDR1 levels.[26] Further miRNAs involved in chemotherapy resistance by affecting drug efflux via different direct targets are miR-7, miR-127, miR-134, miR-196a, miR-221/222, miR-508-5p, miR-129-5p, miR-103/107, miR-9, and miR-519c.[27]

Several other miRNAs are known to sensitise breast cancer cells to chemotherapeutic drugs by inducing apoptosis or preventing DNA damage repair which generally results in cell cycle arrest or apoptosis. One of these miRNAs is miR-193b which increases the sensitivity of breast cancer cells to doxorubicin treatment by directly targeting myeloid cell leukaemia-1, thereby inducing apoptosis.[28] Another miRNA sensitising breast cancer cells to certain chemotherapeutic drugs is miR-489. In addition to VAV3, BCL2, and AKT3, SPIN1 was identified as a direct target of miR-489. Downregulation of SPIN1 or overexpression of miR-489 inhibited activation of the PI3K-Akt pathway and consequently increased sensitivity to doxorubicin. Blockage of the PI3K-Akt pathway enhanced cell death in the cancer cells.[29] Furthermore, high abundance of miR-218 reversed the resistance of breast cancer cells to doxorubicin as well as paclitaxel by inducing apoptosis. Knock-down of survivin (BIRC5), a direct target of the miRNA, was able to phenocopy the increase in apoptotic cells after treatment with the respective drugs.[30] Interestingly, this miRNA also targets BRCA1 to enhance the sensitivity of breast cancer cells to cisplatin treatment by inducing apoptosis and lowering their ability to repair DNA damage.[31] Enhancement of chemosensitivity to doxorubicin and paclitaxel can also be mediated by miR-205 which directly targets VEGFA and FGF2 and thereby induces apoptosis.[32]

In the case of miR-200c, several additional mechanisms to the above-mentioned downregulation of MDR1 have been described to sensitise breast cancer cells to various drugs. For instance, direct targeting of the tyrosine kinase receptor TrkB and the transcriptional repressor Bmi1[33] or inhibition of Akt signalling via E-cadherin and PTEN, which are both upregulated upon ZEB1 suppression by miR-200c, sensitise cells to doxorubicin. Moreover, miR-200c overexpression causes an increase in the sensitivity of breast cancer cells to 5-fluorouracil treatment by lowering Bmi1 levels.[34] Another miRNA targeting Bmi1 and thereby enhancing sensitivity of breast cancer cells to doxorubicin is miR-128. A second direct target of miR-128 is the transporter ABCC5. Overexpression of the miRNA decreases Bmi1 and ABCC5 levels, leading to a significant increase in the number of apoptotic cells and cells with DNA damage enhancing doxorubicin effectiveness.[35]

microRNAs Conferring Resistance to Chemotherapy

miR-181a induction upon treatment with DNA damaging compounds such as doxorubicin was linked to chemoresistance in breast cancer. Upregulation of the miRNA after treatment with doxorubicin required STAT3 activation via the NF-κB pathway. Decreased BAX levels, a direct target of miR-181a, help breast cancer cells to resist apoptosis.[36] Overexpression of miR-141 rendered breast cancer cells resistant to the drug docetaxel. Direct repression of eukaryotic translation initiation factor 4E levels by the miRNA allowed the cells to circumvent drug-induced apoptosis.[37] Breast cancer cells overexpressing the miR-106b~25 cluster acquired resistance to doxorubicin. miR-25 is especially important for developing resistance, however, all three miRNAs in the cluster target the transcriptional E-cadherin activator EP300 and other unidentified targets to reduce sensitivity to anti-cancer treatments.[38]

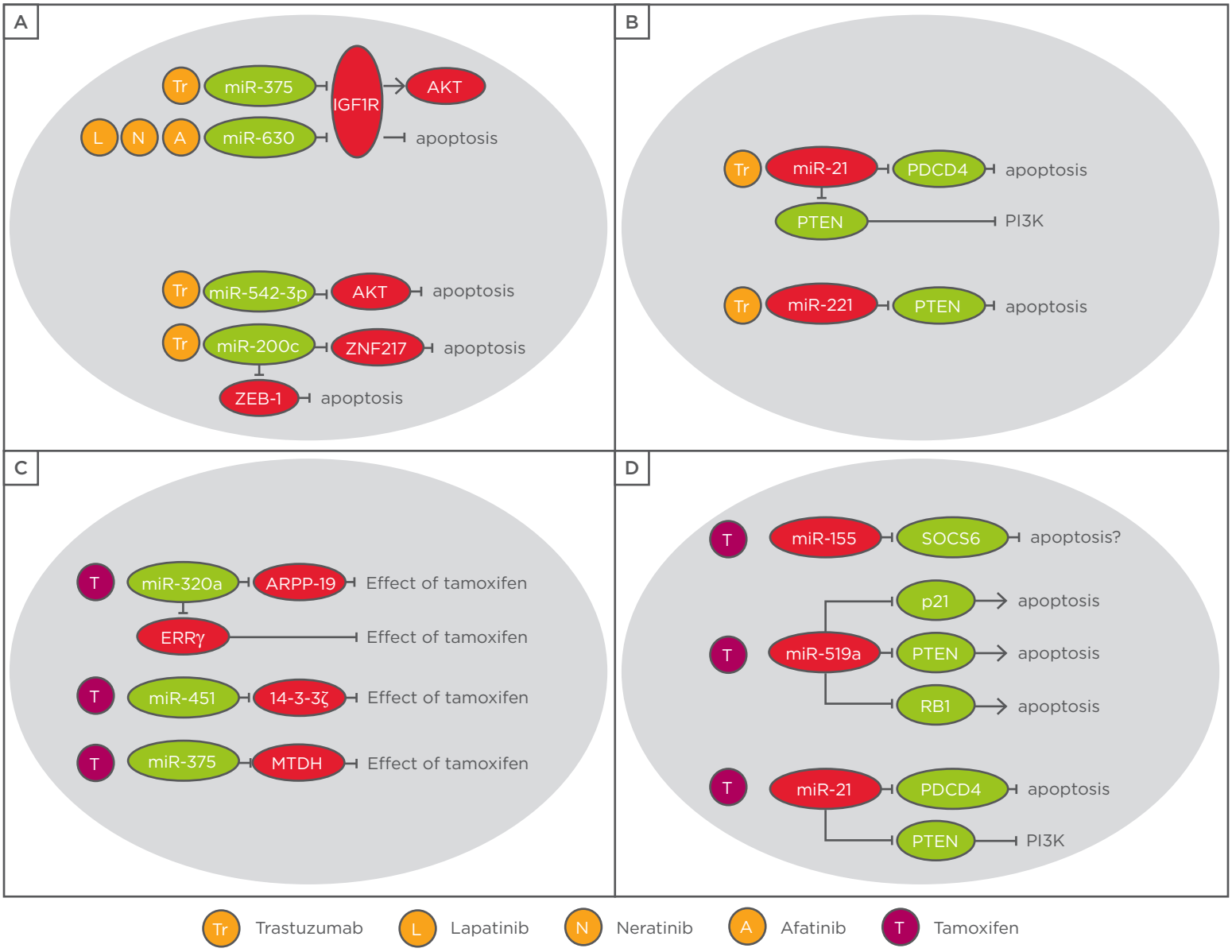


Figure 2: Overview of microRNAs with an impact on targeted therapies in breast cancer patients.
A) and B) microRNAs with a role in HER2 overexpressing patients, C) and D) microRNAs with a role in resistance to endocrine therapy.
ERRγ: oestrogen-related receptor gamma.

microRNAs with a Role in Radiotherapy Resistance

During radiotherapy, beams of ionising radiation are aimed at the tumour and damage the DNA of tumour cells. Resulting DNA double-strand breaks are the predominant lesions caused by radiotherapy.[39] Therefore, the targets of miRNAs mediating radiotherapy resistance or enhancing sensitivity to radiotherapy are mainly connected to the DNA repair machinery or apoptosis. miR-155, for instance, lowers the efficiency of breast cancer cells repairing the radiation-induced DNA damage via homologous recombination by targeting RAD51,[40] whereas overexpression of miR-200c promotes radiation-induced cell death in breast cancer cells and sensitises them to DNA damage upon radiation. TBK1 was identified as a direct target of miR-200c, but *TBK1* knock-down could not account for the complete effect miR-200c has on the cellular response to radiotherapy.[41] The function of miR-302 is also tumour-suppressive since this miRNA directly targets AKT1 and RAD52, both mediators of radioresistance. *In vitro* as well as *in vivo* experiments showed that miR-302 overexpression in TNBC cells reversed resistance to radiotherapy, made the cells even more sensitive to radiation, and suppressed AKT1 and RAD52 levels.[42]

In contrast, high levels of miR-144 enhanced radiotherapy resistance of breast cancer cell lines. A strong decrease in the PTEN levels, a direct target of miR-144, caused AKT activation.[43]

microRNAs and Their Role in Resistance to Chemotherapy and Radiotherapy

So far, few miRNAs have been shown to mediate or counteract resistance to chemotherapy as well as radiotherapy. One example is the tumour-suppressive miR-31, which inhibits the NF-κB pathway by directly targeting PRKCE and thereby inducing apoptosis and increasing sensitivity to chemo and radiotherapeutic treatment in MDA-MB-231 cells, a TNBC cell line. The downregulation of PRKCE leads to a decrease in BCL2 which accounts for the increase in sensitivity to doxorubicin treatment and radiation since the presence of BLC2 exerts an anti-apoptotic effect.[44] miR-21 on the other hand, exerts an oncogenic function by mediating resistance to radiotherapy as well as chemotherapy. miR-21 prevents the breast cancer cells from entering G2/M arrest after radiation. However, the direct targets helping to overcome the G2/M arrest upon radiation have not been identified yet.[45] In terms of chemotherapy resistance, miR-21 has been shown to confer resistance to doxorubicin by directly targeting the tumour-suppressor proteins PTEN[46] and PDCD4[47] which prevents the cells from undergoing apoptosis and mediates the drug resistance.

SPECIFIC MECHANISMS OF microRNAS IN RESISTANCE TO TARGETED THERAPY

Mechanisms and targets of miRNAs impacting the sensitivity of breast cancer cells to targeted therapies are summarised in Figure 2.

microRNAs in Resistance to Targeted Therapy for Human Epidermal Growth Factor Receptor 2 Patients

Targeted therapy approaches for HER2 patients use drugs antagonising or blocking the HER2 receptor. These include trastuzumab or pertuzumab, monoclonal antibodies targeting the HER2 receptor, and the tyrosine kinase inhibitors lapatinib, neratinib, and afatinib.[48] The loss of miR-375 due to epigenetic silencing contributes to trastuzumab resistance. The underlying mechanism involves insulin-like growth factor type 1 receptor (IGF1R) as a direct target of the miRNA. In the absence of miR-375, IGF1R can function as alternative growth factor receptor in breast cancer patients treated with trastuzumab.[49] Another miRNA targeting IGFR1 and thereby increasing the effectiveness of drugs targeting HER2, such as lapatinib, neratinib, and afatinib, is miR-630.[50] miR-542-3p also enhances sensitivity to trastuzumab treatment however, via targeting AKT. The loss of mIR-542-3p renders the HER2$^+$ breast cancer cells more resistant to the drug, reduces the number of apoptotic cells, and enables inhibition of the G1/S checkpoint to be overcome.[51]

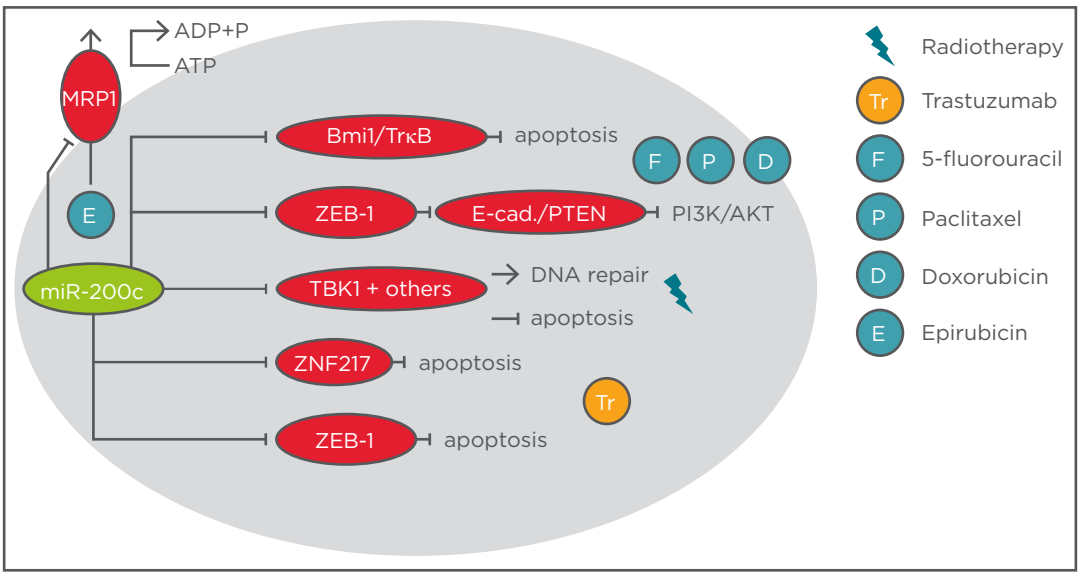


Figure 3: Summary of phenotypes and mechanisms of miR-200c sensitising breast cancer cells to therapy.

The tumour-suppressive function of miR-200c not only sensitises breast cancer cells to chemotherapeutic drugs such as doxorubicin, 5-fluorouracil, and epirubicin,[22,33,34,52] it also sensitises HER2+ breast cancers to trastuzumab via downregulation of ZNF217 and ZEB1.[53] In terms of trastuzumab and lapatinib resistance, miR-16 has been shown to increase the sensitivity of breast cancer cells by targeting cyclin J and far upstream element-binding protein 1. Moreover, miR-16 might serve as a potential biomarker to predict the therapy response of HER2 patients.[54] A miRNA with an oncogenic role in targeted therapy resistance of HER2 patients is miR-221, which prevents breast cancer cells from undergoing apoptosis and mediates trastuzumab resistance in HER2+ breast cancer cells by targeting PTEN.[55] miR-21, another oncogenic miRNA, not only mediates resistance to radiotherapy and doxorubicin,[45-47] but also induces interleukin (IL)-6/STAT3/NF-κB-mediated signalling as well as the PI3K pathway and thereby confers resistance to trastuzumab.[56] In line with other tumour-suppressive miRNAs, miR-450b-3p, 520c-3p, miR-520b-5p, and miR-587-5p were shown to increase the effectiveness of trastuzumab.[54]

microRNAs in Resistance to Endocrine Therapy

Mechanisms of endocrine resistance in breast cancer often involve the loss of ER-α expression, for instance, by hypermethylation of the *ER* gene which mediates resistance to tamoxifen. Moreover, increased activity of the HER2, IGFR1, or FGFR1 signalling pathways activates MAPK or PI3K signalling and is thereby also able to confer resistance to tamoxifen by sustaining proliferation and anti-apoptotic signals in an ER-independent manner.[57] miR-320a is one of the miRNAs which sensitises ER+ breast cancer cells to endocrine therapy. In fact, miR-320a increases the sensitivity of ER+ resistant breast cancer cells to tamoxifen by downregulation of cAMP-regulated phosphoprotein and oestrogen-related receptor gamma.[58] miR-451 is another sensitiser to tamoxifen since the miRNA directly targets 14-3-3ζ[59] which also leads to increased efficacy of doxorubicin treatment as previously described.[20] Overexpression of miR-451 suppressed HER2, EGFR, and MAPK activation and increased apoptosis, leading to an increase in sensitivity to tamoxifen.[59] Besides increasing sensitivity to trastuzumab,[49] miR-375 has also been shown to enhance the effectiveness of tamoxifen treatment. Knocking down metadherin, a direct target of miR-375, enabled the effect of miRNA re-expression to be partially phenocopied.[60] Among the miRNAs with an oncogenic role in endocrine therapy resistance is miR-21. In addition to mediating resistance of breast cancer cells to radiotherapy and doxorubicin as well as HER2+ breast cancers to trastuzumab,[45-47,56] miR-21 decreases the sensitivity of ER+ breast cancer cells to tamoxifen by targeting PTEN.[61] Other miRNAs confer resistance to tamoxifen target SOCS6 and thereby blocking the SOCS6-STAT3 pathway, such as miR-155,[62] or suppress the tumour-suppressor genes *PTEN, CDKN1A/p21*, and retinoblastoma protein in ER+ breast cancer cells, such as miR-519a.[63] Further microRNAs have been shown to act as tumour-suppressors and to sensitise breast cancer cells towards endocrine therapy, such as miR-15a, miR-16, and miR-342-3p, whereas others, for instance, miR-221/222, miR-101, miR-301, and miR-181b, promote resistance to endocrine therapies.[64,65]

CIRCULATING microRNAS IN THERAPY RESISTANCE OF BREAST CANCER PATIENTS

Several microRNAs can be detected in blood plasma and are therefore known as circulating miRNAs. Their detection in blood samples potentially allows their use as biomarkers, e.g. to predict or monitor therapy response. High levels of miR-210 in the plasma of breast cancer patients, for instance, were shown to correlate with high sensitivity to trastuzumab treatment,[66] whereas high levels of circulating miR-125b were associated with an impaired response to the chemotherapeutic drug 5-fluorouracil.[67] However, a panel of biomarkers usually provides more reliable information about how a patient might respond to a certain therapy. In the case of miR-19a and miR-205, high circulating levels of both miRNAs predict a bad response of Luminal A patients to neoadjuvant treatment with epirubicin and paclitaxel.[68]

microRNAS INFLUENCING THERAPY RESISTANCE VIA PLURIPOTENCY, CANCER STEM CELL PROPERTIES, OR EPITHELIAL-MESENCHYMAL-TRANSITION

Since so-called cancer stem cells (CSC) are considered to be tumour-initiating cells and are a major reason for the development of therapy resistance,[69] miRNAs regulating stem cell features

are of particular interest in understanding the impact of the miRNome on breast cancer therapy resistance. These critical cellular features include pluripotency, developmental pathways which are in charge of the self-renewing potential of stem cells in general, and EMT since breast CSC frequently undergo EMT.[70] miR-200c, for instance, targets ZEB-1 as well as Sox2 and Klf4, affecting EMT and pluripotency, respectively.[70] Moreover, other miR-200 family members as well as the miR-183 cluster, the miR-221-222 cluster, miR-142, miR-214, let-7, miR-22, and miR-27b have been described to influence the features of CSC by regulating pathways important for stemness and pluripotency, such as the Wnt and Notch pathways, apoptosis, and EMT.[71,72]

CONCLUSION

In summary, a multitude of miRNAs have been described to sensitise breast cancer cells to chemotherapy, radiotherapy, or targeted therapy or to mediate resistance to diverse treatment strategies. However, the number of miRNAs associated with a tumour-suppressive function exceeds the number of oncomiRs, especially in resistance to chemotherapeutic drugs. This underlines how crucial it is to obtain a better understanding of the complex miRNome and that unravelling further oncomiRs, which could also be explored as potential therapeutic targets, is necessary. Figure 3 summarises the phenotypes and mechanisms by which miR-200c, a tumour-suppressive miRNA, sensitises breast cancer cells to various treatment options. This example teaches us that miRNAs tend to have multiple phenotypes by affecting various cellular mechanisms, it can be expected that in the future, multiple targets of additional studied or uncharacterised miRNAs will have similarly pleiotropic phenotypes.

REFERENCES

1. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature. 2012; 490(7418):61-70.

2. Bastien RR et al. PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers. BMC Med Genomics. 2012;5:44.

3. Singh R, Mo YY. Role of microRNAs in breast cancer. Cancer Biol Ther. 2013; 14(3):201-12.

4. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. Mol Oncol. 2011;5(1):5-23.

5. Sorlie T et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A. 2003;100(14):8418-23.

6. Rakha EA et al. Basal-like breast cancer: a critical review. J Clin Oncol. 2008; 26(15):2568-81.

7. Sabatier R et al. Claudin-low breast cancers: clinical, pathological, molecular and prognostic characterization. Mol Cancer. 2014;13:228.

8. Tryfonidis K et al. Endocrine treatment in breast cancer: Cure, resistance and beyond. Cancer Treat Rev. 2016;50:68-81.

9. Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. EMBO Mol Med. 2012;4(3):143-59.

10. Ryan BM et al. Genetic variation in microRNA networks: the implications for cancer research. Nat Rev Cancer. 2010; 10(6):389-402.

11. Peters L, Meister G. Argonaute proteins: mediators of RNA silencing. Mol Cell. 2007;26(5):611-23.

12. Martí E et al. A myriad of miRNA variants in control and Huntington's disease brain regions detected by massively parallel sequencing. Nucleic Acids Res. 2010;38(20):7219-35.

13. Castanotto D, Rossi JJ. The promises and pitfalls of RNA-interference-based therapeutics. Nature. 2009;457(7228): 426-33.

14. Bottai G et al. Targeting the microRNA-regulating DNA damage/repair pathways in cancer. Expert Opin Biol Ther. 2014; 14(11):1667-83.

15. Garofalo M, Croce CM. MicroRNAs as therapeutic targets in chemoresistance. Drug Resist Updat. 2013;16(3-5):47-59.

16. Korpela E et al. MicroRNA in radiotherapy: miRage or miRador? Br J Cancer. 2015;112(5):777-82.

17. Yadav BS et al. Systemic treatment strategies for triple-negative breast cancer. World J Clin Oncol. 2014;5(2): 125-33.

18. He DX et al. Genome-wide profiles of methylation, microRNAs, and gene expression in chemoresistant breast cancer. Sci Rep. 2016;6:24706.

19. Rapoport BL et al. When and how do I use neoadjuvant chemotherapy for breast cancer? Curr Treat Options Oncol. 2014;15(1):86-98.

20. Kovalchuk O et al. Involvement of microRNA-451 in resistance of the MCF-7 breast cancer cells to chemotherapeutic drug doxorubicin. Mol Cancer Ther. 2008; 7(7):2152-9.

21. Gao M et al. miR-145 sensitizes breast cancer to doxorubicin by targeting multidrug resistance-associated protein-1. Oncotarget. 2016; doi: 10. 18632/ oncotarget. 10845. [Epub ahead of print].

22. Chen J et al. Down-regulation of microRNA-200c is associated with drug resistance in human breast cancer. Med Oncol. 2012;29(4):2527-34.

23. Bao L et al. Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated by miR-298. Am J Pathol. 2012;180(6):2490-503.

24. Liang Z et al. Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1. Biochem Pharmacol. 2010;79(6):817-24.

25. Yang G et al. Upregulation of miR-195 increases the sensitivity of breast cancer cells to Adriamycin treatment through inhibition of Raf-1. Oncol Rep. 2013;30(2):877-89.

26. Zhu X et al. miR-137 restoration sensitizes multidrug-resistant MCF-7/ADM cells to anticancer agents by targeting YB-1. Acta Biochim Biophys Sin (Shanghai). 2013;45(2):80-6.

27. Fanini F, Fabbri M. MicroRNAs and

cancer resistance: A new molecular plot. Clin Pharmacol Ther. 2016;99(5):485-93.

28. Long J et al. miR-193b Modulates Resistance to Doxorubicin in Human Breast Cancer Cells by Downregulating MCL-1. BioMed Res Int. 2015;2015:373574.

29. Chen X et al. Suppression of SPIN1-mediated PI3K/Akt pathway by miR-489 increases chemosensitivity in breast cancer. J Pathol. 2016;239(4):459-72.

30. Hu Y et al. miR-218 targets survivin and regulates resistance to chemotherapeutics in breast cancer. Breast Cancer Res Treat. 2015;151(2):269-80.

31. He X et al. MiR-218 regulates cisplatin chemosensitivity in breast cancer by targeting BRCA1. Tumour Biol. 2015;36(3): 2065-75.

32. Hu Y et al. miRNA-205 targets VEGFA and FGF2 and regulates resistance to chemotherapeutics in breast cancer. Cell Death Dis. 2016;7(6):e2291.

33. Kopp F et al. miR-200c sensitizes breast cancer cells to doxorubicin treatment by decreasing TrkB and Bmi1 expression. PloS One. 2012;7(11):e50469.

34. Yin J et al. A Bmi1-miRNAs cross-talk modulates chemotherapy response to 5-fluorouracil in breast cancer cells. PloS One. 2013;8(9):e73268.

35. Zhu Y et al. Reduced miR-128 in breast tumor-initiating cells induces chemotherapeutic resistance via Bmi-1 and ABCC5. Clin Cancer Res. 2011;17(22): 7105-15.

36. Niu J et al. Induction of miRNA-181a by genotoxic treatments promotes chemotherapeutic resistance and metastasis in breast cancer. Oncogene. 2016;35(10):1302-13.

37. Yao YS et al. miR-141 confers docetaxel chemoresistance of breast cancer cells via regulation of EIF4E expression. Oncol Rep. 2015;33(5):2504-12.

38. Zhou Y et al. The miR-106b~25 cluster promotes bypass of doxorubicin-induced senescence and increase in motility and invasion by targeting the E-cadherin transcriptional activator EP300. Cell Death Differ. 2014;21(3):462-74.

39. Jeggo P, Löbrich M. Radiation-induced DNA damage responses. Radiat Prot Dosimetry. 2006;122(1-4):124-7.

40. Gasparini P et al. microRNA expression profiling identifies a four microRNA signature as a novel diagnostic and prognostic biomarker in triple negative breast cancers. Oncotarget. 2014;5(5):1174-84.

41. Lin J et al. miR-200c enhances radiosensitivity of human breast cancer cells. J Cell Biochem. 2013;114(3):606-15.

42. Liang Z et al. MicroRNA-302 replacement therapy sensitizes breast cancer cells to ionizing radiation. Pharm Res. 2013;30(4):1008-16.

43. Yu L et al. MicroRNA-144 affects radiotherapy sensitivity by promoting proliferation, migration and invasion of breast cancer cells. Oncol Rep. 2015; 34(4):1845-52.

44. Körner C et al. MicroRNA-31 sensitizes human breast cells to apoptosis by direct targeting of protein kinase C epsilon (PKCepsilon). J Biol Chem. 2013; 288(12):8750-61.

45. Anastasov N et al. Radiation resistance due to high expression of miR-21 and G2/M checkpoint arrest in breast cancer cells. Radiat Oncol. 2012;7:206.

46. Wang ZX et al. MicroRNA-21 modulates chemosensitivity of breast cancer cells to doxorubicin by targeting PTEN. Arch Med Res. 2011;42(4):281-90.

47. Bourguignon LY et al. Hyaluronan-CD44 interaction with protein kinase C(epsilon) promotes oncogenic signaling by the stem cell marker Nanog and the Production of microRNA-21, leading to down-regulation of the tumor suppressor protein PDCD4, anti-apoptosis, and chemotherapy resistance in breast tumor cells. J Biol Chem. 2009;284(39): 26533-46.

48. Tsang RY, Finn RS. Beyond trastuzumab: novel therapeutic strategies in HER2-positive metastatic breast cancer. Br J Cancer. 2012;106(1):6-13.

49. Ye XM et al. Epigenetic silencing of miR-375 induces trastuzumab resistance in HER2-positive breast cancer by targeting IGF1R. BMC Cancer. 2014;14:134.

50. Corcoran C et al. miR-630 targets IGF1R to regulate response to HER-targeting drugs and overall cancer cell progression in HER2 over-expressing breast cancer. Mol Cancer. 2014;13:71.

51. Ma T et al. MiRNA-542-3p downregulation promotes trastuzumab resistance in breast cancer cells via AKT activation. Oncol Rep. 2015;33(3):1215-20.

52. Chen Y et al. miRNA-200c increases the sensitivity of breast cancer cells to doxorubicin through the suppression of E-cadherin-mediated PTEN/Akt signaling. Mol Med Rep. 2013;7(5):1579-84.

53. Bai WD et al. MiR-200c suppresses TGF-β signaling and counteracts trastuzumab resistance and metastasis by targeting ZNF217 and ZEB1 in breast cancer. Int J Cancer. 2014;135(6):1356-68.

54. Mao L et al. Involvement of microRNAs in HER2 signaling and trastuzumab treatment. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2016. [Epub ahead of print].

55. Ye X et al. MiR-221 promotes trastuzumab-resistance and metastasis in HER2-positive breast cancers by targeting PTEN. BMB Rep. 2014;47(5):268-73.

56. De Mattos-Arruda L et al. MicroRNA-21 links epithelial-to-mesenchymal transition and inflammatory signals to confer resistance to neoadjuvant trastuzumab and chemotherapy in HER2-positive breast cancer patients. Oncotarget. 2015; 6(35):37269-80.

57. Hayes EL, Lewis-Wambi JS. Mechanisms of endocrine resistance in breast cancer: an overview of the proposed roles of noncoding RNA. Breast Cancer Res. 2015;17:40.

58. Lü M et al. MicroRNA-320a sensitizes tamoxifen-resistant breast cancer cells to tamoxifen by targeting ARPP-19 and ERRγ. Sci Rep. 2015;5:8735.

59. Bergamaschi A, Katzenellenbogen BS. Tamoxifen downregulation of miR-451 increases 14-3-3ζ and promotes breast cancer cell survival and endocrine resistance. Oncogene. 2012;31(1):39-47.

60. Ward A et al. Re-expression of microRNA-375 reverses both tamoxifen resistance and accompanying EMT-like properties in breast cancer. Oncogene. 2013;32(9):1173-82.

61. Yu X et al. Silencing of MicroRNA-21 confers the sensitivity to tamoxifen and fulvestrant by enhancing autophagic cell death through inhibition of the PI3K-AKT-mTOR pathway in breast cancer cells. Biomed Pharmacother. 2016;77:37-44.

62. Shen R et al. MiRNA-155 mediates TAM resistance by modulating SOCS6-STAT3 signalling pathway in breast cancer. Am J Transl Res. 2015;7(10):2115-26.

63. Ward A et al. MicroRNA-519a is a novel oncomir conferring tamoxifen resistance by targeting a network of tumour-suppressor genes in ER+ breast cancer. J Pathol. 2014;233(4):368-79.

64. Muluhngwi P, Klinge CM. Roles for miRNAs in endocrine resistance in breast cancer. Endocr Relat Cancer. 2015;22(5):R279-300.

65. Klinge CM. miRNAs regulated by estrogens, tamoxifen, and endocrine disruptors and their downstream gene targets. Mol Cell Endocrinol. 2015;418 Pt 3: 273-97.

66. Jung EJ et al. Plasma microRNA 210 levels correlate with sensitivity to trastuzumab and tumor presence in breast cancer patients. Cancer. 2012; 118(10):2603-14.

67. Wang H et al. Circulating MiR-125b as a marker predicting chemoresistance in breast cancer. PLoS One. 2012;7(4):e34210.

68. Li Q et al. Circulating miR-19a and miR-205 in serum may predict the sensitivity of luminal A subtype of breast cancer patients to neoadjuvant chemotherapy with epirubicin plus paclitaxel. PLoS One. 2014;9:e104870.

69. Eyler CE, Rich JN. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. J Clin Oncol. 2008;26(17):2839-45.

70. Czerwinska P, Kaminska B. Regulation of breast cancer stem cell features. Contemp Oncol (Pozn). 2015;19(1A): A7-15.

71. Shimono Y et al. MicroRNA Regulation of Human Breast Cancer Stem Cells. J Clin Med. 2015;5(1):E2.

72. Kurozumi S et al. Recent trends in microRNA research into breast cancer with particular focus on the associations between microRNAs and intrinsic subtypes. J Hum Genet. 2016. [Epub ahead of print].

GASTROINTESTINAL STROMAL TUMOURS: A REVIEW ON GENETICS, PATHOLOGY, RISK STRATIFICATION, CLINICAL CHARACTERISTICS, INVESTIGATION, AND TREATMENT

***Md Tanveer Adil,[1,2] Jayesh Sagar,[1] Partha Das,[1] Vigyan Jain[2]**

1. Department of Colorectal Surgery, Luton and Dunstable University Hospital, Luton, UK
2. Department of Upper GI Surgery, Luton and Dunstable University Hospital, Luton, UK
**Correspondence to tanveer.cmc@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 26.07.16 **Accepted:** 24.10.16
Citation: EMJ Oncol. 2016;4[1]:113-121.

ABSTRACT

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, arising from the interstitial cells of Cajal. They are known to occur in all parts of the gastrointestinal tract from the oesophagus to the anorectum, with the stomach being the most commonly affected organ (60%). GISTs are commonly known to occur within the fifth and sixth decades of life, carry an equal predisposition between females and males, and are associated with tyrosine-protein kinase (*KIT*) or platelet-derived growth factor receptor alpha (*PDGFRA*) mutations in 85–90% of cases. Familial syndromes associated with GISTs are neurofibromatosis Type 1, Carney's triad (gastric GIST, pulmonary chordoma, and paraganglioma), Carney–Stratakis syndrome (GIST and paraganglioma), and familial GISTs. Lesions vary in size from a few mm to >30 cm, with a median size between 5 and 8 cm. Immunohistochemical staining with KIT and DOG1 show the highest sensitivity for GISTs. While 20% of GISTs are diagnosed asymptomatically, and 10% at autopsy, 70% are symptomatic. Bleeding followed by abdominal pain and a mass growth are the most common symptoms. Forty to fifty percent of GISTs are biologically malignant. Malignant GISTs spread haematogenously to the liver and peritoneum, while lymphatic spread is rare. Risk stratification subdivides GISTs into very low, low, intermediate, and high-risk groups. Computed tomography (CT) scan is the mainstay of diagnosis, though they are often incidentally detected on endoscopy. Surgery offers the best chance of cure in resectable lesions, while tyrosine kinase inhibitors are the treatment of choice in non-resectable and metastatic GISTs. Neoadjuvant and adjuvant tyrosine kinase inhibitors increase resectability, time to recurrence, recurrence-free survival, and overall survival in GISTs.

Keywords: Gastrointestinal stromal tumours (GISTs), tyrosine kinase inhibitor (TKI), imatinib, tyrosine-protein kinase (KIT), platelet-derived growth factor receptor alpha (PDGFRA).

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract (GIT), arising from the interstitial cells of Cajal (ICC).[1] Neuroenteric networks formed by the ICC are widely distributed within the submucosal, intramuscular (including the deep muscular plexus), and intermuscular layers of the GIT, from the oesophagus to the internal anal sphincter.[2] This explains the diverse location of GISTs found within patients, with the stomach being the most common organ involved (60%).[3] Other sites where GISTs can occur are the small intestine (30%), duodenum (5%), and colorectum (<5%).[3] Rarer locations are the oesophagus and appendix which constitute <1% of all GISTs. Extra-GIT locations like the omentum, mesenteries, and retroperitoneum usually represent metastasis or a possible detachment of the GIST from its GIT origin, even though a small number of primary tumours are reported in these sites.[4] The molecular hallmark of these neoplasms is a kinase-activating mutation in either the receptor tyrosine-protein

kinase (*KIT*) or platelet-derived growth factor receptor alpha (*PDGFRA*) genes, which are present in 85–90% of reported tumours.[5] Surgery offers the best chance of cure in localised disease.[6] Tyrosine kinase inhibitors (TKIs), such as imatinib, offer improved survival rates in metastatic GISTs and decrease recurrence rates in patients with resectable but large tumour burden, with the stratification risk dependent on the location of the tumour and its respective mitotic number.[7] The aim of this article is to provide an evidence-based review on the epidemiology, molecular genetics, pathology, clinical characteristics, investigations, and treatment of GISTs arising in the GIT.

METHODOLOGY

A comprehensive search without language restriction was undertaken using MEDLINE, Scorpus (including Embase), and Cochrane Central Register of Controlled Trials (CENTRAL), from 1st January 1985–30th June 2016. PubMed was also searched for in-process citations. MeSh terms used were 'GIST', 'gastrointestinal stromal tumour', and 'tyrosine kinase inhibitor'. Important clinical trials were searched for on ClinicalTrials.gov and the International Clinical Trials Registry Platform Search Portal (ICTRP). Manual searches were carried out for recent articles in journals with high impact factors and reference lists in key articles. All evidence-based work was carried out in accordance with the standards published in the Centre for Reviews and Dissemination's (CRD, University of York, York, UK, 2008) guidance for undertaking reviews in healthcare.[8] Preference was given to articles of high quality and those with important observations or randomised trials.

EPIDEMIOLOGY

The annual incidence of GIST varies according to geographical location. Incidence of GIST is cited as 11–15 per million population, per year in the West.[9] The incidence is slightly higher in the East, at 16–22 per million, including a relatively higher proportion of extraintestinal GISTs (10%).[10,11] In the UK, the annual incidence of GIST cases is between 1.32 and 1.5 per 100,000, equivalent to approximately 800–900 new cases per year.[12,13] Prevalence of GIST is estimated to be around 120 per million population.[14] Risk stratification, as per the United States National Institutes of Health (NIH) criteria, estimates the prevalence at 18.5% for very low-risk, 43% for low-risk, 20% for intermediate-risk, and 18.5% for high-risk GISTs.[14] GIST is most commonly known to occur in the fifth or sixth decades of life (80%), with a median age of 60 years.[6,9] The disease carries an equal predisposition between males and females, though GISTs as a syndromic component of Carney's triad (gastric GIST, pulmonary chordoma, and paraganglioma) occur more commonly in females.[7]

MOLECULAR GENETICS

The association of *KIT* mutations with GIST has been reported to be between 75% and 90% in various studies, with one showing that 88.2% of GISTs have mutations in the *KIT* gene with a gain of function;[15] a *PDGFRA* mutation is present in 4.7% of GISTs.[15] Both of these genes are located in the long arm of chromosome 4 and encode for homologous receptor tyrosine kinase proteins.[16] Most *KIT* mutations involve exon 11, followed by exon 9, exon 13, and exon 17, in descending order of frequency.[3] Imatinib, a TKI, acts best on exon 11 mutations, and least on exon 17 mutations where the drug is primarily resistant.[3,15] *PDGFRA* mutations have a predilection for gastric GISTs, though duodenal GISTs are also seen with these mutations.[3,17] Exons 18, 12, and 14 are mutated in *PDGFRA* mutations in decreasing order of frequency with the exon 18 *PDGFRA D842V* mutation being resistant to imatinib.[3,17] Mutational analysis is crucial before starting adjuvant imatinib therapy to identify resistant genotypes that will not respond to adjuvant therapy (*PDGFRA D842V* mutation, neurofibromatosis Type I [NF1]-associated GISTs, and wild-type succinate dehydrogenase [SDH]-negative GISTs) and those that would need a higher dose (800 mg/day) of imatinib (exon 9 *KIT* mutation).[18]

FAMILIAL SYNDROMES

GIST is associated with familial syndromes in <5% of cases.[3] NF1 is the most commonly associated syndrome, with 7% of patients developing GISTs.[3,19] Both *KIT* and *PDGFRA* mutations are frequently lacking in these patients.[20] There is a high association of NF1 with duodenal and small intestinal GISTs;[3,21] although the majority of these tumours are benign and clinically indolent, malignant GISTs can occur.[22] GISTs associated with NF1 are resistant to imatinib therapy.[18]

Carney's triad typically lacks *KIT* and *PDGFRA* mutations, along with a distinctive SDH subunit B (SDHB) negativity on immunohistochemistry, with

tumours exclusively occurring in the stomach.[21,22] Recently, SDH subunit C (SDHC) epigenetic hypermethylation has been reported in this syndrome.[23] A vast majority of these GISTs occur at a young age and carry a female preponderance (85%).[3] Although the majority of these tumours are clinically benign, liver metastasis are known to occur as they can behave unpredictably, even after risk stratification.

Carney–Stratakis syndrome (GIST and paraganglioma) also typically lacks *KIT* and *PDGFRA* mutations but can carry a germline mutation in any subunit of the *SDH* gene.[24] Tumourigenesis in this syndrome hinges upon a germline *SDHB*, *SDHC*, or *SDHD* mutation, coupled with a somatic inactivation of the corresponding wild-type allele in the tumour.[25] *SDHA* mutations (30%) have also been identified on immunohistochemical analysis of a few cases.[26]

Familial GISTs are associated with germline mutations of either the *KIT* or *PDGFRA* genes.[3,27] Transmission is autosomal-dominant, and the affected are at a high risk of developing gastric or small bowel GISTs at middle age. Other manifestations associated with familial GISTs due to germline *KIT* mutations include: cutaneous hyperpigmentation, mast cell disorders, diffuse hyperplasia of ICC, and dysphagia, while those due to germline *PDGFRA* mutations include inflammatory fibroid polyps of the stomach and small bowel, gastrointestinal lipomas, and large hands.[28]

PATHOLOGY

GISTs vary in size remarkably, ranging from a few mm to >30 cm in size, with the median size being between 5 cm and 8 cm.[6] Micro-GISTs (<1 cm) are often found incidentally in resected specimens of gastro-oesophageal junction.[29] Micro-GISTs have been found to be present in 10.0–22.5% of resected specimens and autopsy tissue, and there is evidence to suggest that these are precursor lesions to macroscopically relevant GISTs after further molecular alterations.[30-32] Macroscopically relevant lesions usually show an exophytic pattern, often with compression of other intra-abdominal organs. Microscopically, GISTs fall into three basic categories: i) epitheloid; ii) spindle cell; and iii) mixed variety.[14,29] Four subtypes of epitheloid and four of the spindle cell variety have been identified.[3]

Immunohistochemistry is often necessary to confirm the diagnosis. More than 95% of tumours stain positive for KIT (CD117) and DOG1 which are the most sensitive and specific markers for the diagnosis of GISTs.[6,7] DOG1 and PKC-θ expression is especially useful to identify a subset of KIT$^-$ tumours who will respond to KIT-targeted treatment.[33,34] PKC-θ has been found to have a high sensitivity but low specificity in the diagnosis of GISTs, therefore its use for routine diagnosis of these tumours is not recommended.[35] Other markers included in the GIST panel are CD34 (70–80%), smooth muscle actin (30%), desmin (<5%), and S-100 (rare).[34] PDGFRA staining lacks specificity, is technically challenging, and is pushed into the second panel by a few pathologists.[34]

CLINICAL FEATURES

On average, 70% of GISTs are symptomatic, while 20% are diagnosed asymptomatically; 10% are diagnosed only at autopsy.[6] Clinical signs and symptoms depend on the site of the tumour.[36] The most frequent symptoms are vague abdominal discomfort (60–70%), bleeding (30–40%), anaemia, dyspepsia, vomiting, and weight loss.[6] Large tumours present with a palpable lump in the abdomen with mass effect. Bleeding may be chronic where the patient presents with chronic iron deficiency anaemia requiring blood transfusion. Acute bleeding may be intraluminal which manifests as haematemesis and melena, or extraluminal due to tumour rupture, presenting as an acute abdominal catastrophe. Site-specific symptoms include dysphagia for oesophageal GISTs, obstructive jaundice for duodenal or periampullary GISTs, and intussusception or bowel obstruction in small bowel GISTs.[36] Spread occurs either haematogenously or transcoelomically to the liver, mesentery, omentum, and peritoneum. Lymphatic spread is rare, except in wild-type GISTs such as paediatric wild-type GISTs, and those occurring in the setting of Carney's triad where nodal metastasis may occur in 20–30% of cases.[37]

RISK STRATIFICATION

GISTs represent a class of tumours with varied biological behaviour without a sharp distinction between benign and malignant lesions. It is difficult to predict malignancy of a GIST in the absence of metastasis due to lack of absolute histological criteria.[38] It is estimated that 40–50% of GISTs are biologically malignant, and half of these show evidence of metastatic spread to the liver or peritoneum at the time of diagnosis or primary surgery.[39] In a large cohort of 439 patients,[40]

24% of GISTs were locally advanced or metastatic, precluding curative resection. Of those resected, 45% had a recurrence at follow-up, making a total of 69% which were presumed malignant. The overall incidence of liver metastasis was 54%, and peritoneal metastasis was 62%.[40] This observation suggests that a high proportion of GISTs, which are biologically malignant, do not show evidence of loco regional spread at the time of initial diagnosis. Thus, a reliable risk scoring system is thought to be needed to identify lesions that are at a high risk of recurrence and metastasis which would benefit from adjuvant TKI therapy, as well as excluding patients who would not benefit from it.

The National Institutes of Health Scoring System

The NIH Scoring System, also known as the Fletcher's Risk Criteria, is the first risk classification system adopted for GISTs.[41] This incorporates only two risk factors, namely tumour size and mitotic count per 50 high-power field. Even though GIST-specific data were not available at the time of incorporation of this system, NIH criteria are fairly accurate in identifying GISTs which are at high risk of recurrence.[40] However, this system does not include tumour site or rupture as risk factors. The NIH Scoring System tends to overestimate risks in large but biologically inactive gastric GISTs, and underestimates the risks in small duodenal and rectal GISTs which can be biologically aggressive.[42]

The Armed Forces Institute of Pathology Scoring System

The Armed Forces Institute of Pathology (AFIP) scoring system was the first risk classification for GISTs based on evidence which included anatomic site, along with tumour size and mitotic count.[39] It also seeks to establish the size of real risk expressed as a percentage.[39] This system identifies the fact that gastric GISTs have an overall better prognosis than intestinal GISTs.[39,43,44] By virtue of establishment of the quantum of real risk, it helps the oncologist to reliably decide the need for adjuvant TKI therapy.[38] The National Comprehensive Cancer Network (NCCN) GIST Task Force adopted the AFIP scoring system within their clinical practice guidelines regarding GISTs.[45]

Joensuu's Risk Criteria

Joensuu proposed a modification of the NIH criteria in 2008 (Table 1), and incorporated anatomic site (as in the AFIP scoring system) and tumour rupture as criteria for absolute high risk, irrespective of the other risk factors.[46] Tumour rupture can occur either spontaneously (80%) or during surgery (20%).[47] Joensuu's criteria can be applied to all anatomical sites of tumour origin and utilises two cut-offs for mitotic count. It has been found to be particularly advantageous in predicting tumours that are at a high risk of relapse for consideration of adjuvant imatinib therapy.[47]

Table 1: Definition of Joensuu's risk stratification for gastrointestinal stromal tumours.[41]

Risk category	Tumour size (cm)	Mitotic index (per 5 HPF)	Primary tumour site
Very low-risk	≤2.0	≤5	Any
Low-risk	2.1–5.0	≤5	Any
Intermediate-risk	≤5.0 5.1–10.0	6–10 ≤5	Gastric Gastric
High-risk	Any >10.0 Any >5.0 ≤5.0 5.1–10.0	Any Any >10 >5 >5 ≤5	Tumour rupture Any Any Any Non-gastric Non-gastric

HPF: high-power field.

INVESTIGATIONS

Most GISTs are diagnosed either at endoscopy or by an unenhanced or contrast-enhanced computed tomography (CT) scan without a prior clinical suspicion of its presence. A quarter of these are diagnosed asymptomatically (incidental finding).[7] Endoscopy may give a suspicion of GIST by detecting a submucosal lesion warranting further imaging. In a few of these cases, this turns out to be extrinsic compression by a dilated gallbladder or an enlarged spleen. The recommended imaging modalities for GISTs are contrast-enhanced CT scans, endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan. Our strategy is to evaluate suspected tumours following endoscopy with a contrast-enhanced CT scan of the chest, abdomen, and pelvis, as the initial imaging modality which is usually sufficient to guide further management if no metastasis is detected.

The characteristic CT appearance of a primary GIST is a large, hypervascular, and heterogeneously-enhancing mass with areas of haemorrhage, necrosis, and cystic degeneration.[48] MRI is reserved as the preferred imaging modality for anorectal GISTs.[49] We also use MRI to characterise suspected liver metastasis detected on CT scans. EUS is useful in detecting early primary lesions in the oesophagus, stomach, duodenum, and anorectum.[50] Characteristically, they show an echo-poor pattern in the fourth layer (corresponding to the muscularis propria) or rarely in the second layer (corresponding to the muscularis mucosae) as a well-demarcated, homogenous mass. EUS-guided fine needle aspiration can be used for cytological or histological confirmation, though the characteristic sonological appearance in itself often suggests the diagnosis. EUS, unlike a CT scan, does not always offer a complete staging for metastasis even though GISTs can be metastatic at presentation in ≤50% of cases.[14] PET scans are particularly useful for detecting metastatic disease and for rapid assessment of response to imatinib much before the therapeutic response to the drug can be picked up by a CT scan.[51] PET scans however are not sensitive in detecting primary lesions <2 cm in size.[52] A combination of PET and CT scanning (PET-CT) has shown better sensitivity, specificity, and accuracy in the staging and restaging of patients with GISTs and optimising treatment than either modality alone.[53]

TREATMENT

Treatment of GIST depends on resectability, site, size, and presence of metastasis and should be discussed by a multidisciplinary team which should include the relevant specialist surgeon, oncologist, radiologist, and histopathologist.

Resectable/Non-Metastatic GISTs

For resectable/non-metastatic GISTs <2 cm in size, the treatment option is tailored according to the site and risk criteria.[54] All symptomatic gastric GISTs are candidates for surgical resection. Selective asymptomatic gastric GISTs without high-risk criteria on endoscopic ultrasound may be followed-up until 3 cm in size.[55] For tumours in the small bowel, duodenum, or anorectum, surgical resection is advisable due to greater chances of the tumour being symptomatic and at risk of malignancy.

For tumours >2 cm in size, the treatment of choice is surgery with a 1–2 cm margin, aiming for an R0 resection.[7] Organ preservation should be attempted but not at the expense of positive margins. Routine lymphadenectomy is not indicated except in those at high risk. Neoadjuvant imatinib therapy for 2–6 months has shown promise in downstaging treated tumours.[56,57] Tumour shrinkage is especially useful in gastroesophageal junction tumours before gastrectomy, duodenal GISTs before pancreatoduodenectomy, and anorectal GISTs before abdominoperineal resection by facilitating achievement of R0 resection. Response to preoperative therapy is assessed by Choi criteria which has been found to be superior to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria.[6] Responsive tumours show a ≥10% reduction in the size of the tumour, and a 15% reduction in tumour density.[6] Laparoscopic resection has been found to be safe and is advantageous in surgically amenable areas like the anterior wall of the stomach and small intestines, due to lower morbidity and shorter hospital stay.[6] A combined laparoscopic and endoscopic approach (laparoscopic endoscopic-guided surgery) has been found to be an attractive option in selective gastric tumours where the tumour is transilluminated endoscopically for localisation, and resection is carried out laparoscopically.[58]

Adjuvant imatinib therapy has shown survival benefit in lesions of non-gastric origin, lesions >5 cm, tumour rupture, and tumours with high mitotic count.[6] The usual adjuvant dose is 400 mg/day

with an exception being exon 9 *KIT* mutations where, due to partial resistance, a dose of 800 mg/day is preferred. Imatinib therapy is not recommended in patients with resistant mutations like *PDGFRA D842V*, and has a doubtful role in GISTs associated with NF1 or wild-type SDH^{-} tumours.[18] Imatinib therapy is recommended for at least 3 years in patients with high-risk lesions (Table 1, Figure 1).

Non-Resectable/Metastatic GISTs

Treatment of choice for metastatic or non-resectable GISTs is TKI therapy.[5,6] Imatinib is used as the first-line drug in metastatic or non-resectable GISTs at a dose of 400 mg/day, which can be increased by up to 800 mg/day in the case of non-responsiveness at lower dose or in lesions with partially resistant mutations (exon 9 *KIT* mutations).[6,18]

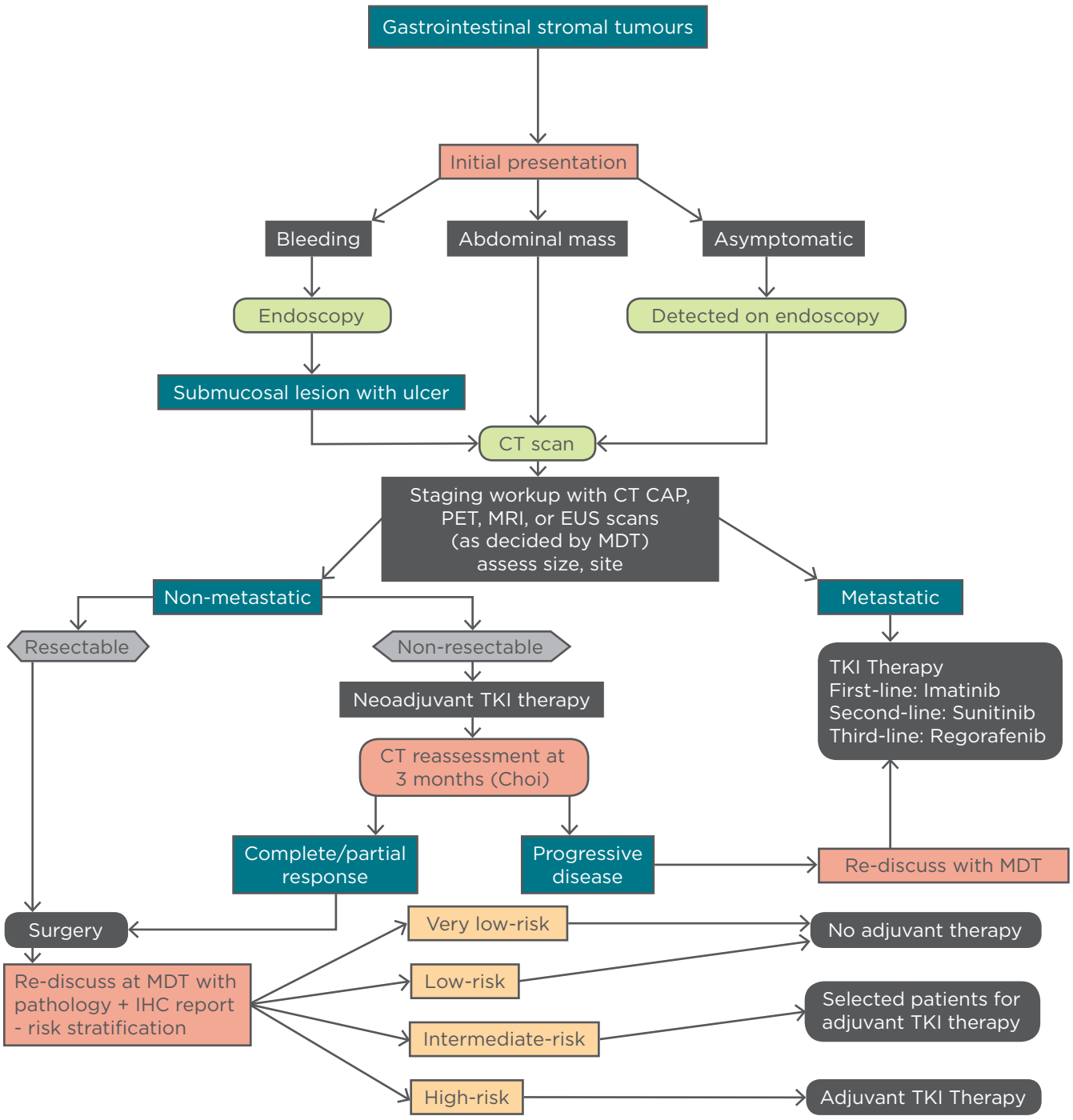


Figure 1 : Management algorithm for gastrointestinal stromal tumours.

CT: computerised tomography; CAP: chest, abdomen, pelvis; PET: positron emission tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; MDT: multidisciplinary team; TKI: tyrosine kinase inhibitor; IHC: immunohistochemistry.

Table 2: Key trials with tyrosine kinase inhibitors in patients with gastrointestinal stromal tumours.

Trial name	Setting	Number	Randomised arms	RFS/PFS	OS	Response
ASOSCOG Z9001, 2009[64]	Adjuvant	713	1-year imatinib vs. placebo	1-year RFS 98% vs. 83% (p<0.0001)	HR=0.816; p=0.438	Not available
SSG XVIII/AIO, 2012[65]	Adjuvant	400	1-year vs. 3-year imatinib	5-year RFS 66% vs. 48% (p<0.0001)	5-year OS 92% vs. 82% (p=0.02)	Not available
EORTC – ISG – AGITG (62005), 2004[66]	First-line metastatic	946	400 mg vs. 800 mg imatinib	2-year PFS 56% vs. 50% (p=0.026)	2-year OS 69% vs. 74%	50% vs. 54%
NORTH AMERICAN SARCOMA INTERGROUP STUDY (S0033), 2005[67]	First-line metastatic	746	400 mg vs. 800 mg imatinib	2-year PFS 50% vs. 53%	2-year OS 73% vs. 78%	43% vs. 41%
DEMETRI et al., 2006[68]	Second-line metastatic	243	Sunitinib vs. placebo	Median 27.3 vs. 6.4 weeks (p<0.0001)	Median 72.7 vs. 64.9 weeks (p=0.306)	Not available
GRID, 2013[60]	Third-line metastatic	199	Regorafenib vs. placebo	Median 4.8 vs. 0.9 months (p<0.0001)	Same (HR=0.77; (p=0.199)	76% vs. 35%

RFS: recurrence-free survival; PFS: progression-free survival; OS: overall survival; HR: hazard ratio.

Sunitinib is recommended by the National Institute for Health and Care Excellence (NICE) guidelines in the UK for patients with metastatic GISTs who do not respond to imatinib.[59] Regorafenib, a multikinase inhibitor, is the third drug licensed by the US Food and Drug Administration (FDA) in patients who have shown progression of the disease alongside imatinib and sunitinib therapy after successful completion of the GRID trial.[60] Sorafenib, also a multikinase inhibitor, has been similarly found to be effective in imatinib and sunitinib-resistant GISTs by the Korean Gastrointestinal Stromal Tumors Group.[61]

The role of cytoreductive surgery in metastatic GISTs is limited and is individualised based on the tumour characteristics and performance status of the patient.[6] Surgical debulking following preoperative imatinib therapy is shown to offer a survival benefit.[6] The addition of adjuvant intraperitoneal chemotherapy with cisplatin and mitomycin C or doxorubicin to surgical debulking has been shown to increase the median time to recurrence from 8 months to 21 months.[6] Radiofrequency ablation and liver transplantation followed by adjuvant imatinib for GIST-related liver metastasis has been attempted with promising results.[62,63] A simplified algorithm for the management of GISTs is enumerated in Figure 1.

FOLLOW-UP

The follow-up strategy for GISTs varies according to the surgical culture and epidemiology of the disease in different countries. Our strategy is to follow the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) Guidelines for the follow-up of GISTs.[52]

- **Very low-risk tumours:** no further imaging
- **Low-risk tumours:** CT at 3 months after surgery, then clinical follow-up
- **Intermediate-risk tumours:** CT at 3 months after surgery, then 6 monthly for 2 years, then annually up to 5 years
- **High-risk tumours:** CT at 3 monthly for 2 years, then 6 monthly for a further 2 years, then annual scans on an indefinite basis
- **Adjuvant therapy with imatinib:** CT at 3 months after surgery, then 6 monthly for 2 years, then annually up to 5 years
- **Clinical suspicion of recurrence:** CT

MRI can be considered as a substitute in patients who are at risk of contrast toxicity, and to reduce radiation dose from annual scans.

PROGNOSIS

Recurrence rates and survival of patients with GISTs are strongly influenced by tumour size, site, mitotic activity, tumour rupture, and extensiveness of resection.[5,43,45] After resection, adjuvant imatinib therapy has been found to improve recurrence-free survival, compared to non-adjuvant therapy, from 83–98% at 1 year with no difference in terms of overall survival between the two groups monitored by the ASOCOG Z9001 trial on 713 patients with tumour size >3 cm.[64] The European SSGXVIII/AIO trial which compared patients on adjuvant imatinib therapy for 3 years with those receiving the same therapy for only 1 year, found a superior recurrence-free survival (66% versus 48% at 5 years) and overall survival (92% versus 82% at 5 years) in patients who received the adjuvant therapy for 3 years.[65] The recurrence-free survival and overall survival observed in the various trials on the effect of TKIs for GISTs are enumerated in Table 2.

REFERENCES

1. Kindblom LG et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol. 1998; 152(5):1259-69.

2. Takaki M. Gut pacemaker cells: the interstitial cells of Cajal (ICC). J Smooth Muscle Res. 2003;39(5):137-61.

3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130(10):1466-78.

4. Miettinen M et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol. 1999;23(9):1109-18.

5. Rubin BP et al. Gastrointestinal stromal tumour. Lancet. 2007;369(9574):1731-41.

6. Rammohan A et al. A gist of gastrointestinal stromal tumors: A review. World J Gastrointest Oncol. 2013;5(6): 102-12.

7. Joensuu H et al. Gastrointestinal stromal tumour. Lancet. 2013;382(9896):973-83.

8. Taccolleni E. Systematic reviews: CRD's guidance for undertaking reviews in health care. Lancet Infect Dis. 2010;10(4):226.

9. Ducimetière F et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS One. 2011;6(8):e20294.

10. Chan KH et al. Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong. World J Gastroenterol. 2006;12(14):2223-8.

11. Cho MY et al. Current trends in the epidemiological and pathological characteristics of gastrointestinal stromal tumors in Korea, 2003-2004. J Korean Med Sci. 2010;25(6):853-62.

12. Ahmed I et al. Gastrointestinal stromal tumours (GIST) - 17 years experience from Mid Trent Region (United Kingdom). Eur J Surg Oncol. 2008;34(4):445-9.

13. Hislop J et al. Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation. Health Technol Assess. 2011;15(25):1-178.

14. Nilsson B et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer. 2005;103(4):821-9.

15. Heinrich MC et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21(23):4342-9.

16. Stenman G et al. Human PDGFA receptor maps to the same region on chromosome 4 as the KIT oncogene. Genes Chromosomes Cancer. 1989;1(2):155-8.

17. Lasota J et al. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest. 2004;84(7):874-83.

18. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3): iii21-6.

19. Zöller ME et al. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. Cancer. 1997;79(11):2125-31.

20. Kinoshita K et al. Absence of c-kit gene mutations in gastrointestinal stromal tumours from neurofibromatosis type 1 patients. J Pathol. 2004;202(1):80-5.

21. Miettinen M et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical and molecular genetic study of 167 cases. Am J Surg Pathol. 2003;27(5):625-41.

22. Miettinen M et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006;30(1):90-6.

23. Haller F et al. Aberrant DNA hypermethylation of SDHC: a novel mechanism of tumor development in Carney triad. Endocr Relat Cancer. 2014; 21(4):567-77.

24. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet. 2002; 108(2):132-9.

25. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. Int J Biochem Cell Biol. 2014;53:514-9.

26. Dwight T et al. Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. Am J Surg Pathol. 2013;37(2):226-33.

27. Chompret A et al. PDGFRA germline mutation in a family with multiple cases of gastrointestinal stromal tumor. Gastroenterology. 2004;126(1):318-21.

28. Ricci R. Syndromic gastrointestinal stromal tumors. Hered Cancer Clin Pract. 2016;14:15.

29. Agaimy A et al. Microscopic gastrointestinal stromal tumors in esophageal and intestinal surgical resection specimens: a clinicopathologic, immunohistochemical, and molecular study of 19 lesions. Am J Surg Pathol. 2008;32(6):867-73.

30. Agaimy A et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol. 2007;31(1):113-20.

31. Abraham SC et al. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. Am J Surg

Pathol. 2007;31(11):1629-35.

32. Rossi S et al. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. Am J Surg Pathol. 2010; 34(10):1480-91.

33. Kang GH et al. DOG1 and PKC-θ are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. Mod Pathol. 2011;24(6):866-75.

34. González-Cámpora R et al. Old and new immunohistochemical markers for the diagnosis of gastrointestinal stromal tumors. Anal Quant Cytol Histol. 2011; 33(1):1-11.

35. Novelli M et al. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours. Histopathology. 2010;57(2):259-70.

36. Goettsch WG et al. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. Eur J Cancer. 2005;41(18):2868-72.

37. Zhang L et al. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal tumors: findings in 104 cases. Am J Surg Pathol. 2010;34(1):53-64.

38. Agaimy A. Risk assessment and pathological reporting of gastrointestinal stromal tumour. Diagn Histopathol. 2013; 19(6):191-7.

39. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70-83.

40. Rutkowski P et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol. 2007;14(7):2018-27.

41. Fletcher CD et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002; 33(5):459-65.

42. Agaimy A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. Int J Clin Exp Pathol. 2010;3(5):461-71.

43. Miettinen M et al. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52-68.

44. Miettinen M et al. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477-89.

45. Demetri GD et al.; NCCN Task Force. NCCN Task force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw. 2007;5(Suppl 2):S1-29.

46. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008; 39(10):1411-9.

47. Rutkowski P et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour – the impact of tumour rupture on patient outcomes. Eur J Surg Oncol. 2011;37(10):890-6.

48. Hong X et al. Gastrointestinal stromal tumor: role of CT in diagnosis and in response evaluation and surveillance after treatment with imatinib. Radiographics. 2006;26(2):481-95.

49. Blackstein ME et al.; Canadian Advisory Committee on GIST. Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. Can J Gastroenterol. 2006;20(3):157-63.

50. Lau S et al. Imaging of gastrointestinal stromal tumour (GIST). Clin Radiol. 2004;59(6):487-98.

51. Stroobants S et al. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer. 2003; 39(14):2012-20.

52. Reid R et al. Guidelines for the management of gastrointestinal stromal tumours (GIST). 2009. Available at: http://www.augis.org/wp-content/uploads/2014/05/GIST_Management_Guidelines_180809.pdf. Last accessed: 26 October 2016.

53. Antoch G et al. Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. J Nucl Med. 2004;45(3):357-65.

54. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: soft tissue sarcoma (version 1.2013). Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Last accessed: 26 October 2016.

55. Bruno M et al. The natural history of gastrointestinal subepithelial tumors arising from muscularis propria: an endoscopic ultrasound survey. J Clin Gastroenterol. 2009;43(9):821-5.

56. Wang D et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol. 2012; 19(4):1074-80.

57. Hohenberger P et al. Neoadjuvant imatinib and organ preservation in locally advanced gastrointestinal stromal tumors (GIST). Abstract 10550. ASCO Annual Meeting. 2009.

58. Walsh RM et al. Combined endoscopic/laparoscopic intragastric resection of gastric stromal tumors. J Gastrointest Surg. 2003;7(3):386-92.

59. National Institute for Health and Care Excellence. NICE technology appraisal guidance [TA179]: Sunitinib for the treatment of gastrointestinal stromal tumours. 2009. Available at: https://www.nice.org.uk/guidance/ta179. Last accessed: 26 July 2016.

60. Demetri GD at al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.

61. Park SH et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs. 2012;30(6):2377-83.

62. Yamanaka T et al. Radiofrequency ablation for liver metastasis from gastrointestinal stromal tumor. J Vasc Interv Radiol. 2013;24(3):341-6.

63. Serralta AS et al. Combined liver transplantation plus imatinib for unresectable metastases of gastrointestinal stromal tumours. Eur J Gastroenterol Hepatol. 2004;16(11): 1237-9.

64. DeMatteo RP et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097-104.

65. Joensuu H et al. Twelve versus 36 months of adjuvant imatinib as treatment of operable GIST with a high risk of recurrence: final results of a randomized trial (SSGXVIII/AIO). Abstract LBA1. ASCO Annual Meeting, 2011.

66. Verweij J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet. 2004;364(9440):1127-34.

67. Rankin C et al. Dose effect of imatinib (IM) in patients (pts) with metastatic GIST – Phase III Sarcoma Group Study S0033. Abstract 9005. ASCO Annual Meeting Proceedings. 2004;22(14):9005.

68. Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.

SOMATIC MUTATIONS IN MYELODYSPLASTIC SYNDROME PATIENTS IN THE CONTEXT OF ALLOGENEIC STEM CELL TRANSPLANTATION

***Olga Blau,[1,2] Rolf Schwarzer,[2] Igor Wolfgang Blau[1]**

1. Department of Hematology, Oncology and Tumourimmunology, Charité Universitätsmedizin Berlin, Berlin, Germany
2. Department of Molecular Genetics in Hematology, Labor Berlin, Berlin, Germany
**Correspondence to olga.blau@charite.de*

Disclosure: The authors have declared no conflicts of interest.
Received: 23.02.16 **Accepted:** 13.05.16
Citation: EMJ Oncol. 2016;4[1]:122-129.

ABSTRACT

Myelodysplastic syndrome (MDS) is a heterogeneous group of myeloid disorders. Allogeneic stem cell transplantation (alloSCT) is the therapeutic approach with a known curative potential for patients with MDS, which allows long-term disease control to be achieved. Despite advances in transplantation technology, there is still a considerable morbidity and mortality associated with this approach. Moreover, numerous controversies still exist regarding alloSCT in MDS. There is significant variability in the management of patients with MDS, especially of the intermediate-risk category and specifically in regards to the timing and use of transplantation. Modern genetic analysis has identified a variety of new mutations, which are associated with clinical phenotype and prognosis. Whether somatic mutations are important prognostic markers of response to alloSCT is little known. It is not clear whether somatic mutations can help to identify groups that are most likely to benefit from alloSCT. In this article, we review the current status of somatic mutations in MDS and focus on the prognostic impact of mutations in the context of alloSCT.

Keywords: Myelodysplastic syndrome (MDS), somatic mutations, allogeneic stem cell transplantation (alloSCT).

INTRODUCTION

Myelodysplastic syndromes (MDSs) are a clinically and molecularly heterogeneous group of clonal stem cell disorders characterised by ineffective and dysplastic myeloid cell differentiation and a high rate of progression to acute myeloid leukaemia (AML). Treatment options for MDS range from observation and growth-factor therapy to more intensive approaches, such as allogeneic stem cell transplantation (alloSCT).[1,2] AlloSCT is the only therapeutic option that has the potential to produce long-term remission and disease-free survival.[3] Furthermore, introduction of reduced intensity conditioning decreased non-relapse mortality, especially in older patients.[4] Nevertheless, alloSCT is a high-risk procedure that is often associated with severe complications.

The main cause of treatment failure in MDS patients after alloSCT is relapse of disease. Although significantly reduced over the last 20 years, mortality and morbidity risks associated with alloSCT continue to represent a major limit to feasibility in a large number of patients.[5] The international prognostic scoring system and the revised version (IPSS-R) are usually used to determine risk stratification.[6,7] Recently it was demonstrated that alloSCT offers optimal survival benefit when it is performed early in the intermediate-risk stage.[8] Other studies have shown that poor and very poor-risk of cytogenetics within the IPSS-R cytogenetic risk categories are strong predictors of adverse outcomes after alloSCT, especially when other risk factors are considered simultaneously.[7]

Table 1: Most common somatic mutations in myelodysplastic syndrome patients.

Mutations	Frequency (%)	Typical clinical phenotype	Prognostic impact	Prognostic impact after alloSCT
RNA splicing machinery				
SF3B1	15–30	RARS	Good overall survival, low-risk of leukaemic evolution	No data
SRSF2	10–20	RCMD, RAEB	Poor overall survival, high-risk of leukaemic evolution	Not shorter OS after alloSCT[37]
U2AF1	5–10	RCMD, RAEB	High-risk of leukaemic evolution	Not shorter OS after alloSCT[37]
ZRSR2	5–10	Subtypes without ring sideroblasts	Shorter OS in co-existing with *TET2* mutation	No data
DNA methylation				
TET2	19–26	All MDS subtypes	No impact on OS, predict response to hypomethylating agents	Shorter OS after alloSCT[19] No prognostic impact[48]
DNMT3A	5–18	All MDS subtypes	Adverse outcome in RCMD and RAEB, but not in RARS	Shorter OS after alloSCT[19] No prognostic impact[48]
IDH1/IDH2	2–9	RCMD, RAEB	Adverse outcome	No prognostic impact[48]
Chromatin modification				
ASXL1	15–20	RCMD, RAEB	Adverse outcome	No prognostic impact[48]
EZH2	5–8	RCMD, RAEB	Adverse outcome	No data
Transcription factors				
RUNX1	5–15	RCMD, RAEB	Adverse outcome	No prognostic impact[48]
BCOR	2–4	RCMD, RAEB	Adverse outcome	No prognostic impact[48]
DNA repair control				
TP53	5–10	Advanced stage of disease, complex karyotype, often in MDS with deletion of the q arm of chromosome 5	Poor overall survival, high-risk of leukaemic evolution, predicts poor response to lenalidomide in MDS with deletion of the q arm of chromosome 5	Shorter OS after alloSCT[19]

OS: overall survival; MDS: myelodysplastic syndrome; alloSCT: allogeneic stem cell transplantation; RARS: refractory anaemia with ring sideroblasts; RCMD: refractory cytopenias with multilineage dysplasia; RAEB: refractory anaemia with excess blasts.

Further disease characteristics such as peripheral cytopenias and a high percentage of blasts in the bone marrow have been shown to affect the prognosis of patients with MDS after alloSCT. Moreover, age-related factors significantly affect the risk of the non-relapse mortality.[9,10] Further successful treatment with hypomethylating agents has been shown to be associated with better

outcome after alloSCT.[11] Due to the fact that MDS has a highly variable course of disease, accurate risk stratification and prognosis becomes crucial for therapeutic decision-making. Selection of patients and choosing the optimal timing of transplantation are areas which require further research to improve use of alloSCT in MDS.

The mutation status of a growing number of genes has recently been found to be an important prognostic factor in MDS patients.[2,4,12-14] Although the prognostic value of mutations has been well studied, little is known about the predictive impact of specific genetic lesions in MDS patients on outcome after alloSCT. In this review, we focus on the prognostic impact of somatic mutations in MDS patients in the context of alloSCT.

MUTATION IN MYELODYSPLASTIC SYNDROMES

Phenotypic heterogeneity of MDS reflects different somatic mutations that cause clonal proliferation and evolution. High-throughput molecular technologies, such as next generation sequencing and high-density single nucleotide polymorphism arrays, provide opportunities for patient stratification and personalised treatment based on individual mutation profiles. Recent genetic analyses have identified a variety of new mutations which present at distinct frequencies in subgroups of patients with MDS.[2,14-17] With the advent of next-generation sequencing recurrent somatic mutations are observed in >90% of patients with MDS, with the number of driver mutations having an independent prognostic impact.[2,4,18,19] Mutations in several genes have been reported to influence overall survival (OS) and risk of disease progression.[2,4,12-14] Knowledge about the nature of genes involved in the mutations may improve the understanding of the evolution and development of MDS.[14] In MDS, somatic mutations affect specific classes of genes. The most common mutations detected in MDS patients include RNA splicing machinery, DNA methylation, chromatin modification, transcription regulation, and DNA damage response (Table 1).

RNA SPLICING MACHINERY

The editing process during transcription of DNA into RNA, which involves removal of non-coding regions, introns, is called splicing.[20] RNA splicing is the most frequently mutated pathway in MDS. The most commonly affected spliceosome genes included *SF3B1* (splicing factor 3b subunit 1), *U2AF1* (U2 small nuclear RNA auxiliary factor 1), *U2AF2* (U2 small nuclear RNA auxiliary factor 2), *SRSF2* (serine/arginine-rich splicing factor 2), *ZRSR2* (zinc finger [CCCH type], RNA binding motif, and serine/arginine rich 2), and some others.[16,18,21-24] Splicing factor mutations, particularly in *SF3B1, U2AF1, SRSF2*, and *ZRSR2*, are present in 50–65% of MDS cases, making them the most common class of mutations in MDS.[18,21,24-26] Mutations in the other spliceosome genes (*U2AF2, SF1, PRPF40B*, and *SF3A1*) occurred with a frequency of ≤1%.[21,23,25,27,28]

A growing body of evidence demonstrates that splice gene mutations define distinct clinical phenotypes and show preferential associations with mutations targeting transcriptional regulation. Recent findings support the role of spliceosome mutations as early mutations that interact with other clonal and sub-clonal events within the same genes during leukaemogenesis in patients with MDS.[29]

SF3B1

SF3B1, together with other factors, forms the U2 small nuclear ribonucleoproteins complex and binds pre-mRNA. Recurrent mutation of the *SF3B1* gene was found in 20–35% of MDS patients and in 70% of MDS patients whose disease is characterised by the presence of ring sideroblasts (in refractory anaemia with ring sideroblasts [RARS]),[4,18,21,22,30,31] although the clonal dominance of mutations in granulocytic cells suggests that oncogenic effects may not be restricted to the erythroid lineage.[21] It was noted that *SF3B1* mutations were frequently associated with an isolated deletion of the q arm of chromosome 5.[18] *SF3B1* mutations are associated with a better clinical outcome.[4] There are no data about the predictive impact of this mutation on outcome after alloSCT. Given the frequent combination of *SF3B1* mutation with favourable prognostic markers and with good clinical outcome, the presence of *SF3B1* mutations as a single aberration should not be an indication for alloSCT.

SRSF2

The protein SRSF2 forms part of the spliceosome. This protein is important for splice-site selection, spliceosome assembly, and both constitutive and alternative splicing.[32] *SRSF2* is currently the second most frequently mutated splicing gene in

the myeloid diseases.[18,33] These genetic aberrations are almost always heterozygous missense mutations that specifically occur at the amino acid residue P95. In MDS, an *SRSF2* mutation was detected in approximately 10% of cases. They are most often observed in refractory cytopenia with multilineage dysplasia (RCMD) and refractory anaemia with excess blasts (RAEB), two subtypes of high-risk MDS.[13,27] In chronic myelomonocytic leukaemia (CMML), *SRSF2* is the most commonly mutated spliceosome gene (28–47%) and has been associated with older age, less pronounced anaemia, and a normal karyotype.[25,33]

MDS harbouring an *SRSF2* mutation is associated with a higher rate of transformation to AML and with lower OS compared with MDS with wild-type *SRSF2*.[30] However, more recently, the frequency of complex karyotypes and adverse cytogenetic risk aberrations were found to be higher in patients with *SRSF2* mutations than in MDS patients with other mutations.[29] Although this mutation was found to be associated with a poor prognosis,[30] significant difference in OS between wild-type and mutated *SRSF2* in transplanted patients was not detected.[34]

U2AF1

U2AF1 encodes the auxiliary factor for the U2 pre-mRNA splicing complex. Eleven distinct mutations have been reported in the *U2AF1* gene.[28,30,35,36] Most of these mutations occur within the two zinc finger domains of *U2AF1*, with S34 and Q157 residues.[34] Using mouse models it was shown that *U2AF1* mutations drive further mutation.[37] In MDS, *U2AF1* mutations are seen in <10% of patients. Although *U2AF1* mutations have been associated with less favourable OS and a higher risk of transformation to AML,[13,23] it is not clear whether the mutation has independent prognostic impact.[25,29] The prognostic effect is known to depend on certain biological factors as well as a combination of cytogenetics and other mutations.

Both the *U2AF1* and *SRSF2* mutations have been associated with poor outcome.[23] Recently, two groups reported no difference in survival between mutated splicing genes and wild-type Wilms' tumour patients undergoing alloSCT.[19,34] Despite some limitations, such as a heterogeneous cohort of patients, these studies provide preliminary evidence to support the theory that alloSCT may potentially reduce the effects of certain poor-risk somatic mutations recurring in MDS.[34]

ZRSR2

ZRSR2 encodes an essential splicing factor which functions in early spliceosome assembly through direct interactions with *U2AF2*.[38] Mutations of the *ZRSR2* gene are present in 10–15% of MDS cases.[18,28] In contrast to other spliceosome gene mutations, *ZRSR2* mutations occur across the entire length of the transcript. Mutations in *ZRSR2* are more prevalent in MDS subtypes without ring sideroblasts and CMML.[25,28] Some authors have shown that *ZRSR2* mutations are associated with an elevated percentage of bone marrow blasts and higher rates of progression to AML.[25,28] However, this was not confirmed by other studies. Furthermore, it was shown that the prognostic impact of *ZRSR2* mutations depends on the mutation status of *TET2*, the gene most commonly combined with *ZRSR2* mutations.[30] There are no data about the prognostic impact of *ZRSR2* mutations on outcome after alloSCT.

DNA METHYLATION

Epigenetic regulation refers to methylation of cytosine residues of DNA, biochemical modifications of histones, and the expression of non-coding RNAs.[39] Mutations in the epigenetic modifiers are of particular importance in MDS.

Ten-Eleven Translocation

The ten–eleven translocation (TET) protein family is responsible for demethylation.[40] In addition, TETs regulate gene expression through modification of chromatin at promoter regions.[41] *TET2* is a tumour suppressor gene, and so loss-of-function mutations support the abnormal haematopoiesis observed in MDS.[42] In MDS, *TET2* mutations affect 19–26% of MDS patients.[43] *TET2* mutations are observed in all types of MDS.[13,44] The clinical implication of *TET2* mutations remains unclear. *TET2* mutations are a neutral or favourable prognostic biomarker[44,45] and have been shown to predict response to hypomethylating therapy in MDS.[43] Some studies demonstrated a higher overall response rate to azacitidine treatment in *TET2* mutated cases with no difference in OS.[46,47]

In MDS patients following alloSCT, *TET2* mutations are associated with shorter OS. Taking into account other risk factors, such as complex karyotype,

high level of bone marrow blasts, donor type, and conditioning regimen, *TET2* mutations together with *TP53* and *DNMT3A*, are significantly associated with shorter OS.[19] However in another study, *TET2* mutations showed no prognostic impact in MDS patients uniformly treated with FLAMSA-busulfan conditioning.[48]

DNMT3A

DNMT3A (DNA methyltransferases 3A) together with other methyltransferases conducts *de novo* methylation of cytosine residues in CpG islands.[49,50] *DNMT3A* mutations occur in approximately 5–18% of MDS patients with the most common mutation involving R882 amino acid residue.[19,43,51,52] These mutations can be found in all MDS subtypes.[13] *DNMT3A* mutations are associated with older age at diagnosis but not with other clinical features or cytogenetics.[52] In RARS, *DNMT3A* mutations more commonly co-operate with *SF3B1* mutations.[13]

Some studies have shown an adverse clinical outcome with a low survival rate and rapid progression to AML in MDS patients with *DNMT3A* mutations.[52] Moreover, it was found that *DNMT3A* mutations have been associated with poor outcomes in some types of MDS, particularly in RCMD and RAEB.[13,52] In RARS, *DNMT3A* mutations often co-occur with *SF3B1* mutations and have no association with adverse outcome.[13,53]

Bejar et al.[19] have identified this mutation as a risk factor, which significantly reduces the OS after alloSCT. The authors observed an increased risk of relapse and death after transplantation, particularly when other predictive variables were considered.[19] In contrast, Christopeit et al.[48] showed no prognostic impact of *DNMT3A* mutations in patients after alloSCT.

IDH1 and IDH2

IDH1 and *IDH2* genes encode cytoplasmic/peroxisomal isocitrate dehydrogenase 1 and mitochondrial isocitrate dehydrogenase 2, respectively. These are $NADP^+$-dependent enzymes that catalyse the oxidative decarboxylation of isocitrate to α-ketoglutarate, generating NADPH from $NADP^+$. Both genes function in a crossroads of cellular metabolism, cellular defence against oxidative stress, oxidative respiration, and oxygen-sensing signal transduction.[54] In MDS, somatic mutations in *IDH1/2* occur in 2–9% of patients.[45,55-58] Mutations preferentially affected the *IDH2* gene. Since these mutations were discovered in early MDS, prior to AML transformation, it has been suggested that *IDH* mutations, especially *IDH2*, may contribute to the pathogenesis of MDS.[56]

The simultaneous presence of *IDH* mutations with other genetic changes is commonly observed in myeloid neoplasms.[57] The close association of *IDH2* mutations with *ASXL1, DNMT3A,* and *SRSF2* suggests that *IDH2* mutations can interact with these aberrations in the development of MDS.[57] The prognostic implication of *IDH* mutations in MDS remains unclear. Some studies have shown an adverse clinical outcome in MDS patients with *IDH* mutations.[45,58] Furthermore, two studies demonstrated *IDH1* mutation as an independent predictor of inferior survival.[55,59] Very little is known about the prognostic impact of *IDH1/2* mutations in MDS patients after alloSCT. Only one study has examined this relationship and suggests that there is no prognostic significance of these mutations.[48]

CHROMATIN MODIFICATION

Two genes involved in chromatin modification and regulation are recurrently mutated in MDS: *ASXL1* (additional sex combs like 1) and *EZH2* (enhancer of zeste 2 polycomb repressive complex 2), which encode chromatin-modifying proteins and interact with the polycomb-group repressive complex 1 and 2. Genomic loss of *EZH2* contributes to overexpression of the Hox gene clusters in MDS through epigenetic modifications.[60] Both mutations are most often observed in higher-risk subtypes of MDS such as RCMD and RAEB.[13,61]

ASXL1 and EZH2

ASXL1 and *EZH2* mutations are closely associated with myeloproliferative disorders. In MDS, *ASXL1* mutations are found in 15–20% of patients.[45,61] These mutations are generally associated with signs of aggressive progression and poor clinical outcome.[45] Mutations of *EZH2* occur in 5–8% of MDS patients.[13,45] Previously, it was reported that *EZH2* mutations are a prognostic biomarker, associated with shorter OS.[45] Although there are no reports on the effect of *ASXL1* and *EZH2* mutations on outcome after alloSCT, the overall relationship of these mutations with poor outcome may be important for risk stratifications.

TRANSCRIPTION REGULATION

Runt-related transcription factor 1 (RUNX1) protein takes part in regulating the expression of multiple

genes involved in normal haematopoiesis.[62,63] *RUNX1* mutations occur in 5–15% of MDS patients,[18,64] and are most often observed in RCMD and RAEB.[13] *RUNX1* mutations are detected during disease progression. Furthermore, this mutation is significantly increased even in secondary AML following MDS. The acquisition of additional mutations in genes such as *MLL-PTD* or *FLT3-ITD* with *RUNX1* appears to be an event precipitating leukaemic transformation.[65] *RUNX1* mutations are associated with unfavourable clinical outcomes.[45] Little is known about the prognostic impact of this mutation after alloSCT. In one cohort of MDS patients uniformly treated with FLAMSA-busulfan conditioning, *RUNX1* mutations showed no prognostic impact.[48]

BCOR (*BCL6* corepressor) and *BCORL1* (BCL6 corepressor-like 1) code for related transcriptional corepressors, that are found tethered to promoter regions by DNA-binding proteins. The proteins interact with several different Class II histone deacetylases to repress transcription. Recently, sequencing of *BCOR* genes in MDS patients identified 2–4% of mutations.[66] *BCOR* mutations are often associated with *RUNX1* and *DNMT3A* mutations. These data suggest that *BCOR* mutations define the clinical course rather than disease initiation.[66,67] In MDS, *BCOR* mutations are associated with adverse outcome, shorter OS, and higher incidence of AML transformation.[66]

DNA REPAIR CONTROL

Tumour protein p53 (TP53) is a tumour suppressor protein that regulates expression of genes involved in cell cycle arrest, apoptosis, senescence, DNA repair, and changes in metabolism.[68] *TP53* is the most frequently mutated gene in many types of cancer. In MDS, *TP53* mutations occur in 5–10% of cases.[13,45] These mutations are most often observed in patients with advanced disease, complex karyotype, or adverse karyotype aberrations.[13,45] MDS patients carrying *TP53* mutation have an unfavourable clinical outcome and a high risk of leukaemic evolution.[4,45]

Bejar et al.[19] have analysed somatic mutations as a potential risk factor in MDS patients following alloSCT. In this analysis, only mutations in *TP53* were significantly associated with shorter OS and progression-free survival. *TP53* mutations are closely associated with complex karyotype. However, in patients with complex cytogenetics, *TP53* mutation showed significantly shorter OS. In contrast, patients with complex cytogenetics without *TP53* mutation had OS comparable to that of patients without complex cytogenetics.[19] Moreover, there are data demonstrating that *TP53* mutations in low-risk MDS with deletion of the long arm of chromosome 5 treated with lenalidomide are associated with an increased risk of leukaemic evolution.[69] In view of the above, this group of low-risk MDS patients could be candidates for alloSCT.

CONCLUSIONS

Currently, little is known about the prognostic value of mutations in MDS patients in the context of alloSCT. Several groups studied the role of alloSCT to overcome the negative impact of mutations in MDS patients. Bejar et al.[19] have found that *TP53, TET2*, and *DNMT3A* mutations are significantly associated with shorter OS following alloSCT. Importantly, the authors observed no adverse prognostic signs such as cytogenetics or bone marrow blasts percentage before transplantation in *DNMT3A* and *TET2* mutated cases. Nevertheless, after alloSCT these patients had an increased risk of relapse and death, particularly when other predictive variables were considered. In this study, *TP53* mutation status was the most significant predictor of mortality after transplantation.

Christopeit et al.[48] analysed MDS patients treated with FLAMSA-busulfan sequential conditioning and alloSCT. *RUNX1, GATA2, TET2,* and *CEBPA* and *TP53* mutations were the most frequently observed in this cohort. None of the mutations showed a prognostic impact in this analysis. Recently, Hamilton et al.[37] examined the effect of alloSCT on the negative prognostic impact of *U2AF1* and *SRSF2* mutations in MDS patients. They reported no difference in survival between mutated splicing genes and wild-type patients undergoing transplantation. Thus, the authors suggest that patients with such mutations could benefit from alloSCT.

All reports have some limitations, such as heterogeneity of patients, conditioning, and others. Despite these limitations, some analysis has provided preliminary evidence to support the hypothesis that alloSCT may mitigate the effects of certain poor risk somatic mutations. In general, somatic mutations such as *TP53, TET2*, and

DNMT3A in MDS patients might be important predictors for adverse outcome after alloSCT.[19,37]

MDS is characterised by mutations in >40 genes. The complex structure of gene crosstalk, multiple mutations, and extensive sub-clonal architecture are common for MDS.[4,25] Recent genetic analysis of large populations revealed some somatic mutations in healthy people in advanced age. These findings support the hypothesis that mutations in genes such as *DNMT3A, ASXL1, TET2*, and others are likely to be initiating events for MDS and/or AML.[17,70-72] These mutations can confer an increased risk of subsequent haematological malignancy diagnosis as well as higher all-cause mortality.[17] The discovery of these mutations in elderly patients with low-risk MDS should be considered in risk stratification very carefully.

Accurate risk stratification, patient selection, and timing of alloSCT are frequently difficult in MDS. The decision on whether or not alloSCT is indicated can be challenging. Integration of somatic mutations into prognostic scoring systems may facilitate risk stratification of individual patients and further refine clinical decision-making in MDS.

REFERENCES

1. de Witte T et al. Value of allogeneic versus autologous stem cell transplantation and chemother-apy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomized European Intergroup Trial. Haematologica. 2010;95(10):1754-61.

2. Malcovati L et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: Recommendations from the European LeukemiaNet. Blood. 2013;122(17):2943-64.

3. Scott BL et al. Results of a Phase III randomized, multi-center study of allogeneic stem cell transplantation after high versus reduced intensity conditioning in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): Blood and Marrow Transplant Clinical Trials Net-work (BMT CTN) 0901. Blood. 2015;126(23):LBA-8.

4. Papaemmanuil E et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616-27.

5. Gooley TA et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010 ;363(22):2091-101.

6. Della Porta MG et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood. 2014;123(15):2333-42.

7. Koenecke C et al. Impact of the revised International Prognostic Scoring System, cytogenetics and monosomal karyotype on outcome after allogeneic stem cell transplantation for myelodysplastic syndromes and secondary acute myeloid leukemia evolving from myelodysplastic syndromes: A retrospective multicenter study of the European Society of Blood and Marrow Transplantation. Haematologica. 2015;100(3):400-8.

8. Alessandrino EP et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. Am J Hematol. 2013;88(7):581-8.

9. Schneidawind D et al. Reduced-intensity conditioning with fludarabine and busulfan for allogeneic hematopoietic cell transplantation in elderly or infirm patients with advanced myeloid malignancies. Ann Hematol. 2016;95(1):115-24.

10. Heidenreich S et al. Allogeneic stem cell transplantation for MDS patients more than 70 years of age: A retrospective study of the MDS Subcommittee of the Chronic Malignancies Working Party (CMWP) of the EBMT. Blood. 2015;126(23):4390.

11. Oran B et al. Cytogenetics, donor type, and use of hypomethylating agents in myelodysplastic syndrome with allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(10):1618-25.

12. Garcia-Manero G. Myelodysplastic syndromes: 2015 Update on diagnosis, risk-stratification and management. Am J Hematol. 2015;90(9):831-41.

13. Cazzola M et al. The genetic basis of myelodysplasia and its clinical relevance. Blood. 2013;122(25):4021-34.

14. Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. Blood. 2014;124(18): 2793-803.

15. Vogelstein B et al. Cancer genome landscapes. Science. 2013;339(6127): 1546-58.

16. Jhanwar SC. Genetic and epigenetic pathways in myelodysplastic syndromes: A brief overview. Adv Biol Regul. 2015; 58:28-37.

17. Steensma DP et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9-16.

18. Haferlach T et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28(2):241-7.

19. Bejar R et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32(25):2691-8.

20. Wahl MC et al. The spliceosome: Design principles of a dynamic RNP machine. Cell. 2009;136(4):701-18.

21. Papaemmanuil E et al. Somatic SF3B1 Mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011; 365(15):1384-95.

22. Malcovati L et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood. 2015;126(2):233-41.

23. Makishima H et al. Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. Blood. 2012;119(14):3203-10.

24. Visconte V et al. SF3B1 haploinsufficiency leads to formation of ring sideroblasts in myelodysplastic syndromes. Blood. 2012;120(16):3173-86.

25. Yoshida K et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011;478(7367): 64-9.

26. Mian SA et al. Spliceosome mutations exhibit specific associations with epigenetic modifiers and proto-oncogenes mutated in myelodysplastic syndrome. Haematologica. 2013;98(7):1058-66.

27. Larsson CA et al. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. Mol Cancer Res. 2013;11(8):815-27.

28. Damm F et al. Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. Blood. 2012;119(14):3211-8.

29. Cho YU et al. Preferential occurrence of spliceosome mutations in acute myeloid leukemia with preceding myelodysplastic syndrome and/or myelodysplasia morphology. Leuk Lymphoma. 2015; 56(8):2301-8.

30. Thol F et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood. 2012;119(15):3578-84.

31. Dolatshad H et al. Disruption of SF3B1 results in deregulated expression and splicing of key genes and pathways in myelodysplastic syndrome hematopoietic stem and progenitor cells. Leukemia. 2015;29(8):1798.

32. Long JC, Caceres JF. The SR protein family of splicing factors: master regulators of gene expression. Biochem J. 2009;417(1):15-27.

33. Meggendorfer M et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood. 2012;120(15):3080-8.

34. Hamilton BK et al. Impact of allogeneic hematopoietic cell transplant in patients with myeloid neoplasms carrying spliceosomal mutations. Am J Hematol. 2016. [Epub ahead of print].

35. Okeyo-Owuor T et al. U2AF1 mutations alter sequence specificity of pre-mRNA binding and splicing. Leukemia. 2015; 29(4):909-17.

36. Walter MJ et al. Clonal diversity of recurrently mutated genes in myelodysplastic syndromes. Leukemia. 2013;27(6):1275-82.

37. Shirai Cara L et al. Mutant U2AF1 expression alters hematopoiesis and pre-mRNA splicing in vivo. Cancer Cell. 2015;27(5):631-43.

38. Madan V et al. Aberrant splicing of U12-type introns is the hallmark of ZRSR2 mutant myelodysplastic syndrome. Nat Commun. 2015;6:6042.

39. Eriksson A et al. Epigenetic aberrations in acute myeloid leukemia: Early key events during leukemogenesis. Exp Hematol. 2015;43(8):609-24.

40. Ito S et al. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. Nature. 2010;466(7310):1129-33.

41. Chen Q et al. TET2 promotes histone O-GlcNAcylation during gene transcription. Nature. 2013;493(7433): 561-4.

42. Solary E et al. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014;28(3):485-96.

43. Traina F et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. Leukemia. 2014;28(1):78-87.

44. Kosmider O et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood. 2009;114(15):3285-91.

45. Bejar R et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364(26):2496-506.

46. Itzykson R et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia. 2011;25(7):1147-52.

47. Pollyea DA et al. Impact of TET2 mutations on mRNA expression and clinical outcomes in MDS patients treated with DNA methyltransferase inhibitors. Hematol Oncol. 2011;29(3):157-60.

48. Christopeit M et al. Correlation of somatic mutations with outcome after FLAMSA-busulfan sequential conditioning and allogeneic stem cell transplantation in patients with MDS. Eur J Haematol. 2015. [Epub ahead of print].

49. Jasielec J et al. The mechanistic role of DNA methylation in myeloid leukemogenesis. Leukemia. 2014;28(9): 1765-73.

50. Li KK et al. DNA methyltransferases in hematologic malignancies. Semin Hematol. 2013;50(1):48-60.

51. Schroeder MA, DeZern AE. Do somatic mutations in de novo MDS predict for response to treatment? Hematology Am Soc Hematol Educ Program. 2015; 2015(1):317-28.

52. Walter MJ et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. Leukemia. 2011;25(7):1153-8.

53. Bejar R et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. J Clin Oncol. 2012;30(27):3376-82.

54. Reitman ZJ, Yan H. Isocitrate dehydrogenase 1 and 2 mutations in cancer: Alterations at a cross-roads of cellular metabolism. J Natl Cancer Inst. 2010;102(13):932-41.

55. Thol F et al. IDH1 mutations in patients with myelodysplastic syndromes are associated with an unfavorable prognosis. Haematologica. 2010;95(10):1668-74.

56. Kosmider O et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. Leukemia. 2010;24(5):1094-6.

57. Lin CC et al. IDH mutations are closely associated with mutations of DNMT3A, ASXL1 and SRSF2 in patients with myelodysplastic syndromes and are stable during disease evolution. Am J Hematol. 2014;89(2):137-44.

58. Lin J et al. IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. Ann Hematol. 2011;91(4): 519-25.

59. Patnaik MM et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic Study of 277 patients. Leukemia. 2012;26(1):101-5.

60. Xu F et al. Genomic loss of EZH2 leads to epigenetic modifications and overexpression of the HOX gene clusters in myelodysplastic syndrome. Oncotarget. 2016;7(7):8119-30.

61. Abdel-Wahab O et al. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell. 2012;22(2):180-93.

62. Kurokawa M, Hirai H. Role of AML1/Runx1 in the pathogenesis of hematological malignancies. Cancer Sci. 2003;94(10):841-6.

63. Taniuchi I, Littman DR. Epigenetic gene silencing by Runx proteins. Oncogene. 2004;23(24):4341-5.

64. Harada H et al. High incidence of somatic mutations in the AML1/RUNX1 gene in myelodysplastic syndrome and low blast percentage myeloid leukemia with myelodysplasia. Blood. 2004;103(6): 2316-24.

65. Dicker F et al. Mutation analysis for RUNX1, MLL-PTD, FLT3-ITD, NPM1 and NRAS in 269 patients with MDS or secondary AML. Leukemia. 2010;24(8): 1528-32.

66. Damm F et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. Blood. 2013;122(18): 3169-77.

67. Yamamoto Y et al. Clarifying the impact of polycomb complex component disruption in human cancers. Mol Cancer Res. 2014;12(4):479-84.

68. Brosh R, Rotter V. When mutants gain new powers: News from the mutant p53 field. Nat Rev Cancer. 2009;9(10):701-13.

69. Jadersten M et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol. 2011;29(15):1971-9.

70. Xie M et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472-8.

71. Jaiswal S et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26): 2488-98.

72. Genovese G et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477-87.

PALLIATIVE RADIOTHERAPY AND HORMONAL DEPRIVATION FOR PROSTATE CANCER INDUCED URINARY OBSTRUCTION AT A SUB-SAHARAN TERTIARY HOSPITAL

***Sam Kaggwa,[1] Israel Luutu,[2] Moses Galukande[1]**

1. Department of Surgery, College of Health Sciences, Makerere University, Kampala, Uganda
2. Department of Radiotherapy, Mulago National Referral Hospital, Kampala, Uganda
**Correspondence to sam.kaggwa@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 23.10.15 **Accepted:** 20.04.16
Citation: EMJ Oncol. 2016;4[1]:130-133.

ABSTRACT

The occurrence of bladder outlet obstruction (BOO) in men with prostate cancer is common. Although relieving the obstruction may not change prognosis, it is highly valued by patients and is generally associated with improvement in general functioning and wellbeing in the short-term. The aim of this study was to assess the efficacy of high-dose external beam radiation therapy (EBRT) combined with bilateral subcapsular orchidectomy (BSO) to relieve BOO due to prostate cancer.

A retrospective study design was employed and conducted at the Mulago National Referral Hospital. Records of all patients with high-risk prostate cancer who presented with urinary obstructive symptoms and treated with the BSO and EBRT were retrieved. The study variables were age, clinical stage, and pathological Gleason score. The endpoint of the study was for patients to be able to pass urine after removing the urethral catheter, analysed as follows: complete failure to pass urine; partial emptying with a post-void volume >100 mL, and passing urine with complete emptying and a post-void volume <100 mL.

In total, 46 patients were analysed in the period of January 2011–December 2012. Mean age was 71 years (range: 63–93). Eight patients failed to pass urine, while six passed urine incompletely (partial emptying). Thirty-two passed urine with a good stream and emptied the bladder completely. The success rate was 32/46 (70%). All patients had T3 and T4 stage disease with Gleason scores >8. In conclusion, orchidectomy combined with EBRT was found to be an effective and feasible option for relieving BOO due to prostate cancer.

Keywords: Prostate cancer, bladder outlet obstruction (BOO), palliative radiotherapy.

INTRODUCTION

Non-communicable diseases, including cancers, are becoming increasingly important as causes of morbidity and mortality in Sub-Saharan Africa, including Uganda. Cancer of the prostate is the most common malignancy in males in Uganda.[1] It is most prevalent in the sixth and seventh decades of life, as it is elsewhere in the world.[2] Bladder outlet obstruction (BOO) is a common presentation in men with high-risk prostate cancer.[3] Whereas the prevalence of advanced and metastatic disease is reduced in high-income countries, this is not the case in low-income countries, especially in Sub-Saharan Africa, where cancer screening services are almost non-existent and access to cancer treatment is limited.[4]

Immediate relief is usually obtained by either suprapubic catheter or an indwelling urethral catheter.[5] Prolonged catheterisation has a major impact on quality of life (QoL) in addition to the risk of urinary tract infections.[5-7] Definitive treatment of the obstruction, according to the standard practice pattern in many countries, is a channel transurethral resection of the prostate (TURP).[8]

Some concerns have been raised about channel TURP and these include intractable postoperative bleeding, prostatorectal fistula, and re-obstruction due to regrowth of the tumour.[9]

There is evidence that urinary obstruction caused by prostate cancer can be relieved by irradiation, however the results of combining radiotherapy and orchidectomy have not been assessed.[10] Given the decreasing incidence of BOO due to prostate cancer in general, this applies mostly to middle and high-income countries. Only a few articles have been published recently on obstructive uropathy from prostate cancer.[11]

This study reports relief of BOO from a combination of bilateral subcapsular orchidectomy (BSO) and external beam radiation therapy (EBRT) in a resource-limited setting.

METHODS

Design

This was a retrospective descriptive study.

Table 1: Age and study outcomes: Palliative Radiotherapy and Hormonal Deprivation Ugandan Study for Prostate Cancer 2015.

Variable	Number
Age	
Mean	71 years
Range	63–93 years
Outcomes	
Complete failure to pass urine	5
Partially emptying and short retention	3
Partially emptying post-void >100 mL	6
Complete empty post-void <100 mL	32
EBRT*	30–45 Gy
Pathologic stage	
T2	0
T3/T4	46
Pathologic Gleason scores	
≤6	0
7	0
≥8	46

EBRT: external beam radiation therapy.
*EBRT in 10–15 fractions.

Setting

This work was conducted at an urban teaching hospital in Kampala, Uganda: a Sub-Saharan Africa resource-limited environment. The Mulago National Referral Hospital is a 1,500 bed hospital with numerous subspecialised units, including urological services, which are largely provided free of charge in this public hospital.

Eligibility

Records of all patients with BOO, as a result of high-risk prostate cancer, who had attended the urology clinic between 4th January 2011 and 31st December 2012, were retrieved and reviewed. A list generated from the operating theatre log of patients who had undergone BSO was used to retrieve the patient files from the records department archives.

The diagnosis of cancer had been proven by histological diagnosis after findings of raised prostate surface antigen (PSA) and digital rectal examination that revealed locally advanced disease. BOO was defined as a self-reported situation when a patient diagnosed with prostate cancer could not void urine partially or completely.

Conventional External Beam Radiation Therapy

Two weeks after BSO, EBRT was delivered by means of a two-field technique. The fields were antero-posterior, postero-anterior, and were designed to include the prostate, the seminal vesicles, and the regional lymphatic channels. EBRT was delivered in 10–15 fractions to a total dose of 35–45 Gy. Two weeks after irradiation, the catheter was removed.

Study Variables

The main outcome measure was the ability to pass urine through the urethra. Other variables such as haematoma, bladder stones, and hydronephrosis were not captured.

Those who reported passing urine satisfactorily underwent an ultrasound examination to assess the post-void residual urine volume. A volume >100 mL was considered significant and indicative of incomplete emptying, and therefore considered as treatment failure. Age, Gleason score, and clinical stage were the other study variables considered.

Ethical Considerations

All patients provided written informed consent for all the procedures that were done. Clearance was obtained from the Mulago Hospital Ethics and Research Review Board.

RESULTS

A total of 46 patients were included in the study analysis. The mean age was 71 years with a range between 63 and 93 years. The median follow-up period was 9 months and the range was 6–12 months.

The final outcome measures were as follows: 32 individuals (70%) reported passing urine satisfactorily and had post-void volumes <100 mL while 5 patients (9%) failed to pass urine at all; the remaining 9 patients (11%) were able to pass urine only partially with post-void volumes >100 mL (Table 1). All prostate specimens had pathological Gleason scores ≥8. The stage was T3 or T4. The patients who failed to pass urine had their urethral catheters reinserted.

DISCUSSION

The study set out to investigate the efficacy of BSO and EBRT in relieving BOO in patients with locally advanced prostate cancer in a resource-limited setting. Assessment was limited to ease or completeness of passage of urine. Results showed that 70% of patients were able to satisfactorily pass urine during the follow-up period (which lasted at least 6 months), a similar outcome to several other studies where a high radiation dose was administered.[12,13] Although numerous studies highlight the treatments of early and advanced stage prostate cancer and its complications, there is a paucity of studies specifically investigating androgen deprivation and EBRT for BOO due to prostate cancer,[14] especially in resource-limited environments.

It is important to relieve urinary obstruction as it generally improves QoL;[5-7] long-term effects depend on the severity of the blockage, its acuity, laterality, and the patient's underlying renal function. Obstructive uropathy from prostate cancer most commonly results from bilateral ureteral blockage or unilateral ureteral obstruction in the setting of a solitary renal unit.[11,15] Obstruction has a deleterious impact on tubular function with diminished urinary concentrating ability, which, if left uncorrected, leads to further interstitial inflammation and ultimately fibrosis.[15] Long-standing (>6 weeks) obstruction may not yield much functional benefit, a factor we take into account when making treatment decisions.[11,15]

The diagnosis of obstructive uropathy is made by history and physical examination, often worsening obstructive voiding symptoms are also used, and in some cases acute urinary retention. Urea and electrolyte levels and imaging can confirm renal insufficiency. In practice, contrast imaging is normally avoided to prevent contrast induced nephropathy, which further impairs renal function.[15]

In this series, management was directed to relieving BOO after physiological derangements were corrected to optimise outcomes.[16,17] Initial relief was obtained by inserting a Foley's catheter and the other relief options were EBRT and BSO.

High-dose EBRT slows down biochemical or clinical progression, more so than a conventional-dose radiation, but no EBRT regimen, whether conventional, high-dose conformal, dose fractionated, or hypofractionated, is superior in reducing androgen deprivation to decrease overall disease-specific mortality. In resource-limited settings such as this, the availability of stents or palliative TURP is limited or non-existent.

STUDY LIMITATIONS

Combination therapy was used, which makes it difficult to delineate which modality had a preferable efficacy and to what extent each therapy contributed to the patient outcome. Though we know radiation is slower than endocrine therapy in diminishing prostate cancer biomarker PSA,[18] this does not conclusively delineate the contribution of each modality. The study design was retrospective and may not bring out the other variables of QoL assessment. Uroflowmetric measurements were not taken due to resource limitations.

CONCLUSION

BSO combined with high-dose palliative EBRT was effective in relieving BOO in high-risk prostate cancer patients. It is an alternative to the often unavailable channel TURP procedure or permanent indwelling suprapubic or urethral catheter drainage among men in resource-limited settings.

Acknowledgements

All staff working at the unit are highly appreciated as are patients that participated. Moses Galukande is supported by THRiVE/Wellcome Trust.

REFERENCES

1. Parkin DM et al. Changing cancer incidence in Kampala, Uganda, 1991-2006. Int J Cancer. 2010;126(5):1187-95.

2. Wabinga HR et al. Trends in cancer incidence in Kyadondo County, Uganda 1960-1997. Br J Cancer. 2000;82(9): 1585-92.

3. Catalona WJ et al. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. JAMA. 1993;270(8):948-54.

4. Ung JO et al. Evolution of the presentation and pathologic and biochemical outcomes after radical prostatectomy for patients with clinically localized prostate cancer diagnosed during the PSA era. Urology. 2002;60(3): 458-63.

5. Willete PA, Coffield S. Current trends in the management of difficult urinary catheterizations. West J Emerg Med. 2012; 13(6):472-8.

6. Ghaffary C et al. A practical approach to difficult urinary catheterizations. Curr Urol Rep. 2013;14(6):565-79.

7. Leidberg H. Catheter induced urethral inflammatory reaction and urinary tract infection. An experimental and clinical study. Scan J Urol Nephrol Suppl. 1989; 124:1-43.

8. Mebust WK et al. Transurethral prostatectomy: immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol. 2002; 167(1):5-9.

9. Mazur AW, Thompson IM. Efficacy and morbidity of "channel" TURP. Urology. 1991; 38(6):526-8.

10. Michigan S, Catalona WJ. Ureteral obstruction from prostatic carcinoma: response to endocrine and radiation therapy. J Urol. 1977;118(5):733-8.

11. Friedlander JI et al. Obstructive Uropathy from Locally Advanced and Metastatic Prostate Cancer: Old problem with New Therapies. J Endourol. 2012; 26(2):102-9.

12. Megalli MR et al. External radiotherapy in ureteral obstruction secondary to locally invasive prostatic cancer. Urology. 1974;3(5):562-4.

13. Wilt TJ et al. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med. 2008;148(6): 435-48.

14. Grimm P et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int. 2012;109 Suppl:22-9.

15. Pais VM et al., "Pathophysiology of obstruction," Wein AJ et al. (eds.), Campbell-Walsh: Urology (2006) 2nd edition, Philadelphia: Elsevier Saunders, pp.1195-226.

16. Tseng TY, Stoller ML. Obstructive Uropathy. Clin Geriatr Med. 2009;25(3): 437-43.

17. Kouba E et al. Management of ureteral obstruction due to advanced malignancy: optimizing therapeutic and palliative outcomes. J Urol. 2008;180(2):444-50.

18. Smith JA Jr et al. Complications of advanced prostate cancer. Urology. 1999; 54(6A Suppl):8-14.

UPCOMING EVENTS

European CanCer Organisation (ECCO) European Cancer Congress 2017

27th–30th January 2017

Amsterdam, Netherlands

At Europe's pre-eminent multidisciplinary congress, there will be presentations on the latest developments from single disciplines from a holistic, multidisciplinary perspective, enabling insight into how these developments affect clinical practice. Hot discussions on the organisation and cost of European cancer care are expected as well as a multidisciplinary perspective on patient situations, which will be a broad theme of the congress.

9th Annual Symposium on Clinical Interventional Oncology (CIO)

4th–5th February 2017

Hollywood, Florida, USA

A tightly focussed, practical programme known for its dynamic learning format and focus on patient care will spotlight the most practical and desirable treatments in clinical interventional oncology as well as previewing novel developments in this field. There are a variety of topics that will be considered, including: lymphatic duct intervention, ablation of lymphadenopathy, liver-directed therapy and the role of Y-90, and therapies for the thyroid.

18th European Congress: Perspectives in Lung Cancer

3rd–4th March 2017

Madrid, Spain

This congress will provide a detailed look at the most topical advances in cancer treatment, particularly focussing on targeted drugs, diagnostics, new treatment algorithms, strategies to use chemotherapy more effectively, and data from key clinical trials on the treatment of patients with lung cancer. This will enable attendees to have confidence in their current practices and facilitate the optimisation of patient care.

Keystone Symposia Tumor Metabolism: Mechanisms and Targets 2017

5th–9th March 2017

Whistler, Columbia, Canada

Experts from a variety of research disciplines will present their most recent discoveries on tumour metabolism, providing a fantastic opportunity to integrate differing viewpoints and research in this interdisciplinary field. This symposium will illuminate the diverse range of metabolic strategies employed by cancer cells and how the tumour microenvironment and distinct genetic events underlying different cancer types affect these metabolic properties.

IMPAKT 2017 Breast Cancer Conference

4th–6th May 2017

Brussels, Belgium

Organised by a consortium of European breast cancer organisations, in collaboration with the Breast International Group (BIG) and the European Society for Medical Oncology (ESMO), IMPAKT 2017 is primarily aimed at breast cancer researchers and clinicians who are especially interested in biomarkers, molecular and functional diagnostics, new agents, translational research, and cutting-edge research applications in the clinical setting.

European Lung Cancer Conference (ELCC)

5th–8th May 2017

Geneva, Switzerland

This conference is a collaboration between the major societies representing thoracic oncology specialists, with the shared ambition to enhance the practice of lung cancer specialists on a global scale. The major topics of focus include: new International Association for the Study of Lung Cancer (IASLC) Staging, immunotherapy as a first-line treatment as well as potential biomarkers and combination approaches, and the management of brain metastases.

European Society of Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer

28th June–1st July 2017

Barcelona, Spain

Held in the vibrant and beautiful city of Barcelona, the world's foremost gastrointestinal cancer event will return in 2017 to provide an overview of malignancies encompassing all sections of the gastrointestinal tract. In addition, it will tackle aspects relevant to the care of patients with gastrointestinal cancer, covering diagnosis, screening, and the very latest management options for both common and uncommon tumours.

European Society for Medical Oncology (ESMO) 2017 Congress

8th–12th September 2017

Madrid, Spain

This renowned congress is the most prominent and influential European annual meeting targeted at medical oncology professionals. Once again, the ESMO Congress will gather leading oncologists together, enabling the sharing of knowledge between the laboratory and clinic, facilitating the alignment of objectives and ensuring greater precision in the direction of research and study which will result in improved treatment options for cancer patients. There will be a huge number of abstract presentations, symposia, and workshops, meaning there will be something to cater for all interests. Online registration will open from February 2017, ensure you remember to book early so as not to miss out on what is sure to be another spectacular event!

EMJ EUROPEAN MEDICAL JOURNAL

EUROPEAN MEDICAL JOURNAL

provides influential articles, presentations of up-to-date scientific research and clinical practice, and in-depth reviews of international medical congresses.

Coming Soon

Please click **here** to:

- subscribe and receive the latest publications, newsletters & updates from **EMJ**
- view each edition in convenient eBook format; desktop, tablet & smartphone compatible

Follow us:

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Buyer's Guide

- ABBVIE
- ADVANCED ACCELERATOR APPLICATIONS
- AGENDIA
- AMGEN (EUROPE) GMBH
- ARIAD PHARMACEUTICALS, INC.
- ASTELLAS PHARMA EUROPE LTD.
- ASTRAZENECA
- BAYER HEALTHCARE PHARMACEUTICALS, INC.
- BIOCARTIS NV
- BOEHRINGER INGELHEIM
- BRISTOL-MYERS SQUIBB
- CELGENE
- CELLDEX THERAPEUTICS
- CHILTERN
- CLOVIS ONCOLOGY
- DAIICHI SANKYO
- EFPIA
- F. HOFFMANN-LA ROCHE
- FRESENIUS KABI DEUTSCHLAND GMBH
- GATC BIOTECH
- GENOMIC HEALTH
- HALIODX
- HELSINN HEALTHCARE
- HELSINN INTEGRATIVE CARE
- IMEDEX
- IMS HEALTH
- INCYTE CORP.
- IPSEN
- JANSSEN
- LILLY ONCOLOGY
- MEDAC GMBH
- MEDIAN TECHNOLOGIES
- MEDICAL PROGNOSIS INSTITUTE
- MEDIVATION, INC.
- MERCK KGAA
- MERCK-PFIZER ALLIANCE
- MSD
- MYRIAD GENETIC LABORATORIES, INC.
- NANOSTRING TECHNOLOGIES
- NOVARTIS ONCOLOGY
- NOVELLA CLINICAL
- NUTRICIA ADVANCED MEDICAL NUTRITION
- ONCODNA SA
- ONCOLOGY VENTURE
- ONCOTHERM
- PAXMAN
- PEREGRINE PHARMACEUTICALS
- PFIZER BIOSIMILARS
- PFIZER ONCOLOGY
- PHARMADAB
- PHARMAMAR
- PIERRE FABRE ONCOLOGY
- PIVOTAL
- PRIME ONCOLOGY
- QIAGEN
- QUINTILES
- SANDOZ
- SANOFI GENZYME
- SERVIER
- SHIRE
- SIRTEX
- SOTIO
- SYSMEX INOSTICS
- TESARO
- TEVA PHARMACEUTICALS EUROPE
- VARIAN MEDICAL SYSTEMS