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ONCOLOGY

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INSIDE
Review of
ESMO 2014
Madrid, Spain

A First-Line BRAF Inhibitor

Tafinlar®
(dabrafenib)

TAFINLAR is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation

- Before taking TAFINLAR, patients must have confirmation of tumour BRAF V600 mutation using a validated test

Prescribing Information

(Please refer to full SmPC before prescribing)
Tafinlar® (dabrafenib) 50mg and 75mg capsules. Each capsule contains dabrafenib mesilate, equivalent to 50mg and 75mg of dabrafenib, respectively. **Indication** In monotherapy for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. **Dosage and administration** Before taking dabrafenib, patients must have confirmation of BRAF V600 mutation using a validated test. 150mg twice daily (b.d.) with interval of ~12hrs between doses (max. total daily dose 300mg), taken until patient no longer derives benefit or develops unacceptable toxicity. Take ≥1 hour before or ≥2 hours after a meal, at similar times every day. Swallow capsules whole with water; do not chew, crush or mix with food/liquids. If dose is missed, do not take if <6 hours until next dose. *Dose modification*: Management of ADRs may require treatment interruption, dose reduction or discontinuation. 1st reduction: 100mg b.d., 2nd reduction: 75mg b.d., 3rd reduction: 50mg b.d. (min. dose). Consider dose re-escalation following same dosing steps as de-escalation when ADR under effective management. *Renal impairment*: No dose adjustment required in mild or moderate impairment. Caution advised in severe renal impairment. *Hepatic impairment*: No dose adjustment required in mild impairment. Caution advised in moderate and severe hepatic impairment. *Elderly*: No initial dose adjustment required in patients >65 yrs. *Paediatrics*: Safety & efficacy not established in patients <18 yrs. **Contraindications** Hypersensitivity to active substance or excipients. **Special Warnings and Precautions** *Pyrexia*: Interrupt treatment if temperature ≥38.5°C and investigate for infection. Restart once fever resolves with anti-pyretics. Restart at reduced dose if fever associated with other severe signs or symptoms as clinically appropriate. *Cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma*: Examine skin prior to treatment, monthly during treatment and for up to 6 months after discontinuation. Patients should inform their physician immediately if a new lesion develops. Dose modifications/interruptions not recommended. *Non-cutaneous secondary/recurrent malignancy*: Head and neck examination and chest/abdominal scan prior to treatment. Monitor as clinically appropriate and for up to 6 months after discontinuation. *Renal failure*: Monitor serum creatinine routinely while on therapy, and interrupt treatment as clinically appropriate if creatinine increases. *Uveitis*: Monitor for signs and symptoms of ophthalmological reactions while on therapy. *Pancreatitis*: Investigate unexplained abdominal pain promptly, including serum amylase & lipase measurements. Monitor closely when re-starting dabrafenib. *QT prolongation*: Treatment not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome or those taking

Treatment with TAFINLAR was proven to significantly extend progression-free survival (PFS) vs dacarbazine[1]

Efficacy in Previously Untreated Patients (BREAK-3 Trial)[1]		
	TAFINLAR (n=187)	Dacarbazine (n=63)
PFS median, months (95% CI)	**6.9** (5.2, 9.0)	**2.7** (1.5, 3.2)
Hazard ratio (95% CI)	0.37 (0.24, 0.58) *P*<0.0001	

6.9 months
Median PFS with TAFINLAR

Investigator assessment, 25 Jun 2012, secondary data cutoff subsequent to primary data cutoff on 19 Dec 2011.

The safety profile is based on data from 5 clinical monotherapy studies and included 578 patients with melanoma. The most frequently occurring adverse reactions (≥15%) of any grade for TAFINLAR included hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash, and vomiting.[1]

TAFINLAR can also cause serious, less common side effects, including increasing the risk of developing new primary cutaneous malignancies, serious febrile drug reactions, uveitis and iritis, and embryofoetal toxicity.[1]

medicinal products known to prolong QT interval. Monitor ECG and electrolytes before treatment, one month after therapy, and after dose modification. Permanent treatment discontinuation recommended if QTc increase is both >500msec and >60msec change from baseline. **Undesirable effects** Please refer to full SmPC before prescribing. *Very common*: papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, PPE syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills, asthenia. *Common*: cuSCC, seborrhoeic keratosis, skin tags, basal cell carcinoma, hypophosphataemia, hyperglycaemia, constipation, dry skin, pruritus, actinic keratosis, skin lesion, erythema, influenza-like illness, LVEF decrease. **Interactions** Avoid co-administration with strong inducers or inhibitors of CYP2C8 and CYP3A4, and agents that increase gastric pH, when possible. Exercise caution when co-administering with digoxin and with warfarin; consider additional INR monitoring. Dabrafenib may reduce efficacy of hormonal contraceptives; use alternative effective contraception and continue for 4 weeks post-discontinuation. **Pregnancy** Do not administer to pregnant women unless benefit to mother outweighs the risk to foetus. **Basic NHS Cost** 50mg x 28-capsule pack £933.33; 75mg x 28-capsule pack £1,400.00. **Marketing authorisation (MA) nos.** EU/1/13/865/001; EU/1/13/865/003. **MA holder** GlaxoSmithKline Trading Services Ltd., Kinsale Road, Cork. **Legal category** POM. UK/MLO/0002/14. March 2014.

Adverse events should be reported. For the UK, reporting forms and information can be found at: http://www.mhra.gov.uk/yellowcard. For Ireland, adverse events should be reported directly to the IMB; Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Tel: +353 1 6764971.

Adverse events should also be reported to GlaxoSmithKline on 0800 221 441 in the UK or 1 800 244 255 in Ireland.

Further information is available from Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone: 0800 221 441.

Please see Summary of Product Characteristics for TAFINLAR.

Reference: 1. GlaxoSmithKline. TAFINLAR Summary of Product Characteristics, May 2014.

TAFINLAR is not currently marketed in all territories and prescribers should check local marketing authorisation status before prescribing. Cost and reimbursement status may also vary.

CONTENTS

ONCOLOGY

Bosulif® ▼ (bosutinib): Meeting an unmet need in all phases of Ph+ CML

For the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options[1]

References: 1. Bosulif, Summary of Product Characteristics.

Bosulif® bosutinib tablets

Bosulif® ▼ (bosutinib) Prescribing Information:
Please refer to the Summary of Product Characteristics (SmPC) before prescribing Bosulif 100mg or 500mg film-coated tablets.

▼ 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. See section 4.8 of the SmPC for how to report adverse reactions.

Presentation: Film-coated tablet containing 100mg or 500mg bosutinib (as monohydrate). **Indications:** Bosutinib is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. **Dosage:** Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML. The recommended dose of bosutinib is 500mg taken orally once daily with food. In clinical trials, treatment with bosutinib continued until disease progression or until it was no longer tolerated by the patient. Dose escalation to 600mg once daily was allowed in the phase 2 clinical trial of adult patients with previously treated Ph+ CML who did not experience severe or persistent moderate adverse reactions, and who did not meet certain early efficacy criteria. For details of dose escalation and dose reduction guidelines for non-haematologic adverse reactions and for haematologic adverse reactions, refer to SmPC section 4.2. Patients with serum creatinine >1.5 x ULN were excluded from CML studies. Increasing exposure (AUC) in patients with moderate and severe renal impairment during studies was observed. For details of dosage in patients with moderate and severe renal impairment please refer to SmPC section 4.2. Caution should be exercised in patients with relevant cardiac disorders and in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4 of SmPC). No specific dose recommendation is necessary in the elderly (≥65 years). Since there is limited information in the elderly, caution should be exercised in these patients. The safety and efficacy of bosutinib in patients under 18 years of age has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hepatic impairment. **Special warnings and precautions for use:** Treatment with bosutinib is associated with elevations in serum transaminases (ALT, AST). Transaminase elevations generally occurred early in the course of treatment. Patients receiving bosutinib should have liver function tests prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated. Treatment with bosutinib is associated with diarrhoea and vomiting, therefore patients with recent or ongoing clinically significant gastrointestinal disorder should use this medicinal product with caution and only after a careful benefit-risk assessment. Patients with diarrhoea and vomiting should be managed using standard-of-care treatment, including an antidiarrhoeal or antiemetic medicinal product and/or fluid replacement. In addition, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see SmPC sections 4.2 and 4.8). The antiemetic agent, domperidone, has the potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; therefore, co-administration with domperidone should be avoided. It should only be used if other medicinal products are not efficacious. In these situations an individual benefit-risk assessment is mandatory and patients should be monitored for occurrence of QT prolongation. Treatment with bosutinib is associated with myelosuppression, defined as anaemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month and then monthly thereafter, or as clinically indicated. Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion and pulmonary oedema. Patients should be monitored and managed using standard-of-care treatment. Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. Bosutinib may predispose patients to bacterial, fungal, viral or protozoan infections. Automated machine-read QTc prolongation without accompanying arrhythmia has been observed. Bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval. Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with Bosutinib and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to bosutinib administration and should be monitored periodically during therapy. Long term treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. It is important that renal function is assessed prior to treatment initiation and closely monitored during therapy with bosutinib, with particular attention to those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, ACE inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). The concomitant use of bosutinib with potent or moderate CYP3A inhibitors/inducers should be avoided as an increase/decrease in bosutinib plasma concentration will occur. Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided. **Drug interactions:** The concomitant use of bosutinib with potent (e.g. ketoconazole, grapefruit products including grapefruit juice) or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur. Refer to section 4.5 of the SmPC for further details. If a potent or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered. The concomitant use of bosutinib with potent (e.g. rifampicin, phenytoin, carbamazepine, St. John's Wort, rifabutin, phenobarbital) or moderate (e.g. bosentan, nafcillin, efavirenz, modafinil, etravirine) CYP3A inducers should be avoided, as a decrease in bosutinib plasma concentration will occur. Caution should be exercised when administering bosutinib concomitantly with proton pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible. Caution should be used if bosutinib is administered with medicinal products that are substrates of P-glycoprotein (P-gp). An *in vitro* study suggests that bosutinib may have the potential to increase the plasma concentrations of medicinal products that are P-gp substrates. Refer to section 4.5 of SmPC for examples of P-gp substrates. Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation. Refer to sections 4.4 and 4.5 of the SmPC for further details. **Fertility, pregnancy and lactation:** Not recommended in pregnancy or whilst breast feeding. Bosutinib has the potential to impair reproductive function and fertility. **Driving and operating machinery:** Bosutinib has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** Very common adverse events are: respiratory tract infection, thrombocytopenia, neutropenia, anaemia, leukopenia, decreased appetite, headache, cough, diarrhoea, vomiting, nausea, abdominal pain, alanine aminotransferase increased, aspartate aminotransferase increased, rash, arthralgia, pyrexia, oedema, fatigue. Commonly reported adverse events are: pneumonia, influenza, bronchitis, nasopharyngitis, febrile neutropenia, drug hypersensitivity, dehydration, hyperkalaemia, hypophosphataemia, dizziness, dysgeusia, pericardial effusion, electrocardiogram QT prolonged, dyspnoea, pleural effusion, gastritis, hepatotoxicity, hepatic function abnormal, blood bilirubin increased, gamma-glutamyltransferase increased, urticaria, acne, pruritus, myalgia, back pain, renal failure, chest pain, pain, asthenia, lipase increased, blood creatinine increased, blood amylase increased, blood creatine phosphokinase increased. Refer to section 4.8 of the SmPC for further information on side effects, including description of selected adverse reactions. **Legal category:** POM. **Basic NHS price:** Bosulif 100mg, 28 tablets [EU/1/13/818/001] £859.17. Bosulif 500 mg, 28 tablets [EU/1/13/818/003] £3436.67. **Marketing authorisation holder:** Pfizer Ltd, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. Further information is available on request from: Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Tel: +44 (0) 1304 616161 **Last revised:** 06/2014 Ref: BO 3_0

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Pfizer

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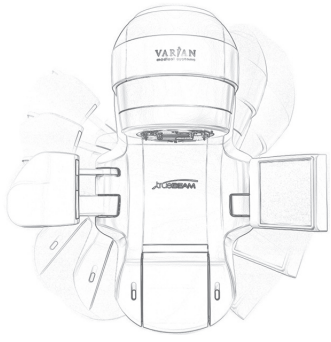
Proven as a Technology. Possibilities as a Result.



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Welcome

Oncology is a tough and demanding discipline, but with the introduction of new therapies and drugs, all for the benefit of the patient, it is one which can be very rewarding. This issue of the *European Medical Journal Oncology* aims to keep you up-to-date with the latest advancements within this area, combining interesting peer reviewed articles and highlights from the European Society for Medical Oncology (ESMO) Congress with other exciting news updates.

"We are at the point where genuinely targeted therapy is now possible for an increasing number of cancers. Practicing precision medicine means we are all working towards a common goal – improved patient outcomes," and this was, as Prof Johann de Bono, Chair of ESMO 2014 Scientific Committee, said, "the ultimate goal of ESMO 2014."

New innovative treatment options for patients, and the progression of knowledge within this area, are extremely important. However, as reported in our 'Congress Review' section, many patients are not informed of current treatment options; in fact, only 23% of healthcare providers believe that their patients are informed of their choices. Another presentation suggested that more research is needed in the area of rare cancers; as these cancers only make up one-fifth of newly diagnosed cancers, there is a lack of evidence and trials within this area. In order to attract drug developers, clinical trial methodology needs to adapt to encourage innovation and increase patient options.

To increase evidence and bring benefits to patients, Dr Niki Karachaliou and Dr Rafael Rosell have recommended in their paper '*Unmet medical needs in non-small-cell lung cancer treatment: how to design pre-emptive combination therapies,*' that a more target-based approach is needed. Combining synthetic lethal approaches and pre-emptive therapies, based on the initial expression of BIM, may greatly improve treatment outcomes for patients with non-small-cell lung cancer. Focusing on inhibitors of specific cellular proteins is crucial for the development of effective treatment design and future clinical studies; this will help us to understand the complex molecular biology in epidermal growth factor receptor mutations in lung cancer.

Along the same lines, Dr Tiziana Vavalà and Dr Silvia Novello hope to improve the knowledge of lung cancer in women in their paper '*Women and lung cancer: literature assumptions and news from recent publication.*' The authors suggest that the identification of specific genetic alterations or hormonal profiles could be targeted by therapies and develop sex-based investigations.

We hope that this edition of the *EMJ Oncology* proves to be beneficial not only to you, but also to your patients, by enabling you to implement what you have learnt into your daily practice; and it is with that, I wish you a most pleasant read.

Spencer Gore

Director, European Medical Journal

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EMJ GORELY NEW MEDIA

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Foreword

Prof Ross Abrams

Hendrickson Professor and Chair,
Rush University Medical Center, USA.

Dear Colleagues,

I would like to introduce another exciting edition of *EMJ Oncology*, which has a stimulating range of peer reviewed articles, the latest news and updates in the rapidly developing field of Oncology, and full review of the European Society for Medical Oncology (ESMO) 2014 Congress.

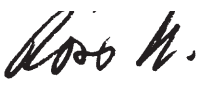
We hope that you enjoyed the recent ESMO Congress, which was held in the beautiful city of Madrid, Spain over a 5-day duration. The theme of this highly prestigious event was based on 'Precision Medicine in Cancer Care,' a widely debated topic in the field at present.

As you review this publication, please consider the meaning of 'precision medicine' in Oncology. I would like to bring your attention to two excellent reviews. The first is by Prof Ciardiello and colleagues[1] for ESMO and beautifully prepares us to think about the necessary component steps for precision medicine in Oncology. The second, by Simonds et al.[2] from the National Cancer Institute, USA, prepares us for rigorous evaluation of our accomplishments as we travel this path. The former article defines precision medicine as "the use of an individual patient's molecular information (including genomics and proteomics) to inform diagnosis, prognosis, treatment, and prevention of cancer for that patient."[1]

The challenges of this process will include: 1) tumour heterogeneity, molecular evolution, and drug resistance; 2) the need for precision diagnostics and predictive biomarkers of response; 3) data analysis and bioinformatics - because large scale genomic data will require integration and translation with clinical data to be useful for clinical decision-making; 4) privacy, data protection, and potential discrimination on a greater scale than ever before; 5) new clinical trial methodologies appropriate to individualised care; and 6) the need to be cost-effective and economically rational.

The 2014 ESMO Congress provided sessions addressing each of these and our current progress. A great adventure in Oncology has begun yet again! May we and our patients increasingly share its continued success and engage its challenges.

Kind Regards,



Ross A. Abrams

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ESMO ANNUAL CONGRESS 2014

IFEMA – FERIA DE MADRID, MADRID, SPAIN

26TH-30TH SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Society for Medical Oncology Congress 2014

EMJ EUROPEAN MEDICAL JOURNAL

ESMO ANNUAL CONGRESS 2014

IFEMA – FERIA DE MADRID, MADRID, SPAIN
26TH-30TH SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Society for Medical Oncology Congress 2014

Madrid, Spain's capital city, which is best known for its great cultural and artistic heritage, along with its striking landmarks and spectacular architecture, was host to the European Society for Medical Oncology (ESMO) Congress, which was held from 26th-30th September 2014. This city was the perfect location for this highly-esteemed Congress, with all its glory and grandeur.

"We are particularly pleased to see participants from 131 countries at the Congress this year," commented Prof Rolf A. Stahel, ESMO President. "Although this is the Congress of the ESMO, it is truly a global Congress with growing participation from countries outside Europe, especially the Far East." Prof Stahel also revealed that to meet the needs of members from across the world, the next ESMO Congress will be held in Singapore.

A record-breaking number of 19,859 delegates were in full attendance with over 2,746 abstracts submitted this year, representing an increase of almost 24% compared to ESMO 2012, in Vienna, Austria. At the Opening Ceremony, it was revealed by Prof Johann de Bono, Royal Marsden Hospital Chair of the ESMO 2014 Scientific Committee, that predictive biomarkers and targeted drugs remained the focal point in more than one-third of the accepted abstracts. Adding to the scientific atmosphere, there was also a wide range of exhibitors showcasing the latest developments within the field of oncology, and increasing opportunities for networking between members from both the clinical and industry fields.

This year's Congress theme, 'Precision Medicine in Cancer Care', will continue to resonate in

delegates' minds since the foundation of this therapy aims to cater to the individual needs of patients. Commenting on this theme, Prof de Bono said: "We are increasingly able to target cancer treatments to the important molecular mechanisms that underpin the malignancy. This is what we mean by precision medicine."

The scientific programme accommodated a variety of cancers (including breast, lung, head and neck, gastrointestinal, and haematological malignancies), oncopolicy forums, paediatric and surgical oncology, and supportive care and palliation. These were all delivered in diverse formats such as presentations, symposia, seminars, and workshops, which catered to a wide spectrum of healthcare professionals. Emphasis was also placed on young oncologists where experts in the field were able to disseminate their advice for career success, which included the value of networking opportunities and how to deal with the stresses that come within the profession.

Other thought-provoking Congress highlights included the safety of cancer treatments during pregnancy, innovations in colorectal cancer screening, supportive care for cancer patients with emphasis on treatments which can potentially minimise the harsh side-effects of chemotherapy, the combination therapy of pertuzumab and trastuzumab in the continuing fight against breast cancer, and the introduction of liquid biopsies which may revolutionise oncology practice.

Cancer treatment is safe for unborn children

ONCOLOGISTS have long been hesitant to administer cancer treatment to patients during pregnancy; however, four recent studies have addressed these concerns, showing that exposure to cancer treatments for unborn babies has no detrimental effects on their health or development.

In the first of the four studies exploring the impact of *in utero* exposure to chemotherapy/radiotherapy, the safety of lymph node biopsy in pregnancy, and the outcomes of unplanned pregnancy during cancer treatment, 38 children prenatally exposed to chemotherapy were recruited and assessed for cardiac health and mental development against 38 controls.

At a median age of approximately 2 years, mental development and cardiac dimensions/functions were within normal ranges for both groups, showing no significant differences. This suggests that treatment is safe, regarding a child's mental and cardiac development.

The second study, containing 16 children and 10 adults exposed to radiotherapy *in utero*, showed that neuropsychological, behavioural, and general health outcomes were again within normal ranges.

The third examined the safety of using sentinel node biopsies for the spread of early breast cancer in 97 women. This method removes the sentinel lymph node (SLN), most likely to contain metastatic cells; if no metastatic disease is present, remaining lymph nodes do not require removal. Subjects underwent sentinel node biopsy. At median follow-up of 35 months, eight patients experienced loco-regional relapses, including two who developed lymph node tumours; and four developed distant metastases, of whom three died of breast cancer.

The fourth investigation highlighted the importance of contraception during cancer diagnosis and treatment. Of 897 women, 29 fell pregnant under these circumstances, including 3 during examinations for suspected malignancy (before definite diagnosis), 18 during treatment, and 7 after diagnosis, before treatment started. Of the 29 women who fell pregnant, contraception methods failed in 24.1%, contraception was unknown in 34.5%, and 41.4% were not using contraception. Thus, there is a need for oncology teams to be educated and aware of adequate contraception methods in young women diagnosed with cancer.

Dr Fedro Alessandro Peccatori, Director of the Fertility and Procreation Unit, Division of Gynaecologic Oncology, European Institute of Oncology, Milan, Italy, commented: "The core message from our results is that it is vital for doctors and patients to discuss contraception during cancer diagnosis and cancer treatment. Although fertility issues are not the focus of attention at this time, it is necessary to provide advice about contraception. And although we know it is possible to treat patients with chemotherapy/radiotherapy during pregnancy when necessary, it is still better to avoid this situation, if possible."

Antibody-based bladder cancer therapy shows promise

HOPES are high for a new and effective treatment strategy which has arisen in the fight against advanced bladder cancer (BLC).

After decades of silence, the engineered anti-PD-L1 antibody MPDL3280A has emerged as a novel immunotherapeutic approach, restoring anti-tumour T cell activity and boosting the cellular immune attack on antigens. Dr Maria De Santis, Medical Oncologist, Centre for Oncology and Hematology, Kaiser Franz Josef Hospital, Vienna, Austria, said: "For the first time in many years exciting news has emerged for patients with BLC.

"Immunotherapy and, more specifically, treatment with the engineered anti-PD-L1 antibody MPDL3280A may offer a new, effective, safe, and well tolerated treatment option for advanced and metastatic BLC patients while preserving quality of life."

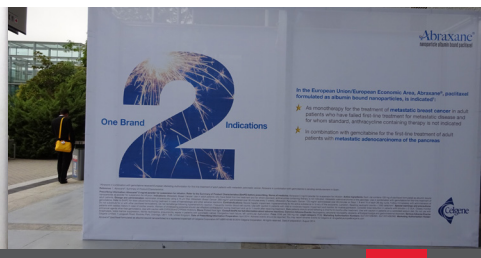
This is a timely development as efforts to tackle this highly aggressive and deadly disease have yielded few results over the past decade. Reinforcing this exciting method is a spate of positive results gleaned from early phase trials involving pre-treated patients with urothelial BLC, the most prevalent form of the disease.

This included a 43% response rate in a subset of patients, of which some were complete and a large number durable; such positive results have been rarer through conventional chemotherapy and may also prove a potent tool for cisplatin-ineligible patients, who constitute approximately half of patients ineligible for standard cisplatin based chemotherapy.

"Looking at the tumour itself, urothelial BLC has a high mutational complexity. This fact makes it more difficult to treat with conventional chemotherapy and specific targeted therapies. This same fact offers the potential for many neo-antigens to be seen as foreign by the host immune system and might be an advantage for immunotherapy to work in BLC," explained Dr De Santis.

The immune system is also active in muscle invasive urothelial BLC, according to Dr De Santis, with CD8 tumour-infiltrating lymphocytes in the primary tumour shown to be predictive of survival. Furthermore, the presence of several immune co-regulatory proteins, such as PD-1, in advanced or metastatic urothelial cancer is regular, with some of these linked to survival.

"Further studies are needed to confirm the preliminary data. Most importantly, these early data are important enough for a breakthrough therapy designation that has been granted by the FDA," concluded Dr De Santis.



Innovations in colorectal cancer screening

SCREENING for biennial colorectal cancer (CRC) has increased diagnosis rates of high-risk pre-cancerous adenomas by 89%, after its introduction to the French region of Côte-d'Or.

Researchers evaluated adenoma diagnosis rates before and after the initiation of a screening programme using faecal occult blood tests (FOBTs), in a study including regional residents aged 50-74 years. Subjects all had a first adenoma identified between January 1997 and December 2008; 38.7% had high-risk adenomas.

For high-risk adenomas, age-standardised diagnosis rates were 136 per 100,000 people before the screening programme and 257 per 100,000 afterwards, correlating a percentage increase of 89%. Corresponding rates for non-advanced adenomas were 235 and 392 diagnoses per 100,000 (percentage increase: 68%).

"It is very important that [the] public follows recommendations and participates in CRC screening campaigns," commented Dr Vanessa Cottet, INSERM Unité 866, Dijon, France. "Participation rate is a major issue for the success of such programmes."

"Immunochemical FOBTs outperform guaiac tests for the detection of CRC and advanced adenoma," continued Dr Cottet. "They have doubled the detection rate of invasive CRC, mostly at early stages, and led to a 4-fold increase in the detection rate of non-invasive CRC and advanced adenomas."

Yet for Prof Hans-Joachim Schmoll, former Head, Division of Hematology and Oncology, and Director, Center for Cell and Gene Therapy, Martin Luther University, Halle, Germany, the question remains as to which method is the most appropriate, regarding access to the target population, maximising participation in screenings, costs, and efficacy. The optimal method for increasing detection rates is currently colonoscopy, though this appears to be less efficient than the use of FOBTs.

In another study, patients at higher risk of CRC (based on family history) were invited to undergo colonoscopy rather than FOBT; of 1,179 patients, 889 underwent colonoscopy, and overall 253 colorectal neoplasias were diagnosed. Researchers calculated that the positive predictive value of colonoscopy was 3.9% for cancer, 12.9% for advanced adenoma, and 25% for overall adenoma – a poor comparison to the positive predictive value in the average risk population selected by a positive FOBT, the researchers said.

"The take-home message is that the positive predictive value for colorectal neoplasia in high-risk patients screened by colonoscopy is lower than it is for average-risk patients screened by FOBT," concluded Dr Sylvain Manfredi, CHU Pontchaillou, Rennes, France.

Plethora of positives in supportive cancer care

SUPPORTIVE care for cancer patients has proven to decrease chemotherapy-induced nausea and vomiting, bleeding in patients with venous thromboembolism (VTE), and cancer anorexia-cachexia syndrome (CACS).

Rolapitant reduced nausea and vomiting in patients receiving cisplatin-based chemotherapy during a Phase III trial; these symptoms often occur in cisplatin patients, leading to dose reductions and treatment termination. Dr Roberto Labianca, ESMO spokesperson and Director of the Cancer Center, Ospedale Giovanni XXIII, Bergamo, Italy, said: "In this well conducted large-scale clinical trial there was a clear advantage in patients receiving rolapitant when treated with highly emetogenic chemotherapy.

"It is remarkable that this effect was observed worldwide across different geographic regions. As the new drug is very selective and long-acting, and also well tolerated, it could be easily introduced in clinical practice in order to prevent both acute and delayed chemotherapy-induced nausea and vomiting."

Anticoagulant therapy is shown to prevent recurrent VTE; however, it is linked to a high risk of major bleeding. Seeking to rectify this, 8,282 cancer patients with acute VTE were enrolled in the EINSTEIN DVT and EINSTEIN PE Phase III trials, which compared rivaroxaban to standard treatment with enoxaparin/vitamin K antagonist.

"Rivaroxaban is an oral drug, with the same antithrombotic effect as compared to the traditional drugs, but with a reduced risk of bleeding. This characteristic can be very important in clinical practice, allowing an easier and more convenient treatment of such a serious complication of cancer," said Dr Labianca.

The efficacy and safety of anamorelin HCl, a novel, selective ghrelin receptor agonist, in treating CACS patients with unresectable advanced non-small cell lung cancer (NSCLC) were analysed in the Phase III trial.

Dr Labianca concluded: "This is really an important advance, as the study emphasises the absolute need of establishing an approach of simultaneous palliative care in patients with advanced disease (such as NSCLC) treated with antitumour drugs and affected with serious symptoms like CACS."

"As the new drug is very selective and long-acting, and also well tolerated, it could be easily introduced in clinical practice in order to prevent both acute and delayed chemotherapy-induced nausea and vomiting."

Dr Roberto Labianca, ESMO spokesperson and Director of the Cancer Center, Ospedale Giovanni XXIII, Bergamo, Italy

Cancer breakthroughs not reaching the masses

> "Oncologists are aware of the importance of molecular testing for the selection of cancer treatment, at least in some cancers, but our results show that they feel there are still economic and organisational problems that are hindering the use of these tests."
>
> *Prof Fortunato Ciardiello, ESMO President-Elect*

OVER three-quarters of oncology specialists in Europe, South America, and Asia believe that their patients are uninformed about available treatment options due to a perceived lack of efforts to publicise them.

The discovery of molecular changes at the heart of many cancers has revolutionised cancer treatment, yet a recent survey of 895 practicing oncology specialists, with more than 3 years' experience, treating over 15 patients per month, from 12 countries, has highlighted that these breakthroughs in personalised medicine are not always adopted into worldwide clinical practice.

Only 23% of physicians believe that their patients are always completely informed about available treatments, despite 82% believing that both doctors and patients should decide on the methods of treatment together. Prof Fortunato Ciardiello, ESMO President-Elect, commented: "Our respondents felt that nurses were the best source of information for their patients, but only 45% thought their patients actually had access to nurse support."

90% of oncologists were shown to be currently exercising biomarker testing to assist in selecting a suitable therapy for patients. KRAS mutations as well as hormone receptor status and HER2 expression, widely used in colorectal cancer and breast cancer, respectively, were the most commonly used tests. 55% of the minority not currently conducting biomarker testing cited cost or scarce reimbursement as limiting factors.

Prof Ciardiello noted: "Although overall we found that 73% of physicians believed their patients knew that it is possible to test tumours to help decide which treatment to give, we noted that this fell to 55% in Germany and Turkey."

"Oncologists are aware of the importance of molecular testing for the selection of cancer treatment, at least in some cancers, but our results show that they feel there are still economic and organisational problems that are hindering the use of these tests," Prof Ciardiello added.

No time for gaps in cancer-drug approval

LIFE-EXTENDING cancer drugs vary significantly in their international accessibility, calling for closer collaboration between doctors and health authorities worldwide.

A survey revealing that patients in some regions of the world have to wait years longer than their international counterparts for new drugs to be approved has sparked a need for coordinated healthcare action to ensure that they are approved more quickly.

A study compared approval times for 41 cancer drugs in Canada, the USA, and the EU; average time to approval by the FDA was 6 months less than for the EU's European Medicine Agency, and 7.6 months shorter than Health Canada. Yet, while approval of regulatory agencies is important for ensuring the safety and efficacy of new drugs, researchers say that delays in the approval process can impact on patient care.

> "We need to balance due diligence to review appropriate treatment by regulatory agencies and providing treatment to our patients that is effective."
>
> *Dr Sunil Verma, Sunnybrook Odette Cancer Center, Toronto, Canada*

Another example can be found in the drug trastuzumab, which targets HER2-positive breast cancer (BC) (accountable for approximately 20% of BCs). Patients in Eastern Europe have less access to this than their Western and USA counterparts; these differences are allegedly linked to discrepancies in cancer survival.

Researchers used national registry data to estimate the number of new cases of HER2-positive BC patients per year in 24 countries, before using procurement data to further estimate the number of likely trastuzumab treatments per year for each. It was seen that Eastern European countries did not acquire sufficient trastuzumab to treat all of the patients who would benefit from it.

Dr Sunil Verma, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada, commented: "Our main aim as clinicians is to ensure that patients are given an opportunity to receive proven, effective, and safe treatment in a timely manner. We need to balance due diligence to review appropriate treatment by regulatory agencies and providing treatment to our patients that is effective."

The next dynamic duo: cediranib and chemotherapy

IMPROVED tumour shrinkage and a modest increase in progression-free survival (PFS) in cervical cancer (CVC) patients whose cancer has recurred after treatment, or has metastasised, have been demonstrated by adding cediranib to standard chemotherapy.

Approximately 70% of CVC patients in Europe can be cured by either surgery or chemotherapy, but the remaining patients who have recurrent or secondary cancer have an ominous prognosis. After conventional chemotherapy, only 20-30% have tumour shrinkage and survival is typically <1 year. Adverse prognostic features include high tumour angiogenesis, along with high levels of intratumoural vascular endothelial growth factor (VEGF). The experimental drug cediranib is a potent tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3.

"CVCs with a well-developed blood supply can have a particularly bad outcome. The experimental drug cediranib blocks the cell surface receptor VEGF, which stimulates the growth of new blood vessels to feed the growth of tumours," said Dr Paul Symonds, study researcher, Department Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK.

69 CVC patients took part in a Phase II, randomised, double-blind CIRCCa trial, and were divided into two groups. Both groups were treated with conventional chemotherapy (i.e. carboplatin and paclitaxel); however, 34 patients also received cediranib, while the remaining 35 received a placebo tablet.

It was observed that those in the cediranib group had greater tumour shrinkage than those in the placebo group (66% versus 42%). There was also a significant increase in median PFS (35 versus 30 weeks) but the median overall survival revealed no statistical significant difference.

Patients in the cediranib group experienced substantial side-effects, in particular increased blood pressure and diarrhoea, while standard medication was used to manage these complications.

The targeting of the tumour's blood supply holds promising potential to increase the effectiveness of chemotherapy in CVC, Dr Symonds stressed: "Recurrent or metastatic cervix cancer is really difficult to treat with a low response rate and poor survival. This study has opened up a new avenue of investigation for a difficult-to-treat cancer."

The next focus of this investigation is to conduct individual patient analyses to correlate responses to chemotherapy with the decreases in VEGF receptor levels in blood. Further investigations into other tumour biomarkers that might be reduced by cediranib will also occur.

Breast cancer faces new foe

ATTACKS on HER2-positive metastatic breast cancer (BC) with pertuzumab and trastuzumab have become increasingly common as the latest weapon of choice against one of the deadliest forms of the illness.

"We should consider this combination as the standard of care for our patients," said Dr Javier Cortes, Director of the Breast Cancer Program, Vall D'Hebron Institute of Oncology, Barcelona, Spain. "I can see no reason to justify the use of trastuzumab without pertuzumab. The impressive overall survival data we have observed at ESMO 2014 will help us, as physicians, to continue working; it will help patients, to fight against their disease; and it will help society to understand that people will not die of cancer in the future."

808 subjects enrolled in CLEOPATRA, a crucial Phase III study testing the safety and efficacy of the antibody pertuzumab, trastuzumab, and docetaxel. Overall survival (OS) and progression-free survival (PFS) were the key determinants as to the effectiveness of this therapy, versus trastuzumab and docetaxel treatment alone. The treatment groups displayed a median OS of 56.5 and 40.8 months, respectively, highlighting a near-16 month improvement with added pertuzumab.

Dr Cortes said: "The median OS data presented by Sandra Swain at ESMO 2014 with pertuzumab and trastuzumab-based therapy in patients with HER2-positive metastatic BC is remarkable. This is one of the biggest steps toward making this disease a chronic condition in the near future...What is more surprising is that the improvement in median OS exceeds the improvement in PFS; maybe because of the different mechanisms of action that monoclonal antibodies have."

These data reinforce results from previous studies which have shown the antibody to prolong PFS and OS, the former having been successfully maintained across a 50-month follow-up, as well as long-term safety profiles. "The safety profile of pertuzumab and trastuzumab plus chemotherapy was consistent with the known safety profile of patients with long-term exposure to dual targeting. It means that we now have a treatment that improves OS and PFS without affecting the quality of life of patients in terms of cardiac safety," said Dr Giuseppe Curigliano, Director of the Division of Experimental Therapeutics, Milan, Italy.

Further research on resistance mechanisms to the combination is required to boost therapeutic activity and spot patients who do not require chemotherapy.

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Dr Javier Cortes,
Director of the Breast Cancer Program,
Vall D'Hebron Institute of Oncology,
Barcelona, Spain

Liquid biopsies: revolutionising oncology practice

RISKS to cancer patients and healthcare costs can now be reduced thanks to the introduction of liquid biopsies; such innovative technology has great diagnostic and treatment implications in the field of oncology.

Tumour genome sequencing is central to the management of cancer care, and patient-tailored therapies rely on identifying the correct molecular tumour target in detecting circulating tumour cells. These cells have been studied in much detail; though they are rare and require sensitive collection, they provide valuable genetic and cellular information.

At present, tumour biopsy tissue is used to determine these targets at a single point in time before commencing treatment. Such biopsies carry significant risks: they are painful, costly, take time, may not provide a tissue sample that truly represents the molecular profile, and are prone to change under selection pressure.

Alternatively, introducing liquid biopsies may capture the entire heterogeneity of a cancer. They offer what the former cannot: the ability to take multiple samples in order to monitor genomic tumour changes in real time, allowing healthcare professionals to ensure that a selected therapy remains relevant and to seek out signs of any resistance to treatment, thus sparing patients any unnecessary toxicities of drugs that provide little-to-no benefit.

These new liquid biopsies offer a unique opportunity to develop our comprehension of metastatic disease development; ultimately, they will be used in the diagnosis of cancer, revolutionising cancer care and optimising treatment choices.

Standardisation will be key to ensuring consistency between centres and in determining the clinical success of liquid biopsies; in fact, standardisation across the board should be aimed for with regards to blood collection, processing, storage, and DNA extraction, quantification, analysis, and reporting of data.

Developing standardised methodologies for cell-free tumour DNA analysis and validation in large prospective clinical trials is mandatory for the implementation of liquid biopsies in the clinical management of cancer patients; the promise of liquid biopsies could soon become a clinical reality.

Combined therapies enhance patient survival

MAGNITUDINAL benefits have been seen in BRAF-mutation positive melanoma patients who undergo a combined therapy of BRAF inhibitor vemurafenib with MEK inhibitor cobimetinib.

Although it is already established that cobimetinib plus vemurafenib could be delivered safely together with promising rates of tumour shrinkage, the potential of this benefit has not been measured until recently.

An ongoing CoBRIM study including 495 treatment-naïve patients with BRAF V600-mutation-positive unresectable locally advanced or metastatic melanoma randomised subjects into three groups, receiving a 28-day treatment cycle of vemurafenib (960 mg, twice daily) and either cobimetinib or placebo (60 mg daily from days 1-21), with a primary endpoint of progression-free survival (PFS).

Patients in the combination arm showed significantly improved median PFS of 9.9 months, compared to 6.2 months in the placebo group, and a 49% reduction in the risk of progression. Response rates of 68% and 45% were seen in the combination and control arms, respectively, including a complete response in 10% of patients treated with combination therapy compared to 4% of those treated with vemurafenib alone.

It is anticipated that combining BRAF and MEK inhibitors will become a new standard treatment for advanced BRAF-mutant melanoma. Combination therapy also achieves longer overall/PFS, and better response rates, with dabrafenib plus trametinib, when compared to vemurafenib alone.

An ongoing two-arm study randomised 704 patients with advanced BRAF V600E/K mutation-positive melanoma to either a combination of dabrafenib (150 mg, twice daily) plus trametinib (2 mg, once daily) or to vemurafenib (960 mg, twice daily) alone; a pre-planned interim analysis shows a 31% improvement in overall survival among patients on combined therapy and a 44% reduction in disease progression risk compared to vemurafenib monotherapy. A median PFS of 11.4 and 7.3 months was also seen for dabrafenib plus trametinib and vemurafenib, respectively, and patients in both arms had similar rates of severe adverse events.

“While monotherapy with BRAF inhibitor is currently considered as a standard of care for patients with BRAF mutated advanced melanoma, the data from these two trials, along with trial data presented earlier this year, provide convincing evidence that combination therapy with either dabrafenib and trametinib, or vemurafenib and cobimetinib will be the standard systemic therapy for this patient population,” said Dr Reinhard Dummer, ESMO Faculty Coordinator for Melanoma.

A potential treatment for malignant pleural mesothelioma

> "It is clear from these two studies that we still have a long way to go, but proper selection of patients, improved techniques in radiotherapy, and new immunotherapy treatments will help us to fight this terrible disease."
>
> *Dr Susana Cedres, Vall d'Hebron Institute Oncology, Barcelona, Spain*

ADDITIONAL survival benefits, such as local relapse and overall survival, may not be achieved by high-dose radiotherapy, even after chemotherapy and surgery for malignant pleural mesothelioma.

A study included 153 patients with surgically-treatable malignant pleural mesothelioma. The first round of patients was subjected to three cycles of chemotherapy; a smaller proportion of these patients were randomly assigned to receive either radiotherapy or no further therapy. The primary endpoint of this investigation was the duration of relapse-free survival (RFS).

There was no difference in RFS between those who were treated with additional radiotherapy and those who were not. "It demonstrates that, like in other solid tumours, when two modalities are not sufficient it is very rare that the third modality added would make a benefit," said Prof Rolf A. Stahel, current ESMO President.

Commenting on these findings, Dr Paul Baas, Department of Thoracic Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands, stressed that although there is no role for this therapy, the investigation is still relatively young while patient selection could influence the outcome.

In another independent study, the expression of a protein called programmed cell-death ligand 1 (PD-L1) in patients with malignant pleural mesothelioma is associated with poorer outcomes, and targeted treatment against this protein may be beneficial.

Tissue samples from 119 patients were analysed using an anti-PD-L1 stain to indicate the level of protein expression; the results revealed that there was PD-L1 expression in 20.7% of patients. Those who were negative for PD-L1 expression survived approximately 11 months longer than their positive counterparts.

Commenting on both studies, Dr Susana Cedres, Vall d'Hebron Institute Oncology, Barcelona, Spain, said: "It is clear from these two studies that we still have a long way to go, but proper selection of patients, improved techniques in radiotherapy, and new immunotherapy treatments will help us to fight this terrible disease."

Added artillery aids cancer campaign

TARGETED and promising approaches involving the use of dabrafenib and inhibition of HER2 may potentially help subsets of non-small cell lung cancer (NSCLC) patients.

Dabrafenib - a BRAF inhibitor - has been shown to demonstrate significant anti-tumour activity in patients with advanced BRAF V600 mutant NSCLC, whose disease has progressed after chemotherapy, in an open-label Phase II study which evaluated 78 patients with the NSCLC mutations who were treated twice daily with 150 mg dabrafenib.

An overall response rate of 32% was achieved in those patients who received one or more prior treatments, and a disease control rate of 56% after 12 weeks of treatment. Some adverse effects observed under the drug therapy were fever, asthenia, hyperkeratosis, nausea, and cough. It was also reported that 18% of patients had cutaneous squamous-cell carcinomas including keratoacanthoma.

The drug received a 'Breakthrough Therapy' designation in lung cancer from the FDA earlier in the year. "These findings establish dabrafenib as an effective treatment option for patients with previously treated advanced BRAF V600E NSCLC," said Dr David Planchard, Pulmonary Oncologist, Gustav-Roussy Cancer Campus, Paris, France.

In a different subset of patients with NSCLC, HER2 mutations are another potential treatment target. According to Dr Benjamin Besse, Head of the Thoracic Cancer Unit, Gustav Roussy, Paris, France, neratinib inhibits the HER2 receptor while temsirolimus inhibits mammalian target of rapamycin (mTOR), a protein belonging to the HER2 signalling cascade.

In a study involving 27 patients with advanced, metastatic NSCLC, whose tumours tested positive for HER2 somatic mutations, patients were randomised into either treatment with oral 240 mg neratinib alone or in combination with intravenous 8 mg/week temsirolimus. The latter dosage was increased to 15 mg/week after one 3-week cycle, if tolerated.

The results showed a 21% overall response rate in 14 patients from the combination group and a median progression-free survival of 4 months. This group also experienced more gastrointestinal effects such as diarrhoea, which was managed with prophylactic loperamide.

Commenting on both studies, Dr Fiona Blackhall, Medical Oncologist and Senior Lecturer, The Christie NHS Foundation Trust, and Manchester University, Manchester, UK, said: "Studies of targeted approaches in molecularly defined subsets of NSCLC are consistently yielding better response rates and survivals than historical studies conducted in non-molecularly selected populations."

Head cancer hammered by afatinib

POTENTIALLY improved progression-free survival (PFS) has been spotted in patients with recurrent or metastatic squamous cell carcinoma of the head and neck who take the second-line tyrosine kinase inhibitor (TKI) afatinib versus methotrexate, following the failure of platinum-based chemotherapy.

"The improvement in PFS was associated with a significant delayed worsening of symptoms (such as pain, swallowing, and global health status) versus chemotherapy. Patients treated with afatinib had less pain over time than patients treated with methotrexate. These are important outcomes for patients with these conditions," said Dr Jean-Pascal Machiels, study author, Medical Oncologist, Institut Roi Albert II, Cliniques Universitaires St. Luc, Brussels, Belgium.

Dr Machiels highlighted the regular poor outcome of recurrent or metastatic squamous cell carcinoma of the head and neck: "This is a poor prognosis population and a disease that does not get enough attention from the scientific community because this group of patients often has severe comorbidities and social problems such as alcoholism and tobacco use.

"Frequently these patients have a relapse in the head and neck area. This location is responsible [for] many symptoms that are difficult to palliate: pain, breath disorder, and swallowing difficulties."

Approximately 90% of squamous cell carcinomas of the head and neck overexpress epidermal growth factor receptor (EGFR), a member of the ErbB family of cell surface receptors that is irreversibly blocked by afatinib. 483 subjects with recurrent or metastatic head and neck squamous cell carcinoma, whose cancer had progressed despite treatment with platinum-based therapy, took part in the Lux-Head and Neck 1 trial which evaluated whether simultaneously inhibiting several ErbB receptors would enhance the clinical efficacy of EGFR-targeted treatment.

322 and 161 subjects took 40 mg/day oral afatinib and 40 mg/m^2/week intravenous methotrexate, respectively, with a 20% decrease in risk of progression or death and 2.6 month median PFS observed in afatinib versus methotrexate. "Afatinib improved PFS and delayed worsening of symptoms, and it is the first TKI to demonstrate a significant benefit in this disease," said Dr Machiels.

Dr Machiels hopes that future trials will underline which patient groups genuinely benefit from afatinib. "We should hope that, based on the new molecular data that is becoming available and through advances in the understanding of the molecular biology of this disease, some new treatments will be investigated in [the] near future," he concluded.

Mutations mar clinical comforts of anti-HER2 drugs

> "We already know that PIK3CA is a prognostic marker but now it also appears to predict response to treatment."
>
> *Dr Evandro de Azambuja, Medical Director of Br.E.A.S.T. Data Centre, Jules Bordet Institute, Brussels, Belgium*

BLUNTED benefits beckon for anti-HER2 drug-taking HER2 positive breast cancer (BC) patients possessing PIK3CA mutations, whose incidence differs across various BC subtypes.

This news comes from trials which have identified a lower pathological complete response for patients with PIK3CA mutations, the effects of which were felt in the lapatinib, trastuzumab, and particularly lapatinib plus trastuzumab, treatment arms.

"All of these data seem to be in line and shows that patients with the PIK3CA mutation derive less benefit from anti-HER2 drugs. This is an important pathway in the cells which leads to proliferation, cell survival, and tumour growth. We already know that PIK3CA is a prognostic marker but now it also appears to predict response to treatment," said Dr Evandro de Azambuja, Medical Director, Br.E.A.S.T. Data Centre, Jules Bordet Institute, Brussels, Belgium.

The ongoing NeoPHOEBE neoadjuvant trial is randomising HER2 positive BC subjects with PIK3CA wild type and PIK3CA mutations to receive the anti-HER2 drug trastuzumab, either alone or in combination with a PI3K inhibitor, over 6 weeks, both in addition to weekly paclitaxel for an extra 12 weeks. Dr de Azambuja noted: "PIK3CA mutations did not predict response to trastuzumab but patient numbers were very small and I think it is a question of power. We need more data before we can be confident about whether or not PIK3CA status predicts response to treatment in the adjuvant setting."

"This research adds to the scientific knowledge on PIK3CA mutations but at the moment will not change clinical practice. There is some evidence that when patients have genetic tests and are directed towards clinical trials focused on their mutation they derive more benefit from treatment. I think we will see more and more use of genetic testing for PIK3CA and other mutations to stratify patients to clinical trials, particularly in the neoadjuvant or metastatic settings. This is the way to move forward in clinical research," added Dr de Azambuja.

Rare cancer discrimination must stop

> "Medical decisions are usually risk averse, for many reasons, but rare cancer patients often argue in favour of relaxing rules so that new treatments can be tried."
>
> *Mrs Kathy Oliver, Founding Co-Director, International Brain Tumour Alliance*

RARE cancers, though they make up one-fifth of new cancer cases, are particularly difficult to study; new methodologies are being called for to address current regulatory criteria that are limiting patient access to new therapies in light of a new consensus paper.

Currently, research methodologies and regulations require new cancer treatments to be proven in large numbers of subjects before patients are permitted access to therapies, yet given the small numbers of rare cancer patients, large studies are not possible; lack of evidence and the costs of small trials are discouraging factors for drug developers.

"Unfortunately, rare cancer patients cannot wait," explained Mrs Kathy Oliver, Founding Co-Director, International Brain Tumour Alliance. "This consensus paper calls, among other things, for rare cancer patients to be allowed earlier access to promising experimental drugs. Rules should be relaxed. Compassionate and off-label use of new drugs should be considered. Of course, access to these drugs should be harmonised across Europe to ensure equitable treatment, supervised by competent bodies and the data compiled from this expanded access approach, made available to researchers. Medical decisions are usually risk averse, for many reasons, but rare cancer patients often argue in favour of relaxing rules so that new treatments can be tried."

Thus, the consensus calls for new, innovative approaches in clinical trials, including the factoring in of pre-clinical evidence, uncontrolled studies, observational evidence, and analysis of retrospective cases, as well as randomised clinical trials (both large and small).

The study claims that patient attitudes concerning 'risk' should be taken into account, and that health systems should avoid discriminating against rare cancer patients by allowing a higher degree of uncertainty than usual.

Additionally, available electronic patient records could allow for the measurement of treatment efficacy via patient-reported outcomes in real-world settings, and new treatments could be used temporarily, adopting surrogate endpoints whilst awaiting final outcomes. Patients should also be able to access information about ongoing trials and be encouraged to participate in them.

Clinical trial methodology now needs to adapt in order to accelerate innovations in the rare cancer field; the consensus reminds us that when rare cancer patients live in the hope that new therapies will be discovered, their decisions (to take risks) and specific needs should to be taken into consideration.

Melanoma tumours beware of nivolumab

SUPERIOR response rates (RRs) and longer durations of response are achieved by a monoclonal antibody, nivolumab, when compared with standard chemotherapy in melanoma patients whose cancer has progressed after ipilimumab treatment.

"Previously-treated advanced melanoma patients have limited options," said Prof Jeffrey Weber, Director, Donald A. Adam Comprehensive Melanoma Research Center of Excellence, Moffitt Cancer Center, Tampa, Florida, USA.

Nivolumab belongs to a class of drugs called 'checkpoint inhibitors' which act to relieve a critical brake enforced on the immune system by the tumour itself. Restoration of patients' anti-tumour response is accomplished by the drug, which also promotes tumour shrinkage.

405 advanced melanoma patients took part in a Phase III randomised, open-label study and were randomised in a ratio of 2:1 to receive either intravenous 3 mg/kg nivolumab or the investigator's choice of chemotherapy regimens: 1,000 mg/m^2 dacarbazine or carboplatin AUC6 plus 175 mg/m^2 paclitaxel.

The primary endpoints of the study were objective RR to treatment and overall survival (OS), but the effect of treatment on the secondary objectives of safety, progression-free survival, health-related quality of life, and expression of programmed death-1 ligand (PD-L1), which is the ligand of PD-1 targeted by nivolumab, was also evaluated.

Patients in the nivolumab group showed a higher clinical activity with a 32% RR, longer-lasting treatment responses, and lower toxicity in comparison to the chemotherapy group which had an RR of 11%. There was only a 9% incidence of higher-grade treatment-related side-effects in the nivolumab group in comparison to the 31% incidence in the chemotherapy group.

"The impressive data on duration of response suggest that there will be significant prolongation of progression-free and OS when the analysis of those data is mature," said Prof Weber. He summarised: "The differences in RR and toxicity markedly favour the use of the PD-1 blocking antibody nivolumab compared to results seen with chemotherapy in patients that have failed ipilimumab."

Commenting on the findings, Prof Olivier Michielin, Department of Oncology, University of Lausanne, Lausanne, Switzerland, said: "These results demonstrate that PD blockade, contrary to a common and old dogma of immunotherapy, can produce rapid and deep responses even in advanced and bulky disease. This opens exciting new opportunities to widen the scope of application of immune-oncology for the treatment of Stage 4 melanoma."

Lenvatinib: the potential saving grace for difficult-to-treat thyroid cancer

PROMISING results such as tumour shrinkage and prolonged progression-free survival (PFS) have been observed in the Phase III SELECT trial, assessing the effect of lenvatinib on radioiodine-refractory differentiated thyroid cancer (DTC).

DTC, which includes papillary and follicular, account for a staggering 90% of all cases. Yet, while most DTC patients are curable with surgery and radioactive iodine treatment, those who do not respond to treatment tend to have a poor prognosis; there are very limited options for this difficult-to-treat, life-threatening, and treatment-refractory form of thyroid cancer.

An investigational drug that hopes to address this need for treatment is an oral multiple receptor tyrosine kinase inhibitor (TKI) called lenvatinib. Its novel binding mode selectively inhibits the kinase activities of all vascular endothelial growth factor receptors (VEGFRs) and other pathway-related TKIs that are involved in tumour proliferation, especially angiogenesis.

Due to the inhibiting actions of the drug, the level of baseline angiopoietin-2, a protein which regulates angiogenesis, can be a predictive factor in the response to lenvatinib. "To date, there are no established prognostic or predictive biomarkers for radioiodine-refractory DTC or its treatment, so these studies are crucial in helping to understand further this disease and the best approach to treatment," said Prof Lori Wirth, Assistant Professor of Medicine, Harvard Medical School, and Medical Director, Center for Head and Neck Cancers, Massachusetts General Hospital, Boston, Massachusetts, USA.

Radioiodine-refractory DTC patients who were under lenvatinib therapy for 1 year or more saw rapid tumour shrinkage within the first 8 weeks of treatment. This shrinkage was then maintained but at a slower continuous rate. Promising activity including boosted PFS was observed across all subtypes of advanced thyroid cancer.

A common adverse event that was experienced by 73% of lenvatinib-treated patients was hypertension, a known adverse event of VEGFR inhibition. Prof Wirth mentioned: "Although hypertension is a significant adverse event that must be carefully monitored and managed, it may be an important indicator of the efficacy of treatments such as lenvatinib.

"Further studies are needed to investigate hypertension as a predictive indicator of lenvatinib response so that people with radioiodine-refractory DTC can be managed appropriately to ensure they get the most out of their treatment."

Tumour-infiltrating lymphocytes: treatment and prognosis

PROMISING evidence has arisen, indicating the use of tumour-infiltrating lymphocytes (TILs) as both predictive indicators and treatments of cancer.

TILs may be used to control tumour growth when they are initiated into the tumour itself; thus, depending on TIL expression, patients could potentially gain benefits from certain treatments (such as chemotherapy in breast cancer). The number of TILs at a patient's diagnosis is associated with prognosis, therefore an individual's TILs may be manipulated as a cancer treatment.

According to research, adoptive cell therapy (ACT) with TILs is particularly effective in treating metastatic melanoma. TILs are reintroduced in patients after lymphodepletion, in the presence of interleukin-2 (IL-2). Yet despite its successes, this technique is not currently widely adopted.

A Phase II trial explored the use of low dose IL-2 in subjects who received TILs for metastatic melanoma. Toxicity was considerably lower than expected in the first 20 patients with high-dose IL-2, and there were 2 complete and 7 partial responses.

Such results imply that using low-dose IL-2, in the context of ACT and TILs, is not only well endured by patients, but also clinically competent; other data from clinical research have shown that marked infiltration of tumours by specific immune cell populations is an indicator of good prognosis.

As well as this, scientists established an interaction between higher levels of TILs and an increased benefit from trastuzumab, when they used data from an adjuvant trial to examine the implications and associations of TILs in triple-negative breast cancer (TNBC); each 10% increase in lymphocyte infiltrate saw an 18% reduction in the relative risk of distant recurrence.

Therefore, the role of TILs in the prognosis of TNBC may be the outcome of several factors. The genetic instability and diversity of tumours leads to a number of variants that may strongly stimulate a host immune response against the tumour, and responses to chemotherapy are, at least partly, dependent on an immunological reaction against the dying tumour cells.

Oncotype DX®: revolutionising personal cancer care

PERSONALISING treatment decisions for patients of different cancer types has been given a helping hand by a test that potentially predicts disease aggressiveness and risk of recurrence after surgery; this comes as welcome news to patients and clinicians alike.

"Each year, more than 400,000 men in Europe are diagnosed with prostate cancer (PrC). However, existing methods of examining small amounts of needle biopsy tissue are not adequate for predicting which cancers will be aggressive. This limitation leads many physicians and patients to pursue immediate PrC treatment, even when patients display low-risk features with minimal risk of the advancement of PrC and its known sequelae," said Dr Jennifer Cullen, lead investigator, Center for Prostate Disease Research, Rockville, Maryland, USA.

Yet the launch of the Oncotype DX sees a cancer test which bases its predictions on the assessment of tumour biopsies, and is able to provide information beyond available risk factors, further predicting adverse pathology.

A first-of-its-kind multi-gene test, the assessor measures the level of expression of 17 genes across 4 biological pathways in predicting prostate cancer aggressiveness, and results are given as a Genomic Prostrate Score (GPS) in the range of 0-100. Other clinical factors are also taken into consideration so as to further clarify one's risk prior to treatment intervention.

Thus far, Oncotype DX has been validated to guide treatment decisions using prostate needle biopsy samples, taken before the prostate is removed, thereby providing opportunities for low-risk patients to avoid invasive treatments, such as radical prostatectomy or radiation. Additionally, several studies have been performed in order to test Oncotype DX against other kinds of cancer.

Results from the PACS01 trial demonstrated that the test was able to predict risks of recurrence and survival in pre and post-menopausal patients treated with adjuvant taxane-containing chemotherapy; the recurrence score was a significant predictor of distant recurrence and disease-free survival. Another study confirmed that the Oncotype DX test may help to identify which early-stage breast cancer patients have greater potential to benefit from extended hormonal treatment beyond 5 years.

"The results of this study confirm that the information provided by the Oncotype DX PrC test can help physicians and patients choose the most appropriate treatment approach, based on an individualised risk assessment," concluded Dr Cullen.

Strings added to bow in prostate cancer crusade

MULTIPLE therapies, designed to take prostate cancer (PC) treatment to the next level, are beginning to take centre stage.

Androgen deprivation therapy (ADT) remains a key component of therapy for patients with high-risk non-metastatic, and also metastatic, PC. However, many men will eventually develop castration-resistant prostate cancer (CRPC), which currently carries a poor prognosis, in spite of an overall positive response of metastatic disease to ADT-based treatment.

A first-line combination therapy of antiandrogen and docetaxel triggered a formidable improvement in overall survival (OS) versus ADT therapy alone for patients with 'high-volume', castration-sensitive metastatic PC in randomised Phase III trials. Prof Giuseppe Curigliano, European Institute of Oncology, Milan, Italy, said: "The investigators demonstrated that patients with 'high-volume', castration-sensitive metabolic disease benefit from upfront docetaxel, and it appears to confer a survival benefit that is superior to docetaxel given for metastatic castration-resistant disease.

"However, there is a need to develop better models to determine who 'high' and 'low' volume disease groups should include to avoid, for example, discrimination between a patient with several small lesions and one with a single large lesion."

Dr Eleni Efstathiou, MD Anderson Cancer Center, Houston, Texas, USA, said: "This confirms previously reported trials on locally advanced disease. Importantly, data suggest that lymph node-positive, non-metastatic disease may warrant more aggressive combinatorial strategies incorporating radiotherapy and systemic treatment.

"Data will need to mature and a confirmatory trial is likely warranted for current practice to be altered. Importantly, safety of such an approach is of the essence, given the involved field and diversity in radiation treatment rendered based on availability. Undoubtedly, the data presented is in line with the biology of the disease."

During a separate study, OS was extended by 17 months through abiraterone acetate plus prednisone therapy versus prednisone alone in patients with chemotherapy-naïve metastatic CRPC. However, no added OS or other therapeutic benefit was recorded when custirsen, a second-generation antisense oligonucleotide that targets a pro-survival cellular protein (clusterin) which is overexpressed in response to cellular stress, was added to docetaxel plus prednisone in patients with metastatic CRPC.

Further research into the range of molecular subtypes, revealed by biopsies, is required to tailor treatment as the involvement of various signalling pathways and tumours carrying changes in DNA damage repair may, perhaps, play a significant role in therapy customisation.

Double trouble for advanced melanoma

Patients should be positive about the future clinical application of the combination therapy. The results represent welcome news for individuals with BRAF mutation-positive advanced melanoma, since this can be a promising treatment option.

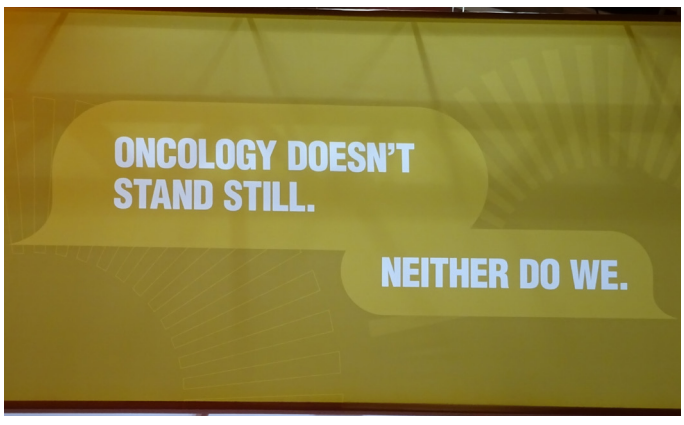
BREAKTHROUGHS in cancer therapy have shown that combining mitogen activated kinase inhibitor cobimetinib with Zelboraf® (vemurafenib) can reduce the risk of disease worsening by half, when compared to Zelboraf alone; the benefits of this could be experienced by thousands of advanced melanoma patients across the world.

The two drugs were combined in order to hinder a major cancer growth pathway, and thus improve clinical outcomes. Results from a Phase III study revealed that subjects with previously untreated BRAF V600 mutation-positive, advanced melanoma, receiving the combination therapy, lived significantly longer without their disease worsening.

Melanoma, though less common, is more aggressive and far more deadly than other forms of skin cancer. If diagnosed early, the disease is generally curable; yet most patients suffer at the hands of poor prognosis, and currently more than 232,000 people a year worldwide are diagnosed with the cancer. In the study, patients were randomised to receive Zelboraf every day for 28 days, plus either cobimetinib or placebo on days 1-21; investigator-assessed progression-free survival was the primary endpoint.

There was a higher overall frequency of Grade 3 or higher adverse events (AEs) such as diarrhoea, nausea, photosensitivity, and lab abnormalities in the combination arm, with almost half of these due to lab abnormalities. Other select AEs, such as serous retinopathy, were also observed at a higher frequency in this arm, with most of these events either Grade 1 or 2 and temporary in nature, though cutaneous squamous cell carcinomas and keratoacanthomas were lower in frequency. AEs leading to withdrawal from treatment were similar in both study groups.

According to Dr Sandra Horning, Chief Medical Officer and Head of Global Product Development, Roche, Basel, Switzerland, patients should be positive about the future clinical application of the combination therapy. The results represent welcome news for individuals with BRAF mutation-positive advanced melanoma, since this can be a promising treatment option.



Gastric cancer meets its match

> "We are encouraged by the signals of anti-tumour activity in advanced GC, and are eager to move ahead with the Phase II study to better understand the potential of pembrolizumab in advanced GC."
>
> *Dr Alise Reicin, Vice President, Oncology, Merck Research Laboratories, Boston, USA*

EXCITING findings may bring new treatment options for advanced gastric cancer (GC) patients as the use of anti-programmed cell death protein 1 (PD-1) therapy, pembrolizumab, is investigated.

Pembrolizumab is a humanised monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Through binding to the PD-1 receptor and blocking the interaction with the receptor ligands, the drug releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

Data from a cohort of the ongoing Phase Ib KEYNOTE-012 study evaluated pembrolizumab monotherapy at 10 mg/kg every 2 weeks in patients with advanced GC, whose tumours were determined to be positive for PD-L1 expression.

Tumours were classified based on the percentage of tumour cells demonstrating expression of the PD-L1 marker (≥1), or any positive staining with the same reagent in tumour stroma, and measured by MSD's proprietary immunohistochemistry clinical trial assay; enrolment included an equal number of Asian and non-Asian subjects.

Tumour shrinkage was demonstrated in 41% of evaluable patients who had measurable disease with one post-baseline scan, per investigator assessed RECIST v1.1 criteria; adverse events were consistent with the drug's previously reported safety data. No infusion-related reactions were observed and no patients discontinued treatment because of drug-related adverse reactions; one death was reported, due to hypoxia, the investigators reported.

The study is ongoing, evaluating the safety, tolerability, and anti-tumour activity of pembrolizumab in patients suffering triple negative breast cancer, advanced head and neck cancer, advanced urothelial cancer, or advanced GC. Secondary endpoints include progression-free survival and duration of response.

"MSD is advancing the development of pembrolizumab across different tumour types and lines of therapy," said Dr Alise Reicin, Vice President, Oncology, Merck Research Laboratories, Boston, Massachusetts, USA. "We are encouraged by the signals of anti-tumour activity in advanced GC, and are eager to move ahead with the Phase II study to better understand the potential of pembrolizumab in advanced GC."

ESMO ANNUAL CONGRESS 2014

IFEMA – FERIA DE MADRID, MADRID, SPAIN
26TH-30TH SEPTEMBER 2014

ESMO AWARDS 2014

ESMO celebrates outstanding work within the field of clinical research and practice by awarding the finest dignitaries for their work each year. These prestigious awards were presented at the Opening Ceremony among world-renowned peers, and represent a symbol of their continuing endurance in the fight against cancer. These awardees will continue to leave their imprint on oncological advances for many years to come.

ESMO AWARD

Prof Carsten Bokemeyer, Germany

Prof Carsten Bokemeyer received this prestigious award for his commitment to accelerating the transition of cancer discovery into real benefit at patient level. He is the world leader in the pathogenesis and biology of malignant germ cell tumours and has developed new therapeutic concepts with cytostatic drugs and immunotherapy in solid tumours.

On receiving this award, Prof Bokemeyer commented: "Being recognised by such an important award always means there were many good teachers, role models, and important co-workers who have contributed to my role in oncology. I would like to cordially thank them at this moment."

ESMO LIFETIME ACHIEVEMENT AWARD

Prof Peter Boyle, UK

This prominent award was bestowed upon Prof Peter Boyle for his long-standing contribution to cancer epidemiology, education, and prevention. He led the EUROCAN+PLUS project for the European Parliament, which developed priorities for coordination of cancer research in Europe.

On receiving this esteemed award, Prof Boyle said: "First, I was surprised. Then, I was delighted. Now I am honoured; both for myself and for my discipline of epidemiology and prevention. To be recognised for my contributions to oncology motivates me to redouble my efforts."

HAMILTON FAIRLEY AWARD

Prof Heikki Joensuu, Finland

Prof Heikki Joensuu was presented with this distinguished award for his significant contribution to improvements in breast cancer and gastrointestinal stromal tumour diagnostics and care.

"I feel very privileged and honoured to receive the Hamilton Fairley Award from ESMO. I have been blessed with a chance to work with many talented collaborators, keen scholars, and brilliant scientists, without whom I could not have achieved much. I do not know how to thank them enough," remarked Prof Joensuu on receiving his award.

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– The only mTOR inhibitor indicated for adult patients with relapsed and/or refractory MCL[1]
– Proven significant progression-free survival benefit vs investigator's choice of treatment[2]

TORISEL® (temsirolimus) injection

Trust in evidence[1]

Torisel® temsirolimus

Prescribing Information: Before prescribing Torisel please refer to the full Summary of Product Characteristics. **Presentation:** Torisel 30 mg concentrate and diluent for solution for infusion. Each vial of Torisel concentrate contains 30 mg temsirolimus dissolved in a total volume of 1.2 ml. **Uses:** Treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). **Dosage:** 175mg infused over a 30 to 60 minute period once weekly for 3 weeks followed by weekly doses of 75mg, infused over a 30 to 60 minute period. To be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Administer an anti-histamine intravenously approximately 30 minutes before the start of each dose of temsirolimus. Treatment should continue until the patient is no longer clinically benefiting or unacceptable toxicity occurs. Suspected adverse reactions may require temporary interruption and/or dose reduction. The starting dose of 175mg should be reduced to 75mg and then 50mg. The continuing dose of 75 may be reduced to 50mg and then 25mg as necessary. In elderly, renal impairment and mild hepatic impairment patients, temsirolimus should be used with caution but there is no specific recommended starting dose adjustment. **Contra-indications:** Hypersensitivity to temsirolimus, its metabolites (including sirolimus) polysorbate 80 and any of the excipients. Use of temsirolimus in patients with mantle cell lymphoma with moderate or severe hepatic impairment is not recommended. **Warnings and Precautions:** The incidence and severity of adverse events is dose dependent. Patients receiving the starting dose of 175mg weekly for the treatment of MCL must be followed closely to decide on dose reductions/delays. Not recommended for paediatric patients. Elderly patients may be more likely to experience certain adverse reactions. Use with caution in severe renal impairment patients. Patients on temsirolimus who develop thrombocytopaenia may be at increased risk of bleeding events, including epistaxis. Patients on temsirolimus with baseline neutropaenia may be at risk of developing febrile neutropaenia. Live vaccinations should be avoided. Use carefully in patients with CNS tumours and/or those receiving anticoagulation therapy due to an increased risk of intracerebral bleeding. Cataracts have been observed in some patients who received a combination of temsirolimus and interferon-α. Hypersensitivity/infusion reactions including some life-threatening and rare fatal reactions have been associated with the administration of Torisel. In all patients with severe infusion reactions, Torisel infusion should be interrupted and appropriate medical therapy administered. Use with caution in patients with known hypersensitivity to antihistamines or in those who cannot receive antihistamines. Torisel may be associated with an increase in blood glucose levels in diabetic and non-diabetic patients. This may result in the need for an increase in dose of, or initiation of, insulin and/or hypoglycaemic agent therapy. Use of Torisel is associated with increases in serum triglycerides and cholesterol. Torisel has also been associated with abnormal wound healing, so care should be taken in the peri-operative period. Patients may be immunosuppressed and should be carefully observed for the occurrence of infections, including opportunistic infections such as pneumocystis jiroveci pneumonia (PCP). For patients who require use of corticosteroids or other immunosuppressive agents, prophylaxis of PCP may be considered. Among patients receving 175mg/week, infections were substantially increased compared to lower doses and compared to conventional chemotherapy. Patients on temsirolimus with baseline neutropaenia may be at risk of developing febrile neutropneia. Grade 3/4 thrombocytopenia have been observed. Patients on temsirolimus who develop thrombocytopenia may be at an increased risk of bleeding events, including epistaxis. Cases of non-specific interstitial pneumonitis, including fatal reports, have been reported in patients receiving weekly intravenous Torisel; empiric treatment with corticosteroids and/or antibiotics may be considered. Opportunistic infections such as PCP should be considered in the differential diagnosis. Patients should undergo baseline radiographic assessment prior to the initiation of Torisel therapy. Patients should be followed closely for occurrence of clinical respiratory symptoms. The concomitant use of Torisel with ACE inhibitors may increase the risk of angioneurotic oedema-type reactions. Torisel contains 35% volume ethanol and this should be considered in patients suffering from alcoholism and high-risk groups, such as patients with liver disease or epilepsy. For patients with mantle cell lymphoma, it is recommended that coadministration of CYP3A4/5 inducers should be avoided due to the higher dose of temsirolimus. Concomitant treatment with agents that have strong CYP3A4 inhibition potential should be avoided. Concomitant treatment with moderate CYP3A4 inhibitors should only be administered with caution in patients receiving 25mg and should be avoided in patients receiving temsiorolimus at a higher dose. **Pregnancy and Lactation:** Torisel must not be used during pregnancy. Men should use medically acceptable contraception while recieving Torisel. Breast-feeding should be discontinued during Torisel therapy. **Interactions:** Sunitinib, CYP3A inhibitors and inducers, amphiphilic agents and ACE inhibitors. **Undesirable Effects:** There have been reports of serious reactions observed with Torisel, these include hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycaemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipaemia, intracranial haemorrhage, renal failure, intestinal perforation, wound healing complication, thrombocytopenia, neutropenia (including febrile neutropenia), pulmonary embolism. Very common (≥1/10):Bacterial and viral infections, Pneumonia, Neutropaenia, Thrombocytopaenia, Anaemia, Hyperglycaemia, Hypercholesterolaemia, Hypertriglyceridaemia, Decreased appetite, Hypokalaemia, Insomnia, Dysgeusia, Headache, Dyspnoea, Epistaxis, Cough, Nausea, Diarrhoea, Stomatitis, Vomiting, Constipation, Abdominal pain, Rash, Pruritus, Dry Skin, Arthralgia, Back pain, Fatigue, Oedema, Asthenia, Mucosal inflammation, Pyrexia, Pain, Chills, Chest pain, blood creatinine increased. Common (≥1/100 to <1/10): Sepsis, Candidiasis, Urinary Tract infection, Upper respiratory tract infection, Pharyngitis, Sinusitis, Rhinitis, Folliculitis, Leukopaenia, Lymphopaenia Allergic/hypersensitivity reactions, Diabetes mellitus, Dehydration, Hypocalcaemia Hypophosphataemia, Hyperlipidaemia, Depression, Anxiety, Dizziness, Paresthaesia, Somnolence, Ageusia, Conjunctivitis, Venous thromboembolism, Thrombophlebitis, Hypertension, Interstitial lung disease (includes pneumonitis, alveolitis, alveolitis allergic, pulmonary fibrosis and eosinophilic pneumonia), Pleural effusion, Gastrointestinal haemorrhage, Gastritis, Dysphagia, Abdominal distension, Aphthous stomatitis, Oral pain, Gingivitis, Dermatitis, Exfoliative rash, Acne, Nail disorder, Ecchymosis, Petechiae, Myalgia, Renal failure, Increased aspartate aminotransferase, Increased alanine aminotransferase. Please refer to the SmPC for all other reported side-effects. **Legal category:** POM. **Package Quantities:** Pack contains 2 x glass vials, 1 vial x 1.2ml of concentrate and 1 vial x 2.2ml of diluent. **Basic NHS Cost:** £620. **Marketing Authorisation Holder:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. **Marketing Authorisation number(s):** EU/1/07/424/001. For full prescribing information and details of other side effects see Summary of Product Characteristics. Further information is available on request from Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. **Date of Prescribing Information:** August, 2014. **Ref: TO 6_2**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Pfizer Medical Information on 01304 616161.

1. Pfizer. TORISEL (temsirolimus) Summary of Product Characteristics. 2. Hess G, Herbrecht R, Romaguera J *et al*. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009;27:3822–9.

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TORM 013

SEQUENTIAL ANDROGEN RECEPTOR PATHWAY INHIBITOR IN PROSTATE CANCER: PILING-UP THE BENEFITS OR A CASE FOR CROSS-RESISTANCE?

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ABSTRACT

In the last 10 years, there has been accumulating evidence that, even in a low serum testosterone environment, the androgen receptor (AR) remains the main driver of prostate cancer progression. This has led to the discovery and clinical development of new anti-androgens and androgen biosynthesis inhibitors. Enzalutamide and abiraterone acetate are the lead compounds of this new generation of agents, but multiple other agents are on their way. Because they both target the ligand-dependent regulation of AR activity, it is plausible that cross-resistance may exist when both drugs are used sequentially, and that the benefit of these agents may fade away when sequencing them. As the exact mechanisms for cross-resistance between AR-targeted agents remain unclear at this point, additional clinical studies are crucial to define the exact combination or sequencing order that could yield highest clinical benefits. Moreover, new molecular targets are needed in order to address these resistances, as well as establishing biomarkers to improve patient selection that could most benefit from AR-targeted therapies, but also help develop novel agents to improve and optimise the management of castration-resistant prostate cancer and metastatic, castration-resistant prostate cancer.

Keywords: Enzalutamide, abiraterone, androgen receptor, anti-androgens, cross-resistance.

INTRODUCTION

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has been profoundly modified with the discovery of new androgen receptor (AR) pathway inhibitors. Until 2010, docetaxel-based chemotherapy was indeed the only option to improve overall survival (OS) of patients progressing under androgen-deprivation therapy. However, for diverse reasons including age and comorbidities, it appears now that many patients do not receive docetaxel, and more options are needed.[1]

In the last 10 years, there has been accumulating evidence that, even in a low serum testosterone environment, the AR remains the main driver of prostate cancer (PrCa) progression. This has led to the discovery and clinical development of new anti-androgens and androgen biosynthesis inhibitors (ABIs). Enzalutamide and abiraterone acetate are the lead compounds of this new generation of agents, but many others are on their way (ARN-509, ODM-201, TOK-001).[2-7] In contrast to docetaxel, these new AR pathway inhibitors are orally available and easy to manage with a very favourable toxicity profile. It is not surprising then that these agents have been widely adopted by physicians as soon as they became available. Because they both target the ligand-dependent regulation of AR activity, it is plausible that cross-resistance may exist when both drugs are used sequentially.

Indeed, the development programmes of abiraterone and enzalutamide were conducted quasi in parallel, therefore not addressing that

important question for the clinician. One of the main inclusion criteria of these four pivotal clinical trials, supporting indication approval for either abiraterone or enzalutamide, is that the patients enrolled in the studies could not have previously received the other agent. Enzalutamide has recently been approved by the FDA and EMA in the pre-docetaxel setting,[8,9] similarly to abiraterone, which means that a patient can sequentially receive abiraterone or enzalutamide, then docetaxel, and finally the other one of these two AR-targeted agents. This is an important factor as it means that should a cross-resistance exist, it could not have been unveiled by these trials; this was raised in an editorial by Goldkorn et al.,[10] and up until last year, the issue remained unaddressed.

Understanding the level of cross-resistance between these drugs is crucial for the clinicians but also for regulators and reimbursement authorities. Most importantly, this may severely hamper the development of the newer generation of AR pathway inhibitors. Repeating agent versus placebo in a setting where enzalutamide or abiterone will be used later is unlikely to produce positive trials as demonstrated by the recent failure of the TAK-700 programme, in which TAK-700 therapy failed due to a high degree of cross-over to abiraterone, enzalutamide, and chemotherapy.[11] To date, there has been no direct head-to-head trial comparing abiraterone and enzalutamide.

While other cross-resistances have also been identified between AR-targeted agents and taxane chemotherapy, this review will investigate the potential mechanisms for cross-resistance between AR-targeted agents and their impact on clinical implications in CRPC and mCRPC management within this therapeutic class.

THE AR SIGNALLING PATHWAY FOR CRPC

In the last few years, novel agents targeting AR signalling have been developed to address the unmet medical needs generated by CRPC and mCRPC.

ABIs: Abiraterone Acetate

A few years ago, several research groups demonstrated that, in the absence of exogenous testosterone, PrCa cells were capable of expressing enzymes, encoding androgen-synthesising enzymes, and maintaining intratumoural androgens at concentrations capable of activating AR target genes, as well as maintaining tumour cell survival. One of these important enzymes is CYP17A1, or 17α-hydroxylase/17,20 lyase/17,20 desmolase, a key enzyme in the androgen pathway.[12] Abiraterone acetate (Zytiga®, Janssen) is the prodrug of abiraterone that is a selective and irreversible inhibitor of CYP17A. Oral administration of abiraterone increases levels of adrenocorticotropic hormone (ACTH) and steroids upstream of CYP17A, and suppresses serum testosterone, downstream androgenic steroids, and estradiol. Through feedback mechanisms, ACTH increases, potentially resulting in a syndrome of secondary mineralocorticoid excess, hence justifying the association with low-dose daily prednisone.

The Cougar 301 (COU-AA-301) Phase III trial was a pivotal clinical trial conducted in 1,195 mCRPC patients who had failed docetaxel therapy.[13] At the final analysis, with median follow-up of 20.2 months, median OS was 15.8 months for abiraterone/prednisone and 11.2 months for prednisone (HR, 0.74; 95% CI, 0.64-0.86; p<0.0001; Table 1).[14] These results led to the approval of abiraterone by the FDA in April 2011 and by the EMA in September 2011.

The Cougar 302 (COU-AA-302) trial was conducted in 1,088 mCRPC patients who had not previously received chemotherapy, thus challenging docetaxel as a primary modality.[15] At a median follow-up duration of 27.1 months, radiological progression-free survival (rPFS) was significantly improved from 8.2 months in the prednisone group to 16.5 months in the abiraterone/prednisone group (HR, 0.52; 95% CI, 0.45-0.61; p<0.0001). For the patients, however, one of the most relevant benefits was that abiraterone delayed the time to administration of cytotoxic chemotherapy by 9.7 months (HR 0.61; 95% CI, 0.51-0.72; p<0.0001).[16] When the results were initially released, the predefined endpoints for OS were not met (p=0.01). However, the results were considered strong enough to grant label-extension for pre-chemotherapy clinical settings in December 2012, both by the FDA and the EMA.

The final OS results were released at the latest European Society of Medical Oncology meeting.[17] With median follow-up of 49.4 months at final analysis, abiraterone/prednisone significantly prolonged OS versus prednisone alone (median OS, 34.7 versus 30.3 months; HR, 0.80; 95% CI, 0.69-0.93; p=0.0027).

Table 1: Main findings from key clinical studies on abiraterone and enzalutamide.

Study	Population	Active therapy arm containing	Median follow-up	OS (versus comparator arm)	PSA response rate*
COU-AAA-301	1,195 CRPC patients with previous docetaxel therapy	Abiraterone	12.8 months[13]	14.8 versus 10.9 months; HR, 0.65; 95% CI, 0.54-0.77; p<0.001	29% versus 6% in the placebo arm; p<0.0001
			20.2 months[14]	15.8 months versus 11.2 months; HR, 0.74, 95% CI 0.64-0.86; p<0.0001	29.5% versus 5.5 in the placebo arm %; p<0.0001
COU-AAA-302	1,088 mCRPC patients chemotherapy-naïve	Abiraterone	22.2 months[15]	OS was improved with abiraterone–prednisone (median not reached, versus 27.2 months for prednisone alone); HR, 0.75; 95% CI, 0.61-0.93; p=0.01	-
			27.1 months[16]	35.3 versus 30.1 months; HR, 0.79; 95% CI, 0.66-0.95; p=0.0151	-
			49.4 months[15]	34.7 versus 30.3 months; HR, 0.80; 95% CI, 0.69-0.93	-
Loriot et al.[30]	38 mCRPC patients who had received treatment with docetaxel and enzalutamide in the AFFIRM trial	Abiraterone	-	-	8% (triple sequential therapy) and 29% (abiraterone without prior enzalutamide)
Noonan et al.[31]	30 patients with progressing disease following treatment with docetaxel and enzalutamide	Abiraterone	-	11.8 months (Cougar 301 study, 14.8 months)	3% (triple sequential therapy) and 60% (enzalutamide only)
AFFIRM[20]	1,199 CRPC patients with previous docetaxel therapy	Enzalutamide	14.4 months	18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR, 0.63; 95% CI, 0.53-0.75; p<0.001)	54% versus 2% in the placebo arm, p<0.001
PREVAIL[21]	1,717 mCRPC patients chemotherapy-naïve	Enzalutamide	49.4 months	-	78% versus 3%; p<0.001

Table 1 continued.

Study	Population	Active therapy arm containing	Median follow-up	OS (versus comparator arm)	PSA response rate*
Schrader et al.[33]	35 mCRPC patients who had received abiraterone and received enzalutamide after failure	Enzalutamide	-	-	43.8% (patients who were initially abiraterone-sensitive) and 15.8% (patients who were initially abiraterone-insensitive) versus 45.7% (abiraterone only)

*PSA response rate: proportion of patients with a decrease of ≥50% in the PSA concentration from baseline.

CI: confidence interval; HR: hazard ratio; (m)CRPC: (metastatic) castration-resistant prostate cancer; OS: overall survival; PSA: prostate-specific antigen.

Second-Generation AR Antagonist: Enzalutamide

Enzalutamide (Xtandi®, Medivation and Astellas Pharma) is a second-generation nonsteroidal anti-androgen that retains activity in the setting of increased AR expression, one of the most common features of mCRPC.[18,19] In contrast to abiraterone, enzalutamide does not require steroid protection, so a placebo was chosen as the comparator in the clinical trials. Consequently, this hampers the comparison between the relative benefit of abiraterone and enzalutamide versus their chosen comparator.

The FDA approved enzalutamide in August 2012 following the promising results of the Phase III AFFIRM trial.[20] The study was conducted in 1,199 CRPC patients who had previously failed chemotherapy treatment with docetaxel. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR, 0.63; 95% CI, 0.53-0.75; p<0.001). A subsequent Phase III clinical trial, the PREVAIL study,[21] aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were chemotherapy-naïve. Median OS (risk of death, HR=0.71; p<0.0001) was significantly improved in the enzalutamide group compared with placebo. This trial led to an extension of indication in chemotherapy patients by the FDA and the EMA, in September and October 2014 respectively.[8,9]

As for abiraterone, the main benefit of enzalutamide in chemotherapy-naïve patients is to delay radiographic progression and time to chemotherapy. At 12 months, median rPFS was not reached in the enzalutamide group, as compared with 3.9 months in the placebo group; the rate of rPFS was significantly improved in the enzalutamide group compared to the placebo group (65% versus 14%; HR, 0.19; 95% CI, 0.15-0.23; p<0.001). The median time to initiation of cytotoxic chemotherapy was 28.0 months in the enzalutamide group, as compared with 10.8 months in the placebo group (HR 0.35; 95%CI, 0.3-0.40; p<0.001).[21]

THE POTENTIAL FOR CROSS-RESISTANCE AMONG ANDROGEN-BLOCKING AGENTS

Molecular Evidence of Cross-Resistance between Anti-Androgens and Steroidogenesis Inhibitor

The most prominent rationale for enzalutamide resistance is the F867L mutation, a missense mutation in the ligand-binding domain of the AR receptor, which acts like an antagonist-to-agonist switch, thus converting enzalutamide into an AR agonist in preclinical models.[22,23] Furthermore, the AR F876L mutant encoding DNA was found in the plasma of patients progressing on ARN-509, a novel AR antagonist.[23]

Efstathiou et al.[24] recently reported the results of a very interesting prospective Phase II study on bone marrow biopsies of 60 mCRPC patients, obtained before and after 8 weeks of treatment with enzalutamide. In most patients, enzalutamide was effective in blocking nuclear translocation of AR, but interestingly enough, testosterone increased following 8 weeks of treatment in the majority of patients with evaluable paired samples in both blood (40 of 51, 78%) and bone marrow aspirate plasma (34 of 44, 77%). This suggests an adaptive physiologic feedback mechanism that could contribute to enzalutamide resistance.

In a previous work by Efstathiou et al.,[25] conducted in a cohort of 57 patients with CRPC, the same group showed that abiraterone depleted blood and bone marrow aspirate testosterone, the latter remaining suppressed at progression, thus indicating the strong action of abiraterone in inhibiting intratumoural production of androgen. The authors suggested that in patients progressing in the presence of a depleted environment, persistent androgen signalling could be explained by native ligand-independent mechanisms or by altered steroid biosynthesis.

While it is still unclear what drives resistance to abiraterone, preliminary results show that it could be explained by the reactivation of intratumoural androgen synthesis through upregulation of CYP17A1 transcripts, or other transcripts encoding enzymes involved in androgen synthesis within tumour cells. Other investigated mechanisms include the involvement of the glucocorticoid receptor[26] and the induction of AR splice 7 variant with a ligand-independent AR transactivation ability, as detected in circulating tumour cells from CRPC patients with resistances to enzalutamide or abiraterone.[27-29]

Current Clinical Evidence for Cross-Resistance between Abiraterone and Enzalutamide

Abiraterone therapy following docetaxel plus enzalutamide treatment

Loriot et al.[30] reported the results of a French study evaluating the efficacy and safety parameters of abiraterone in 38 mCRPC patients following treatment with docetaxel and enzalutamide in the context of the AFFIRM trial (triple sequential therapy arm).[20] The control arm (n=16) comprised patients from this trial who had been originally assigned to the placebo arm, which means they received abiraterone without prior enzalutamide. Main results revealed that patients who had received both active therapies had shorter and poorer responses than patients who had only received abiraterone. Median PFS was 2.7 and 6.5 months in the triple sequential therapy arms and the control arm, respectively. Similar results were observed in terms of median OS (7.2 and 11.4 months, respectively), prostate-specific antigen (PSA) response >30% (18% and 36%, respectively), and PSA response >50% (8% and 29%, respectively) decrease from baseline.

In a Canadian study, Noonan et al.[31] also evaluated 30 patients receiving abiraterone for progressing disease following treatment with docetaxel and enzalutamide. Median PFS (time to progression [TTP]) with abiraterone was 3.6 weeks (Cougar 301 study, 5.6 months), while median OS was 11.8 months (Cougar 301 study, 14.8 months).[13] PSA responses as >30% and >50% decreases from baseline were 11% and 3%, respectively (Cougar 301 no available data, and 29%, respectively).

Both of these studies highlighted the fact that abiraterone therapy following docetaxel and enzalutamide could be associated with shorter and poorer responses to therapy, as well as weaker PSA responses. While the safety of abiraterone following enzalutamide appears to be acceptable, the underlying mechanism to explain poorer responses for sequential use of novel therapies could be acquired cross-resistances. However, larger cohort data are required to firmly establish a link between prior enzalutamide therapy and abiraterone resistance, as these studies lacked in statistical power and presented selection bias. In the meantime, these findings are the only clinical data that physicians can rely on to select and choose appropriate therapy for mCRPC.

Enzalutamide therapy following docetaxel plus abiraterone treatment

As abiraterone was approved sooner than enzalutamide, a large majority of patients received sequential enzalutamide following abiraterone in the context of expanded-access programmes and compassionate use, and were therefore involved in many clinical studies. The clinical benefits and safety of enzalutamide in patients with mCRPC (n=61) who failed docetaxel and abiraterone therapy were evaluated in a retrospective study.[32] Enzalutamide had a modest clinical activity, as demonstrated by a median PFS of 12.0 weeks.

Median time to PSA progression was 17.4 weeks and the OS was 31.6 weeks. The safety profile of enzalutamide was consistent with those of previous clinical trials.

In a retrospective study conducted at a German centre, 35 mCRPC patients who had received abiraterone for a median duration of 9.0 months were evaluated.[33] 45.7% of them had achieved a ≥50% PSA decline. Then, after failure of abiraterone, they received enzalutamide for a median duration of 4.9 months. Enzalutamide achieved a modest response, with 43.8% of the patients who were initially abiraterone-sensitive and 15.8% of patients who were initially abiraterone-insensitive having a ≥50% PSA decline. Median TTP was 4.0 months among patients with at least one declining PSA value while taking enzalutamide. A similar retrospective study in the UK also suggested limited activity for enzalutamide as second-line in mCRPC (n=39) following failure of abiraterone and docetaxel therapy.[34] 41% of patients achieved a ≥30% PSA decline and, among patients who were refractory to abiraterone, only 9% of patients achieved a ≥50% PSA decline with enzalutamide.

At the 2014 Genitourinary Cancers Symposium held on 30th January-1st February, 2014 in San Francisco, USA, many new findings were made available on this pathway. Roeder et al.[35] presented the results of a study on 24 mCRPC Danish patients who received enzalutamide following disease progression with docetaxel and abiraterone in the setting of a compassionate use program. Median OS (minimum follow-up of 3 months) was 4.8 months, 46% of patients had a PSA response >30% decrease from baseline, and the best median PSA response was -22%. These results were less marked than those in the AFFIRM study,[20] therefore being consistent with the possibility of a cross-resistance for this sequential order as well. At the same meeting, Cheng et al.[36] presented the results of a retrospective study on 195 mCRPC patients from 7 centres. A marked difference was observed in terms of PSA response as 39% of previously treated patients with abiraterone experienced a ≥30% PSA decline, compared to 55% of abiraterone-naïve patients (odds ratio 2.3; 95% CI 1.0–5.5; p=0.06).

A retrospective study from 7 UK centres evaluated the sequential use of enzalutamide following abiraterone and taxane chemotherapy failure in 79 mCRPC patients.[37] Preliminary results revealed a TTP for abiraterone of 37.44 weeks and a TTP of 15.87 weeks for enzalutamide (at the time of the abstract presentation, 55% of patients had discontinued enzalutamide therapy because of disease progression). In another study, 23 mCRPC patients received enzalutamide therapy as part of an expanded access programme, following failure to docetaxel and abiraterone therapy.[38] Median biological PFS was 11.9 weeks, while 39% of patients showed enzalutamide sensitivity, as defined by a PSA response >50% decrease from baseline.

A Canadian study reviewed the cases of 26 patients with mCRPC and who received the same sequential therapy.[39] 27% of patients had a PSA response >50% decrease from baseline, and an additional 27% had a PSA response >30% decrease from baseline. Median time to treatment failure was 4.9 months. A retrospective chart review was conducted on 63 patients progressing on abiraterone and docetaxel, in order to determine the PSA response rates of enzalutamide.[40] After a median follow-up of 12.5 weeks, ≥30% PSA decline was observed in 29% of patients.

At the 2014 American Society of Clinical Oncology Annual Meeting held 30th May-3rd June in Chicago, USA, Zhang et al.[41] presented the results of a prospective study conducted at Duke University on mCRPC patients (n=20) who had received pre-chemotherapy abiraterone, and then went on to receive either enzalutamide or docetaxel therapy. Median PFS was 3.6 and 5.1 months for the enzalutamide and docetaxel groups, respectively. Median OS was 8.5 months for the enzalutamide group, while the median OS for the docetaxel was not reached. A ≥50% PSA decline was observed in 12.5% and 50% of patients, respectively. These findings also highlight the high probability for cross-resistance between both novel agents, while confirming the higher additional radiographic and clinical benefits of docetaxel following first-line abiraterone.

The Current Consensus on Sequential Monotherapy

In April 2014, a European Expert Consensus Panel[42] published some recommendations on the management of mCRPC, including guidance in the selection and sequencing of available therapeutic options. The advisors worked according to a modified Delphi method; a strong consensus (90% of the votes) was made as the advisors agreed on the fact that there are cross-resistances between

approved AR-targeted agents, and that patients with disease progression on either abiraterone or enzalutamide should not be prescribed the other novel agent (85-86% agreed) due to cross-resistance, or should be prescribed the novel agent only if a 'durable' response to the first agent had occurred (76% agreed).

CONCLUSION

As the exact mechanisms for cross-resistance between AR-targeted agents remain unclear at this point, additional clinical studies are crucial to define the exact combination or sequencing order that could yield highest clinical benefits. Moreover, new molecular targets are needed in order to address these resistances, as well as establishing biomarkers to improve patient selection that could most benefit from AR-targeted therapies but also help develop novel agents to improve and optimise the management of CRPC and mCRPC.

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UNMET MEDICAL NEEDS IN NON-SMALL-CELL LUNG CANCER TREATMENT: HOW TO DESIGN PRE-EMPTIVE COMBINATION THERAPIES

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ABSTRACT

The rapidly expanding catalogue of human oncogenic mutations, coupled with difficulties in identifying the cellular targets of active compounds in phenotypic screens, has refocused drug discovery efforts on inhibitors of specific cellular proteins. This new 'target-based' approach has enjoyed some spectacular successes in several types of tumours, including non-small-cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) mutations occur in 17% of NSCLC patients, with notable response to single agent therapy. Unfortunately, all patients eventually develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), while complete remission rate to EGFR TKIs monotherapy is low. Priming BIM, a proapoptotic signalling BH3-only protein, induces sensitivity to erlotinib [Tarceva®] in EGFR-mutant cell lines. Synthetic lethal approaches and pre-emptive therapies based on the initial expression of BIM may significantly improve treatment outcomes. EGFR mutations result in transient pro-death imbalance of survival and apoptotic signalling in response to EGFR inhibition. Src homology 2 domain-containing phosphatase 2 is essential to the balance between extracellular signal-regulated kinase, phosphoinositide-3-kinase/protein kinase B and signal transducer and activator of transcription 3 activity. Furthermore, stromal hepatocyte growth factor confers EGFR TKI resistance and induces inter-receptor crosstalk with Ephrin Type-A receptor 2, CDCP1, AXL, and JAK1. A better understanding of the complex cancer molecular biology of EGFR mutant lung cancer is crucial for development of effective treatment and design of successful future clinical studies.

Keywords: Lung cancer, epidermal growth factor receptor (EGFR) mutations, synthetic lethal combinations.

INTRODUCTION

Attempts to treat cancer with drugs that target mutated proteins have been met with mixed success. Lung adenocarcinoma is a typical example in which systemic therapy is personalised based on predictive molecular biomarkers. Anti-cancer treatments are dominated by targeting genetic abnormalities such as oncogenes or non-oncogenic genetic defects. Historically, the standard of care for advanced non-small-cell lung cancer (NSCLC) has been platinum-based combination chemotherapy. This 'one-size-fits-all' approach to treatment has plateaued in terms of efficacy and has been largely supplanted by a 'personalised' approach, primarily due to the discovery that certain subsets of patients have a mutated or overexpressed receptor tyrosine kinase (RTK) gene responsible for initiation and maintenance of their cancer.[1,2] Erlotinib, gefitinib (Iressa®), and the second-generation, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) afatinib (Giotrif®), have

offered a therapeutic alternative for patients with metastatic EGFR positive lung cancer; an approach that has proven superiority over standard platinum-based chemotherapy.[3-5]

A recent meta-analysis of patients with NSCLC and EGFR activating mutations showed that first-generation EGFR TKIs significantly delayed disease progression but had no effect on overall survival (OS).[6] However, targeting genetic defects such as EGFR mutations with a personalised strategy is limited by the high degree of intra-tumour heterogeneity, adaptation of genetic networks, and high somatic mutation rates in cancer.[7] In this short review we will try to demonstrate that, 10 years after the discovery of EGFR mutations, first-line EGFR TKI monotherapy for patients with mutant EGFR NSCLC is incomplete, and EGFR inhibitors, reversible or irreversible, are unlikely to provide cures for the majority of patients.

SYNTHETIC LETHALITY APPROACHES FOR IMPROVING SURVIVAL IN NSCLC

The Spanish Lung Cancer Group performed the first large scale screening of EGFR mutations for erlotinib treatment.[8] We were also able to examine the expression levels of the proapoptotic signalling BH3-only protein, BIM, in pretreatment tumour samples from 83 patients included in the EURTAC trial.[3] BIM expression was low or intermediate in 53 (63.96%) and high in 30 (36.14%) of these patients. Progression-free survival (PFS) to erlotinib was 12.9 months for those with high and 7.2 months for those with low/intermediate BIM expression levels, while among chemotherapy-treated patients, it was 5.8 and 5.5 months, respectively (p=0.0003).[9] OS was 28.6 months for patients with high BIM expression and 22.1 months for those with low/intermediate BIM expression (p=0.0364).[9]

Multivariate analyses showed that erlotinib was a marker of longer PFS (HR=0.35, p=0.0003), while high BIM expression was a marker of longer PFS (HR=0.49, p=0.0122) and OS (HR=0.53, p=0.0323).[9] The levels of all three major splicing isoforms - BIM extra-long (BIM-EL), BIM long, and BIM short - are induced after erlotinib treatment in drug-sensitive PC-9 cells, but not in drug-resistant H1650 and H1975 cells. EGFR signalling influences BIM expression and phosphorylation status mainly via the ERK pathway, and erlotinib appears to induce significant dephosphorylation of BIM-EL, resulting in an increase in its pro-apoptotic function.[10,11] Although pretreatment BIM expression levels may not be enough to predict outcome to EGFR TKIs, they may serve as a companion diagnostic marker for synthetic lethal combinations in lung cancer with EGFR mutations.

RESISTANCE TO EGFR TKIS, EVEN WITH HIGH BASELINE BIM LEVELS

The two primary signalling pathways activated by EGFR include the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) axes. Src tyrosine kinases and activation of the signal transducer and an activator of the transcription 3 (STAT3) pathway, as well as downstream signalling, have also been well documented.[12] EGFR phosphorylation leads to recruitment of multiple effecter proteins through recognition and binding of Src-homology 2 domain-containing phosphatase 2 (SHP2) to phosphotyrosine motifs on the receptor.[12] SHP2 (encoded by PTPN11) is a ubiquitously expressed SH2 domain-containing protein tyrosine phosphatase. Despite its direct function in protein dephosphorylation, SHP2 plays an overall positive role in transducing signals initiated from growth factors/cytokines and extracellular matrix proteins and initiating various downstream signalling cascades, including the PI3K and MAPK.[12,13] By contrast, SHP2 functions as a negative regulator of the Janus kinase (JAK)/STAT pathway.[14]

In 2004, Sordella and colleagues[15] were able to demonstrate the differential EGF-induced tyrosine phosphorylation pattern seen with wild-type (WT) and mutant EGFR receptors. For instance, Y845 is highly phosphorylated in the L858R missense mutant, but not in the WT or deletion mutant, and hence, appears to be unique in distinguishing between the two types of EGFR mutations.[15] Y845 (pY845) phosphorylation stabilises the activation loop, maintains the enzyme in an active state, and regulates STAT3/5 activity.[15] Surprisingly, the EGFR L858R mutation leads to a decreased ability to activate ERK compared to WT EGFR, which correlates with decreased EGFR internalisation, reduced phosphorylation of SHP2, hyperactivity of STAT3, and reduced sensitivity to gefitinib.[16] Lazzara and colleagues[16] found that SHP2 Y542 phosphorylation was not induced in response to EGF in the H3255 cells, which harbour the missense L858R exon 21 mutation, suggesting that SHP2 activity may be less efficiently promoted by EGFR L858R and the STAT3 pathway may be more active.

The main problem is that STAT3 signalling is not inhibited with EGFR TKI monotherapy.[15] According to our experience, the combination of gefitinib + ruxolitinib (Jakavi®: a JAK inhibitor) is additive in the 11-18 cell line which also harbours the EGFR L858R mutation (unpublished data). Even the second-generation irreversible EGFR TKIs, such as afatinib or dacomitinib, do not abrogate, and may also induce STAT3 phosphorylation in gefitinib or erlotinib-resistant cell lines such as H1975 or PC9-R.[17] Afatinib activates interleukin-6 receptor (IL-6R)/JAK1/STAT3 signalling via autocrine IL-6 secretion in both cells. Blockade of IL-6R/JAK1 significantly increases sensitivity to afatinib through inhibition of afatinib-induced STAT3 activation. The role of the paracrine IL-6R/JAK1/STAT3 loop between stroma and cancer cells in the development of drug resistance is crucial.[17] Yao et al.[18] uncovered the existence of a subpopulation of cells, intrinsically resistant to erlotinib, which display features suggestive of epithelial-to-mesenchymal transition in NSCLC-derived cell lines and early-stage tumours before erlotinib treatment. Activation of TGF-β-mediated signalling was sufficient to induce these phenotypes. Increased TGF-β-dependent IL-6 secretion released previously addicted lung tumour cells from their EGFR dependency. Therefore, both tumour cell-autonomous mechanisms and/or activation of the tumour microenvironment could contribute to primary and acquired erlotinib resistance and, as such, treatments based on EGFR inhibition may not be sufficient for effective treatment of EGFR mutated lung cancer patients.[18] Furthermore, tumour cells exposed to reversible or irreversible EGFR TKIs display early resistance dependent on MET-independent activation of B cell lymphoma-2 (BCL-2)/BCL-extra-large (BCL-XL) survival signalling.[19]

According to the study of Fan and colleagues,[19] such cells display a quiescence-like state that is readily reversed after withdrawal of targeted inhibitors. BCL-2 induction and p-STAT3 (Y705) activation are found within the residual tumour cells surviving the initial antitumour response to targeted therapies. Niclosamide (Niclocide®) is a teniacide in the anthelmintic family, approved by the US FDA for the treatment of tapeworms.[20] This safe, inexpensive drug, used in humans for nearly 50 years, reduces expression of the transcription factor STAT3.[20] Microtubule-targeted drugs, such as paclitaxel (Taxol®), inhibit cytokine-induced STAT3 and disrupt the interaction of STAT3 with tubulin.[21] Docetaxel (Taxotere®) or paclitaxel, act as STAT3 inhibitors, shedding light on 'flare' after stopping EGFR TKIs and indicating that addition of taxanes can have a benefit through STAT3 inhibition.[21] Finally, the JAK inhibitors AZD1480 or ruxolitinib block STAT3 signalling, resulting in suppression of tumour cell growth and survival.[22] Combining EGFR TKIs (reversible or irreversible) with STAT3 inhibitors or upstream (pan-JAK) or downstream (BCL-2/BCL-XL) constituents can be more efficient in inducing apoptosis, regardless of MAPK/ERK abrogation, for EGFR mutant patients with high levels of BIM possibly related to early adaptive resistance (Figure 1).[17-19]

NSCLC EGFR MUTANT PATIENTS WITH LOW BIM LEVELS AT BASELINE

BIM expression in treatment naïve cancers predicts responsiveness to EGFR TKIs, but almost two-thirds of patients have low BIM mRNA levels at baseline.[9] SHP2, which is downstream of EGFR and several other tyrosine kinase receptors, is required for sustained activation of ERK and BIM downregulation.[23,24] Upon activation of MET by its ligand hepatocyte growth factor (HGF), provided by stromal cells, EGFR signalling is dramatically altered.[25] HGF anticipates the mode of action in EGFR mutant tumours since EGFR tyrosine kinase activity, along with classical downstream signalling, is no longer required for tumour growth.[25] Specifically, HGF confers EGFR TKI resistance by inducing two novel cancer-promoting functions: firstly, it abolishes classical EGFR signalling, which makes cancer cells independent of these signalling mechanisms and neutralises the point of action for EGFR TKI-targeted drugs. Secondly, it enables EGFR to interact with proteins known to be markers of a highly metastatic phenotype such as the CUB domain containing protein 1 (CDCP1), Ephrin Type-A Receptor 2 (EphA2), JAK1, AXL, and Mer, interactions that cannot be affected by EGFR TKI treatment. EphA2 is a member of the erythropoietin-producing hepatocellular (Eph) family of RTKs. Unlike traditional oncogenes that often function only in tumour cells, EphA2 mediates cell-cell interactions both in tumour cells and tumour stroma and vasculature. EphA2 is often overexpressed in a variety of malignant cancers, including breast, lung, prostate, and colon cancers.[23]

EphA2 phosphorylates Tyr542 and Tyr580 of SHP2 to enhance and prolong ERK activation downstream of RTKs in the cells stimulated with

growth factors, such as EGF, HGF, or Gas6.[23] Miura et al.[23] were able to demonstrate that prolonged and enhanced ERK activation in cells stimulated with growth factors was reduced in cells depleted of EphA2 with simultaneous reduction of Tyr542/580 phosphorylation.

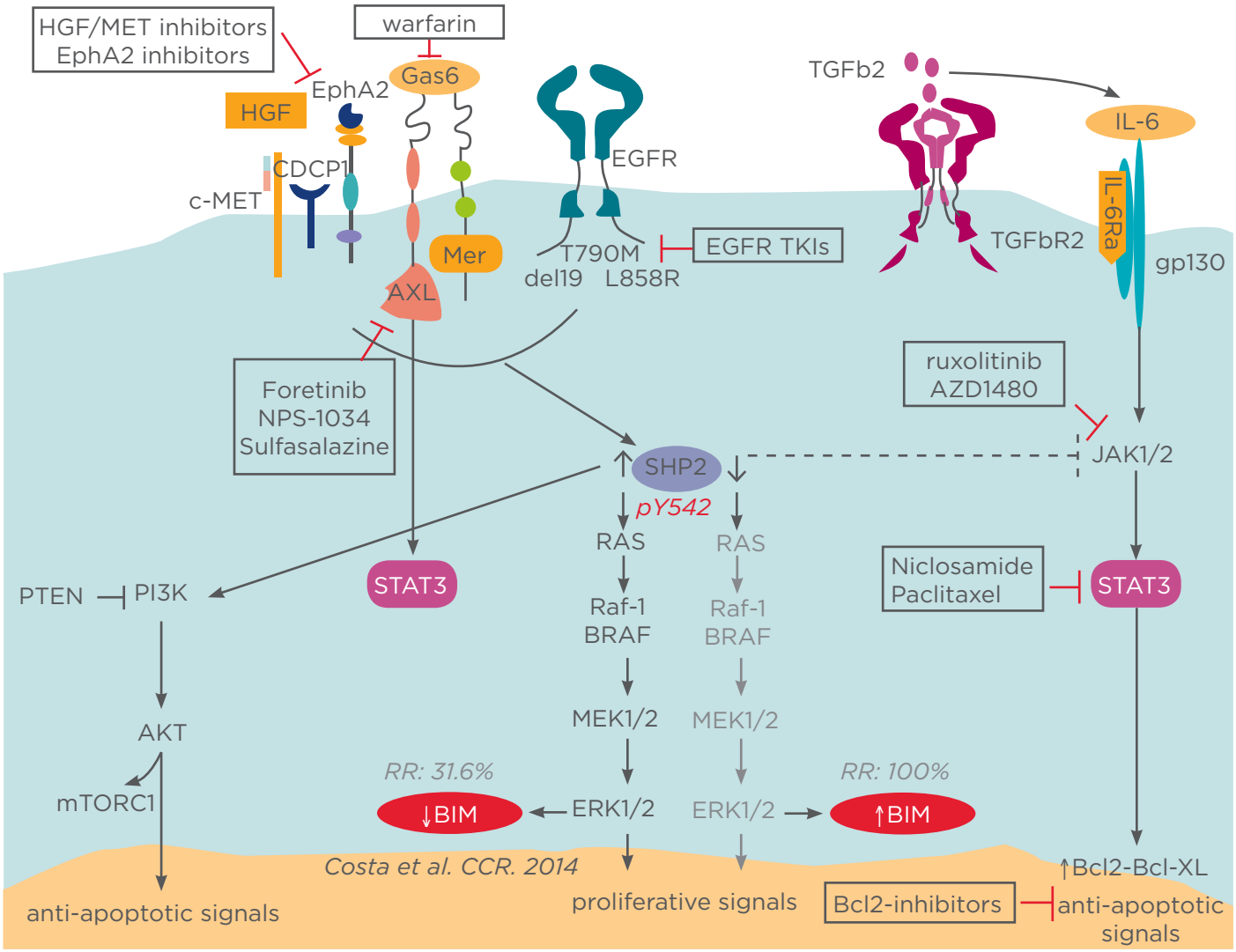

Figure 1: Potential mechanisms of resistance to EGFR tyrosine kinase inhibitors (TKIs).
The main signalling pathways activated by epidermal growth factor receptor (EGFR) include the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and signal transducer and activator of transcription 3 (STAT3) axes. Src homology 2 domain-containing phosphatase 2 (SHP2) plays a positive role in transduction of signals initiated from growth factors/cytokines, and extracellular matrix proteins, and initiation of various downstream signalling cascades. By contrast, SHP2 functions as a negative regulator of the Janus kinase (JAK)/STAT pathway. Combining EGFR TKIs with STAT3 inhibitors or upstream or downstream (BCL-2/BCL-XL) constituents can be more efficient in inducing apoptosis, regardless of MAPK/extracellular signal-regulated kinase (ERK) abrogation, in EGFR mutant patients with high levels of BIM, possibly related to early adaptive resistance. Combining EGFR TKIs with MET, AXL, or ephrin type-A receptor 2 (EphA2) inhibitors can be a rational and innovative synthetic lethality approach for EGFR mutant non-small-cell lung carcinoma (NSCLC) patients with low baseline BIM expression and high SHP2 activity.

HGF: hepatocyte growth factor; Gas6: growth arrest-specific 6; TGFb2: transforming growth factor-beta 2; IL: interleukin; CDCP1: CUB domain-containing protein 1; PTEN: phosphatase and tensin homologue; AKT: serine/threonine protein kinase; mTORCI: mammalian target of rapamycin complex 1; Raf: rapidly accelerated fibrosarcoma; BCL-2: B cell lymphoma 2; XL: extra-large; BIM: B-cell lymphoma 2 interacting mediator of cell death; MEK: MAPK/ERK kinase.

SHP2-dependent ERK activation signal pathway was hyperactivated, promoting cancer cell proliferation in tumours with EphA2 overexpression, measured by mRNA or immunohistochemistry.[23] Thus, treatment with HGF/MET inhibitors, together with EGFR-targeted therapies, and targeting HGF/MET-induced EGFR interactors may be necessary for the elimination of tumour growth.[25] At the same time, Gas6/AXL-mediated stimulation of ERK is attributed, in part, to its ability to activate SHP2.[24] There are several AXL or Gas6 inhibitors that can be combined with EGFR TKIs as preventive synthetic lethal therapies. Interestingly, warfarin prevents γ-carboxylation of TAM ligands, rendering Gas6 unable to activate TAM receptors (AXL and Mer).[26] Foretinib (GSK1363089), NPS-1034 but also sulfasalazine (Salazopyrin®), a synthetic nonsteroidal anti-inflammatory drug commonly used in the management of inflammatory bowel diseases and rheumatoid arthritis, are potent AXL inhibitors.[27-30]

Combining EGFR TKIs with MET, AXL, or EphA2 inhibitors can be a rational and innovative synthetic lethality approach for EGFR mutant NSCLC patients with low baseline BIM expression and high SHP2 activity. It seems that immunohistochemical staining and mRNA expression of SHP2 are well correlated and can be used as a biomarker for response.[31,32] Interestingly, STAT3 signalling can be hyperactive due to upstream pathways including not only IL-6 and JAK but also AXL, providing further opportunities for combination therapies (Figure 1).

CONCLUSIONS

Targeting genetic defects using a personalised strategy is limited by the high degree of intra-tumour heterogeneity, adaptation of genetic networks, and high somatic mutation rates in cancer. If we wish to radically change treatment of EGFR mutant NSCLC to the benefit of our patients, we should start thinking about a different approach based on information derived from additional biomarkers. BIM may serve as a companion diagnostic marker for successful synthetic lethal combinations. Patients with high BIM levels at baseline may have a hyperactive JAK/STAT pathway through either the L858R mutation or loss of SHP2 activity. The combination of EGFR TKIs + a JAK, STAT3, or BCL-2/BCL-XL inhibitor should be seriously considered in these cases. Patients with low BIM levels at baseline may benefit from the combination of EGFR TKIs with compounds that downregulate or abrogate activity of SHP2, such as MET, AXL, or EphA2 inhibitors. It should be seriously considered whether, at time of progression, a JAK or a STAT3 inhibitor could be added in order to overcome loss of the negative impact of SHP2 on the JAK/STAT3 pathway. We propose this line of research at the level of cell lines and xenograft models, and at the level of biomarker discovery in tumour samples, in order to verify our assumptions as accurately as possible and contribute to radically transforming treatment of EGFR mutant lung cancer.

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WOMEN AND LUNG CANCER: LITERATURE ASSUMPTIONS AND NEWS FROM RECENT PUBLICATIONS

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ABSTRACT

For a long period of time, lung cancer (LC) was considered as a malignancy affecting only males, but epidemiological data have shown a dramatic increase of the incidence of this disease among women, and the gender gap has been narrowing steadily since the 1980s, mainly as a consequence of the huge spread of tobacco consumption during the past 70 years. In 2013, the percentage of current cigarette smokers among adults aged 18 and over in the US was 19.9% for men and 15.2% for women (selected estimates based on data from the January-June 2013 National Health Interview Survey), reflecting the earlier and more marked decline in the prevalence of tobacco use in men. Nowadays, cigarette smoking accounts for >90% of LCs in men and 75-85% of LCs in women in the US and Europe, but 20% of women with LCs have never smoked. Many studies describe differences between males and females in the clinical presentation and biology of LC, suggesting that the disease should be considered a specific entity in women, where adenocarcinoma is the most common histological subtype, and prognosis and response to treatment appear to be different. In line with these findings, hormonal receptors have been isolated in LC tissues: the interaction of oestrogen receptors with growth-factor-receptor signalling is an emerging area of investigation and - considering the potential impact of hormonal factors - lung carcinogenesis appears distinctive in women. Despite these considerations, no 'gender driven' diagnostic or therapeutic approaches are available nowadays. Improving knowledge of LC in women will allow identification of specific genetic alterations or hormonal profiles which could be targeted by therapy in order to stimulate research progress towards personalised sex-based investigations.

Keywords: Women, gender, sex, lung cancer, cigarette smoking, never smokers, biological abnormalities, hormones, oestrogen receptors.

INTRODUCTION

At the beginning of the 20th century only a few hundred cases of lung cancer (LC) were diagnosed annually, but the largely progressive spread of tobacco consumption caused a dramatic increase of the incidence of this disease among men, and then later among female smokers, in Western countries.[1] Trends in LC incidence and mortality have reflected changing habits in cigarette smoking during the past years, but it has been known that women have a 1 in 16 lifetime risk of developing LC regardless of smoking status, and a higher percentage of LC in non-smoking women, as compared with non-smoking men, suggests that LC behaves differently in female patients.[2]

The purpose of this paper is to review recent scientific assumptions concerning LC in women, exploring more recent data about smoking susceptibility, as well as biological and hormonal features, in order to discuss the future implications of gender-related approaches and therapeutic options. To be eligible for this systematic review,

a publication had to fulfil the following criteria: to deal with LC, gender, and biological and hormonal aspects; to have been published as a full paper in English, Italian, or French language. Abstracts were also included. Studies were identified by an electronic search on Medline databank using the following keywords: "lung cancer", "lung adenocarcinoma", "lung squamous carcinoma", "NSCLC", "SCLC", "women", "sex", "gender", "never smokers", "cigarette smoking", "tobacco", "molecular issues", "biological abnormalities", "next-generation sequencing", "hormones", "oestrogen receptor", "progesterone receptor", "lung cancer risk", "antioestrogen", "EGFR", "K-Ras", and "ALK". The search ended in April 2014.

Epidemiology

In the last decades, LC incidence rates worldwide have decreased or levelled-off among men, being instead dramatically risen among women by 600% in the last 50 years.[3] Particularly, in this population in the US, a significant increase in smoking habit started in 1973, reaching a plateau in the late 1990s - over a decade later than men - while LC mortality stabilised for the first time in 2003, two decades later than men, and has yet to decline.[4,5] The International Agency for Research on Cancer estimated 1.8 million new LC cases worldwide in 2012 (12.9% of the total). This disease is still the most common cancer in men (1.2 million, 8.74% of the total) and the third most frequent in women (583,000 cases, 4.16% of the total). It is the most common cause of death from cancer worldwide in men and the second cause in women with 1.59 million deaths, of which, 491,000 were female patients.[6] Nowadays in the US, LC is the leading cause of cancer death for this population, with >108,000 new estimated cases and >72,000 estimated deaths in 2014, while in European countries there are >79,000 new cases of LC in the female sex per year and 82,000 have been estimated in 2013[4,7-9] (Figures 1-4). Thus, compared to the historical data, recent publications confirm that the epidemiology of LC is still changing and that sex differences, in terms of incidence and mortality, are still present with increasing rates for women in many countries.

SMOKING HABITS

Currently, tobacco smoking accounts for >90% of LCs in men and 75-85% of LCs in women, in the US and Europe; it is the most well-established risk factor for this disease.[10-12] Several case–control studies have found a higher relative risk among women when compared with men for the same level of smoking exposure.[13-16] In contrast, other cohort studies have not shown higher smoking-related risks, evidencing that the incidence of LC among female smokers was approximately the same as that in male smokers, after standardising for the amount smoked.[17,18] To address this issue, two recent publications evaluated analogous populations (European subjects, similar gender distribution) using different metrics. De Matteis et al.[19] evaluated the interaction between female sex and tobacco smoking in association with LC risk within 2,100 cases and 2,120 controls. LC odds ratios (OR) for pack-years were higher in men than in women, with a negative female sex-smoking interaction (p=0.0009). The association within former and current smokers was also explored and no major difference was seen. In the analyses for the main LC histological types, OR for pack-years among adenocarcinoma cases were higher in men than in women, with a negative female sex-smoking interaction (p=0.005), while, in the analyses restricted to former and current smokers, there was no evidence of interaction (p=0.76 and p=0.47, respectively).[19] Papadopoulos et al.[20] evaluated 2,276 male/650 female cases and 2,780 male/775 female controls, estimating lifetime smoking exposure by the comprehensive smoking index (CSI), which combines the duration, intensity, and time since cessation of smoking habits. They found that the LC risk was similar among men and women, but evidenced that women had a 2-fold greater risk associated with a 1-unit increase in CSI than men of developing either small cell carcinoma (OR=15.9, 95% CI 7.6-33.3 and 6.6, and 95% CI 5.1-8.5, respectively; p<0.05) or squamous cell carcinoma (OR=13.1, 95% CI 6.3-27.3 and 6.1, and 95% CI 5.0-7.3, respectively; p<0.05), while the association was similar between men and women for adenocarcinoma.[20]

Active cigarette smoking is the most important risk factor for LC, but it is only one of a well-characterised set of established risk factors that include: smoking types of tobacco other than cigarettes (e.g. cigars, pipes), passive smoking, occupational exposure to lung carcinogens such as radon, asbestos, arsenic, radiation, outdoor, and indoor air pollution (e.g. coal-fuelled stoves and cooking fumes), family history, and infections.[21,22] Biological explanations have also been proposed to demonstrate sex differences in LC susceptibility:

oestrogen receptors (ERs) are present in both normal and neoplastic lung tissues and could accelerate the metabolism of smoke-related carcinogens in a dose-dependent way, as suggested by higher levels of polycyclic aromatic hydrocarbon–DNA adducts in female smokers compared with males, or inherited, gender-related polymorphisms could affect activating and detoxifying enzymes.[12,23-25]

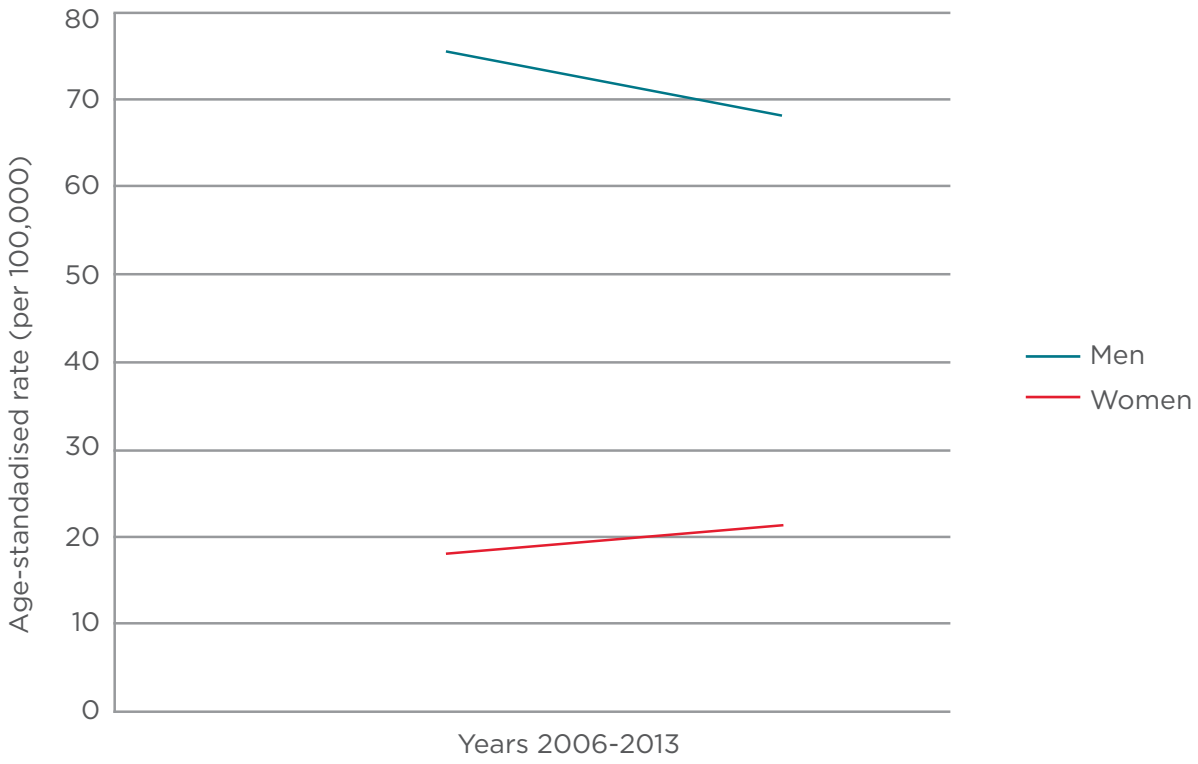

Figure 1: Lung cancer incidence trends by sex in Europe during 2006-2013.

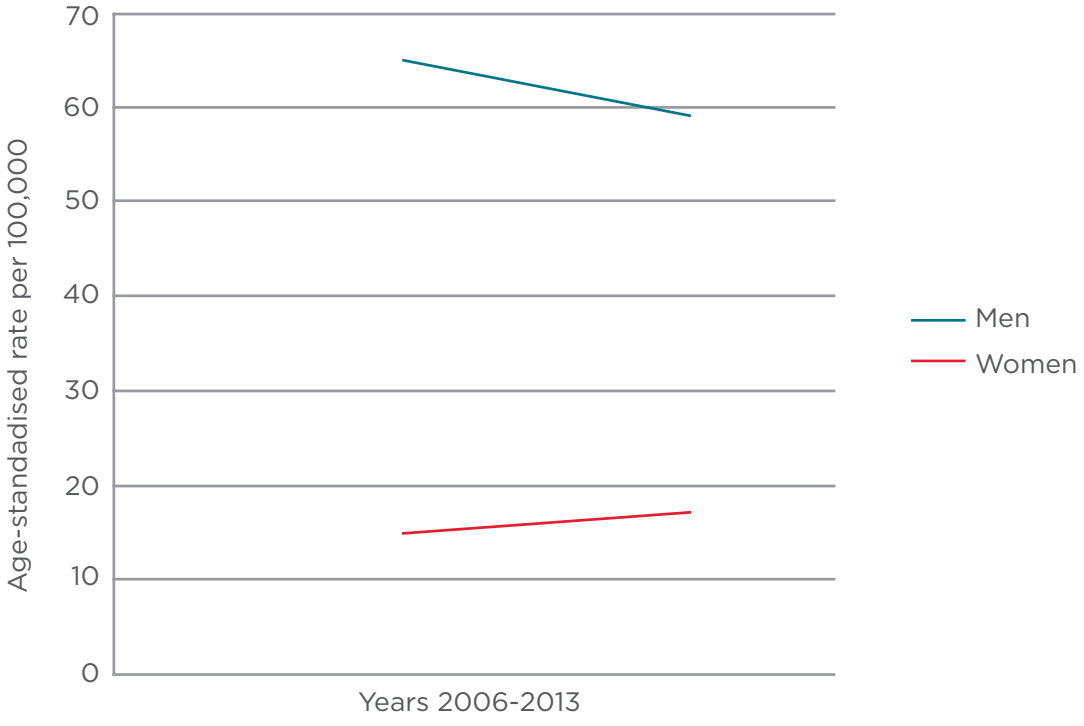

Figure 2: Lung cancer mortality trends by sex in Europe during 2006-2013.

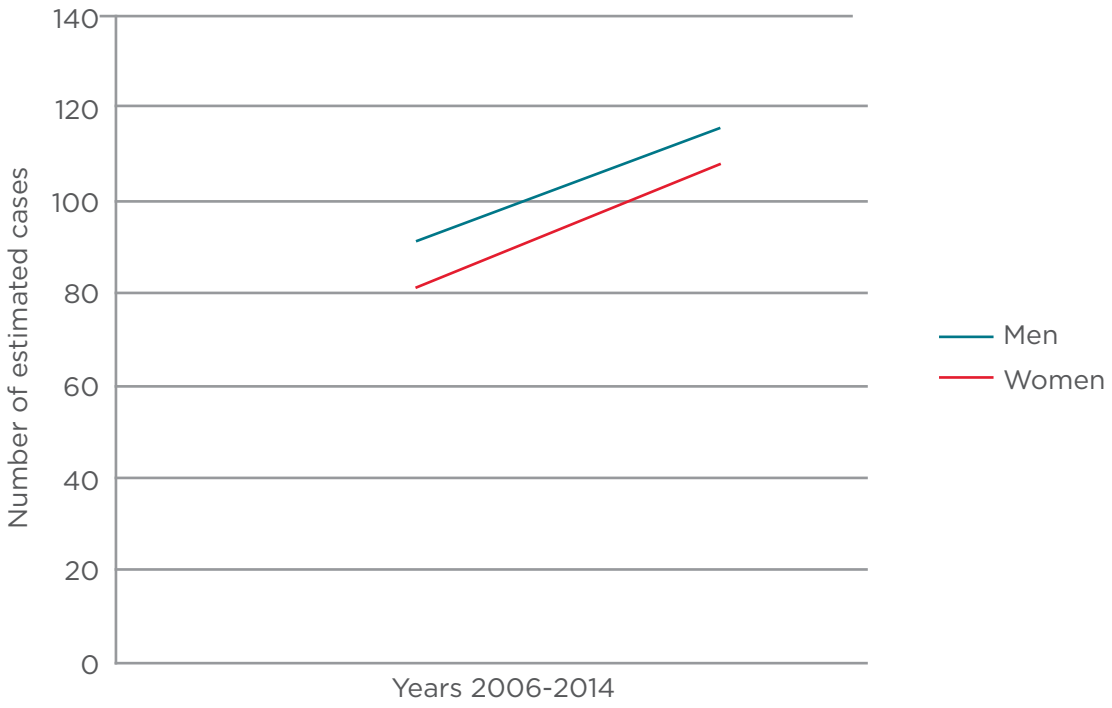

Figure 3: Lung cancer incidence trends by sex in US during 2006-2014.

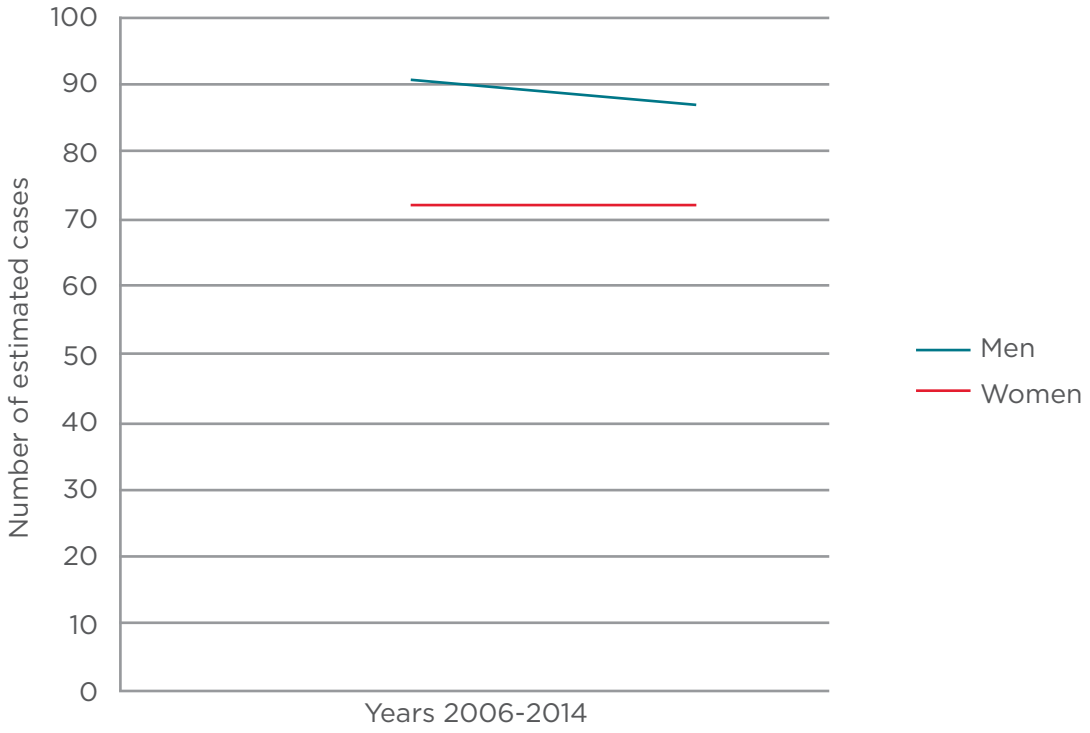

Figure 4: Lung cancer mortality trends by sex in US during 2006-2014.

Chlebowski et al.[26] examined oestrogen plus progestin (E+P) association with LC incidence and outcome in >30,000 postmenopausal women, and evidenced that in non-users of E+P, LC incidence, deaths from LC, and deaths after LC were significantly and substantially greater in current smokers versus never smokers ($p<0.0001$ for all comparisons) and, in current smokers, the same variables were significantly and substantially greater in E+P users versus non-users ($p=0.0021$, 0.0005, and 0.0002, respectively), nearly doubling a smoker's already high risk of death from LC and

after LC. Thus, compared to the historical data, recent publications confirm the prominent role of smoking habit as a risk factor of LC, even in female population, but no conclusions are yet available regarding the potential difference in susceptibility to the carcinogenic effects of cigarette smoke on women's lungs when compared with their male counterparts.

NEVER SMOKERS AND MOLECULAR ABNORMALITIES

Tobacco smoking is the main cause of LC, but it also occurs in people who have never smoked, ranking as the seventh most common cause of cancer death worldwide.[25] LC in never smokers is more frequently observed in women: in the US and Europe, approximately 20% of women with LCs have never smoked and this trend is further accentuated in Asian populations where 60-80% of women with LC, in contrast to 10-15% of men with LC, have never smoked.[5,27] Passive smoking is the most widely studied and confirmed risk factor of LC among non-smokers. Furthermore, in this cohort of patients, a higher rate of gene mutations involving epidermal growth factor receptor (EGFR) or echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4–ALK) translocations has also been evidenced. Mazières et al.,[28] in an evaluation of 140 women with adenocarcinoma (63 were never smokers), evidenced EGFR mutation more frequently and mutated K-Ras less frequently in women who had never smoked; more precisely, 50.8% of never smokers displayed the mutation compared with 10.4% of former or current smokers ($p<0.001$). In contrast, K-Ras mutation was more frequent in smokers (33.8%) compared with never smokers (9.5%; $p=0.001$). It also described a higher percentage of ER alpha expression ($p=0.03$; and $p=0.008$ with two different antibodies) in women who never smoked when compared with smokers.[28]

No definitive data are currently available about the EML4-ALK translocation or *ROS1* gene regarding a possible difference between men and women. From prospective trials and from retrospective evaluation, EML4-ALK has been evidenced to occur more frequently in young patients, light or never smokers, and male subjects, while *ROS1* seems to occur slightly more often in the young female population.[29,30] On the contrary, mutations in *HER2* gene are identified in approximately 2% of non-small-cell lung cancer (NSCLC) and in a recent publication, Mazierès et al.,[28] who retrospectively collected clinicopathologic characteristics, patient outcomes, and treatments of 65 NSCLC, diagnosed with a *HER2* in-frame insertion in exon 20, evidencing a higher proportion of women (45 women versus 20 men).[31] Finally B-Raf (V600) is described in 2% of patients with lung adenocarcinoma in Western countries; it seems to be slightly more frequent in women and represents a negative prognostic factor.[32]

At a molecular level, the Tumor Sequencing Project revealed that smokers suffer mutations at rates 5 to 10-times higher than never smokers; as a consequence, the smaller number of mutations among never smoker patients suggested the opportunity to easily isolate driver mutations.[33] In this regard, Kim JH et al.[34] conducted a genome-wide association study of non-smoking Korean women with LC to identify the effect of genetic polymorphisms on LC risk. They analysed 440,794 genotype data of 285 cases and 1,455 controls, and evidenced that 19 single nucleotide polymorphisms (SNPs) were associated with LC development ($p<0.001$); however, only rs10187911 on 2p16.3 was significantly associated with LC development ($p=0.025$). The effect of this SNP was found to be consistent only in adenocarcinoma patients (1.36 and <0.001 in the additive model, 1.49 and <0.001 in the dominant model, and 1.54 and <0.001 in the recessive model). This is a novel genetic locus in the 2p16.3 region, associated with susceptibility of adenocarcinoma in Korean never smoking females.[34] Further replication studies in larger populations are needed to confirm this hypothesis, considering that Kim SC et al.,[35] performing a high-throughput, multidimensional sequencing study of primary lung adenocarcinoma tumours (EGFR, KRAS, and EML4-ALK negative) in six Korean female never smoker patients, found that none of the mutations or fusion genes were present in more than one patient.[35] This evaluation suggests that, at the present time, for the large proportion of NSCLC cases, negative for the established 'driver' mutations, it is difficult to predict the function of a given mutation (i.e. gain in oncogenic activity or a loss of tumour suppressor activity, or neither) unless an extensive characterisation of the gene activity is performed *in vitro* and *in vivo*, the first step to propose potential target pathways for establishing effective and personalised therapies.

Thus, compared to the historical data, recent publications confirm LC in never smokers as a

different disease per se; this remains to be clarified in the role of sex in this context, even if some interesting preclinical data are already available showing specific molecular features.

HORMONAL FEATURES

Hormonal status is one of the most cited potential explanations for differences in LC between men and women. There are several lines of biological evidence that suggests oestrogen acts as a promoter for LC.[36-38] Experimental data are still conflicting due to the presence of two ER isoforms (α and β) and the expression of ER β isoforms (mainly ER β1), the range of antibodies used, and the absence of a validated threshold or score. In fact, Wu et al.[39] observed an overexpression of ER β in lung tumours significantly more frequently in female patients (53.8%) than in males.[39] In contrast, Schwartz et al.[40] found that ER β was preferentially expressed in men, while Rouquette et al.[41] described ER β overexpressed in the majority of patients, regardless of gender (Table 1).[40,41] For the same reasons the impact of reproductive and hormonal factors on the aetiology of LC in women is still unclear, even if it is hardly debated.

Table 1: Hormones and lung cancer (selected studies).

References	Methodology	n	Principal Findings
Rodriguez-Lara et al.[51]	IHC	90	ER β and *CXCL12/CXCR4* expression in lung adenocarcinoma depends on sex and hormonal status.
Verma et al.[52]	IHC	169	Co-expression of ER β and aromatase in NSCLCs of Japanese males may result in tumour progression.
Rouquette et al.[41]	IHC	100	Positive link between EGFR expression and expression of ER α and ER β, both men and women.
Abe et al.[53]	IHC	105	ER expression associated with aromatase expression in NSCLC.
Raso et al.[54]	IHC	317	ER expression associated with EGFR mutations in NSCLC.
Wu et al.[39]; Schwarz et al.[40] Skov et al.[55]	IHC	278/301 104	ER expression associated with better clinical outcome in NSCLC.
Niikawa et al.[56]	IHC	59	Aromatase expression was associated with intratumoural estradiol concentrations in NSCLC.
Hershberger et al.[57,58] Jarzynka et al.[59]	*in vitro* (NSCLC cell lines)		ER demonstrated tumour promoting features in the absence of ER.
Hammoud et al.[60]; Jarzynka et al.[59]	*in vivo* (mouse)		Estradiol stimulated the growth of lung carcinoma xenografts.
Mah et al.[61]	IHC	442	Lower levels of aromatase predicted a better survival in females >65.
Márquez-Garbán et al.[62]; Weinberg et al.[63]	*in vitro* *in vivo*		Aromatase inhibitor suppressed the lung tumour growth.
Issa et al.[64]	Southern blot	46	Lung cancer patients with a history of smoking had a significantly lower incidence of ER promoter methylation than non-smokers.

IHC: immunohistochemistry; ER: oestrogen receptor; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor.
Modified and updated from Verma et al.[50]

Endogenous Hormones

A meta-analysis by Zhang et al.[42] evaluated 25 articles in order to estimate the impact of menstrual and reproductive factors on LC risk. Older age at menarche in North American women and a longer length of menstrual cycle were associated with a significant decreased risk of LC (rate risk [RR]= 0.83; 95% CI: 0.73-0.94 and RR=0.72; 95% CI: 0.57-0.90, respectively). Particularly, shorter length of menstrual cycle indicated an overall increase in the period of unopposed oestrogen exposure; younger age at menarche implied more menstrual cycles over the lifetime and hence longer periods of oestrogen exposure in total. Women who undergo shorter length of menstrual cycle and younger age at menarche may have an increased risk of LC, possibly due to more cumulative exposure to endogenous oestrogen, which may be involved in the aetiology of this disease.[42]

Pesatori et al.[43] examined 407/499 female cases/controls and observed a reduced risk of LC among women with a later age at first live birth (≥31 years: OR=0.57, 95% CI=0.31-1.06, p-trend=0.05), later age at menopause (≥51 years: OR=0.49, 95% CI=0.31-0.79, p-trend=0.003), and longer reproductive periods (≥41 years: OR=0.44, 95% CI=0.25-0.79, p-trend=0.01).[43] Finally, Gallagher et al.[44] evaluated a cohort of 267,400 female textile workers in Shanghai, enrolled in a trial of breast self-examination where information on reproductive history, demographical factors, and cigarette smoking were collected at enrolment. The cohort was followed until July 2000 for incidence of LC and 824 cases were identified. Nulliparous women were at increased risk compared to parous women (HR=1.33, 95% CI 1.00-1.77). Women who had gone through menopause at baseline were at an increased risk compared to women of the same age who were still menstruating. Risk was higher in women with a surgical menopause (HR=1.64, 95% CI 0.96-2.79) than in those with a natural menopause (HR=1.35, 95% CI 0.84-2.18), and risk was highest in those postmenopausal women with a hysterectomy and bilateral oophorectomy at baseline (HR=1.39, 95% CI 0.96-2.00), although the risk estimates were not statistically significant.[44]

Exogenous Hormones

It is important to underline that endogenous and exogenous sex hormones could play different roles in lung tumourigenesis.[45] In a Women's Health Initiative randomised, placebo-controlled clinical trial it has been evidenced that more women died from LC in the combined hormone therapy group than in the placebo group (HR 1.71, 1.16–2.52, p=0.01).[26] Based on these data, Bouchardy et al.[46] argued that the use of anti-oestrogens should be associated with decreased LC mortality risk. The authors compared LC incidence and mortality among 6,655 women diagnosed with breast cancer between 1980 and 2003, treated with and without anti-oestrogen therapy; 46% (3,061) of them received anti-oestrogens and 0.6% (40) developed LC. Standardised incidence rates for LC were not significantly decreased among breast cancer patients treated with and without anti-oestrogens (0.63, 95% CI, 0.33-1.10; and 1.12, 95% CI, 0.74-1.62, respectively) while standardised mortality ratios decreased among women with anti-oestrogens (0.13, 95% CI, 0.02-0.47, p<0.001) but not for women without anti-oestrogens (0.76, 95% CI, 0.43-1.23).[46]

The same concept has been applied by Lother SA et al.[47] who performed a retrospective population-based study identifying all women diagnosed with NSCLC in 2000-2007 and suggesting that anti-oestrogen use may influence survival in NSCLC female patients. They evaluated 2,320 women (of which 156 had received anti-oestrogens) to compare survival among anti-oestrogen users and nonusers. Exposure to anti-oestrogens was associated with a significantly decreased mortality in those exposed both before and after the diagnosis of NSCLC (adjusted HR: 0.42, p=0.0006). This association remained consistent across age and stage groups. Anti-oestrogen use before and after the diagnosis of NSCLC was also associated with decreased mortality.[47]

Oestrogens still represent a potential key player in the biology and outcomes of NSCLC and, consequently, a possible therapeutic approach. Garon et al.[48] evidenced, in NSCLC cell lines, that sensitivity to fulvestrant (Faslodex®) correlates with greater baseline ER α gene expression, and tumour xenografts regress significantly when both ER and EGFR pathways are inhibited.[48] Furthermore, Siegfried et al.[49] confirmed that the combination of vandetanib (Caprelsa®) (a multi-target inhibitor) with fulvestrant maximally inhibits cell growth when compared to single agents (p<0.0001), decreases tumour xenograft volume by 64%, compared to 51% for vandetanib (p<0.05) and 23% for fulvestrant (p<0.005) alone, and finally, produces a significant increase in apoptotic cells when compared to single agents.[49] Thus, compared

to the historical data, recent publications confirm the hormonal status as one of the major causes for sex differences in LC. Even without the possibility to make any final statements, women who continue to produce oestrogens seem to have a lower LC risk, and anti-oestrogens were shown to have a potential therapeutic implication, from preclinical and clinical experiences.

CONCLUSIONS

A better understanding of the genetic, metabolic, and hormonal factors in women still represents a research priority. Further and larger investigations with biomarkers of oestrogen and molecular classification of LC will help for a more comprehensive view of LC development in women. In the era of targeted drugs, variations in response to EGFR inhibitors and antiangiogenesis drugs between men and women are intriguing but insufficient to allow the gender of the patient guide the choice of therapy, and larger oncogenic platforms associated to dedicated protocols should represent an answer to the question.

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RITUXIMAB AND OTHER NEW ANTI-CD20 MABS FOR NON-HODGKIN'S LYMPHOMA TREATMENT

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ABSTRACT

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of different haematological cancers with a wide range of aggressiveness. NHLs represent >80% of lymphomas and the majority of NHLs involve B cells. CD20 represents a good target for NHL immunotherapy because it is largely expressed on B cell NHL and not on B cell precursors and plasma cells. The anti-CD20 monoclonal antibody (mAb) rituximab (RTX) was the first antibody approved by the FDA for lymphoma therapy and has revolutionised B cell lymphoma treatment. Several clinical trials have demonstrated the high efficacy of RTX, resulting in a significant improvement in overall response rates and in NHL patient survival. However, RTX, both as a single agent and in combination with chemotherapy, induces several side-effects and resistance mechanisms. Remarkable efforts have been made to improve RTX efficacy, including conjugation to an active moiety (radionuclide, toxin, enzyme, or drug) and the development of new anti-CD20 mAbs. This review summarises the characteristics of RTX and other anti-CD20 mAbs for NHL treatment; the results of the main clinical trials are reported.

Keywords: Non-Hodgkin's lymphoma, CD20, rituximab, immunotherapy, monoclonal antibodies.

INTRODUCTION

Lymphoma is the general term used to define blood cancers that develop mainly in the lymphatic system. Lymphoma is not a single type of cancer but a group of related tumours. There are approximately 30 different types of lymphoma that are divided into two main categories: Hodgkin's lymphoma (HL; or Hodgkin's disease) and non-Hodgkin's lymphomas (NHLs), which are the most common (approximately 80%). HL is a specific type of cancer characterised by the presence of Reed-Sternberg cells in the cancerous tissue; these are large and multinucleated cells, usually derived from B lymphocytes, and their presence is required for HL diagnosis. NHLs are a heterogeneous group of different haematological cell malignancies with a wide range of aggressiveness; >80% of NHLs are B cell lymphomas. NHLs usually occur in adults and can be further classified by growth rate; fast-growing subtypes are defined as aggressive, slow-growing NHLs are defined as indolent. The two most common forms of NHL are diffuse large B cell lymphoma (DLBCL), an aggressive type accounting for 30% of NHL cases, and follicular lymphoma (FL), an indolent type that accounts for 25-30% of cases.[1] NHLs are often cured by combined therapies including chemotherapy and radiotherapy and, rarely, surgery and transplants (autologous or allogeneic). However, indolent lymphomas, when in advanced clinical stages, are incurable in most cases. The classic chemotherapeutic approach is CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Chemotherapy's efficiency is limited by non-specific toxicity to normal tissues and by the development of resistance to therapeutic agents. Moreover, a percentage of patients treated

with chemotherapy and radiotherapy develop secondary malignancies due to the lowering of immunosurveillance induced by conventional antiblastic agents and radiation and to the therapies' transformative actions. Approximately 50% of NHL patients either relapse or become refractory to conventional therapy.[2] For these patients with poor outcomes, the use of new therapeutic strategies, such as immunotherapy, is required.

The use of monoclonal antibodies (mAbs) for anti-cancer therapy has been widely explored since mAbs were initially developed by Kohler and Milstein. The specificity of immunotherapy is based upon characteristics (surface antigens) that are completely independent from the parameters that allow for the differential toxicity of chemotherapy and radiotherapy. This specificity results in a non-superimposition of side-effects and unimpaired cytotoxicity towards cell clones resistant to chemotherapy and radiotherapy. The choice of the target antigen for antibody-based therapy should take into account important factors; the antigen should be easily accessible, highly expressed on unwanted cells and possibly restricted to these cells, and the antigen should not be shed into the blood. Because most lymphomas have vascular accessibility, they are a favourable setting for this treatment modality. Furthermore, haematological cells represent the ideal target for antibody-based immunotherapy due to the presence of clusters of differentiation (CD) on their surface. CD are well-characterised molecules against which a multitude of mAbs are available. In fact, the first successful use of mAbs for cancer treatment was demonstrated in lymphoma, and mAbs are now employed to benefit thousands of patients with NHL.[3,4]

CD20 ANTIGEN AS A TARGET FOR IMMUNOTHERAPY

CD20 (B1) is a highly expressed transmembrane surface antigen with a molecular weight of approximately 35 kDa. The function of CD20 is not completely understood; however, this antigen seems to be involved in the regulation of B cell growth and differentiation via intracellular signalling or by functioning as a calcium channel in association with antigen stimulation of the B cell receptor. The CD20 molecule has been studied extensively as an appealing target for mAb-based immunotherapy due to several favourable properties: 1) CD20 is expressed on nearly 90% of B cell NHLs and on normal B cells, but neither on B cell precursors and plasma cells nor on other tissues; 2) the antigen is highly expressed on the cell surface; 3) CD20 is not normally shed from the cell; and 4) CD20 is internalised after antibody binding.[5] Anti-CD20 mAbs cause cell death through different pathways. After binding to the antigen, these mAbs can activate complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), which are mediated by the Fcγ receptors on effector cells, such as granulocytes, macrophages, and natural killer (NK) cells. Moreover, some antibodies can directly kill the target cell by triggering the apoptotic pathway, thus having a direct cytotoxic effect.[6] These effects make anti-CD20 antibodies essential tools in lymphoma therapy, both alone and in combination with chemotherapy.[7]

Clinically active anti-CD20 mAbs can be divided into two groups based on the triggered cell death pathway. Type I antibodies (rituximab [RTX], ofatumumab [OFA], veltuzumab, ocrelizumab, ocaratuzumab, and rhumAb v114) induce CD20 translocation into lipid rafts with consequent ADCC, CDC, and weak apoptosis. Type II mAbs (tositumomab and obinutuzumab) do not redistribute CD20 on the cell surface and induce strong ADCC and apoptosis but weak CDC.[8]

RTX

RTX, a mouse-human chimeric mAb, was the first anti-CD20 mAb showing clinical effectiveness for lymphoma patients. This mAb is composed of a human immunoglobulin G1 (IgG1) Fc region and human kappa constant regions with variable regions derived from the 2B8 murine Ig.[8] RTX was the first antibody approved by the FDA for use in cases of relapsed or indolent NHL. The primary cell death mechanism induced by RTX is CDC, but RTX can also lead to ADCC and apoptosis. In addition, RTX is able to raise the T cell response against malignant clones.[9] RTX treatment improves response rates in several types of B cell NHL, including DLBCL, FL, and mantle cell lymphoma. The treatment has also resulted in a significant increase of progression-free survival (PFS) and overall survival (OS), unlike the combination of different chemotherapies.[10] RTX has been investigated both as a single agent and in association with standard chemotherapy. The combination of RTX with CHOP treatment has been evaluated in patients with

aggressive NHL (MabThera International Trial); 824 patients with DLBCL were randomly selected to receive six cycles of either CHOP + RTX (R-CHOP) or standard CHOP alone. After a 3-year follow-up period, R-CHOP-treated patients had a 79% improved rate of PFS versus 59% of those treated with CHOP alone. The 3-year OS rates were 93% (R-CHOP) versus 84% (CHOP).[11]

In indolent NHL, such as FL, RTX has been investigated both as a single agent and combined with standard chemotherapy.[12] First, RTX was investigated as a single agent in a 166-patient clinical trial; the response rate was 48%, which was similar to chemotherapy alone.[13] In a larger Phase III trial, 428 patients with advanced FL were randomly treated with either R-CHOP or CHOP alone. Significant increases in OS rates (96% for R-CHOP versus 90% for CHOP alone) and estimated survival rates at 2 years (95% for R-CHOP versus 90% for CHOP alone) were reported.[14]

RTX as single agent or in combination with chemotherapy has revolutionised lymphoma therapy. Unfortunately, RTX is not effective in all cases, and some patients experience severe side-effects; the main side-effects reported for RTX treatment are listed in Table 1. The frequency of side-effects may vary among the first and subsequent infusions (for a complete list of these rates see the web page http://www.rxlist.com/rituxan-side-effects-drug-center.htm). In addition, acquired resistance to RTX is another observed clinical problem. The mechanism of RTX resistance is not completely clear. Alterations in host immunologic factors could be implicated in tumour resistance to RTX, such as: 1) CDC resistance due to the alteration of expression of complement-regulatory proteins (CD46, CD55, and CD59) on tumour cells; 2) ADCC resistance due to changes in the lipid raft causing failed recognition of the CD20/antibody complex by effector cells and FcγRIIIa polymorphisms; 3) selection of apoptosis resistant clones as a consequence of repeated exposure to RTX; and 4) selection of CD20-negative tumour clones.[15] For these reasons, different strategies have been explored to obtain higher response rates and remission duration for mAb-based immunotherapy. For example, mAb efficacy can be augmented by conjugation to an active moiety, such as radionuclide (radioimmunoconjugate),[16] toxin/enzyme or drug (immunotoxin).[17-19]

Table 1: Main adverse effects of rituximab treatment.

Side-Effects	Symptoms
Infusion reactions	Headache, breathing difficulty, urticaria, angioedema, chills, and fever. Rapid onset respiratory failure, heart attack.
Skin and mouth reactions	Painful sores or ulcers on skin, lips, or in mouth; blisters, peeling skin, pustules. Acute whole-body allergic reaction.
Progressive multifocal leukoencephalopathy (infection caused by John Cunningham virus)	Death or severe disability.
Reactivation of hepatitis B virus	Serious liver problems and death.
Tumour lysis syndrome	Kidney failure, altered heart rhythm.
Cytopaenias and hypogammaglobulinaemia	Late-onset neutropaenia, leukopaenia, thrombocytopaenia, lymphopaenia, anaemia, hypogammaglobulinaemia.
Others	Bowel obstruction and perforation.

RTX-Containing Radioimmunoconjugates

Immunoconjugate toxicity is based on the involvement of different pathways that only minimally depend on ADCC and CDC. The response rates observed in Phase I/II trials have often been higher than those reported for unconjugated antibodies and conventional drugs. Radioimmunoconjugates can kill not only the target cells but also surrounding cells. This can represent an advantage because tumour cells not expressing the antigen or expressing a mutated antigen can also be eliminated, but it represents also a disadvantage due to the non-specific toxicity towards normal cells near the tumour. Two radioimmunoconjugates, ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, have been approved by the FDA to treat relapsed/refractory FL and low-grade lymphomas. Compared to RTX, in clinical trials radioimmunotherapy (RIT) increased complete responses (CR) in low and intermediate-grade refractory NHLs, while the addition of RIT after chemotherapy in maintenance therapy produced effects comparable to or better than RTX. Several Phase III clinical trials have been conducted with these two radioimmunoconjugates and many others are still ongoing in lymphoma patients.[20] The most common side-effects are hypothyroidism and marrow suppression, but there is also a risk of acute myeloid leukaemia and myelodysplastic syndrome. In other experimental approaches, RTX has been conjugated to a toxic moiety to obtain immunotoxins. For this purpose, plant toxins[21] and chemotherapy agents[22] have been utilised.

SECOND-GENERATION ANTI-CD20 MABS

The second generation of anti-CD20 mAbs (OFA, veltuzumab, and ocrelizumab; see Table 2) are humanised or fully human molecules developed with the purpose of reducing immunogenicity. These mAbs have often been tested in contemporary clinical trials on NHL and chronic lymphocytic leukaemia (CLL) patients; better results were reported in the latter patients. As a consequence, in some cases, second-generation anti-CD20 mAbs have been approved by FDA for CLL therapy.

OFA (Arzerra, HuMax-2F2) is a completely human Type I anti-CD20 mAb that binds a different epitope than that recognised by RTX. OFA targets CD20 with greater avidity than RTX, causing similar ADCC but stronger CDC in both RTX-sensitive and RTX-resistant cells.[23,24] The first Phase I/II clinical trial for OFA conducted with 40 relapsed/refractory FL patients showed an overall response rate (ORR) ranging from 20-63%.[25]

Table 2: Cytotoxic mechanisms of RTX and other new anti-CD20 mAbs.

	Cytotoxic Mechanisms Compared To RTX	Clinical Trials	FDA Approval
First Generation			
RTX	CDC, ADCC, apoptosis	I, I/II, II, III, IV	Yes
Second Generation			
Ofatumumab	↑CDC	I/II, II, and III	In development
Veltuzumab	↑CDC	I/II	In development
Ocrelizumab	↑ADCC, ↓CDC	I/II	In development
Third Generation			
RhumAb v114	↑affinity to FcγRIIIa (↑ADCC)	I	Terminated
Ocaratuzumab	↑affinity to FcγRIIIa (↑ADCC), ↑CDC	I	In development
Obinutuzumab	↑affinity to FcγRIIIa (↑ADCC)	I, I/II, II, III, and IV	Yes
TRU-015	Apoptosis	I/II	Terminated
EMAB-6	↑affinity to FcγRIIIa (↑ADCC)	I and I/II	In development

RTX: rituximab; mAbs: monoclonal antibodies; CDC: complement-dependent cytotoxicity; ADCC: antibody-dependent cell-mediated cytotoxicity.

In a further Phase II study, OFA was evaluated in 116 patients with RTX-refractory FL, but only a limited response was reported with an ORR of approximately 11% and a median PFS of 5.8 months.[26] When OFA was used in combination with CHOP in untreated advanced-stage FL patients, OFA showed greater efficacy (ORR of 90%).[27] The most common side-effects reported with OFA were neutropaenia, thrombocytopaenia, and anaemia. In response to the good results reported in Phase III clinical trials in CLL patients, OFA was approved by the FDA in 2009 for fludarabine and alemtuzumab-refractory CLL treatment.

Veltuzumab (IMMU-106, hA20) is a Type 1 humanised anti-CD20 mAb with a single amino acid difference in the CDR3 variable region of the heavy chain compared to RTX. This substitution causes a significant improvement in CDC and the off-rate reduction in different preclinical models.[28] Veltuzumab was evaluated in a Phase I/II trial in 82 patients with relapsed/refractory NHL (55 with FL) that showed high tolerance to weekly infusions. The FL patients showed an ORR of 44% (CR/CR unconfirmed rate 27%) despite the failure of previous RTX treatment. Interestingly, objective responses were obtained for marginal zone lymphoma and DLBCL with ORRs of 83% and 43%, respectively.[29] The most commonly observed adverse events included transient infusion-related reactions.

Ocrelizumab (PRO70769, rhuH27) is a Type 1 humanised anti-CD20 mAb with different amino acids at several positions within CDRs of variable heavy and light chains compared to RTX. These differences allow ocrelizumab to bind to a different but overlapping epitope. In contrast to RTX and most Type 1 mAbs, ocrelizumab causes stronger ADCC and lower CDC. Ocrelizumab's efficacy was evaluated in a Phase I/II trial in FL patients previously treated with RTX. The ORR was 38% with a median PFS of 11.4 months; Grade 3/4 toxicity was observed in 9% of patients. In many cases, infusion-related reactions were reported (74%).[30]

THIRD-GENERATION ANTI-CD20 MABS

The third-generation anti-CD20 mAbs (rhumAb v114, ocaratuzumab, obinutuzumab, TRU-015, EMAB-6; see Table 2) have humanised CDR and engineered Fc regions, resulting in enhanced binding affinity for the FcγRIIIa receptor expressed on NK cells with a consequent augmentation of ADCC. RhumAb v114 (PRO131921) is a Type 1 humanised anti-CD20 mAb. This mAb is derived from ocrelizumab and has better binding affinity for FcγRIIIa than RTX. A Phase I trial was conducted with dose escalation in 24 patients with relapsed/refractory indolent lymphoma previously treated with RTX. The maximum tolerated dose was not determined but the study showed a correlation between drug exposure and tumour reduction. A partial response (PR) was observed in 6 out of 22 evaluable patients. Infusion-related reactions were the most frequently reported side-effects. In addition, three patients had temporary neutropaenia.[31]

Ocaratuzumab (LY2469298, AME-133v) is an anti-CD20 mAb used to treat NHL and other B cell malignancies. Ocaratuzumab is a Type 1 humanised IgG1 mAb that binds CD20 more efficiently than RTX. This mAb has been optimised by protein engineering to improve both CDC and ADCC with respect to RTX. In a Phase I study, ten patients with relapsed/refractory FL received the mAb with dose escalation; three patients had a CR, one patient had an unconfirmed response, and one patient had a PR.[32] Another Phase I clinical trial with ocaratuzumab in 23 patients previously treated with FL showed that ocaratuzumab is well tolerated. A CR was observed in 2 out of the 23 patients, and the median PFS was 25.4 weeks. The main side-effects were chills and fatigue and transient tumour lysis syndrome; one patient showed a dose-limiting toxicity.[33]

Obinutuzumab (GA101, RO5072759) is a Type II humanised anti-CD20 mAb. Compared to RTX, obinutuzumab recognises CD20 antigen on a larger surface area, binding a different epitope. The Fc region has been engineered with a consequent higher ADCC compared to that of RTX. Obinutuzumab induces cell death more efficiently than other anti-CD20 mAbs. In a Phase I study, obinutuzumab was administered to 22 patients with relapsed NHL or CLL that had received a median of 4 prior regimens; 86% of the patients had received at least 1 RTX treatment. No dose-limiting or unexpected adverse effects were observed. At the end of induction, 5 patients achieved PR and 12 patients had stable disease; 8 patients received maintenance therapy, and the ORR was 32% (6 PR/1 CR). Injection reactions were the most common adverse event, followed by infection, neutropaenia, headache, and nausea.[34]

Obinutuzumab is currently being evaluated in several clinical trials, one of which (NCT00576758) has recently been completed. In this Phase II trial, 175 patients with relapsed indolent NHL were randomised to receive either obinutuzumab or RTX given as four weekly infusions. Many other clinical trials with this mAb are ongoing or recruiting patients, and it has been approved by FDA for the treatment of CLL (Phase IV clinical trial: NCT01868893).

TRU-015 (CytoxB20G) consists of a single-chain Fv specific for CD20 linked to the human IgG1 hinge domain and the heavy-chain constant region domains CH2 and CH3. TRU-015 has shown pro-apoptotic activity against B lymphoma cells.[35] Clinical development efforts for the treatment of lymphoma and inflammatory disease are ongoing. The first Phase I/II dose escalation study (NCT00521638) of TRU-015 in subjects with relapsed or refractory B cell NHL was recently terminated, but no data are available. EMAB-6 (LFB-R603) is a novel chimeric anti-CD20 mAb that is able to induce similar apoptosis and CDC but higher ADCC compared to RTX.[36] A Phase I clinical trial (NCT01098188) involving 33 CLL patients was completed in 2012, and other clinical trials for the treatment of NHL, CLL, and other B cell lymphomas are ongoing. To date, the clinical results have not been made available. Some other Phase I/II trials are ongoing.

CONCLUSIONS

The above summarised clinical trials show the efficacy of RTX and the clinical potential of the other new anti-CD20 mAbs in NHL therapy. The availability of a panel of new human mAbs will surely lead to a reduction in the side-effects associated with RTX. Moreover, the clinical efficacy of these new mAbs has not yet been completely explored because the results of several clinical trials have not been disclosed and many trials are ongoing. In the near future, it will be possible to match the more effective and tolerated agents to a single lymphoma subtype to obtain personalised therapies for each patient.

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FUNDAMENTAL PRINCIPLES OF RAISING AN ANTITUMOUR IMMUNE RESPONSE *IN VIVO*: A COMPLEX MODEL, A CASE REPORT, AND A PERSPECTIVE

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ABSTRACT

In preclinical model systems, the fundamental principles underlying a successful and durable anti-tumour immune response are well demonstrated. In clinical practice, significant successes in Phase III trials have been few over the last decades, but the field has gained tremendous interest following recent advances showing the activity of checkpoint blockade inhibitors. Still, at this time we do not fully understand why some people respond while others do not; nor do we completely understand which clinical and immunological monitoring tools we need to put in place to make immunotherapy a more controlled medical science. Reviewing recent evidence suggests that for a successful and controlled immunotherapy, we may need to juggle with several conditions at the same time; there is a need for the endogenous or exogenous addition of tumour antigens for a favourable tumour microenvironment, and for an immune system which remains actionable towards T cell (effector) activity by checkpoint blockade inhibitors.

Keywords: Immune response, vaccines, tumour antigens, tumour microenvironment, checkpoint blockade.

INTRODUCTION

Mellman et al.,[1] in their review: '*Cancer immunotherapy comes of age*', explore the advances in the understanding and regulation of anti-tumour immune responses, and explain the sequence of events that need to occur for a successful immune response to take place. Immune tolerance and immunosuppression are frequent features in cancer patients, but these can be bypassed and immunity restored as supported by recent successes,[2] which strongly suggest that active immunotherapy does indeed represent a valid therapeutic option and is a path towards a durable and long-lasting response in cancer patients. In the present review we shall compare the fundamental theoretical basis to the clinical practice of immunotherapy, the past failures in large Phase II and III clinical trials, incipient results, and fledgling success stories. We can model our endeavours to harness the immune system in the right direction by equating immunotherapy to the multi-parametric model of sustained flight with a device heavier than air.

Theoretical Basis behind the Biology of the Immune Response

Over the past decades, most of our clinical efforts were directed towards providing sufficient fuel in the form of tumour specific antigens, exogenously in a variety of flavours (tumour cell lysates, peptides, whole genes in viral carriers, DNA vaccines, etc.) or endogenously by tumour-cell lysis following standard targeted therapies or oncolytic viruses.[2] The immune-stimulatory process is enhanced by the association of a so-called 'adjuvant', which is meant to deliver a maturation signal to antigen presenting cells (APCs) such as immature dendritic cells (DCs). This 'adjuvant' might be pictured as a catapult, able to provide uplift to our model plane (a glider here) from the ground. The endogeneous approach also necessitates the recruitment of APC into the tumour area. Following effective maturation, DCs may

move towards immune organs such as tumour-draining lymph nodes, where they prompt T cells to become engaged in the battle against specific antigen-bearing cancer cells and to mature into effector T cells.

Effector T cells recirculate - passing fleetingly in circulation where they may be monitored - and re-enter the tumour bed, usually facing an array of immunosuppressive defence mechanisms such as suppressive myeloid cells and T regulatory cells (Tregs), which oppose their lytic function.[1] If the suppressive microenvironment can be blocked, and if all necessary steps of immune activation are fulfilled according to plan, T cells may infiltrate the tumour and lyse tumour cells. In our model, tolerigenic or immunosuppressive actions might be pictured as strong crosswinds or violent thunderstorms, which are known to jeopardise take offs and landings.

THE REALITY OF IMMUNE THERAPY IN CLINICAL PRACTICE

The detection of a viable tumour signifies that the immune system has failed. This may be due to failed antigen recognition. Human leukocyte antigen (HLA) dysregulation, as well as absent HLA Type 1 glycoprotein expression (preventing antigen-specific T cell recognition), have been described in tumours and cancer cell lines[3] while HLA Type 2, which is normally not expressed (for instance in normal squamous epithelium), has been shown to be expressed in >80% of carcinomas.[4,5] There exists now a wealth of data in the literature documenting active immunosuppression through the secretion of immunosuppressive mediators by the tumour and leading to induction of Tregs and subtypes of suppressive myeloid-derived cells in close association with growing tumours.[6] While natural Tregs have a role in maintaining self-tolerance and in regulating responses to infectious agents, transplantation of atypical glandular cells (AGCs), and tumour AGCs, induced Tregs are able to prevent a robust antitumour cytotoxic T lymphocyte (CTL) response.[7]

Tregs appear to be exquisitely sensitive to chemotherapy,[8] but they tend to reappear over time in the presence of a persistent tumour. Similarly, subsets of 'M2 Type' APCs, in the tumour microenvironment (TME), were shown to be relevant to poor outcome. Depletion of tumour-associated macrophages (TAM) in an animal model, restored tumour-infiltrating CTL responses and suppressed tumour growth,[9-11] while depletion of tissue resident macrophages had no effect. It has been suggested that the presence of colony stimulating factor-1 (CSF-1), a macrophage-specific growth factor which is abundant in many tumours, will lead to TAM and may divert effective maturation from DCs, which are potent APCs, thereby perturbing efficient immune stimulation.[12,13] However, in some instances there are signs of an effective immune response occurring at the tumour site. Thus, the presence of specialised CD4+ T cells in the TME, when found to localise to the germinal centres of peri-tumoural tertiary lymphoid structures in extensively infiltrated neoplastic lesions, predicted improved outcome in breast carcinoma patients.[14,15]

Similarly, during neoadjuvant chemotherapy in patients with breast cancer, the increase of a CD25-CD127- CD4+ T cell population in circulation correlated with tumour regression.[16] In a recent paper assessing the microenvironment of cervical cancer patients, the quantification of different subsets of myeloid cells revealed that a strong intraepithelial infiltration of CD14+ cells, and more specifically, the population of CD14+ CD33- CD163- matured 'M1' (activating phenotype) macrophages, were associated with a large influx of intraepithelial T lymphocytes (p=0.008), and with improved disease-specific survival (p=0.007). This factor retained an independent prognostic value for improved survival in a multi-parametric analysis (p=0.033).[17] Recently, 84-gene signature on genes involved in immune function was shown as being able to predict outcomes in patients with melanoma.[17] In practical terms, the immunological monitoring of patients is most often based on sampling of lymphocytes from circulation, rather than from the tumour or from tumour draining lymph nodes, while a more accurate assessment of tumour infiltrating lymphocytes would be based on a biopsy at the crucial tumour site.

PAST CLINICAL DEVELOPMENTS IN CANCER IMMUNOTHERAPY

There are many different types of immunotherapies, and a great variety of reagents to choose from. What did we accomplish in a century of immunotherapy and what should be adapted to future clinical trials? A recent review article listed 41 Phase II or Phase III trials, some with quite significant numbers of patients, all asking questions

concerning clinical efficacy and a prolonged disease-free period, or overall survival.[2] In many cases, trials were abandoned at interim analysis because there was no significant survival benefit in the intention to treat population, compared with an active comparator or best supportive care.

When subgroups of patients were analysed, signs of activity could be seen in so-called 'favourable' patient groups, with either a favourable prognostic score, as in a prostate cancer group with a Halabi score predicted survival of >18 months,[18,19] or for patients who had combined treatments with hormone therapy, chemotherapy, or radiation. Importantly, after many early failures, some recent very clear successes in clinical trial responses[20,21] could be achieved by using so called 'checkpoint modulators' directed against programmed death-1 (PD-1) T cell co-receptor and its ligands. PD-1 is expressed on antigen-experienced T cells in the periphery, and serves in the normal host to limit the activity of T cells at the time of an inflammatory response, thereby protecting normal tissues from collateral destruction. By blocking its effect in cancer patients, the immunosuppressive effect in the TME may be lifted.

A Model Perspective

While controlled flight has been a preoccupation of mankind over many centuries, it was only at the beginning of the last century (1903) that we grasped the multiple parameters that need to be fulfilled to not only lift an object heavier than air into the air but, more importantly, to control all actions of safe flying. To put immunotherapy in historical perspective, at the time the Wright brothers were building their plane, the New York surgeon William Coley used live bacteria as antigens to immunise against tumours (1893). What are the essential ingredients for controlled flight and can we transpose this model to immunotherapy? To fly an airplane, we need fuel for propulsion, we need wings, and we need balance; we need those three main ingredients all together at the same time. Each one, taken on its own, will not allow an airplane to fly (Figure 1). Ifwe try to transpose that idea to immunotherapy, we may submit that antigens and adjuvants represent the fuel, whilst lift/wings to remain airborne may be equated with an 'adjuvant', and with correct DC maturation.

Powerful crosswinds can be likened to an unfavourable TME, favouring DC maturation toward tolerance, rather than toward activation, while violent thunderstorms would be the immunosuppressive microenvironment mediated by Tregs and myeloid derived suppressor cells. Finally, the last, but crucial aspect of flying has to do with balance and centre of gravity, which also affect the stability of the aircraft. When the centre of gravity is 'out of range', the aircraft may pitch uncontrollably down or up. This tendency may exceed the control capacity of the pilot and cause a loss of control. To ensure the aircraft is safe to fly, the centre of gravity must fall within specified limits established by the aircraft manufacturer, and may be compared in our model to immune checkpoints whose normal function is to prevent excessive and uncontrolled immune responses. An extreme loss of control through a checkpoint modulation is already reported in the literature in 2006, when six healthy volunteers (within 90 minutes of receiving a single intravenous dose of an anti-CD28 antibody), all had a systemic inflammatory response, characterised by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhoea, erythema, vasodilatation, and hypotension.[22]

Within hours, they became critically ill with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes from circulation occurred within 24 hours. All six patients were transferred to an intensive care unit, where they received intensive cardiopulmonary support. Despite evidence of the multiple cytokine-release syndrome, all six patients survived. Immune checkpoint modulation may thus be compared to releasing a brake on immune control. While interfering with CD28 was very poorly tolerated, similar actions on other checkpoints such as cytotoxic T lymphocyte antigen 4 (CTLA4) or PD-1 have been shown to be an advantage in the treatment of cancer patients.

Modulations – adaptations to the individual immune response settings

- Possible actions to avoid turbulence are to fly on a calm day. By analogy, only treat patients with a good Halabi score, or take DCs out of the compromised TME and grow them *in vitro*, and re-inject matured (finally differentiated) DCs that are loaded with the desirable antigen. A number of clinical trials using DCs have shown some activity in the clinic, leading to

the registration of Provenge.[23] A variant from this scheme is to expand T lymphocytes *in vitro* from the patient T lymphocytes which have already shown some ability to kill the patient's own tumour or natural killer T cells directed against a tumour antigen. Steve Rosenberg's laboratory has been a leader in that field and has done remarkable work for many years.[24]

- A good pilot may also make use of flaps and elevator trim to give some leverage in controlling crosswinds. Flaps may be equated to assistance by standard therapies in the control of Tregs and myeloid suppressors. It is documented that myelosuppressive chemotherapy[25] may improve the disturbances in the microenvironment, rendering it less tolerigenic. *In vivo* measures, other than myelosuppressive chemotherapy, to specifically block the differentiation of inflammatory macrophages may be considered in the future via specific blockade of the CSF1 receptor. CSF1 is a chemotactic cytokine for the recruitment of monocytes to an area of intense tissue turnover, and for their differentiation into macrophages. It has a major role in wound repair. We have previously shown that it modifies DC differentiation prior to the terminal differentiation step by tumour necrosis factor, while fully mature DCs will not be modified by CSF1.[13]
- Finally, we can use the notion of checkpoint modification as analogous to the balance of the centre of gravity of the immune response. Similarly, just as we carefully monitor the stability of an aircraft, we can stimulate activating receptors on T cells or block inhibitory receptors such as block interaction of PD1 with PD-L1, or expand T cell numbers with anti CTLA4. Establishing an immunological 'grade' for tumour stratification and therapeutic decision before treatment with vaccines +/- checkpoint inhibitors could be equivalent to the pilot doing preflight checks, particularly for weather conditions, prior to take-off.

Case History

While we are still some distance from curing patients with immunotherapy in a regular and controlled fashion, the way aspirin cures most headaches, there are occasional success stories which are worth exploring in depth. Ten metastatic breast cancer patients, who had previously progressed on chemotherapy, were treated in 1999 at Institut Curie, Paris, France, with the Transgene TG4010 vaccine product (containing the MUC1 gene + interleukin-2 in a Vaccinia Virus vector). Injections had been administered every 3 weeks. Two of ten patients achieved a partial response, which lasted 11 months for patient '204'. Patient '207', after surgical resection of residual disease remains in complete remission in 2014.[2] Injections were administered every 3 weeks. 15 years ago, we knew that patients with a 'healthy' immune response had on average >1,000 total peripheral lymphocyte counts, and that these have a tendency to drop during metastatic tumour progression, that immunosuppression (in relation to AIDS) was correlated with a low CD4 count in circulation, and that T effector cells were CD8+. We routinely evaluated CD4+ and CD8+ total counts in circulation, as well as serum CA153 marker and CSF1 levels.

Figure 1: Three-dimensional dynamics of anti-tumour immune response.

While treatment tolerance was excellent, patient 207 complained of increasing fatigue at 6-8 months, which led to a diagnosis of hypothyroidism. Retrospectively we tested all the stored serum samples (Table 1) showing that the increase in circulating CD4+ T cell counts paralleled the appearance of thyroid auto antibodies, a failing thyroid function, but most importantly, of tumour regression. Interestingly, CSF1 serum levels, an inflammatory macrophage differentiation, and survival factor were consistently low throughout.[26] The patient has been in complete remission for >14 years. It is striking that the unique single patient who developed signs of autoimmune thyroiditis in parallel with vaccination, which peaked with the maximal tumour shrinkage, achieved a durable remission and, very likely, a cure. Her MUC1 specific immune function could unfortunately not be tested due to a technical problem[26] but additional genomic testing of her tumour is presently ongoing. In the present case, the specificity of these CD4+ T cells is unknown, but in a recent publication, adoptive transfer of CD4+ T helper 1 cells, recognising a specific mutated epitope on cancer cells, was shown to be able to mediate a regression of metastatic epithelial lesions.[27]

Table 1: Quantitative changes in circulating PBMC of CD4/CD8 phenotype and rising autoantibodies during an effective vaccine based tumour regression.

Variations of CD4 levels of anti-thyroid and anti-nuclear antibodies, of thyroid function tests and breast cancer tumour marker CA153									
		Real-time assessment			Retrospective assessment				
					Antibodies				
Injection number	Date	**CD4 Fresh blood**	CD4/CD8 **Fresh blood**	CA153 serum	**Anti-TPO serum**	Anti-nuclear serum	Anti-DNA serum	T4 serum	TSH serum
		counts/ mm^3	ratio	U/ml	U/ml	inverse ratio	U/ml	ng/ml	ug/ml
BL	20th Jan 99	680		26	179	0	0		
1	28th Jan 99			23		0	0	10.7	1.18
2	18th Feb 99	908		18		0	0	10.3	1.94
3	11th Mar 99	1,160	4.7	18		0	0		
4	1st Apr 99	1,081	5.2	17		0	0		
5	17th May 99	1,172	5.6	16		0	0	12	2.92
6	28th June 99	1,305		18		80	14	15.2	2.23
7	9th Aug 99	1,224	4.7	17		160	15		
8	**20th Sept 99**	**1,444**	**5.5**	**18**	**11,529**	**320**	**13**	**5.8**	**51.29**
9	2nd Nov 99	1,345	3.5	18	11,052			11.9	9.14
10	13th Dec 99	966	4.7	18	6,667	260	260	12	0.97

PBMC: peripheral blood mononuclear cells; Anti-TPO: anti-thyroid peroxidase; T4: total thyroxine; TSH: thyroid stimulating hormone.

CONCLUSIONS AND PERSPECTIVES

While many isolated observations of tumour responses to immunotherapy do exist, and while some statistically significant successes in Phase III trials have been reported, we do not, at present, fully understand why some people respond and others do not; nor do we understand which clinical monitoring tools we could put in place to make immunotherapy a more controlled science. If the model of aviation holds true, then we would need to fulfil several conditions at the same time, such as the presence of tumour antigens, a favourable microenvironment, and an immune system geared towards T cell effector (lytic) activity. Modern techniques, allowing assessment of the likelihood of immune responsiveness by an immune activity signature, will be helpful for the selection of patients in a first instance.[17] To bring on board immunotherapy for all, we will need to not only add fuel, but also think about the microenvironment and checkpoint blockade. Whether it will take us another century to control immunotherapy - to expand and fold wings at leisure - remains to be seen.

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IMMUNOTHERAPY OF CANCER: TOWARDS A NEW ERA

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ABSTRACT

In the past two decades, immunotherapy of cancer has developed into an established treatment option. At first, the development of monoclonal antibodies - targeting overexpressed cell surface molecules on tumour cells - resulted in improved survival when combined with standard chemotherapy or radiotherapy. More recently, T cell immunotherapy has impacted on survival of certain cancer types. In melanoma especially, but now also in renal cell cancer and non-small cell lung cancer, immune checkpoint inhibitors, such as cytotoxic T lymphocyte–associated antigen-4 (anti-CTLA4) and blockade of programmed death receptor-1-PD-ligand 1 (PD1-PD-L1) interaction, represent a completely new treatment paradigm, lowering the threshold for an anticancer immune response and breaking self-tolerance. Adoptive T cell transfer using tumour-infiltrating lymphocytes or genetically modified T cells are under development, but have shown impressive clinical efficacy in several Phase II studies. These emerging but highly promising treatments can give rise to durable tumour control in diseases that were lethal in all patients only a few years ago.

Keywords: Immunotherapy, cancer, T cell, checkpoint inhibitor, adoptive cell therapy, cytokine, monoclonal antibodies, melanoma.

INTRODUCTION

Immunotherapy of cancer goes back to the beginning of the previous century with a famous pioneer in the field, Dr William Coley, who observed that occasionally cancer could regress following a severe bacterial infection (erysipelas).[1] Based on these observations, he started treating cancer patients with bacterial toxins, sometimes with great success.[2] Despite these early observations and treatments, however, immunotherapy of cancer remained in its infancy for a very long time. Only very recently, immunotherapy of cancer made a breakthrough when immune checkpoint inhibitor ipilimumab (Yervoy®) demonstrated an improvement in overall survival (OS) in pretreated metastatic melanoma patients, and was approved for this disease.

T CELL IMMUNOTHERAPY

T cell based immunotherapy has been promising for decades as a minority of patients appear to benefit from this strategy. However, studies testing vaccines, for example, never showed any improvement in survival in large randomised controlled clinical trials. One may ask the question: why has T cell immunotherapy been tried for so many years? Firstly, some cancers are associated with spontaneous regressions, even metastatic disease. Well-known examples are melanoma and renal cell carcinoma.[3,4] In melanoma, around 5% of patients with metastatic disease present without a primary tumour. Based on a highly similar genetic make-up as cutaneous primary melanomas, it is likely that these primary tumours have regressed spontaneously by an effective immune response.[5] Secondly, for many tumour types, the presence of lymphocytic infiltrates in the primary tumour or metastatic lesions has been correlated with improved outcome.[6,7] These observations have been clearly shown for melanoma, colorectal cancer, and ovarian cancer.[8-10] Especially in the case of melanoma, many tumour-associated antigens that are recognised by these infiltrating T cells have been defined.

These antigens are mostly derived from tumour-associated proteins that are shared between patients. Examples of these antigens are the melanocyte differentiation antigens (MDAs), such as: MART-1, gp100 and tyrosinase, the cancer/testis gene products from (for example) the MAGE family, from NY-eso-1, or from the SSX family, and overexpressed proteins such as MELOE-1 and telomerase.[11-16] Now that genomes of many human cancers have been sequenced, one has learned to appreciate that some tumours harbour many more mutations than others.[17] Of all tumour types, melanomas have the highest somatic mutation rate. These mutations have been induced by exposure to ultraviolet irradiation.[18] Next come non-small cell lung cancer (NSCLC) and other smoking induced cancers. When a mutation occurs in an expressed gene, this may lead to single amino substitution, and therefore, a potentially truly foreign neoantigen for the immune system. Recently, CD8 T cells, specific for these mutation-induced, tumour-specific antigens, have been found within tumour infiltrating lymphocytes. It is tempting to speculate that tumour types with the highest mutation rate are the most immunogenic tumours. Evidence is accumulating that supports this hypothesis.[19,20]

VACCINE-BASED STRATEGIES

Several of the shared tumour-associated antigens have been part of a vaccine strategy. Many different vaccine-based strategies have been explored: short peptide vaccines, containing 8-10-mer peptides that can directly bind to major histocompatibility complex (MHC) Class 1 molecules, and thus, be presented to the T cell immune system; synthetic long peptides (20-40-mer) that require intracellular processing before presentation to the T cell immune system; viral vaccines engineered to express peptides from, or the tumour-associated antigens themselves; DNA vaccines, bacterial plasmids engineered to contain TAA sequences; and dendritic cell (DC) vaccines, consisting of autologous or allogeneic *ex vivo* cultured DCs that are loaded with TAA or tumour derived RNA, before injection or infusion into patients. Until recently, these strategies failed in randomised controlled trials (RCTs) despite the high number of promising early phase trials. In 2010, the FDA, because of a statistically significant impact on survival, approved Sipuleucel-T (Provenge®), an autologous DC vaccine for patients with castrate-resistant prostate cancer. One double blind, placebo controlled, Phase III study showed that Sipuleucel-T prolonged OS from 21.7 months to 25.8 months (HR: 0.775; CI: 0.61-0.98).[21] This was confirmed in a smaller, second study with the same design.[22]

CYTOKINE TREATMENT

The use of cytokines to treat cancer goes back >30 years. High-dose interleukin-2 (HD IL-2) was approved in 1992 for metastatic renal cell cancer (mRCC) and in 1998 for metastatic melanoma (MM). This was not based on results from randomised, controlled, Phase III clinical trials, but on Phase II data.[23] In both mRCC and MM, the overall objective response rate (RR) is around 15%. 4-7% of patients treated with HD-IL-2 obtain a complete remission (CR).[24] These patients tend to do extremely well and can be considered cured in the majority of cases. Interferon-alpha (IFN-α) was studied in many types of cancer and was approved for the treatment of melanoma (adjuvant setting in the US), mRCC, and haematological malignancies (including chronic myeloid leukaemia and hairy cell leukaemia). Cures during IFN-α, however, are rare. In mRCC, IFN-α has provided a 3-month improvement in OS compared to medroxyprogesterone acetate (considered a placebo).[25] In melanoma, the debate has been ongoing for many years about the benefit of IFN-α in melanoma as adjuvant treatment, between study groups in the US and Europe.[26-28] An OS benefit could not be demonstrated. Based on subgroup analyses, patients with ulcerating primary melanomas may benefit from adjuvant IFN-α.[29] A Phase III trial in Stage 2 (ulcerating disease) will investigate the role of IFN-α in this patient population.

IMMUNE CHECKPOINT INHIBITORS

Anti-CTLA4

Almost 30 years ago, CTLA4 was discovered.[30] CTLA4 is an inhibitory cell surface receptor expressed on activated CD4 and CD8 T cells. Mice deficient of CTLA4 succumb to severe lymphoproliferative disease a few weeks after birth, indicating that CTLA4 is required to dampen an ongoing immune response.[31] CTLA4 binds two receptors present on antigen presenting cells (APCs), predominantly DCs in lymph nodes. For proper T cell activation, apart from the interaction between the T cell receptor - unique for every T cell - and the MHC-peptide complex on the APC, a second signal is required. This signal is delivered

by the co-stimulatory molecule CD28 on the T cell, upon interaction with CD80 or CD86 on the APC. Hours after full T cell activation, T cells start expressing CTLA4, which also binds to CD80/CD86 on the APC. Due to a higher binding affinity, CTLA4 outcompetes CD28 for interaction with CD80/CD86, therefore resulting in an inhibitory signal, dampening the T cell response.[32]

It has been demonstrated that blocking the interaction between CTLA4 and CD80/CD86 results in potentiation of a T cell response, especially against self-antigens. In preclinical models, anti CTLA4 treatment showed anti-tumour activity, either as single agent or in combination with a vaccine depending on the tumour model that was used.[33,34] Ipilimumab is a fully human monoclonal antibody (mAb) with high affinity for human CTLA4. Early phase clinical studies already showed activity of this drug as a single agent in patients with MM and mRCC.[35] Indeed, side-effects observed in at least half of patients appeared immune related and resembled autoimmune diseases such as Crohn's disease, autoimmune hepatitis, thyreoiditis, uveitis, and an otherwise extremely rare disease, hypophysitis.[36] Impressive objective responses were shown in 10% of patients. In 2010, the mature data from the first RCT were published, demonstrating a 4-month gain in median OS in favour of ipilimumab compared to the gp100 peptide vaccine as treatment for MM patients that had received one prior systemic therapy for advanced disease.[37] Ipilimumab is the first drug after decades of clinical research to show improvement in survival in MM. Importantly, the Kaplan-Meier survival curves reached a plateau at 3 years after initiation of ipilimumab treatment. At that time, around 20% of patients were still alive, which was about 10% more than in the control group. Adverse events (AEs) were similar, as was already observed in Phase II trials, mostly immune related, with about 15-20% Grade 3-4 (colitis, hepatitis, etc.), but manageable mostly with high dose steroids. Only very few treatment-related deaths were reported. Based on these data, both FDA and European Medicines Agency approved ipilimumab for the treatment of MM. Ipilimumab is administered as four consecutive infusions at a dose of 3 mg/kg, every 3 weeks. The results from the first RCT were confirmed by a second trial in which dacarbazine was compared to the combination of dacarbazine and ipilimumab. In the ipilimumab-treated group of patients, the median OS was 2 months longer when compared to the control arm.[38]

Anti-PD-L1

Several other immune checkpoint molecules have been discovered that may be displayed by T cells and other cells from the immune system during an immune response. Programmed death receptor-1 is expressed by activated CD4 and CD8 T cells.[39] In contrast to CTLA4, which appears to play a role at an early stage during T cell activation, PD1 expression is important at the effector stage, within peripheral tissues or at tumour sites. PD1 can bind two ligands, PD-L1 and PD-L2.[40,41] PD-L1 can be expressed on many cell types including tumour cells, whereas, so far as we know now, PD-L2 expression is limited to haematopoietic cells. Interaction of PD-L1 on tumour cells with PD1 on T cells results in an inhibitory signal to the T cell with diminished T cell receptor (TCR) signalling and the shutting down of cytolytic activity. Blockade of PDL1-PD1 interaction can prevent this negative signalling and reinvigorate previously suppressed anti-tumour T cell activity. Several antibodies have been developed against PD1 and PD-L1 and all of these are either in early phase clinical trials or in Phase III RCT.

Nivolumab (Opdivo®), a fully human IgG4 mAb, has been shown to effectively bind PD1, and has been tested in several cohorts of patients, including patients suffering from MM, mRCC, and NSCLC. In all three tumour types objective responses (18% in NSCLC and 27% in mRCC) have been observed.[42] Interestingly, nivolumab is associated with fewer immune related AEs when compared to ipilimumab. The drug is well tolerated and is administered intravenously every 2 weeks. In melanoma, the objective RR observed in an extended Phase I study was 31%.[43] In this cohort of 107 MM patients, the majority of whom were heavily pretreated, the median OS was 16.8 months, with impressive 1 and 2-year survival rates of 62% and 48%, respectively. Another anti-PD1 mAb, MK-3475 or pembrolizumab, a humanised IgG4 antibody, has demonstrated similarly impressive results in patients with MM and NSCLC.[44] In a cohort of 113 MM patients, the objective RR was 40%. In NSCLC, monotherapy with pembrolizumab resulted in an objective RR of 21% (n=38), with a median OS of 12.8 months. Apart from anti-PD1, anti-PD-L1 antibodies have also been developed for clinical application. The first antibody, MDX-1105, was tested in a Phase I study in a large variety of cancer patients. In patients with MM, mRCC, NSCLC, and ovarian cancer, objective responses were observed. Also,

MDX-1105 was well tolerated and induced fewer immune related side-effects when compared to ipilimumab. MPDL3280A, another anti-PD-L1 antibody has been tested in patients with, among others, MM, mRCC, and NSCLC.[45] Also, in these studies, objective responses were seen, some of which were durable. Initially, PD-L1 expression by the tumour appeared to be correlated with response to PD1/PD-L1 blockade. More recent (mostly unpublished) data indicate that patients with PD-L1-expressing tumours have a higher chance of responding to PD1/PD-L1 blockade, but that PD-L1 low or negative tumours can have objective responses as well. In addition, PD-L1 staining is complicated: several antibodies and companion diagnostic tests are being developed, but the inter and intra-test variability seems high, and apart from tumour cells expressing PD-L1, also stromal cells and lymphocytic infiltrates can stain positive. Next to CTLA4 and PD1/PD-L1, inhibitors of other immune checkpoint molecules such as LAG-3, TIM-3, BTLA, and others are (or will be) further developed.

ADOPTIVE CELL THERAPY

Anecdotally, infusion of *ex vivo* cultured T cells has been successful; however, it was not until 2002 that Dudley and colleagues[46] published an objective RR of 50% in pretreated MM patients using autologous *ex vivo* grown tumour-infiltrating lymphocytes (TIL) in a Phase I/II trial.[46] TIL were isolated from a resected metastatic lesion and cultured to high numbers (1-10x10^{11} T cells) before reinfusion. Prior to infusion, patients received non-myeloablative chemotherapy consisting of high-dose cyclophosphamide (Cytoxan®) and fludarabine (Fludara®). Apart from generating physical space for the infused cells, preclinical studies had shown that prior lymphodepletion also removed so-called cytokine sinks and suppressive cell types such as regulatory T cells, so that the infused cells could have a head start before repopulation of the normal lymphocyte pool.[47] In later studies this protocol was amended either by adding total body irradiation to the chemotherapy, requiring peripheral stem cell support for bone marrow recovery, or by culturing the TIL for a much shorter period of time.[48-51] Despite these changes, the objective RR averaged around 50% (40-70%) with a median OS of about 16 months in patients with MM. Interestingly, about 10% of these patients achieved CR; they tend to have an excellent prospective. For many years, investigators have tried to culture TIL from tumour types other than melanoma. This has been successful only recently so that adoptive cell therapy with TIL can now be tested in other cancers as well.[52,53]

As it is still difficult to culture TIL from tumour types other than melanoma, an off-the-shelf product to treat many patients over many tumour types would be a solution to this problem. By genetically transferring TCR genes, encoding a receptor specific for a certain tumour antigen, into peripheral blood T cells, one can create a large army of tumour-specific T cells.[54] This so-called TCR gene therapy has been, and is being, studied in several clinical trials. In the first trials, TCR derived from T cell clones specific for MART-1 or gp100 (MDA) were used for genetic transfer.[55,56] The used transfer platform was a retrovirus that is capable of transducing T cells upon division and insert the TCR genes into the genome. Thus, obtained T cells do express this novel TCR and are specific for tumours that express the tumour antigen in the context of mostly HLA-A2. The objective response rates obtained with this versatile strategy, however, were lower than what was seen in TIL trials but the transduced T cells appear to be able to persist in the treated patients. Next to the use of TCR, others have used chimeric antigen receptors (CAR) instead.[57] CAR are single chain antibodies that are linked to TCR signalling molecules such as CD3 zeta and CD28 or CD137. T cell transduction with CAR specific for the B cell antigen CD19 were able to recognise and lyse CD19+ B cells and B cell malignancies. Early clinical trials targeting CD19+ haematological malignancies have shown very promising results and will be further studied in larger patient cohorts.[58-60] CAR targeting other cell surface tumour antigens are under development.

IMMUNE ESCAPE

Despite these amazing recent successes in immunotherapy of cancer, it is clear that immunotherapy is not a panacea as not all patients will respond to immunotherapy. Additionally, patients who respond originally may show disease progression later on. Therefore, one can distinguish intrinsic and acquired resistance to immunotherapy. Intrinsically resistant tumours are characterised by either lack of tumour immune infiltrates, or by strong local immune inhibiting mechanisms. The tumour microenvironment (TME) that has been recognised as equally important as the cancer cells themselves in tumour progression, invasion,

and metastasis formation may be highly hostile for effector T cells and prevent their homing and infiltration. TME consists of endothelial cells, stromal cells, myeloid cells, and immune cells. It is now well-established that many of these cell types may have tumour growth-promoting and immunosuppressive properties, rendering these tumours invisible for, or unresponsive to, the immune system. Among these cells are myeloid derived suppressor cells, tumour associated macrophages, and DCs that are highly immunosuppressive by production of immunosuppressive factors, including arginase-1, nitric oxide synthase, and indoleamine 2,3-dioxygenase.[61,62] Other cell types that appear to play a role in preventing an effective anti-tumour immune response are the recently described regulatory B cells or Bregs. These B cells that may reside in the TME invariably produce IL-10, an immune-inhibitory cytokine that impairs normal DC and T cell function.[63] Next to Bregs, regulatory T cells (Tregs), CD4+CD25+FoxP3+ T cells, which inhibit normal effector T cell function, can reside within the TME (Figure 1). Oncogene induced expression of T cell inhibitory molecules by tumour cells such as PD-L1 can also paralyse tumour-infiltrating lymphocytes. In some tumour types, PD-L1 expression is associated with PTEN deletion or an activating mutation in the phosphoinositide 3-kinase signal transduction pathway.

With acquired resistance, there is no evidence for altered T cell activation or homing. This type of resistance is enforced by mechanisms that interfere with T cell function within the TME. Many inhibitory mechanisms can be involved - including the induced expression of T cell checkpoint molecules and their ligands - that reduce the immune response, such as LAG-3 and its ligand MHC Class 2, TIM-3 and its ligand galectin-9, BTLA, and PD-L1.[39]

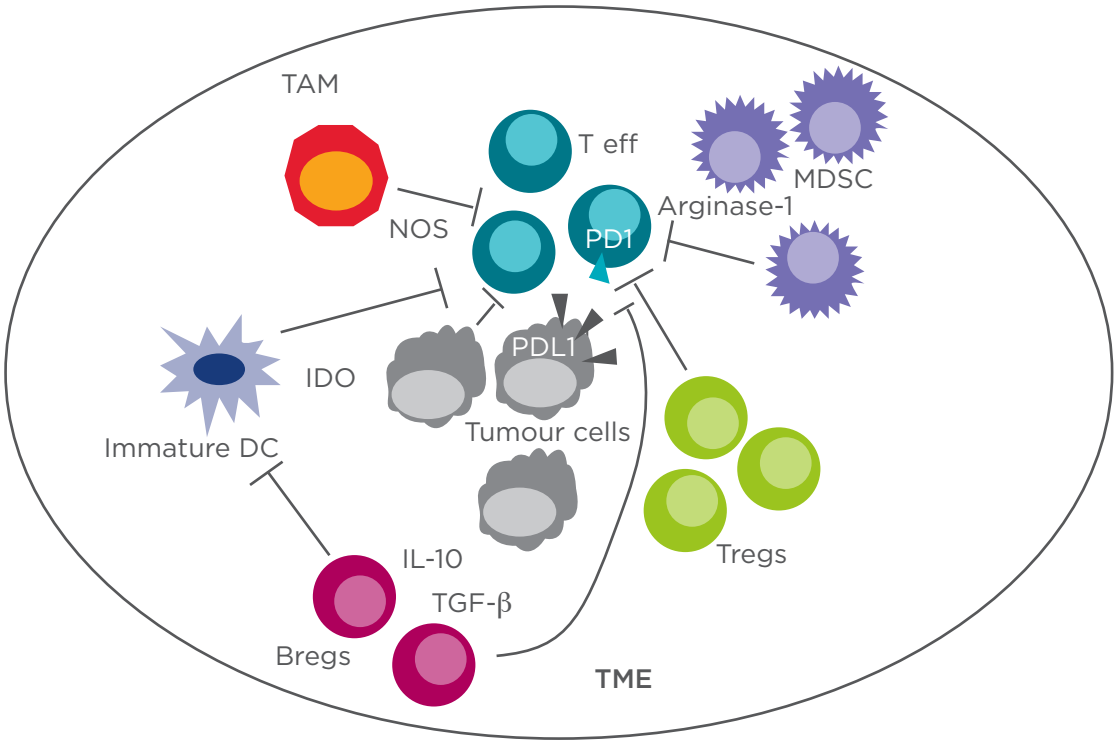

Figure 1: Cancer immune escape mechanisms.
Within the tumour micro-environment (TME) several mechanisms that help tumours to escape immune attack: regulatory B cells (Bregs) produce immunosuppressant cytokines including interleukin (IL)-10 and transforming growth factor-beta (TGF-β); regulatory T cells (Tregs) directly inhibit the function of effector T cells (Teff); myeloid derived suppressor cells (MDSCs) suppress effector T cells through arginase-1; tumour-associated macrophages (TAM) inhibit effector T cells through nitric oxide produced by NO synthase (NOS); immature dendritic cells (immature DC), but also tumour cells highly express indoleamine 2,3-dioxygenase (IDO) leading to tryptophane deprivation, which inhibits effector T cell function.

PD1: programmed death receptor

The latter may be induced at the tumour cell surface as the result of IFN-α signalling upon recognition and binding of cognate tumour antigen by the infiltrating T cells, which limits further T cell effector function by engaging its ligand PD-1 on the T cells.[64] In addition, an effective immune response may select for tumour cell subpopulations with loss or defects in the antigen processing and presentation machinery, like loss of MHC Class 1 expression, thereby hiding the tumour cell from the immune system.[65-67] Similarly, immune evasion may occur through a process called immune-editing: selection of tumour subclones present within heterogeneous tumours, lacking one or multiple antigens that are subject to strong Darwinian selection.[68-70]

CONCLUSION

Immunotherapy has developed from a promising treatment strategy to an adult and established cancer therapy. In the next decade, it is expected that immunotherapy will become a standard of care for many cancer patients beyond melanoma. First results coming from patients treated for mRCC and NSCLC are promising, and it is highly likely that other tumour types will follow. This can be achieved by single agent treatment, but more likely by combination therapy, such as combination of immune checkpoint inhibitors with chemo or targeted therapy, and ACT in combination with immune checkpoint inhibitors.

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RADIOTHERAPY FOR BREAST CANCER: HOW CAN IT BENEFIT FROM ADVANCING TECHNOLOGY?

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ABSTRACT

There have been significant technological and technical advances in radiotherapy over the last 20 years. This paper presents the pertinent advances and examines their application in contemporary breast cancer (BC) radiotherapy, particularly for reducing the long-term toxicity, using intensity-modulated radiation therapy, image-guided radiation therapy, and management of breathing motion. These modern technologies and techniques enable precise delivery of a highly conformal radiation dose distribution to the target volume in real-time, to optimise tumour control, and minimise treatment toxicity. They have been used for the treatment of BC in selected centres around the world. Although there is insufficient high-level evidence to support their routine application in BC at present, implementation of these technologies has been shown to be feasible, and could result in clinically meaningful long-term benefits for selected patients with BC.

Keywords: Breast cancer radiotherapy, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), motion management.

BACKGROUND

Radiotherapy is an established adjuvant treatment for breast cancer (BC), after conservative surgery or mastectomy, to reduce the risk of local recurrence and BC mortality in selected patients.[1,2] The target volume for radiotherapy typically includes the ipsilateral whole breast after conservative surgery or the chest wall after mastectomy, and regional lymph nodes form part of the target volume in selected patients. Conventionally, the radiation dose used for the adjuvant treatment of BC is 45-50 Gy delivered in 25 daily fractions over 5 weeks, followed by a tumour bed boost in selected patients. Dose escalation to improve tumour control, which is often a driver for the introduction of new technology for other cancer sites, is not a critical priority for BC. The radiation doses used in adjuvant therapy for BC are relatively low compared to definitive radiotherapy for some other tumour sites, and severe acute radiation toxicity is uncommon. However, in the context of the growing number of BC survivors, the key challenge is to minimise the risk of long-term toxicity, secondary due to the irradiation of non-targeted critical organs especially the heart, lungs, and the contralateral breast.[3-5] The long-term toxicities of radiation-related second malignancy and cardiac morbidity are uncommon but even low-level radiation exposure of these normal organs may be harmful.[6]

More recently, radiation target volumes and dose fractionation used in BC have been evolving as a result of several randomised clinical trials. These trials of adjuvant whole breast irradiation showed the non-inferiority of hypofractionated schedules, including 40.0-42.5 Gy delivered in 15-16 daily fractions to the biologically equivalent 50 Gy in 25 daily fractions in terms of tumour control and treatment toxicity.[7,8] The overall treatment time is further decreased to 1 week or less with the increasingly widespread use of accelerated partial breast irradiation, which also entails a

change in target volume from the whole breast to the tumour bed only, in selected patients with early BC.[9] Although the delivery of larger fraction sizes in a shorter overall treatment time improves patient convenience, this benefit needs to be carefully balanced against the risk of more long-term adverse effects, highlighting the importance of judicious application of radiation technical advances for reducing this risk in patients with BC.[10]

The evolving practice of radiotherapy for BC has brought into focus the importance and relevance of new technologies and techniques to improve its efficacy and safety. The conventional technique of whole breast radiotherapy primarily involves two parallel opposed tangential radiation beams (main picture in Figure 1). They are often supplemented by smaller 'fields-in-field' to improve dose homogeneity in the target volume by delivering additional radiation doses to the parts that do not receive the prescribed dose from the two primary tangential beams.[11] In comparison to the other tumour sites, whole breast radiotherapy has been delivered at many centres without contouring of the target volume and critical structures explicitly on 3D computerised tomography (CT) scans to improve dose distribution throughout the target volume and reduce treatment toxicity. Although 3D CT planning was proposed for BC treatment two decades ago,[12] it was not until recent years that it became more routinely used.

The aim of the present review is to examine the impact of the following technical advances of radiotherapy for BC:

1. Intensity-modulated radiation therapy (IMRT);
2. Image-guided radiation therapy (IGRT);
3. Management of breathing motion affecting the target volume and critical organs, especially the heart.

CONTEMPORARY TECHNOLOGIES AND TECHNIQUES OF RADIOTHERAPY

The past two decades have witnessed significant technological advances in radiation oncology, enabled by the increasing availability of computer technology to improve the characterisation of target volume, precision of its localisation, accuracy of radiation delivery, and homogeneity of dose distribution in the target volume. The improvements in target volume characterisation and localisation are beyond the scope of the present review. IMRT, IGRT, and motion management primarily concern treatment delivery. IMRT improves homogeneity of radiation dose distribution in the target volume and enables delivery of highly conformal radiotherapy. IGRT is essential for accurate and reproducible positioning of radiation beams during treatment. Motion management is related to IGRT, as the same imaging tools could also be utilised to assess movements of the target, in order to improve treatment accuracy, and critical normal organs, to minimise radiation exposure. We present a general review of the three techniques with particular reference to BC. More in-depth reviews are presented elsewhere.[13-16]

IMRT

The application of IMRT in the discipline of radiation oncology is increasing rapidly. The concept of IMRT was developed in the early 1980s, and involved subdivision of radiation beams into segments of different intensity, to increase the freedom of shaping radiation dose distribution and optimise its conformity and homogeneity in the target volume.[17] The subdivision became easily achievable when multileaf collimators (MLCs) became a standard accessory of most linear accelerators used in radiotherapy delivery.[18] The MLCs consist of many thin tungsten leaves that move independently of each other to shape the radiation fields. They effectively function as variable internal blocks in the beam, and conform to the target volume of individual patients quickly and automatically during treatment to enable radiation delivery to multiple small fields in rapid succession. The leaf pattern may also be dynamically modified during treatment to further decrease the time required for delivery of each fraction. More recently, this dynamic delivery was further enhanced by the capacity of linear accelerators to dynamically modify the MLC patterns whilst rotating the radiation source around the patient, a process called volumetric modulated arc therapy (VMAT).[19]

The design of target volumes and sequence of delivery of IMRT or VMAT are, in most cases, not possible without computer aid.[20] In the process of 'inverse treatment planning', the required radiation dose distribution is clinically defined, and the best possible method to achieve this distribution is yielded by a computer optimisation process. This has a number of important consequences:

- Contouring of all target volumes and relevant normal organs is required for the computer optimisation process,[21] increasing the workload of clinicians with resource implications in individual radiotherapy centres.

- An IMRT plan typically consists of at least seven radiation fields, each of which is subdivided into multiple segments. Treatment plans of this complexity cannot intuitively be understood and verified. They require additional quality assurance measures, which could be additional calculations or physical measurements, further increasing resource requirements.[13]

- The overall beam-on time for delivery of IMRT is longer than in conventional radiotherapy, resulting in more radiation leakage. Improvement in conformality of radiation dose distribution to the target volume is often countered by an increase of low radiation doses to normal organs distant to the target. The potential long-term adverse effects of low radiation dose exposure of normal organs, particularly the risk of radiation-related second malignancy, are an important consideration in the application of IMRT in patients with early BC, many of whom are long-term survivors.[22]

- Since the margins applied around target volumes to account for uncertainties in planning and treatment delivery in IMRT are typically smaller than in conventional radiotherapy, reproducibility of patient set-up and regular verification imaging become correspondingly more important.[23]

There is some inconsistency in the definition of IMRT in the literature. In whole breast radiotherapy, the use of two parallel opposed tangential radiation beams, supplemented by one or more smaller beams in the same direction (field-in-field approach; Figure 1), is sometimes referred to as IMRT, even if inverse treatment planning and complex field design is not a prerequisite.[24] This field-in-field approach was used in the IMRT arm of two randomised trials of early BC, which showed a decrease in acute radiation toxicity such as moist desquamation in the IMRT arm compared to 2D radiotherapy.[25,26] This was associated with an improved cosmetic outcome in the IMRT arm.[26] Including these results, a systematic review has found that radiotherapy for BC is one of the few areas where the benefit of IMRT is proven.[24]

The more contemporary definition of IMRT involves the use of more than two beam directions and inverse treatment planning. For whole breast irradiation, multi-field inverse-planned IMRT may provide additional degrees of freedom to optimise dose distribution, particularly when the target volume also includes the regional lymph nodes,[27,28] or to reduce radiation doses to the heart for patients with left-sided BC.[29] Heart sparing has been one of the main drivers for the introduction of inverse-planned IMRT in BC.[28,30] It is difficult to achieve in some patients using two tangential beams; in particular, if the target volume includes the internal mammary lymph nodes.[31] However, the inclusion of additional beam directions requires caution as it may paradoxically increase radiation doses to the contralateral breast, lung, and heart.[32]

The role of IMRT in radiotherapy for BC

The use of a field-in-field approach for whole breast irradiation is well-established as it not only reduces treatment time compared to the use of conventional wedges, but also optimises radiation dose distribution in the target volume: a key benefit of multifield inverse-planned IMRT without its disadvantage of increased doses to the distal non-targeted organs. Thus, implementation of inverse-planned IMRT and VMAT for BC is likely to be limited, with careful patient selection based on anatomy and the need for regional nodal irradiation rather than a 'one size fits all' approach informing their utilisation.

IGRT

Verification imaging is a quality assurance measure undertaken to confirm if the target volume is accurately localised for treatment delivery. There is no uniformly accepted distinction between conventional verification imaging and IGRT.[33,34] However, there is general agreement that IGRT should include the following features:

- Availability of high quality imaging equipment in the treatment room;

- Ability to visualise the actual target volume (and not just the external markers or bony anatomy) with the patient in treatment position, immediately prior to treatment;

- Presence of predefined protocols to indicate the necessary corrective measures in the presence of inaccurate target volume localisation on verification images.

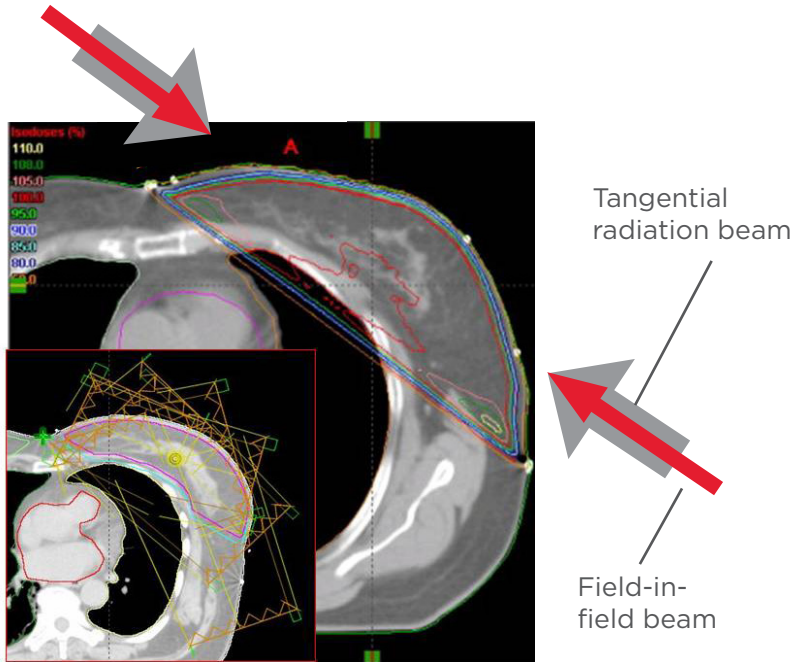

Figure 1: Conventional whole breast radiation treatment plan using a two tangential, parallel-opposed beam arrangement supplemented by field-in-field.
The insert demonstrates a treatment plan for multifield, inverse-planned, intensity-modulated radiation therapy.

Most modern linear accelerators are equipped with imaging equipment. A commonly available piece of equipment is the electronic portal imaging (EPI) device, which uses the megavoltage treatment beam to generate an image in a detector system, built into the gantry of a linear accelerator on the opposite side of the beam, without exposing patients to additional radiation doses.[35] Figure 2b shows an EPI of an anthropomorphic phantom which is depicted in Figure 2a. EPI uses megavoltage X-rays, a radiation quality optimised for treatment and not imaging. A dedicated diagnostic imaging unit using kilovoltage X-rays is now available on high-end linear accelerators to deliver high quality images as shown in Figure 2c.[36] The figure shows the surgical clips implanted in the phantom clearly. This can enable more precise targeting of the tumour bed, delineated by surgical clips, for the delivery of additional radiation doses to this site, to improve tumour control in patients undergoing breast conserving therapy.[37,38]

Projection images from many different directions, generated by the integrated diagnostic imaging unit of a linear accelerator, can be combined to form a reconstructed 3D cone beam CT (CBCT) image set prior to treatment delivery.[39] Comparison of this image set to the image acquired during the preceding treatment planning process verifies not only correct positioning of the patient but also the target volume and critical organs.[40,41] However, the following disadvantages of CBCT may limit its application in BC:

- A CBCT delivers approximately 1 Gy of radiation dose to the imaged site. Over the course of 25 fractions, the total additional dose to the heart, lungs, and contralateral breast is of the order of 0.25 Gy, which is approximately 100 times higher than the annual radiation exposure from natural sources.[42]
- A CBCT is acquired over approximately 1 minute during which motion artefacts may be introduced. Digital tomosynthesis may be a faster low-dose alternative in the future.[43]
- CBCTs from different manufacturers have different fields of view, some of which may not cover the entire region of interest.
- Shifting of the patient to a different position on the treatment unit may be necessary to acquire a CBCT with sufficient clearance of the linear accelerator's gantry in its rotation around the patient, potentially introducing positioning errors.

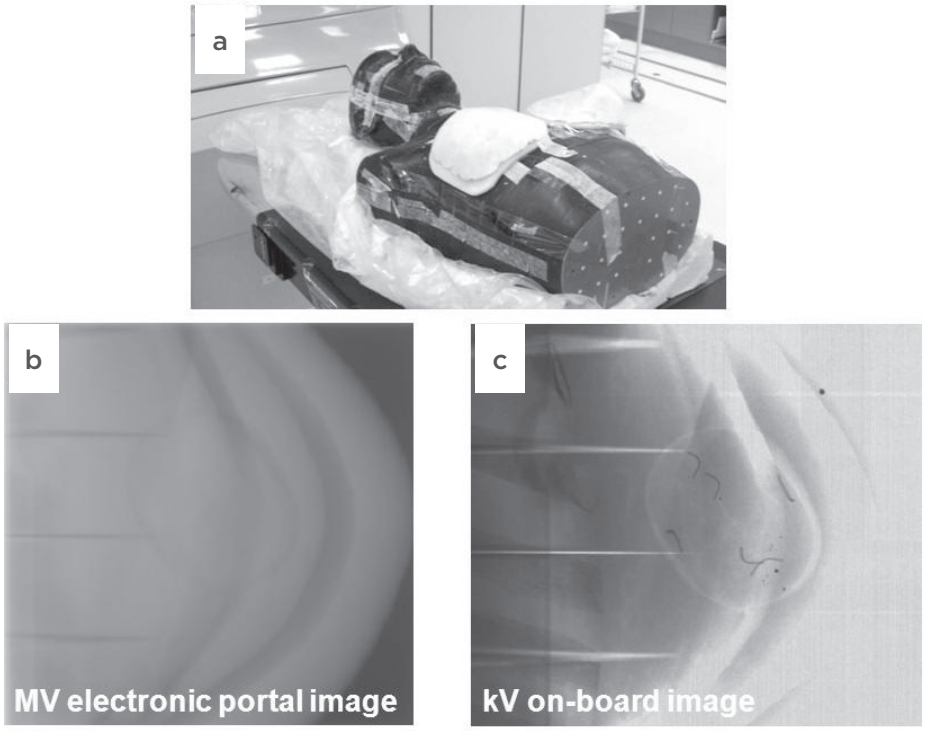

Figure 2: Image guidance in an anthropomorphic phantom with customised breast attachments.
A) The phantom on a radiation treatment couch. Customised breast attachments were made from wax. B) Electronic portal image of the breast attachment acquired using megavoltage (MV) treatment beam. C) Image of the breast attachment acquired using diagnostic X-ray equipment integrated into the gantry of a linear accelerator. The surgical clips implanted into the phantom are visible only in this image.
Taken from Willis et al.[48]

The other modalities that may be used for IGRT of BC are ultrasound[44] and, most recently, magnetic resonance imaging.[45,46] However, these modalities require new skill sets and are not widely available at present.

The role of IGRT in radiotherapy for BC

Although CBCT offers high quality verification images, this benefit needs to be balanced against the potential harm of additional radiation exposure to normal organs of patients and introduction of motion artefacts during its acquisition. Its application will likely increase if complex IMRT[47] and partial breast irradiation[48] become more widely used. However, EPI is currently the preferred option for verification imaging in most patients undergoing radiotherapy for BC.

Motion Management

Motion management could improve the precision of radiation delivery to targets that move, particularly with the breathing cycle.[16,49] As chest wall motion is typically relatively limited during quiet breathing,[50] the aim of motion management in whole breast radiotherapy is to reduce radiation doses to normal structures; in particular, the heart, which moves with breathing in relation to the target volume.[51,52] Motion management can be achieved using a variety of approaches, ranging from increasing the target volume to take motion into account, to immobilisation, gated delivery, and deep inspiration breath hold (DIBH).[16] In gated delivery the radiation beam is turned on only during predetermined phases of the breathing cycle to effectively 'freeze' the organ motion during radiation delivery and decrease treatment set-up uncertainty.[53] Its application in BC is predicated on the movement of the heart away from the high dose region of the target volume during inhalation.[50,54] DIBH capitalises further on this movement during deep inhalation, as illustrated in Figure 3.[55-59]

An additional benefit of DIBH radiotherapy is that lung density is reduced and, as such, there is less healthy lung tissue in the radiation field, potentially reducing the probability of lung toxicity.

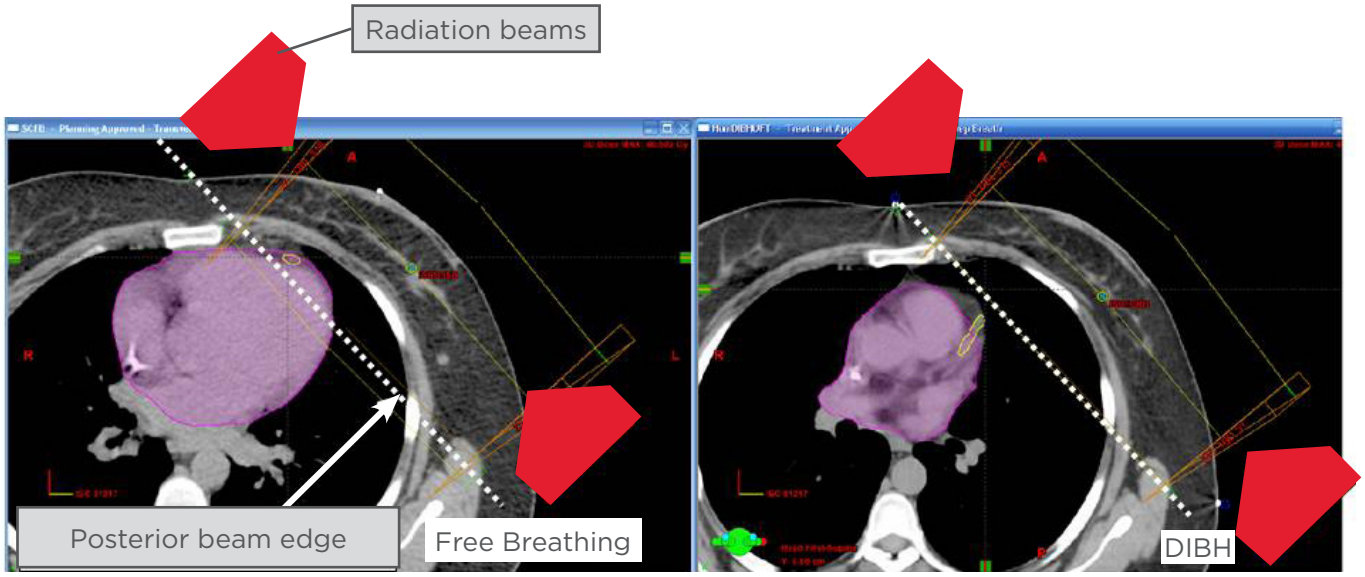

Figure 3: Planning computerised tomography scans of a patient with left-sided breast cancer after breast conserving surgery, demonstrating the decrease in cardiac volume in the target volume during deep inspiration compared with free breathing. The heart moved inferiorly on the diaphragm and out of the radiation field during deep inhalation.
DIBH: deep inspiration breath hold.

It is also important to note that DIBH, in the commonly used supine treatment position but not in the prone position, confers benefit to patients irrespective of the treatment technique used. In addition, a recent review of heart sparing approaches indicated that different techniques could complement each other.[30] For example, IMRT may further improve heart sparing in patients treated using DIBH.[59] However, as with other new techniques, DIBH must be implemented in practice carefully as treatment planning needs to be aligned with the DIBH state, and the breathing cycle of the patient should be monitored to ensure reproducible treatment set-up.

The role of motion management in radiotherapy for BC

Cardiac toxicity is an important consideration for patients undergoing left-sided breast radiotherapy, particularly with the increasing use of potentially cardiotoxic systemic therapeutic agents, including anthracyclines and trastuzumab (Herceptin®).[60] Motion management using DIBH can be an effective method of reducing radiation dose to the heart to decrease the risk of cardiac toxicity. It is anticipated that DIBH will become increasingly used in radiotherapy for BC.

CONCLUSION

New radiation technologies and techniques have the potential to improve the efficacy and safety of radiotherapy for patients with early BC. However, the maxim of '*primum non nocere*' is particularly relevant in these patients as the majority of them are long-term survivors. Thus, implementation of new radiation technologies and techniques must be scientifically rigorous and measured with patient safety as a key consideration. As IMRT and IGRT involve the delivery of additional low radiation doses to normal organs distal to the target volume, identification of patients who would derive the most benefit from the techniques is critical. An important consideration in implementing new radiation technologies and techniques is that they are often complementary to each other. For example, motion management would not be possible without high quality image guidance, and delivery of the highly conformal radiation dose distribution of IMRT is dependent on IGRT. Thus, it is necessary that new technological and technical advances in radiation oncology are not examined in isolation from each other. A multidisciplinary approach is key to their successful implementation to improve patient outcomes.

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MANAGEMENT OF PATIENTS WITH HIGH-GRADE GLIOMA

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ABSTRACT

The scientific basis for the surgical management of patients with glioma is rapidly evolving. The infiltrative nature of these cancers precludes a surgical cure, but despite this, cytoreductive surgery remains central to high-quality patient's care. In addition to tissue sampling for accurate histopathological diagnosis and molecular genetic characterisation, clinical benefit from decompression of space-occupying lesions and microsurgical cytoreduction has been reported in patients with different grades of glioma. By integrating advanced surgical techniques with molecular genetic characterisation of the disease and targeted radiotherapy and chemotherapy, it is possible to construct a programme of personalised surgical therapy throughout the patient's journey. The goal of therapeutic packages tailored to each patient is to optimise patient safety and clinical outcome, and must be delivered in a multidisciplinary setting. Here we review the current concepts that underlie surgical management of patients with high-grade glioma.

Keywords: High-grade glioma, surgery, adjuvant therapy, prognosis.

INTRODUCTION

Gliomas are the most common primary central nervous system tumours. Malignant gliomas account for 60-75% of all gliomas and comprise glioblastoma multiforme (GBM) (incidence 5/100,000, World Health Organization [WHO] Grade 4), anaplastic astrocytoma (AA) (WHO Grade 3), mixed anaplastic oligoastrocytoma (AnO) (WHO Grade 3), and anaplastic oligodendroglioma (AO) (WHO Grade 3).[1] These tumours can develop at any time, the peak incidence being in the fifth and sixth decades of life.[2] Despite continuous improvements in therapeutic modalities, outcome remains poor with a median survival (MS) of <15 months.[3] The most common and aggressive malignant glioma is GBM with an average survival of 1 year.[4] Patients with anaplastic glioma have a moderately better prognosis with a MS of approximately 3-7 years for AA and AO, respectively.[5,6] The initial management of malignant gliomas involves maximal safe resection utilising modern technology. Because of high propensity of malignant gliomas for local invasion, adjuvant therapies are recommended. Recent studies have suggested that the grouping of patients, based on their molecular genetic signatures, will enable more efficacious targeted therapies.

HETEROGENEITY AND MOLECULAR MARKERS IN GBM

GBM is widely known for its immense inter and intratumoural heterogeneity in terms of cellular, genetic, epigenetic, and molecular composition.[7-9] There are four different subtypes: classic, proneural, neural, and mesenchymal. The first is associated with extensive epidermal growth factor receptor (EGFR) amplification and expression of EGFRvIII, accompanied by loss of phosphatase and tensin homologue (PTEN). The proneural type

exhibits platelet-derived growth factor receptor amplification and enriches for mutations in p53, isocitrate dehydrogenase (IDH) 1 and 2, and cyclin-dependent kinase (CDK) 6 and 4. Neural GBMs are connected to markers such as NEF1 and elevated ERBB2 levels. Lastly, mesenchymal GBM are associated with loss of PTEN and CDK inhibitor 2a. A hierarchical cancer stem cell model has not yet been identified for GBM. Although the identification of brain cancer stem cells has been linked to the expression of several cell surface markers, none of them appear to be universal or specific.[7,10,11]

Identification of molecular changes in high-grade glioma (HGG) provides an advanced understanding for survival and treatment response. There are specific biomarkers that have been studied in recent years such as O6-methylguanine methyltransferase (MGMT) promoter methylation (Figure 1), 1p/19q chromosomal co-deletion, mutations of IDH 1 and 2, and EGFR alterations. MGMT encodes a DNA repair protein that removes alkyl groups from the O6 position of guanine counteracting alkylating agent chemotherapy.[12] The epigenetic methylation of the MGMT promoter is proven to be a predictive biomarker of response to temozolomide (TMZ) chemotherapy with longer overall survival (OS) and response to alkylating chemotherapy in patients with GBM.[13,14] In patients with anaplastic gliomas, MGMT promoter methylation is prognostic for those receiving chemoradiotherapy.

Combined loss of heterozygosity on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is the molecular signature of oligodendroglial tumours.[15] This aberration is seen in 60-80% of AO, and 20-30% of AnO.[16] Loss of chromosome 1p and 19q is prognostically significant for Grade 3 glioma patients who receive chemoradiotherapy, and predictive to benefit from procarbazine, lomustine, and vincristine (PCV) in patients with AO.[17,18] Its value in GBM is not known. Most IDH mutations involve the *IDH1* gene. IDH1 mutations are found in a vast majority of diffuse low-grade and anaplastic glioma and secondary GBM, and rarely in primary GBM.[19] It was shown that IDH1 mutation represents a very early oncogenic event, and is a strong prognostic marker in patients with HGG.[20]

The most common EGFR alteration in malignant gliomas is amplification. Approximately 40% of GBMs with EGFR amplification have EGFR mutations, most commonly deletion of exons 2-7 that produce EGFRvIII, leading to constitutive receptor activation.[21,22] EGFR inhibitors have been studied in Phase II trials with either recurrent or newly diagnosed malignant gliomas, but neither showed improved survival.[23-25] Haas et al.[26] reported that EGFR amplification was predictive of erlotinib response. However, other studies have not confirmed this result, or have suggested different markers.[27-29] Rindopepimut, a peptide vaccine against EGFRvIII is currently being evaluated in a Phase III trial.[30]

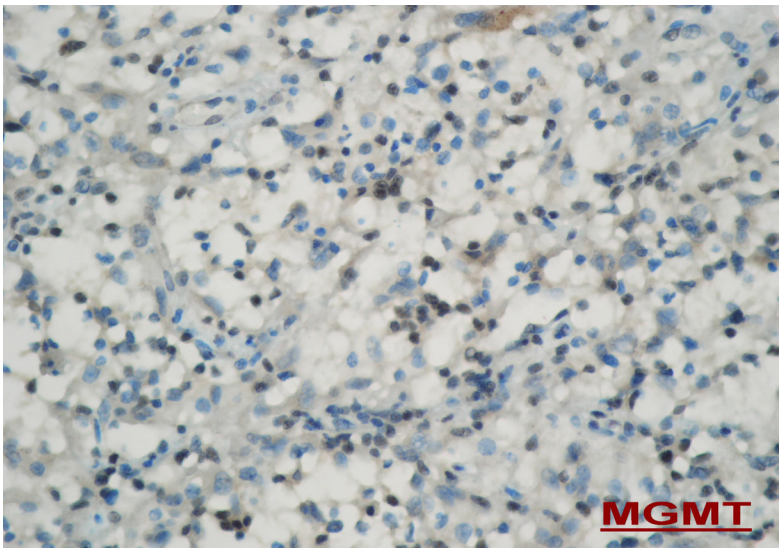

Figure 1: O6-methylguanine methyltransferase (MGMT) promoter methylation is a strong prognostic factor in patients with glioblastoma (MGMT; streptavidin-biotinylated complement; x200).

SURGICAL RESECTION

Rationale for Surgery

Surgical resection is the initial step. Studies have shown that the extent of resection is an important prognostic factor for OS.[31] Cytoreductive surgery of HGG also provides a more representative histological sample[32] and enables a rapid log kill of tumour cells.[33] Reduction of tumour load leads to relief of increased intracranial pressure and peritumoural oedema (PO).[34] It also decreases preoperative epileptic seizures that are observed in 25-40% of patients with HGG.[35] Recently, post-hoc analysis of three large prospective randomised controlled trials (RCTs) has provided valid evidence for the effect of resection on patient survival.[36-39] This also illustrated the facilitation of adjuvant treatments with extensive resection.

In a study by Westphal et al.,[40] 240 patients with newly diagnosed malignant glioma were randomised to receive resection with biodegradable 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) wafer or placebo wafer implantation, followed by radiotherapy. Complete resection was defined as removal of >90% of tumour tissue on postoperative radiographs. In both the BCNU wafer group and the placebo wafer group, complete resections led to longer survival. The BCNU wafer arm resulted in longer survival compared to the placebo wafer arm in both subgroups (13.9 versus 11.6 months). In addition, MS for the BCNU wafer group was longer in the complete resection subgroup (14.8 versus 12.1 months). This result indicated that the efficacy of BCNU wafer therapy increased with extensive resection.

The European Organization for Research Trials in Cancer (EORTC)-National Cancer Institute of Canada (NCIC) trial study randomised 573 patients with newly diagnosed malignant glioma to receive concomitant radiochemotherapy, followed by adjuvant TMZ or radiotherapy alone.[38,41] Patients with complete resections survived longer. However, the extent of resection was assessed subjectively. Analysis of 5-year OS favoured combined chemoradiotherapy over radiotherapy alone (14.6 versus 12.1 months). Furthermore, median gain in survival time was greatest in the complete resection subgroup (plus 4.1 months) compared to the partial resection subgroup (plus 1.8 months) and the biopsy subgroup (plus 1.5 months). Thus, this study has shown that more extensive surgery enhances the effect of radiochemotherapy.

In another study by Stummer et al.,[36] patients with newly diagnosed malignant glioma were randomised to receive 5-aminolevulinic acid (5-ALA) fluorescence-guided resection or conventional microsurgery, followed by radiotherapy. Patients with complete resections survived longer (16.7 versus 11.8 months). In a more recent prospective study of 166 patients with GBM, the completeness of resection was determined by magnetic resonance imaging (MRI) obtained within 72 hours of operation.[37] The absence of visible contrast-enhancing disease was associated with prolonged progression-free survival (PFS) and OS. The median OS of patients without residual enhancing disease exceeded the follow-up period of 24 months (mean 23.6 months; range 21.4–25.8). The extent of resection is an important predictor of OS. Gross resection at recurrence might be able to overcome the negative prognostic effect of an incomplete initial resection.[30]

Intraoperative Techniques for Patient Safety

Maximal resection with minimisation of postoperative neurological deficit is an important goal in the initial management.[42] In order to more reliably identify tumour and functionally important brain areas, advanced intraoperative techniques have been developed. Awake craniotomy with intraoperative cortical/subcortical mapping and monitoring is the gold standard.[43,44] Intraoperative neuronavigation has also become a commonly used surgical adjunct. However, its accuracy is compromised by brain shift.[45] Integration of real-time updated imaging data sets from intraoperative MRI into neuronavigation can minimise this error.[46]

A simpler and more cost-efficient intraoperative tool for maximal safe resection is the use of 5-ALA fluorescence.[47-50] Fluorescence has a high predictive value to detect contrast-enhancing HGG and anaplastic foci of low-grade glioma. The principle behind this is the accumulation of fluorescent porphyrins in malignant glioma led by the metabolic precursor, 5-ALA.[51] Clinical application has been validated in the RCT by Stummer et al.,[47] where its use almost doubled the number of patients with complete resections.[47] Despite these improvements, complete surgical resection is impossible due to the invasive nature of malignant gliomas. In order to prevent recurrence, surgery must be followed by adjuvant therapies such as radiotherapy, chemotherapy, or both (Figure 2).[52,53]

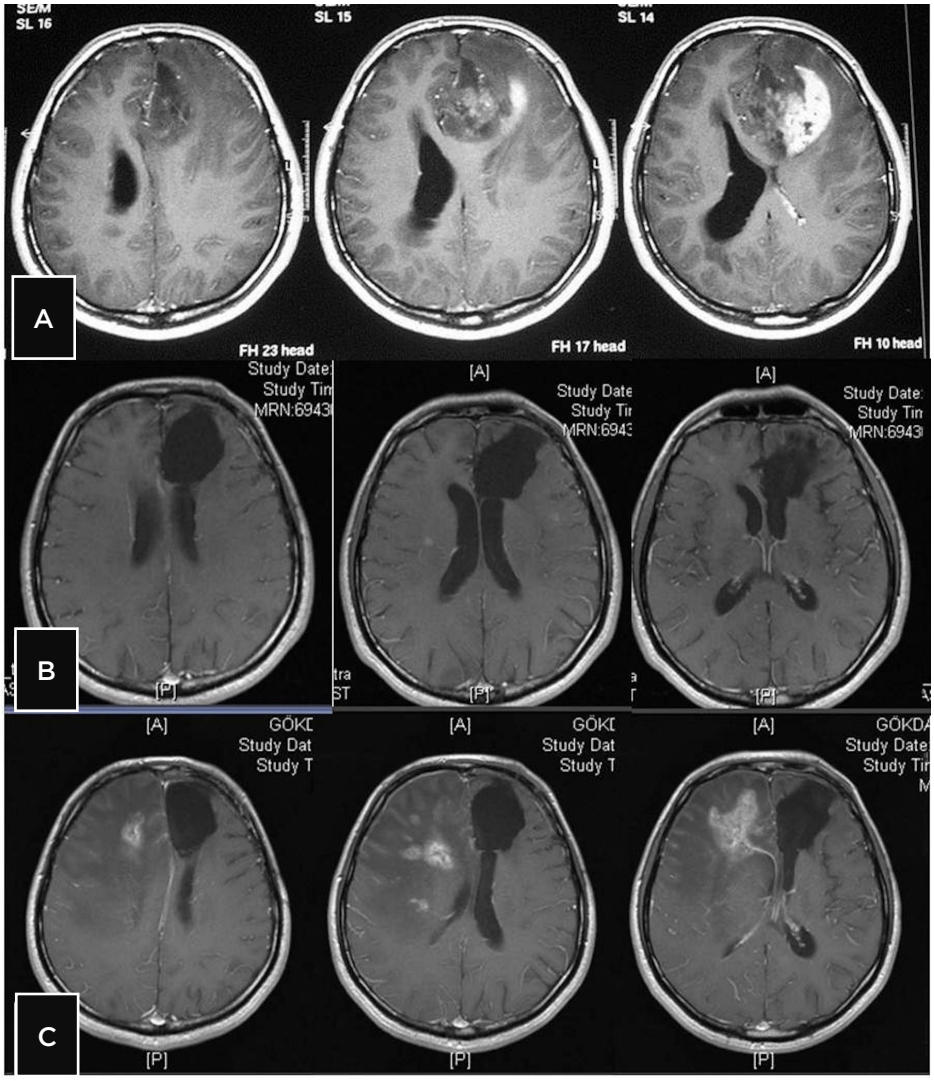

Figure 2: A) A 30-year-old male with a newly diagnosed glioblastoma multiforme (GBM) underwent an initial resection. Preoperative gadolinium-enhanced magnetic resonance imaging (MRI) showed a heterogeneously enhancing lesion in the left frontal lobe. B) Post-operative gadolinium-enhanced MRI at 3 months showed total resection of the tumour. C) Gadolinium-enhanced MRI at 18 months revealed multiple ring-enhancing lesions in the right frontal lobe after chemoradiation. The patient underwent a second resection due to clinical deterioration. Histological analysis performed for multiple regions of the lesion revealed radiation necrosis.

RADIOTHERAPY

The rationale for radiotherapy after surgical resection is a significant enhancement in survival. Due to its powerful survival benefit, radiotherapy has been implemented as a central treatment modality. Based on adjuvant radiotherapy studies, standard radiotherapy for HGG has been defined as fractionated focal radiotherapy with a dose of 60 Gy in 1.8-2.0 Gy daily fractions in 6 weeks.[54] In 1978, the Brain Tumor Study Group randomised patients with malignant glioma to one of four study arms after surgical resection.[55] The arms were: best supportive care after surgery, BCNU chemotherapy alone, whole brain radiotherapy (WBRT) alone to a dose of 50-60 Gy, and BCNU chemotherapy combined with radiotherapy. MS was 4.3 months for the best supportive care arm, 6.3 months for the chemotherapy alone arm, 9.4 months for the radiotherapy alone arm, and 10.1 months for the chemoradiotherapy arm. These results showed a significant survival benefit for patients receiving adjuvant radiotherapy.

In order to maximise the survival benefit, the brain volume of radiation delivery has been investigated. It was observed that recurrent HGG after WBRT

occurred within 2 cm of the original tumour site in 80–90%,[56] while <10% developed multifocal recurrence.[57] Therefore, radiation delivery has evolved to focal radiotherapy called involved field radiotherapy. Involved field radiotherapy is delivered not only to radiographically defined tumour volume but also to 1-2 cm margin of the tumour in order to prevent local recurrence.[58]

CHEMOTHERAPY

GBM

Concomitant chemoradiation with TMZ followed by six cycles of adjuvant TMZ constitutes the current standard management for the adjuvant therapy of GBM.[59] This is based on the pivotal EORTC-NCIC trial that yielded results favouring combined chemoradiotherapy with TMZ over radiotherapy alone.[41] According to a 5-year analysis of the trial, for patients with MGMT methylation the 2-year survival rates were 49% and 24% with chemoradiotherapy and with radiotherapy alone, respectively, whereas, for those without MGMT methylation, the 2-year survival rates were 15% and 2%, respectively.[60] This confirms that MGMT promoter methylation is correlated with response of GBM to TMZ chemotherapy.[61] TMZ itself is also a powerful MGMT-depleting agent, so higher doses could possibly overcome resistance of non-MGMT methylated tumours, although hematotoxicity remains a dose-limiting problem.[62] The Phase III Radiation Therapy Oncology Group 0525 trial stratified 833 patients with GBM according to clinical factors and MGMT methylation status.[60] Patients were randomly assigned to standard (150-200 mg/m^2 daily for 5 days, every 28 days) or dose-dense TMZ (75 to 100 mg/m^2 days 1-21, every 4 weeks). Although results confirmed the prognostic role of MGMT status, no statistically significant difference was observed. Nevertheless, this demonstrated the feasibility of large-scale, prospective tumour collection and molecular stratification that is promising for further research.[61]

BCNU wafers have been approved as a treatment option for malignant glioma.[63] Implantation of BCNU wafer into the resection cavity, prior to radiotherapy, has been shown to prolong survival compared to radiotherapy alone.[64] Although retrospective studies showed positive results for the safety and efficacy of the combination of BCNU wafer with standard TMZ chemotherapy,[64] Phase III prospective randomised trials are needed to evaluate the place of BCNU wafers in modern neuro-oncology practice.

Anaplastic Glioma

Radiotherapy with concurrent and adjuvant TMZ is recommended for most patients with AA, especially for the ones with negative prognostic factors including wild-type IDH1/IDH2 and older age. Adjuvant chemotherapy alone with delayed radiotherapy was compared to adjuvant radiotherapy alone with delayed chemotherapy in the Neuro-Oncology Working Group of the German Cancer Society (NOA)-04 trial.[65] 318 patients with anaplastic gliomas were randomised to adjuvant chemotherapy, with radiotherapy delayed until progression or to adjuvant radiotherapy, with chemotherapy delayed until progression. Patients were randomly assigned to either TMZ or PCV for chemotherapy, either as the initial or the delayed treatment. Analysis of 54 months follow-up showed that the time to treatment failure of those receiving chemotherapy initially and those receiving radiotherapy first was similar (44 versus 43 months). There was no significant difference in time to treatment failure between those managed by TMZ and those managed by PCV. In a retrospective analysis of patients with AA, adjuvant TMZ was as effective and better tolerated than PCV.[66] Therefore, it is frequently used in lieu of PCV in combination with postoperative radiotherapy.[67,68]

MANAGEMENT OF PATIENTS WITH RECURRENT HGG

Despite the highest standard of care, the recurrence rate remains high. A decision to re-operate should be made in a multi-disciplinary team setting, as the role of surgery in recurrent HGG remains controversial. There are insufficient data to support specific practice guidelines,[69] a situation that has not changed in over 10 years.[70] Validated criteria for patient selection have not been established, but focal recurrence, good performance status, and a multi-disciplinary rationale constitute good clinical practice. Unfortunately, the number of appropriate patients remains limited.[71]

In a prospective, single-arm, uncontrolled Phase II study that recruited 40 patients with recurrent HGG (WHO Grade 4 and 3),[72] 5-ALA fluorescence had a predictive value of 97.2% (95% CI: 85.5-99.9%) in tissue that had a pathologic appearance under white light. Sample analysis revealed 342/

354 biopsies taken from fluorescing areas showed tumour histopathologically (positive predictive value [PPV] of 96.6%). Stratified by fluorescence quality, histopathological analysis showed primarily solid tumour for strong fluorescence and infiltrative tumour for weak fluorescence. For normal appearing tissue with strong as well as weak fluorescence, 146/157 biopsies (93% PPV [95% CI: 87.8-96.5%]) showed infiltrating tumour. Scar tissue and areas of necrosis did not fluoresce. These data support the use of 5-ALA as an adjunct to surgery in recurrent HGG.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), a key promoter of tumour neovascularisation. In a randomised non-comparative Phase II trial for recurrent GBM, 167 patients received either bevacizumab alone or in combination with irinotecan.[73] The objective response rates with bevacizumab alone or in combination with irinotecan were 28% and 38%, respectively. The 6-month PFS rates and OS were 43% and 50%, and 9.2 and 8.7 months, respectively. The high response rate and 6-month PFS led to its approval by the FDA in the United States in 2009 as a single-agent chemotherapy for recurrent GBM. However, it was rejected by the European Union due to the lack of data for improved OS. Recently, two Phase III trials on newly diagnosed GBM have investigated the use of bevacizumab with standard chemoradiotherapy with TMZ.[74] They have demonstrated improved PFS in patients treated with both bevacizumab and standard chemoradiotherapy, but they have failed to demonstrate a prolonged overall survival. Other anti-angiogenic agents such as cediranib, a VEGF receptor 2-inhibitor, and cilengitide, an integrin inhibitor, exhibited promising results in Phase II trials on recurrent GBM.[75-77] But both agents failed to deliver in subsequent Phase III trials, where they were combined with other drugs,[78,79] as neither PFS, nor OS, were improved.

Re-irradiation is another treatment option for recurrent HGG but its efficacy is limited. Although no RCTs have been performed, retrospective studies indicated stereotactic radiotherapy and stereotactic radiosurgery as the most effective approaches for re-irradiation.[80,81]

Patients suffering from HGG often exhibit seizures caused by the high extracellular glutamate concentration, which can reach up to 20 mM, causing excitotoxicity in peritumoural areas.[82,83] Patients can be treated with seizure medication to relieve the symptoms, although side-effects have to be taken into account and weighted against their benefit.[84] In a new clinical Phase II trial, levetiracetam and pregabalin have been found to exhibit a good antiepileptic effect without causing any intolerable side-effects.[85] Another treatment option, often part of palliative care, is the use of steroid based medication, such as dexamethasone.[86] Steroids are normally used to relieve symptoms of PO, but cause a variety of unwanted side-effects.[87] Therefore, other treatment modalities are taken into consideration, such as angiotensin II inhibitors, which interfere with the VEGF pathway, a key driver of oedema and angiogenesis.[88]

MANAGEMENT OF HGG IN THE ELDERLY

The incidence of HGG increases with age, with nearly 60% of cases occurring in patients over the age of 70.[89] The role of surgery in the elderly patient remains controversial. Due to concerns over elderly patients' ability to cope with therapy and its toxicity, they may receive less intensive treatment: diagnostic biopsy rather than debulking surgery,[90] and less radiotherapy and chemotherapy.[91-95] Thus, elderly patients are under represented in clinical trials. For instance, in a trial assessing the role of carmustine wafers in addition to surgery the median age was 53 years.[96] The EORTC undertook a study assessing the benefit of adding TMZ to radiation and adjuvant chemotherapy for patients aged 18-70 with GBM, which demonstrated a significant survival benefit.[97] The median age at entry was 56 years and the MS was 14.6 months. 83 patients were older than 60 and had a MS of 10.9 months.

More recent data incorporating modern surgical techniques, including the use of fluorescence guided cytoreduction, are available for 130 GBM patients with a median age of 68. The MS for those who went on to receive radiotherapy and chemotherapy was 16.3 months (range 12-17.2) compared to 11.2 months for those receiving radiotherapy alone.[98] Two recent studies have further advanced our understanding of the management of the elderly population with HGG.[95,96] Both NOA-08 and the Nordic studies support the use of TMZ alone in MGMT ethylated elderly GBM and radiotherapy alone for unmethylated patients, although this has yet to become established in UK practice.[97]

These prospective data are supported by a retrospective analysis,[99] and suggest that elderly patients will benefit from more aggressive management that incorporates biomarker-based treatment stratification.

CONCLUSION

Malignant gliomas should be removed via technological adjuncts that maximise tumour resection and minimise neurologic injury. Surgical resection should be pursued by adjuvant therapies for prevention of recurrence. However, despite recent improvements in management of HGGs, the MS still remains poor. In order for more effective interventions to take place, further studies should focus on targeted therapies and personalised care. Previously tested targeted drugs have failed to improve survival.[77] However, advancements in genomic profiling of gliomas and detection of molecular signatures might lead to the discovery of new targets for personalised therapy.

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STATE-OF-THE-ART TREATMENT IN CASTRATION-RESISTANT PROSTATE CANCER

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ABSTRACT

Prostate cancer (PrCa) is the most common cancer type in men in developed countries. In the last few years, a dramatic change has occurred in the understanding of castration-resistant PrCa which has led to the development of new drugs that have an impact on patient survival. This review summarises the recent advances in the management of the disease.

Keywords: Prostate cancer, renal cancer, bladder cancer, testicular cancer, treatment options.

PROSTATE CANCER (PRCA)

PrCa is the second most common cancer and the sixth leading cause of cancer mortality in men worldwide.[1] In most developed countries, PrCa has become the leading cancer in men, mainly due to lifestyle factors and the spread of prostate specific antigen (PSA) screening. During the last 25 years, the advances in PrCa diagnosis and treatment have improved 5-year survival rates from 68.3% to almost 95% when all stages are considered. Nonetheless, up to 90% of PrCa diagnosed in the developed countries are organ-confined, and the 5-year survival rates approach 100% following conventional treatments.[2] Management of localised disease includes active surveillance, radical prostatectomy, and radiation therapy (external beam radiotherapy and brachytherapy). At this time, cryosurgery or other local therapies are not recommended as primary treatments outside of a clinical trial due to the lack of long-term data comparing these treatments with radiotherapy or prostatectomy.[3] The availability of several therapeutic options for localised stages warrants careful consideration when planning treatment with curative intent. Patients need to be active participants in decision-making, and they must be aware of the benefits and possible complications of the different types of treatment. With better survivorship, the focus is now towards the reduction of treatment-related morbidities and better individualisation of treatment options according to disease biology.[2]

Androgen deprivation therapy (ADT) is the cornerstone of treatment for patients with advanced PrCa. Unfortunately, in the majority of cases this will only provide temporisation and palliation. The natural evolution of PrCa is due to castration-resistant prostate cancer (CRPC), a lethal form of the disease. Significant gains in our understanding of the pathogenesis of CRPC have occurred in the last decade, which has led to the development of new agents that impact on overall survival (OS). Docetaxel + prednisone, every 3 weeks, is the preferred first-line chemotherapy treatment for symptomatic CRPC.[3] No consensus exists for the best subsequent therapy for metastatic CRPC (mCRPC) after docetaxel failure. Options include abiraterone, enzalutamide, cabazitaxel, radium-223, docetaxel rechallenge, mitoxantrone, sipuleucel-T, and participation in clinical trials.

Cytotoxic Chemotherapy

Docetaxel

Docetaxel was the first chemotherapy approved for mCRPC that showed a survival benefit. In 2004, two studies compared docetaxel with mitroxantrone, the previous standard of care. In the SWOG 99-164 and TAX3275 studies, docetaxel extended OS by 2 months and showed a significant improvement in time to progression and PSA decline. The TAX327 study compared docetaxel given every 3 weeks and weekly docetaxel with mitoxantrone given every 3 weeks (all drugs were administered with prednisone). Only 3-week docetaxel demonstrated survival benefit over mitroxantrone, whilst PSA response rate and quality of life (QoL) scores were significantly improved in both docetaxel groups. Since these studies, multiple trials have been conducted with different agents in combination with docetaxel for mCRPC (e.g. bevacizumab, aflibercept, lenalidomide, dasatinib, and sunitinib) but none have shown improvement in OS compared with docetaxel and prednisone.[6]

Docetaxel has not been commonly used for asymptomatic patients, except for those with signs of rapid progression or liver involvement,[3] and with the advent of new treatments such as abiraterone and enzalutamide, which have proven to benefit chemo-naïve mCRPC patients, the administration of docetaxel tends to be delayed. Interestingly, a new study has recently addressed the question of whether upfront chemotherapy also confers an OS advantage for PrCa patients. The CHAARTED trial randomised 790 patients with hormone-sensitive metastatic PrCa to ADT alone versus ADT + docetaxel 75 mg/m^2 every 3 weeks for six cycles. The primary endpoint was OS. It was found that ADT + docetaxel resulted in a median OS of 57.6 months versus 44 months in the ADT alone arm (HR 0.61, p=0.0003). Although ADT + docetaxel was beneficial in all subgroups analysed, the benefit was more important for patients with high-volume disease. In this subgroup of patients median OS was 49 months with docetaxel + ADT versus 32 with ADT alone (HR 0.60, p=0.0006). Median time to clinical progression was 33 months when docetaxel was added versus 20 for ADT alone (HR 0.49, p<0.0001). Similarly, median time to CRPC was 21 months in the ADT + docetaxel arm versus 15 in the ADT-only arm.[7]

There is a need for better identification of which patients should be considered with 'high' and 'low' metastatic volume disease. To date, the 17-month difference in OS, observed in the high-volume disease group, is the greatest improvement in survival reported for PrCa.

Cabazitaxel

The Phase III trial (TROPIC)[8] that led to the approval of cabazitaxel by the regulatory agencies in 2010, randomised 775 mCRPC patients to cabazitaxel 25 mg/m^2 or mitroxantrone 12 mg/m^2 each with daily prednisone.[9] Patients had previously received docetaxel. At 2.4 months, improvement in OS was demonstrated with cabazitaxel compared to mitoxantrone (HR 0.72; p<0.001). Febrile neutropaenia was observed in 7.5% of cabazitaxel-treated men versus 1.3% in the mitroxantrone arm, indicating the need for vigilance and treatment, or prophylaxis to prevent febrile neutropaenia.[8] The incidences of severe diarrhoea (6%), fatigue (5%), nausea/vomiting (2%), anaemia (11%), and thrombocytopaenia (4%) were also higher in cabazitaxel-treated men.[9]

Second-Generation Anti-Androgens

Abiraterone

Abiraterone acetate is an irreversible inhibitor of CYP17 that blocks androgen synthesis in the testis, adrenal glands, and prostate, but also leads to undetectable intratumoural androgen levels.[10] Abiraterone has an antitumour effect on both chemotherapy-treated and chemotherapy-naïve CRPC patients. The COU-AA-301 study[11] randomised mCRPC patients who had progressed post-docetaxel to abiraterone + prednisone or placebo + prednisone. The use of prednisone with abiraterone is necessary due to the mineralocorticoid-related adverse events (AEs). Abiraterone demonstrated prolonged OS (14.8 versus 10.9 months, HR 0.65, p<0.001), time to PSA progression (10.2 versus 6.6 months), progression free survival (5.6 months versus 3.6 months), and a greater PSA response rate (29% versus 6%).

Abiraterone has also been investigated in the chemo-naïve setting. In the COU-AA-302 study, CRPC patients with PSA or radiographic progression were randomised to abiraterone + prednisone or placebo + prednisone.[12] Most patients in this trial were not taking opiates for cancer pain and none had visceral metastatic disease or ketoconazole exposure. Primary endpoints were

radiographic progression free survival (rPFS) and OS. The study was unblinded at the time of a planned interim analysis after 43% of the expected deaths had occurred. The rPFS was significantly improved in the abiraterone group (16.5 versus 8.3 months, HR 0.53, p<0.001). There was a 25% decrease in the risk of death in the abiraterone group, which showed a trend toward OS improvement from 27.2 months for placebo to not reached (HR 0.75, p=0.01). However, this did not meet pre-specified statistical significance. Abiraterone prolonged median time to initiation of cytotoxic chemotherapy, median time to opiate use for cancer-related pain, PSA progression, and decline in performance status.

The most common adverse reactions seen with abiraterone were fatigue (39%), back or joint discomfort (28-32%), peripheral oedema (28%), diarrhoea, nausea or constipation (22%), hot flushes (22%), hypertension (22%, severe hypertension 4%), hypokalaemia (17%), and atrial fibrillation (4%). Increased aspartate aminotransferase, and/or alanine aminotransferase, or cardiac disorders (heart failure, arrhythmias, and myocardial infarction in 19%, serious in 6%) were the most common adverse drug reactions that resulted in drug discontinuation; therefore, potassium levels and blood pressure readings on a monthly basis are warranted during abiraterone acetate therapy. Symptom-directed assessment for cardiac disease is also warranted, particularly in patients with pre-existing cardiovascular disease.[3] Although the use of abiraterone in the pre-docetaxel setting in patients with asymptomatic or minimally symptomatic CRPC is supported by these results, its use in men with symptomatic or visceral disease has not been formally assessed in a controlled trial or compared with docetaxel chemotherapy yet.[3]

Enzalutamide

Enzalutamide is a pure androgen receptor (AR) antagonist and, unlike first-generation anti-androgens such as bicalutamide and flutamide, it has a greater affinity for the receptor and no known agonistic effect.[13]

The AFFIRM study compared enzalutamide to placebo in mCRPC patients previously treated with docetaxel and who had biochemical or radiographic progression.[14] This trial randomised 1,199 patients to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. Median OS was 18.4 months in the enzalutamide arm compared to 13.6 in the placebo group (HR 0.63, p<0.001), with a 37% reduction in risk of death. Survival was improved in all subgroups analysed, including men with poor performance status, high or low PSA levels, visceral metastasis, significant pain, and more than two prior chemotherapy regimens. Enzalutamide was also superior to placebo in the proportion of patients with >50% PSA decline (54% versus 2%), time to PSA progression (8.3 versus 3.0 months), radiographic response (29% versus 4%), rPFS (8.3 versus 2.9 months, HR 0.40, p<0.001), and the time to the first skeletal-related event (16.7 versus 13.3 months, HR 0.69, p<0.001). QoL was also improved with enzalutamide compared to placebo. AEs were mild and included fatigue (34% versus 29%), diarrhoea (21% versus 18%), hot flashes (20% versus 10%), and headache (12 versus 6%). Five patients on enzalutamide had seizures compared to none in the placebo group (0.6 versus 0%). The incidence of cardiac disorders did not differ between the two arms.

In the pre-docetaxel setting, the PREVAIL study[15] randomised 1,717 patients with asymptomatic or mildly symptomatic metastatic chemo-naïve CRPC to enzalutamide or placebo. Approximately 12% of patients had liver and/or lung metastasis. Primary aims were OS and rPFS. The interim analysis at 539 deaths showed a statistically significant benefit of enzalutamide over placebo with a 29% reduction in risk of death and an 81% reduction in risk of radiographic progression. In addition, enzalutamide showed success in completely or partially reducing soft tissue disease on imaging in 59% of patients (20% complete responses and 39% partial responses). Enzalutamide also delayed the median time to chemotherapy initiation by 17 months.

Grade 3-4 AE rates were similar in both arms; AEs that occurred slightly more often with enzalutamide included all-grade fatigue (36% versus 26%), back pain (27% versus 22%), constipation (22% versus 17%), and arthralgia (20% versus 16%). Although patients with a history of seizure were excluded from the study, one seizure occurred in each arm of the trial, both in patients with a history of seizure that was unknown at time of enrolment.[15] To assess the real incidence of seizures and monitor the safety of enzalutamide, the 9785-CL-0403 Phase IV study is currently enrolling CRPC patients known to have risk factors for seizure.[16]

Both abiraterone and enzalutamide have independently demonstrated clinical benefit, and thus, represent a standard of care for CRPC after docetaxel failure, provided these agents were not used pre-docetaxel. Aside from practical considerations (i.e. contraindications to steroids, and potential side-effects), there are currently no head-to-head data informing which agent may excel in a given patient. However, despite their efficacy, not all patients respond to these treatments, and neither abiraterone nor enzalutamide are curative, and resistant disease eventually develops.

The AR isoform encoded by splice variant 7 (AR-V7) lacks the ligand-binding domain, which is the target of both enzalutamide and abiraterone, and remains constitutively active as a transcription factor. The detection of AR-V7 in circulating tumour cells from patients with CRPC has been associated with resistance to both abiraterone and enzalutamide.[17] Several studies have also shown that mutant AR can become promiscuously activated by very low levels of androgens, other steroid metabolites, and drugs that bind the AR. These models support co-targeting combinations of CYP17 inhibitors with other enzymatic inhibitors or with potent second-generation AR antagonists. Combined therapy of abiraterone + enzalutamide is currently an area of great interest, although there are some data suggesting cross-resistance between abiraterone and enzalutamide.[18,19] On the other hand, given the evidence of a reciprocal feedback loop between the AR and the PI3K/Akt pathway,[20] combination of novel AR-targeted drugs enzalutamide and abiraterone acetate with PI3K/Akt inhibitors appears to hold great promise.[21] Further understanding of the mechanisms that underlie acquired and primary resistance is a priority to inform on the development of the next therapeutic strategies.

Inmunotherapy

Sipuleucel–T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. It is an autologous cancer 'vaccine' that involves a collection of the white blood cell fraction containing antigen-presenting cells from each patient; exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP_GM_CSF recombinant fusion protein); and subsequent reinfusion of the cells. The pivotal study (D9902B) randomised patients with minimally symptomatic or asymptomatic mCRPC to receive sipuleucel-T or placebo. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk, with 25.8 months median OS in the vaccine arm versus 21.7 in the control arm. AEs included mild-to-moderate chills, pyrexia, and headache. Additional data showed that this benefit was present in almost every subset of patients; across Gleason score, PSA, extent of disease, age, and laboratory values. Sipuleucel-T is recommended for mCRPC patients without symptoms, with good performance status (ECOG 0-1), and at least 6 months of estimated life expectancy. Treatment subsequent to sipuleucel-T should proceed as clinically indicated, particularly in the occurrence of symptoms.

Ipilimumab is a fully human monoclonal antibody that inhibits CTLA-4. In mCRPC post-docetaxel patients, a Phase III study randomising patients to receive bone-directed RT, before either ipilimumab or placebo, failed to show OS benefit.[22] Subset analyses showed that ipilimumab may be most active in men with lower disease burden, similarly to sipuleucel-T.

Agents Related to Bone Health in CRPC

Bone metastases are a major cause of morbidity and mortality in men with PrCa including pathologic fracture, spinal cord compression, and debilitating bone pain requiring additional therapy. Besides, ADT results in accelerated bone resorption, leading to bone loss and an increased risk of fracture. Excessive osteoclast activity plays a central role in the pathophysiology of bone disease at each stage of PrCa disease progression. Zoledronic acid, a highly potent inhibitor of osteoclast-mediated bone resorption, increases bone mineral density in men receiving ADT. In a multicentre study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were randomised to 4 mg zoledronic acid every 3 weeks or placebo.[23] At 15 months, 33% of patients on zoledronic acid presented with skeletal related events (SRE) compared with 44% of patients in the placebo arm (p=0.02). Zoledronic acid also delayed the occurrence of first SRE. No significant differences were found in OS.[24] Zoledronic acid is restricted in patients with renal impairment as it has the potential to cause renal insufficiency. Other bisphosphonates (pamidronic and clodronic acid) have not shown to be effective in preventing disease-related skeletal complications.[3]

Denosumab, a fully human monoclonal antibody with high affinity and specificity for human RANKL, inhibits bone resorption, including in those who failed prior bisphosphonate treatment. Denosumab has been compared to zoledronic acid in men with CRPC.[25] The absolute incidence of SREs was similar in the two groups; however, the first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid. Although the rates of important SREs and treatment-related toxicities were similar with both compounds, including osteonecrosis of the jaw (1% versus 2%, p=0.09) and arthralgias, hypocalcaemia was more common with denosumab (13% versus 6%, p<0.0001). Zoledronic acid, or denosumab, is recommended for men with CRPC and bone metastases to prevent or delay disease-associated SRE, although the optimal duration of the therapy remains unclear.[3] Clinical research continues on the prevention or delay of disease spread to bone. In a Phase III randomised trial involving patients with non-mCRPC, denosumab increased bone-metastasis-free survival by a median of 4.2 months compared with placebo and delayed time to first bone metastasis, but failed to improve OS, and the regulatory agencies have not approved this indication for denosumab.[26]

Recently, a first-in-class radiopharmaceutical compound has been approved for treatment of mCRPC in patients with symptomatic bone metastasis and unknown visceral metastatic disease. In these patients, radium-223 has shown to improve OS by almost 4 months, and to prolong time to first symptomatic SRE.[27] Radium-223 dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 µm). As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases. The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localised cytotoxic effect in the target areas. The short path of the alpha particles also means that toxic effects on adjacent healthy tissue, and particularly the bone marrow, may be minimised.

In the pivotal Phase III study (ASYMPCA) that led to the drug's approval, patients that had previously received docetaxel - or were ineligible for it - were randomised 2:1 to six monthly radium-223 intravenous or placebo every 4 weeks. The primary endpoint was OS. The main secondary efficacy endpoints included time to the first symptomatic SRE and various biochemical endpoints. Radium-223 significantly improved OS as compared with placebo (14.9 versus 11.3 months, HR 0.70, p<0.001) and prolonged time to first symptomatic SRE (15.6 versus 9.8 months). Grade 3-4 haematologic toxicity was low (3% neutropaenia, 6% thrombocytopaenia, 13% anaemia). Radium-223 can be used with denosumab or a bisphosphonate, but its combination with chemotherapy outside of a clinical trial has the potential for additive myelosuppression.[3]

CONCLUSION

The significant gains in our understanding of the pathogenesis of PrCa have led to the development of new agents that have an impact on OS of CRPC patients. These treatments that are currently available in daily clinical practice have totally changed the management of the disease in barely 5 years. There remain many questions, particularly regarding the optimum timing and the most appropriate sequencing and/or combinations of second-generation anti-androgens and immunotherapeutics with conventional anti-androgen therapy and cytotoxic chemotherapy therapy. The overall therapeutic goal is to maximise treatment effect while minimising toxicity. Further research to select those patients most likely to benefit from each therapy are urgently needed.

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RAPIDPLAN™: VARIAN'S NEXT LEVEL OF KNOWLEDGE-BASED OPTIMISATION OF INTENSITY-MODULATED AND VOLUMETRIC ARC THERAPY

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Background

Among the components of the radiation-oncology treatment chain, the treatment planning process is a key step where many decisions and information shall merge, leading to the most appropriate technique and dose distribution for all individual patients. The process can be factorised in several sub-elements (e.g. contouring, dose prescription, dose-volume objectives definition, treatment technique choice, dose calculation, and plan evaluation/acceptance), where different levels of 'knowledge' are used as input of decision-making elements. Much of this 'knowledge-based' information is derived from consolidated consensus and evidence-based sources, but many are subtly linked to trade-off decisions between population-based data, clinical and patient preferences, technical constraints, and so forth.

The determination of the best combination of all the variables into a 'perfect' solution for an individual patient is then challenging, particularly when manual, operator-dependent, experience-based methods are applied. Also, a completely automatic decision system incorporating all of the ingredients might be difficult to be realised in practice. Nevertheless, for some of the steps broadly defined above, automatic or semi-automatic support systems can be prefigured and have been realised (e.g. contouring tools or even the concept of inverse planning itself). The basic principle is to develop information technology tools which can incorporate clinical experience, be reproducible, and be as general as possible. Self-learning and 'adaptive' capability would be desirable as well. In the treatment planning process, the determination of the ideal dose-volume constraints for organs at risk (OARs) and target volumes is a typical problem that could be 'modelled' if the following questions could be translated into mathematical-statistical methods: given a population, what are the 'features' which cause inter-patient variability of dose distributions? Which geometric, anatomical, and dosimetric features are capable of being good predictors?

Several groups investigated these problems, and solutions have been proposed. A group at Duke University, Durham, North Carolina, USA, developed so-called knowledge-based methods in order to solve this problem, and applied it to clinical experiments[1-5] and inter-institutional validation. Similarly, another group at the Washington University, St. Louis, Missouri, USA, developed similar architectures to automatically appraise the quality of treatment plans and to predict automatically appropriate dose-volume constraints for any patient.[6,7] One of the earliest experiences in the practical application of knowledge-based approaches has been described by Good et al.[5] for the intensity-modulated radiotherapy treatment (IMRT) planning of prostate. It showed that knowledge-based plans resulted in a better target homogeneity, improved sparing of organs at-risk and, in general, superior or equivalent plans in 95% of the cases when compared to manual planning. Data also demonstrated the possibility to transfer the planning expertise from a more experienced to a less experienced institute. Moore et al.[6] demonstrated improved plan quality and reduced inter-clinician variability, and suggested that the automatic tools might be used as a quality assurance method for IMRT planning.

A Novel Technology

A new optimisation engine was introduced in the Eclipse treatment planning system (Varian Medical

Systems, Palo Alto, CA, USA) starting from the release 13. This is made of three main components: 1) a model building and training engine; 2) a model-based dose-volume and automated constraints prediction tool; and 3) a new volumetric modulated arc therapy and IMRT optimisation algorithm to manage the above.

With this new environment, to generate a predictive, knowledge-based model, it is necessary to identify a set of treatment plans supposed to adequately represent the clinical problem, and to have sufficient quality to constitute a robust benchmark set. These plans are then associated to a model layout (where target and OARs [ontology], dose prescriptions, and some descriptive elements can be defined). The dataset is then processed in the training phase where, from principal component analysis methods, essential features are extracted from the dose plans. These features primarily include geometrical characteristics of the various targets and organs, as well as their mutual position and their relationships with the treatment fields or arcs. The principal components used in the model derive from the determination of the mean features (e.g. mean dose in a dose volume histogram [DVH]), from progressive minimisation of the variance in the training set (first component), and from the second and further order approximations describing the residual variance. The resulting regression model is used to perform predictive estimation of the DVHs achievable for a given new test case and, from these, to determine the best planning constraints. As per construction, the predicted constraints are located just below the lower limit of a 1 standard deviation (SD) range of the distribution of potential DVHs achievable from the model for the test case. Figure 1 presents a schematic view of the model determination steps. Figure 2 exemplifies the resulting model-based predictive objectives with the estimation range and automatic objectives (line objectives in this example).

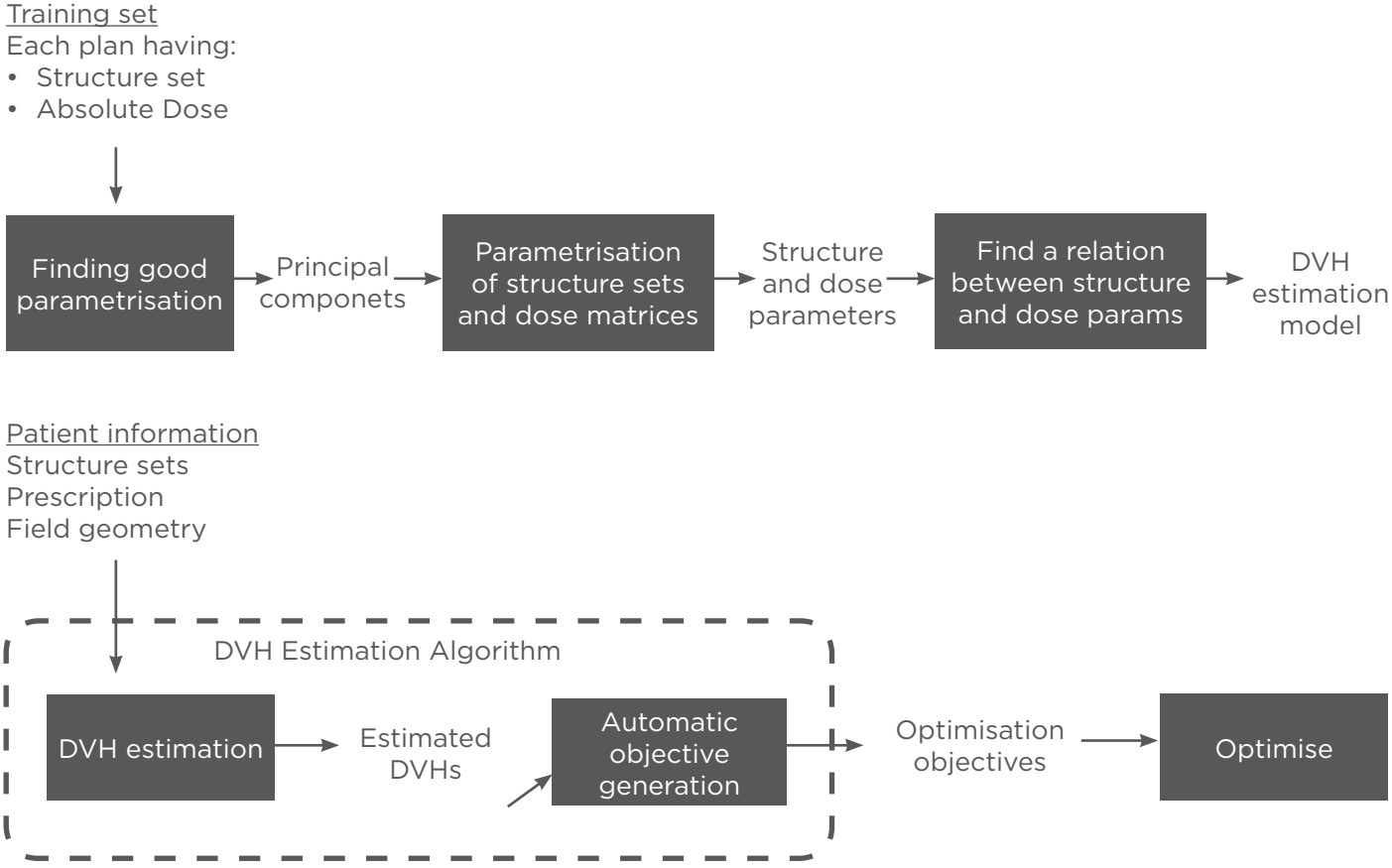

Figure 1: Schematic view of the model determination steps showcasing the levels taken to both achieve DVH estimation model and optimising DVH estimation algorithm.
DVH: dose volume histogram.

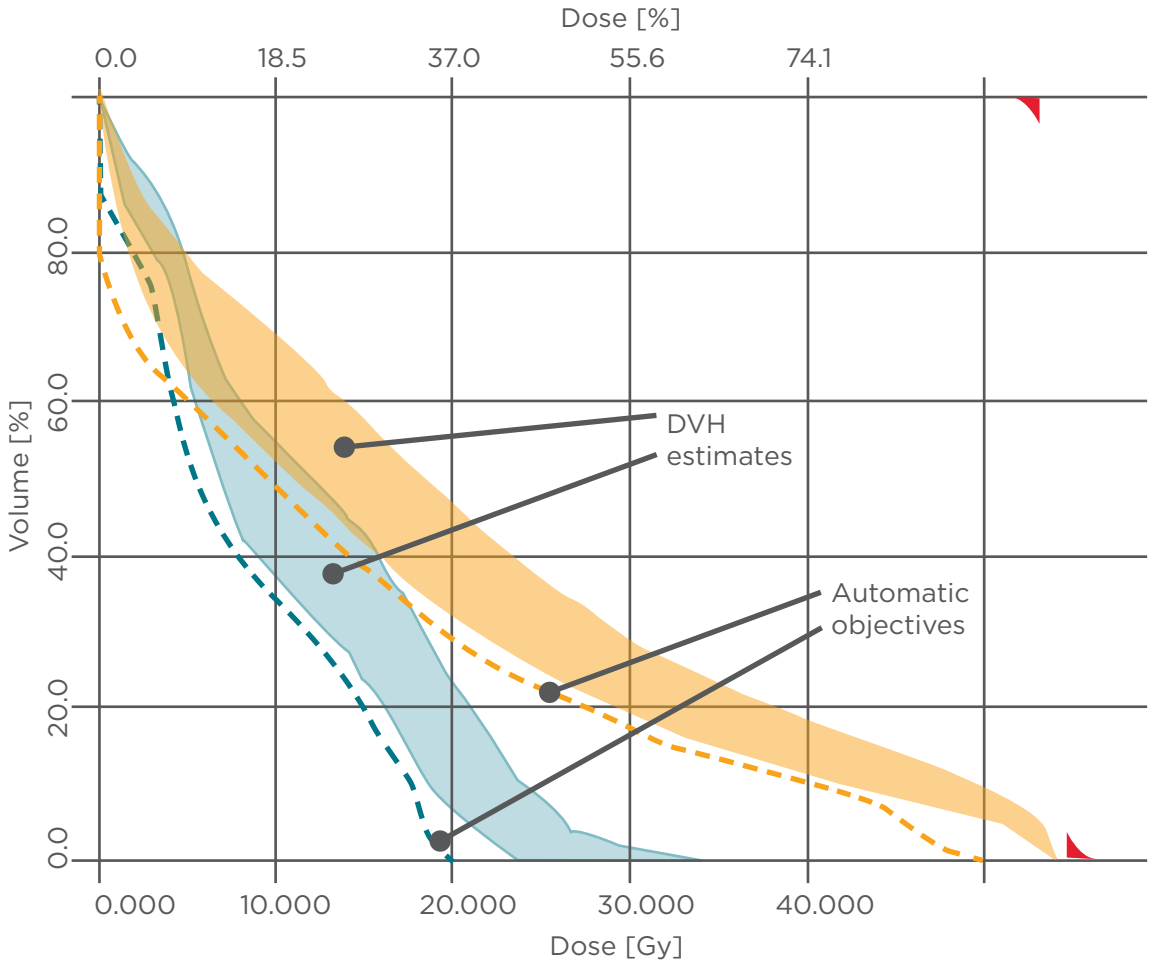

Figure 2: The resulting model-based predictive objectives with the estimation range and automatic objectives.
DVH: dose volume histogram.

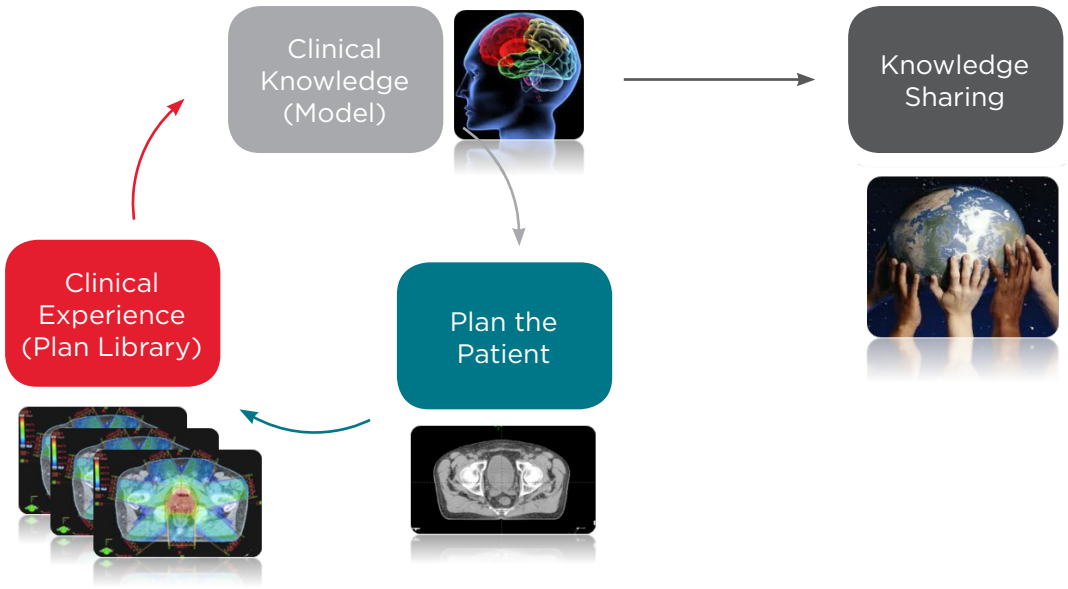

Figure 3: The illustration shows the impact of knowledge-based planning in the clinical routine setting.

Role in Radiation Oncology

Knowledge-based planning (KBP) can effectively contribute to streamlining the process in clinical routine along two parallel pathways. In first instance, KBP will contribute to organise and model the workflow from earlier clinical experience and/or from multi-institutional guidelines (trials, consensus reports, international recommendations). Simultaneously, KBP will act as a support to decision-making phases. Treatment individualisation will be made possible based on a patient's features, best practice, and reduced subjective assessment of plan quality (e.g. questions will be inherently solved, such as: how was it done in the past? What are the options? Am I sure this plan is the best?). Figure 3 illustrates the concept expressed above.

In practice, several application strategies can be envisaged for KBP according to the type of clinical environment and the needed outcome. Education for beginners, residents, peripheral centres; harmonisation, for trials, large clinics, cooperative activities; innovation, to facilitate the development and the validation of new treatment strategies and to benchmark them against earlier methodology. These are some of the areas where KBP will play a major role in radiation oncology. Figure 4 summarises these principles.

Figure 4: The principles of knowledge-based planning in various levels of research applications and their potential outcomes.

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One test diagnoses all

IDENTIFYING patients at risk of cancer can be difficult but a simple blood test may now be able to correct this, avoiding misdiagnosis and unnecessary procedures, thus saving both time and money.

The researchers analysed blood samples from 208 participants using a Lymphocyte Genome Sensitivity (LGS) test, which assesses white blood cells (WBCs) and measures the damage done to DNA when it is subjected to different intensities of ultraviolet A (UVA) light, which is known to damage DNA.

Of the 208 samples, 94 healthy individuals were recruited and 114 samples were collected from patients referred to clinics. The samples were coded, anonymised, randomised, and then exposed to UVA light.

"WBCs are part of the body's natural defence system," said Prof Diana Anderson, lead researcher and Professor of Biomedical Science, School of Life Sciences, University of Bradford, Bradford, UK.

"We know that they are under stress when they are fighting cancer or other diseases, so I wondered whether anything measurable could be seen if we put them under further stress with UVA light," continued Prof Anderson. "We found that people with cancer have DNA which is more easily damaged by UVA light than other people, so the test shows the sensitivity to damage of all the DNA – the genome – in a cell."

The UVA damage was noticed when pieces of DNA were pulled toward the positive end of an electric field, resulting in a 'comet-like' tail. The results indicated that if a tail was longer, then there was more DNA damage.

Differences between samples were noted at a statistically significant level ($p<0.001$); 58 patients were eventually diagnosed with cancer, 56 with a precancerous condition, and 94 were healthy.

While this is just an early stage in the research, and more needs to be conducted, this test has a huge potential and shows a lot of promise.

"We found that people with cancer have DNA which is more easily damaged by UVA light than other people, so the test shows the sensitivity to damage of all the DNA – the genome – in a cell."

Prof Diana Anderson,
School of Life Sciences,
University of Bradford,
Bradford, UK

Cancer therapy evolution:
self-assembling anti-cancer molecules

"Nature uses this kind of self-assembly to make complex asymmetric molecules like proteins all the time, but doing it artificially is a major challenge."

Prof Peter Scott, Department of Chemistry, University of Warwick, Coventry, UK

ARTIFICIAL anti-cancer molecules that mimic the properties of one of the body's natural defence systems have been developed using the properties of molecular self-assembly.

Structurally similar to natural peptides, due to their similar three-dimensional helix form, the new peptide mimics - called triplexes - have proved to be effective against colon cancer cells *in vitro*. The production of such stable molecules was developed utilising a new method based on the principles of complex chemical self-assembly.

The team of chemists at the forefront of this revolutionary development are led by Prof Peter Scott, Professor of Chemistry, Department of Chemistry, University of Warwick, Coventry, UK, and in collaboration with Dr Roger Phillips, Reader in Cancer Pharmacology, Institute for Cancer Therapeutics, School of Life Sciences, University of Bradford, Bradford, UK.

Describing the self-assembly process, Prof Scott said: "When the organic chemicals involved - an amino alcohol derivative and a picoline - are mixed with iron chloride in a solvent, such as water or methanol, they form strong bonds and are designed to naturally fold together in minutes to form a helix. It is all thermodynamically downhill. The assembly instructions are encoded in the chemicals themselves.

"Once the solvent has been removed we are left with the peptide mimics in the form of crystals, there are no complicated separations to do, and unlike a Lego model kit, there are no mysterious bits left over.

"In practical terms, the chemistry is pretty conventional. The beauty is that these big molecules assemble themselves. Nature uses this kind of self-assembly to make complex asymmetric molecules like proteins all the time, but doing it artificially is a major challenge."

To build on the success achieved in the laboratory setting, more research will be required before progressing onto the clinical trial stages.

Tumours: the key to unlocking new therapies

HIDDEN information in imaging tests could help doctors to more accurately choose radiation therapy doses required to kill tumours, research reveals.

In the largest study to date, using radiomics to predict the likely progression of cancer and its response to treatment (based on positron emission tomography [PET] scans of patients with various forms of cancer), 163 non-small cell lung cancer patients and 174 head and neck cancer patients received PET scans before and after treatment.

A variety of information was extracted from each tumour, including the intensity value of the PET image, the roughness of the image, and how round the tumour was; in PET, the brighter an area is, the higher the intensity, thus, the tumour consumes greater amounts of energy from the injected radioactive glucose substitute tracer.

The information gathered from the scans before and after treatments was then compared and factors such as whether the tumour had shrunk and how long the patient survived were taken into consideration so that researchers could create models to help direct future therapy. For example, it was determined that lung tumours with a higher uptake of the tracer need to be treated with a higher dose of radiation than is typically prescribed.

"Standard protocol today is to only use PET imaging to define the extent of a tumour to be treated," commented Dr Joseph Deasy, senior author and Chair of the Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York City, New York, USA.

"Based on the information from this study, the data would be extracted from those images and put into models that would tell the physician what dose was required to kill the tumour with a high probability," Dr Deasy continued.

Dr Deasy further noted that radiomics is a team effort, requiring great collaboration between physicians and computer scientists.

"Based on the information from this study, the data would be extracted from those images and put into models that would tell the physician what dose was required to kill the tumour with a high probability."

Dr Joseph Deasy,
Chair of the Department of Medical Physics,
Memorial Sloan-Kettering Cancer Centre,
New York City, USA

Long-anticipated cancer detection technique finally arrives

'IMMUNOSIGNATURING', an innovative new technique for early cancer detection which has recently emerged, takes a different approach in detecting early immunological signs of cancer.

"For years we have seen remarkable results from immunosignatures, but introducing the technology to the scientific community has required a lot of patience," said lead author Dr Phillip Stafford, Associate Professor of Research, Center for Innovations in Medicine, Biodesign Institute, Arizona State University, Phoenix, Arizona, USA.

Previous research efforts, such as identifying individual biomarkers, have lacked sensitivity, and resolution for positive diagnosis and diagnostic molecules have been presented in vanishingly small amounts, making detection particularly challenging.

The immunosignaturing method depends on a multiplexed system where an entire population of antibodies circulating in the blood at a given time is profiled, and a microarray of thousands of random sequence peptides are imprinted on a glass slide; when a droplet of blood is spread across the microarray, the antibodies in it bind with peptides, forming an image of immune activity – an immunosignature.

In order to test the technique's ability to identify multiple disease types, immunosignaturing was assessed in a study containing >1,500 historical samples comprising 14 different diseases, including 12 cancers; 75% of the samples were also used in a 'training' phase prior to the investigation.

Remarkably, an average diagnostic accuracy of >98% was achieved, and in one experimental trial researchers were able to detect Stage 4 breast cancer, relative to four other cancers and healthy controls. In another trial, 14 separate diseases were distinguished from one another, as well as from healthy controls.

Thus, immunosignatures are an attractive and potential means of capturing disease complexity, providing a marked improvement in cancer detection over traditional methods.

"For years we have seen remarkable results from immunosignatures, but introducing the technology to the scientific community has required a lot of patience."

Dr Phillip Stafford, Center for Innovations in Medicine, Biodesign Institute, Arizona State University, Phoenix, USA

New genetic risk markers for pancreatic cancer

FIVE new genetic markers have been identified that raise the risk of developing deadly pancreatic cancer (PC); this discovery results from the third project in a series of genome-wide association studies which began in 2006 under the National Cancer Institute (NCI) Cohort Consortium.

"Currently, there is no population screening programme for PC, which in 80% of cases is discovered when it is too late to allow curative surgery – the cancer has already spread," commented Dr Brian Wolpin, lead author and Assistant Professor, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

However, the PanScan project, set up by the NCI in 2006, is beginning to identify both genetic and environmental factors which contribute to the development of PC in order to improve screening, disease detection, and diagnosis.

The study, PanScan III, analysed DNA from 7,638 patients with PC and 14,397 controls from the USA, Europe, Canada, and Australia. Scientists used sequencing technology to examine >700,000 locations on the genome to find single-nucleotide polymorphisms associated with PC susceptibility, and found 5 new markers where a single letter variation occurs.

The discovery of these markers is important not only in helping to develop a screening test for PC, but to further help researchers look for molecular explanations as to why some people are more susceptible to the disease than others.

Dr Wolpin noted that a screening tool, used to identify those individuals at increased risk of PC, could help to reveal patients who require magnetic resonance imaging or ultrasound scanning to look for early, treatable, pancreatic tumours.

The long-term aim is to develop a tool that can stratify the risk of developing PC so that doctors in primary care can identify patients who require further screening techniques.

"Currently, there is no population screening programme for PC, which in 80% of cases is discovered when it is too late to allow curative surgery – the cancer has already spread."

Dr Brian Wolpin,
Department of Medical Oncology,
Dana-Farber Cancer Institute,
Boston, USA

Vasectomy could risk prostate health

"The decision to opt for a vasectomy as a form of birth control is a highly personal one and a man should discuss the risks and benefits with his physician."

Dr Kathryn Wilson,
The Harvard School of Public Health,
Harvard University,
Boston, USA

VASECTOMY is associated with a small increased risk of prostate cancer (PrC), and a larger increased risk for advanced or lethal PrC, a large comprehensive study has found.

PrC is a major cause of cancer-related death in men in the USA, where vasectomy is a common form of contraception and approximately 15% of American males undergo the minor procedure every year. However, thought-provoking research has shown that vasectomy may actually be linked to the development of PrC.

Prof Lorelei Mucci, Associate Professor of Epidemiology, Department of Epidemiology, the Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA, and colleagues analysed data from 49,405 American men, aged 40-75 years at baseline, who were followed between 1986 and 2010, as participants of the Health Professional Follow-up Study.

During the 24-year follow-up, 6,023 men were diagnosed with PrC, including 811 who died of the disease; one in four of the participants reported having undergone a vasectomy, and, when analysed, the data showed a 10% overall increased risk of PrC in these subjects.

However, further analysis found that vasectomy was linked to a stronger increased risk of more aggressive forms of PrC – a 19% higher risk of advanced cancer and a 20% higher risk of the lethal form (with 16 out of every 1,000 men developing this).

Concerns have been raised that the links could be a result of bias, yet the researchers maintain that their analyses accounted for diverse information that meant potential biases could be ruled out.

Dr Kathryn Wilson, co-author and Research Associate, Harvard University, summarised: "The decision to opt for a vasectomy as a form of birth control is a highly personal one and a man should discuss the risks and benefits with his physician."

Pelvic examinations:
causing more harm than good

HEALTHY women are likely to experience more harm than good by undergoing pelvic exams included in standard gynaecologic check-ups, causing the doctors group to issue new guidelines advising against them.

Dr Linda Humphrey, member of the American College of Physicians (ACP) Clinical Practice Guidelines, Philadelphia, Pennsylvania, USA, and co-author of the new guidelines, commented: "Routine pelvic examination has not been shown to benefit asymptomatic, average risk, non-pregnant women. It rarely detects important diseases and does not reduce mortality and is associated with discomfort for many women, false positive and negative examinations, and extra cost."

Dr Humphrey noted that the new guidelines apply only to pelvic exams and not to other tests such as cervical cancer screenings, which the ACP suggests should be restricted to visual inspection of the cervix and taking cervical swabs, and should not include a bimanual examination.

Additionally, a team of researchers from the University of California – San Francisco (UCSF) found that many physicians mistakenly believe that pelvic exams are important for ovarian cancer screening; their survey showed the continuation of doctors performing exams simply because women have come to expect them as routine.

Yet the latest analysis of evidence has found that pelvic exams have a low success rate of detecting gynaecologic cancers and infections.

"With the current state of evidence," Dr George Sawaya and Dr Vanessa Jacoby, Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, UCSF, San Francisco, California, USA, said, "clinicians who continue to offer the examination should at least be cognisant about the uncertainty of its benefits and its potential to cause harm through false-positive testing and the cascade of events it prompts."

Finally, in cases where women have symptoms such as abnormal bleeding, urinary bleeding, and vaginal discharge, the doctor's group maintains that pelvic examination is still appropriate.

"Routine pelvic examination has not been shown to benefit asymptomatic, average risk, non-pregnant women."

Dr Linda Humphrey, Member of the American College of Physicians (ACP) Clinical Practice Guidelines, Philadelphia, USA

Breast cancer beast knows no gender

> "I always say that under the microscope, BC is BC. It does not make a difference if you are a man or a woman."
>
> *Mr Bob Riter, Breast cancer survivor*

MEN with breast cancer (BC) are more likely to die from the illness than women; a current lack of knowledge on how to treat male BC is undermining a particularly serious issue.

BC is rare in men; however, the survival rate among men is lower than that for women, according to an assessment of >13,000 men with BC from the US National Cancer Data Base. Of an estimated 2,360 new BC cases diagnosed in men in the USA this year, around 430 will die from the illness. Men are more likely to have far larger breast tumours at diagnosis, with the cancer more likely to have disseminated to other parts of the body.

A perceived lack of awareness by men as to the dangers of male BC and an inability to spot symptoms besides a lump in the breast are seen as major contributors to this high mortality rate. Men are also more likely to be embarrassed of being diagnosed with a condition viewed as being intrinsically feminine.

"This may be attributed to the fact that awareness of BC is so much greater among women than men," said Dr Jon Greif, study leader, DO, Cancer Surgery, Sutter Health, Oakland, California, USA. "Guidelines call for regular screening, both clinical and mammographic, in women, leading to earlier detection."

There are presently no routine screening regimens for men. The American Cancer Society, Atlanta, Georgia, USA, explained: "Because BC is so uncommon in men, there is unlikely to be any benefit in screening men in the general population for BC with mammograms or other tests."

However, BC survivor Mr Bob Riter told the Huffington Post: "I always say that under the microscope, BC is BC. It does not make a difference if you are a man or a woman."

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Promoting cancer cell suicide

"One way to avoid this is to administer the agent in conjunction with an otherwise innocuous compound that makes cells more vulnerable to its deleterious effects, and induces them to undergo programmed cell death."

Prof Angelika Vollmar, Professor of Pharmaceutical Biology, Ludwig Maximilian University of Munich, Munich, Germany

CHEMICAL compounds referred to as T8 have been discovered which have the potential to increase the sensitivity of cancer cells to chemotherapeutic drugs. Additionally, researchers have identified a relevant enzyme, protein disulphide isomerase (PDI), which could be a promising target for anti-tumour agents.

The new class of compounds, T8, are non-toxic and function to stimulate the killing capacity of chemotherapeutic drugs. Due to this heightened stimulation, chemotherapeutic drugs can be used in lower doses, making it less likely that targeted rapidly dividing cancer cells will eventually become resistant to the cancer-killing effects of therapy.

"One way to avoid this is to administer the agent in conjunction with an otherwise innocuous compound that makes cells more vulnerable to its deleterious effects, and induces them to undergo programmed cell death," said Prof Angelika Vollmar, Professor of Pharmaceutical Biology, Ludwig Maximilian University of Munich (LMU), Munich, Germany.

Another new drug target is PDI, which is an enzyme that changes the spatial conformation, and thus the functional state, of proteins involved in a wide variety of cellular functions. These potentially significant discoveries were recorded by an interdisciplinary collaboration of researchers from LMU, Technical University of Munich, Munich, and the Saarland University, Saarbrücken, Germany.

The researchers commented: "Our studies show that T8 is a very promising lead compound, as it is capable of exercising a chemosensitising effect on diverse types of cancer cells. The drug has been tested on a variety of different tumour cells including leukaemia, pancreatic, and breast cancer cell lines.

"In the next phase of the project, this new class of chemosensitisers will be optimised and tested in a variety of *in vivo* animal models, and the compounds will be used to probe the functional significance of PDI as a drug target for tumour therapy."

New imaging technique for neuroblastoma

"Offering children a single PET scan instead of multiple scans would take a lot of the stress out of getting neuroblastoma diagnosed, while still providing doctors with the information they need to decide on the best course of treatment."

Dr Sue Chua,
The Royal Marsden NHS Foundation Trust,
London, UK

RADIOACTIVE iodine tracer, 124I-metaiodobenzylguanidine ([124I]mIBG), has the potential to revolutionise how children with neuroblastoma are treated and diagnosed in positron emission tomography (PET)/computerised tomography (CT) scans.

Neuroblastoma annually affects 100 children in the UK, typically aged 5 or under. Although survival rates have significantly increased from 17% in the early 1970s to 64% today, it is very difficult to treat the most aggressive form of the disease.

Doctors tend to carry out multiple tests which employ a variety of techniques to determine the best possible treatment, but this is deemed distressing to very young patients, especially when certain tests require the use of general anaesthetic.

Typically, a planar scintigraphy scan, involving the injection of young patients with a small amount of [123I]mIBG, is absorbed by the neuroblastoma cells to make them visible on the scan. Another tracer called [124I]mIBG is chemically identical to [123I]mIBG, but a different type of radiation is emitted which can be traced on a PET/CT scan.

This new [124I]mIBG PET/CT scan will allow a more accurate three-dimensional picture to identify where the neuroblastoma has grown or spread. The best treatment options can be decided upon as a result, based on how well the cancer has responded to therapy and the possibility of its recurrence.

"Offering children a single PET scan instead of multiple scans would take a lot of the stress out of getting neuroblastoma diagnosed, while still providing doctors with the information they need to decide on the best course of treatment. Often the more aggressive form of the disease is not picked up until conventional treatments fail, so we also hope this trial will help diagnose the disease earlier so treatment can be adapted accordingly," said Dr Sue Chua, study leader, consultant radiologist and nuclear medicine physician, The Royal Marsden NHS Foundation Trust, London, UK.

War of words over emerging prostate cancer treatment

APPROVAL of a high-intensity focused ultrasound (HIFU) device for treating recurrent prostate cancer (PrC) patients has been postponed by the FDA, although the governing body has expressed satisfaction with the progress of the equipment.

SonaCare Medical Devices, Charlotte, North Carolina, USA, had sought FDA approval for its *Sonablate 450*, a computer-controlled machine carrying a probe, which allows clinicians to transport HIFU energy via thermal ablation to the prostate. Its purpose is to treat biopsy-proven recurrent cancer in low-to-high-risk patients who have failed primary external beam radiation therapy, with prostate-specific antigen (PSA) measurements below 10 ng/ml. However, SonaCare has been encouraged to continue research and not to report back until it has completed a crucial ongoing trial.

Of the first 100 of a proposed 200 subjects enrolled in the trial, 78 finished 12 months of follow-up and had biopsy, while 22 did not. SonaCare presented findings based on both the 100 subject intention to treat (ITT) group and the 78 subjects in the per protocol (PP) group.

50 subjects in the ITT set attained local control, defined by the trial as obtaining a PSA nadir of 0.5 ng/ml or lower, and possessing a negative prostate biopsy at 12 months, with the lower boundary of a 97.06 confidence interval (39%) dropping just short of a 40% performance goal target. Conversely, 78 subjects in the PP group allegedly obtained >40% success, while just 1 more subject had to hit this target in the ITT group to ensure goal completion in this subset.

Results drew scepticism from the FDA, which highlighted the failure of the ITT group to hit its target. FDA members suggested that a 5-year follow-up, rather than 12-months, should be used with PrC constituting a slow-growing disease. However, some believe that the device could yet play a pivotal role in PrC treatment.

Featured Suppliers

Oncology

Pursuing a goal of delivering ground-breaking, life-altering therapies to patients in over 50 countries worldwide, Celgene seeks to establish itself as a major player in the global pharmaceuticals industry. A plethora of immune-inflammatory related conditions, including cancer, constitute the targets set by Celgene for the finding, development, and marketing of patented products. These are tested rigorously at key medical centres in over 300 clinical trials. Multiple myeloma, myelodysplastic syndromes, and chronic lymphocytic leukaemia are among the incurable haematological and solid tumour cancers currently being targeted through the development of investigational treatments.

GlaxoSmithKline (GSK) is one of the world's largest research-based pharmaceutical and healthcare firms, developing and supplying medicines to vastly improve patient health worldwide. GSK has a 97,000-strong workforce covering more than 100 countries, and leads innovative projects in the manufacturing of prescription medicines, vaccines, and over-the-counter medicines. GSK produces medicines that treat major diseases including: asthma, virus control, infections, mental health, diabetes, and cardiovascular and digestive conditions. GSK enjoys a fruitful relationship with the NHS, and has managed to stay true to its strong British heritage.

Pfizer is one of the world's largest pharmaceutical companies, and has always been committed to applying its vast array of global resources toward improving the health and wellbeing of all patients at every stage of life. The company has a leading portfolio of products and medicines which support wellbeing and prevention, as well as a selection of treatment options covering a wide range of therapeutic areas. Pfizer currently possesses an industry-leading pipeline of promising new products, which have the potential to challenge some of the world's most feared diseases including Alzheimer's disease and cancer.

Dedicated to providing a range of medicines, vaccines, and innovative therapeutic solutions to patients worldwide, Sanofi is forever pursuing the goal of providing healthcare and hope to people everywhere. The company, which employs 45,000 individuals across 41 countries, focuses its time and resources on the strategic growth platforms of: diabetes, vaccines, consumer healthcare, rare diseases and multiple sclerosis, other innovative products, animal health, and emerging markets. Central to ambitions is the research and development branch of Sanofi, fuelled by funds from continued growth, which is built on improved global access to quality healthcare.

Varian Medical Systems is the world's leading manufacturer of medical devices and software for treating cancer. The company is responsible for supplying a range of informatics software designed for managing comprehensive cancer clinics, radiotherapy centres, and medical oncology practices. Varian is also a key supplier of tubes and digital detectors used in X-ray imaging for medical, scientific, and industrial applications. Varian's company vision places emphasis on saving lives, and through partnerships with customers it has managed to develop leading solutions for advancing cancer treatment, radiosurgery, X-ray imaging, and security.

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Societies

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- ANTICANCER FUND
- AOG- ASSOCIATION OF ONCOLOGISTS OF GEORGIA
- ASCO- AMERICAN SOCIETY OF CLINICAL ONCOLOGY
- BIG- BREAST INTERNATIONAL GROUP
- CDDF- CANCER DRUG DEVELOPMENT FORUM
- COS- CZECH SOCIETY FOR ONCOLOGY
- CSCO- CHINESE SOCIETY OF CLINICAL ONCOLOGY
- DGHO E.V.- DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE
- ECANCER
- ECCO- THE EUROPEAN CANCER ORGANIZATION
- EORTC- EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER
- ESMO- EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY
- ESO- EUROPEAN SCHOOL OF ONCOLOGY
- ETOP- EUROPEAN THORACIC ONCOLOGY PLATFORM
- HESMO- HELLENIC SOCIETY OF MEDICAL ONCOLOGY
- 10TH INTERNATIONAL SYMPOSIUM ON ADVANCED OVARIAN CANCER: OPTIMAL THERAPY. UPDATE
- IUCT-O INSTITUT UNIVERSITAIRE DU CANCER TOULOUSE ONCOPOLE
- JSMO- JAPANESE SOCIETY OF MEDICAL ONCOLOGY
- MASCC- MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER
- MOGA- MEDICAL ONCOLOGY GROUP OF AUSTRALIA
- MOT- HUNGARIAN CANCER SOCIETY
- RSRMO- ROMANIAN SOCIETY OF RADIOTHERAPY AND MEDICAL ONCOLOGY
- RUSSCO- RUSSIAN SOCIETY OF CLINICAL ONCOLOGY
- SEOM- SOCIEDAD ESPAÑOLA DE ONCOLOGÍA MÉDICA
- SLACOM- LATIN AMERICAN & CARIBBEAN SOCIETY OF MEDICAL ONCOLOGY
- SONK- ST. GALLEN ONCOLOGY CONFERENCES
- SPO- PORTUGUESE SOCIETY OF ONCOLOGY
- STO- SOCIETY FOR TRANSLATIONAL ONCOLOGY
- TAT2015- 13TH INTERNATIONAL CONGRESS ON TARGETED ANTICANCER THERAPIES
- TSMO- TURKISH SOCIETY OF MEDICAL ONCOLOGY
- UICC- THE UNION FOR INTERNATIONAL CANCER CONTROL

UPCOMING EVENTS

Union for International Cancer Control (UICC) World Cancer Congress 2014

3rd-6th December 2014

Melbourne, Australia

'Joining forces: accelerating progress' is this year's conference theme which will attract all cancer related professionals in the global fight against cancer. This Congress promises to provide participating delegates with opportunities to interact with an impressive range of experts from all over the world. The scientific programme will include plenary, symposia, discussion panels, clinical sessions, debates, poster presentations, and much more.

2015 Gastrointestinal (GI) Cancers Symposium

15th-17th January 2015

San Francisco, USA

Fresh perspective on the diagnosis, treatment, and management of GI cancers is the main goal of this symposium. With a commitment to reviewing the latest research and science, the symposium ensures oncologists of all subspecialties are provided with the most pertinent information to enhance the quality of patient care. Those attending include: medics, oncologists, radiologists, gastroenterologists, pathologists, and laboratory scientists.

3rd Global Congress on Prostate Cancer

4th-6th February 2015

Rome, Italy

This Congress aims to bring together top experts and delegates for an in-depth discussion on the different aspects of prostate cancer, with a focus on the difficulties and dilemmas of clinical decision-making. The target audience includes urologists, radiologists, radiotherapists, and medical oncologists. There will be a range of stimulating satellite symposia, lectures, poster presentations, clinical case discussions, and debates.

10th International Symposium on Advanced Ovarian Cancer: Optimal Therapy Update

6th March 2015

Valencia, Spain

This 1-day event will cover all hot topics concerning diagnosis, biology, and therapy of ovarian cancer. The symposium is based on classic educational activity where many specialists will come to teach, learn, and also discuss the value of how standardised and new approaches are being incorporated into the management of ovarian cancer. This event will benefit specialists in: oncology, gynaecology, and molecular biology.

14th St. Gallen Breast Cancer Conference 2015

18th-21st March 2015

Vienna, Austria

Worldwide experts will present their latest data in both basic and clinical research, as well as in the clinical management of breast cancer. Attending participants will be oncologists, surgeons, gynaecologists, pathologists, epidemiologists, nurses, and basic scientists, making it ideal for scientific networking. The programme consists entirely of invited lectures by internationally renowned experts, extensive poster exhibitions, and symposia.

13th International Conference on Malignant Lymphoma

17th-20th June 2015

Lugano, Switzerland

Haematologists, clinical oncologists, pathologists, and leading researchers involved in the study and treatment of lymphoid neoplasms will benefit from this event. The aim of this conference is to discuss all aspects relating to basic research, clinical data, and the results of trials in the treatment of malignant lymphoma worldwide. This will take the form of a stimulating range of plenary sessions, symposia, poster presentations, and ongoing trials sessions.

2nd European Association for Cancer Research (EACR) Summer Conference: Cancer Genomics

28th June-1st July 2015

Cambridge, United Kingdom

The objective of this conference will be to cover recent developments in cancer genomics, as well as to provide an overview of the field. It will bring together scientists from different disciplines, such as cancer biology, translational research, bioinformatics, and epigenomics. Importantly, it will also provide ample opportunities for early-stage researchers to present their work to the international community and to increase scientific networking.

The European Society for Medical Oncology (ESMO) 17th World Congress on Gastrointestinal Cancer 2015

1st-4th July 2015

Barcelona, Spain

Dedicated to all aspects of GI cancers, this is the pinnacle event for healthcare professionals involved in GI and those with a budding interest in the field. The focus will be on the care of patients with GI cancer, including diagnosis, screening, and the management options for common and uncommon tumours. This will be delivered in the form of educational clinical conferences, satellite symposia, presentations, and state-of-the-art lectures.