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ONCOLOGY

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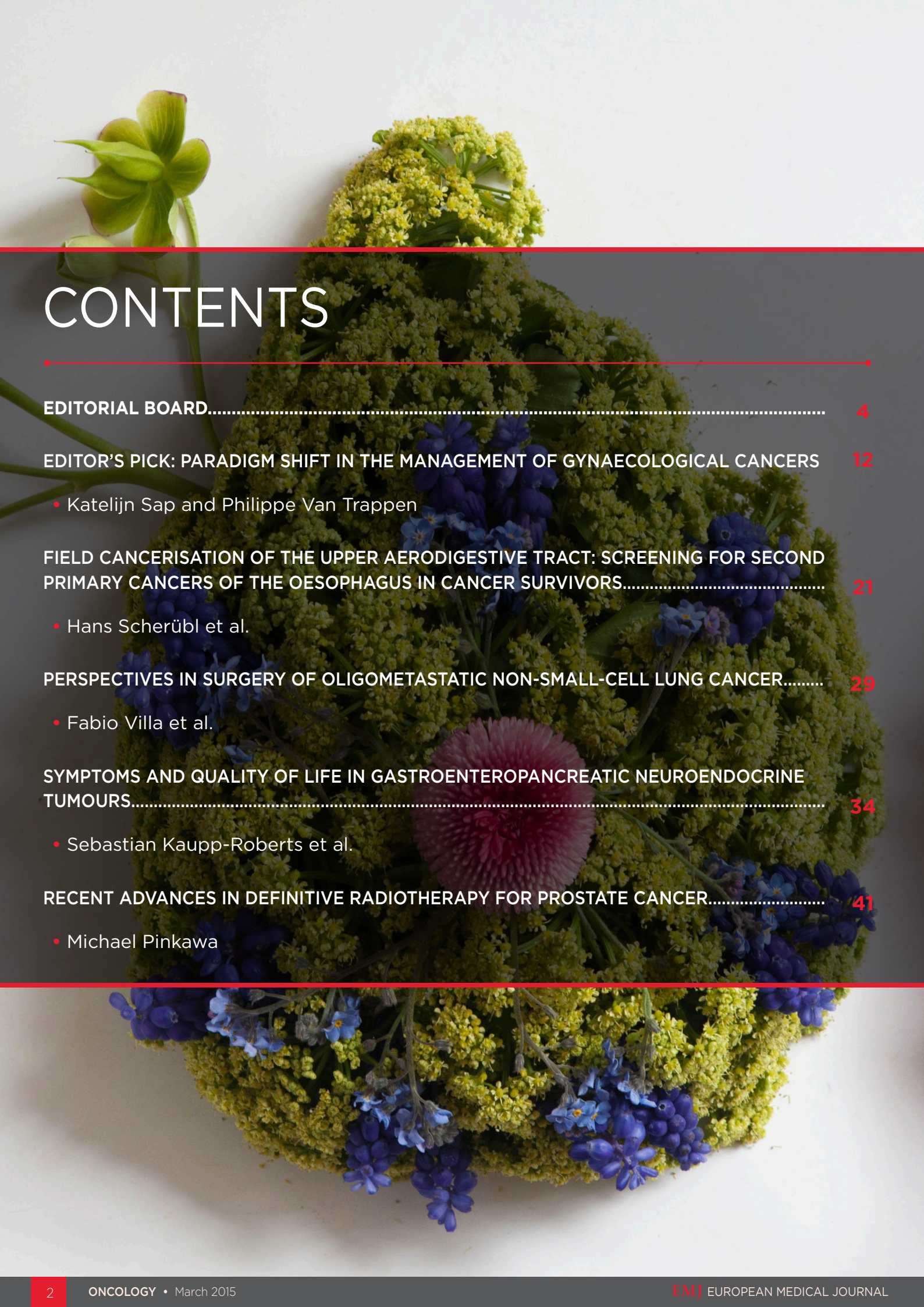

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EMJ GORELY NEW MEDIA

European Medical Journal
EMJ Oncology Vol 3.1
March 2015

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Welcome

Hello, and a very warm welcome to this edition of *European Medical Journal Oncology,* the first of two volumes this year. This edition contains high-quality, peer-reviewed papers bringing you the latest developments and addressing future issues in the oncological field; the second edition will feature a review of the highly anticipated European Cancer Conference (ECC2015) which will take place on 25th-29th September in picturesque Vienna, Austria.

Oncology can be a challenging field to work in at times, but as new treatments are developed that improve prognoses, it can also be extremely rewarding. Case in point: renal failure (RF) occurs in 20-30% of patients with multiple myeloma (MM) and in more than 50% of patients with advanced disease. Historically, the prognosis for patients with MM and RF was considered poor, but things are now looking up. In their paper *'Multiple myeloma and renal failure',* Tosi et al. discuss the introduction of novel drugs and treatments that look set to curb the trend of mortality associated with MM and RF.

In addition, the paper *'Recent advances in definitive radiotherapy for prostate cancer'* by Pinkawa includes a strong case for hypofractionated radiotherapy as a curative treatment option; and Sap and Van Trappen highlight the novel aspects of diagnostic imaging in gynaecological cancers in their paper *'Paradigm shift in the management of gynaecological cancers',* as well as new molecular targeted therapies.

It is a sad truth that in many cases, survivors of cancer face the continued possibility of further problems. Indeed, in the wake of head and neck squamous cell cancer or lung cancer, survivors are at increased risk of developing second primary malignancies, including second primary cancers of the oesophagus. In *'Field cancerisation of the upper aerodigestive tract: screening for second primary cancers of the oesophagus in cancer survivors',* Scherübl et al. discuss the best approaches to testing for, managing, and preventing such unfortunate outcomes.

Oncology is a constantly evolving field and it is the aim of this journal to provide you with an invaluable forum for discussion, the generation of ideas, and the acquirement of knowledge, all of which might positively influence both your practice and your patients. With that in mind, we very much hope that you find this edition of *EMJ Oncology* informative and useful, and wish you all the best in your future endeavours.

Spencer Gore

Team Principal, European Medical Journal

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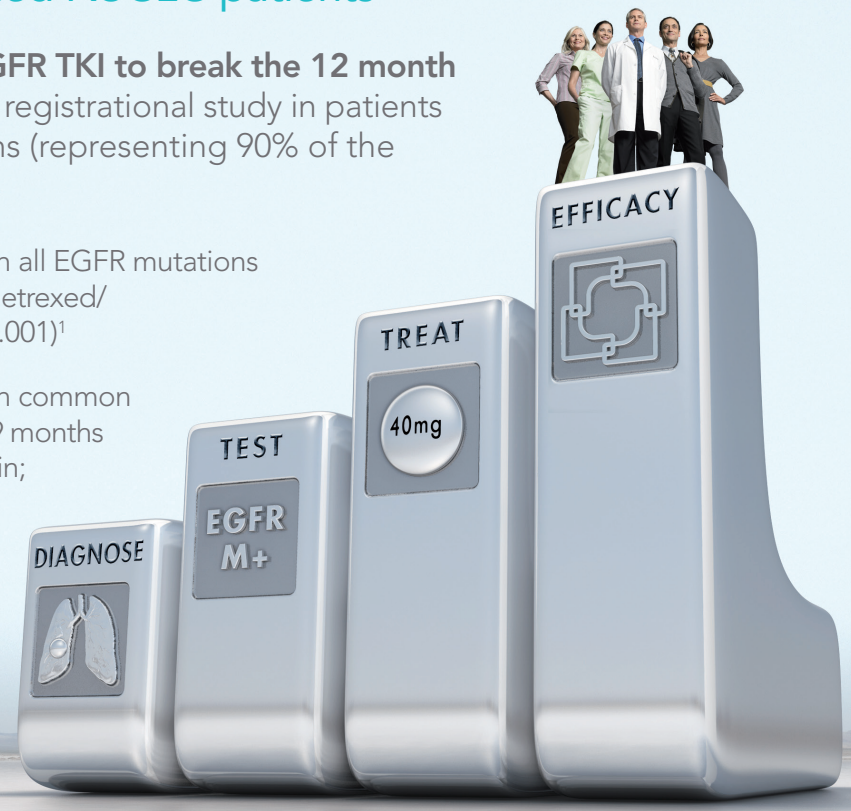

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Left ventricular dysfunction has been associated with HER2 inhibition. Cardiac risk factors, conditions that can affect LVEF and those who develop cardiac signs/symptoms during treatment: cardiac monitoring including LVEF assessment should be considered. Ejection fraction below the institution's lower limit of normal: cardiac consultation and treatment interruption or discontinuation should be considered. Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib. Contains lactose. Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **Interactions:** Administer strong P-gp inhibitors (e.g. ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF. Strong P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort *(Hypericum perforatum)*) may decrease exposure. Afatinib is a moderate inhibitor of P-gp. It is unlikely that treatment will result in changes of the plasma concentrations of other P-gp substrates. Afatinib may increase the bioavailability of orally administered BCRP substrates (e.g. rosuvastatin and sulfasalazine). **Fertility, pregnancy and lactation:** Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with GIOTRIF. There are no or limited amount of data from the use in pregnant women. Mothers should be advised against breast-feeding while receiving this product. An adverse effect on human fertility cannot be excluded. **Undesirable effects:** The most frequent adverse drug reactions were diarrhoea and skin related adverse events as well as stomatitis and paronychia. 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References 1. Sequist L, *et al. J Clin Oncol* 2013;31(27):3327–3334. **2.** Yang J C-H, *et al.* Presented at: 50th Ann Meeting of the American Society of Clinical Oncology (ASCO), Chicago, 30 May–3 June 2014. Oral presentation; Abstract 21366. **3.** Wu L, *et al. Lancet Oncol* 2014;15(2):213–222. **4.** Mok TS, *et al. N Engl J Med* 2009;361:947–957. **5.** Fukuoka M, *et al. J Clin Oncol* 2011;29:2866–2874. **6.** Rosell R, *et al. Lancet Oncol* 2012;13:239–246. **7.** Sebastian M, *et al. Eur Respir Rev* 2014;23:92–105.

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UK/GIO-151009 February 2015

Foreword

Prof Ahmad Awada

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

Dear Colleagues,

I would like to welcome all readers to another exciting issue of *European Medical Journal Oncology,* brimming with interesting peer-reviewed papers dealing with current oncological issues that are of great interest for clinical and therapeutic practice.

Molecular-targeted therapies that emerged years ago continue to steadily increase our armamentarium in the treatment of solid and haematological malignancies. In this edition, PI3K inhibitors in the haematological malignancies are reviewed, as well as the molecular profiling of gastrointestinal stromal tumour, a tumour where one of the first targeted therapies was prescribed (imatinib). Surgery of oligometastatic lesions is an emerging field and its role in non-small-cell lung cancer (NSCLC) is discussed. Here, randomised clinical trials are needed to document the potential of this approach. Immune function modulators (e.g. checkpoint inhibitors) are very promising therapies in 'difficult-to-treat' solid tumours such as recurrent head and neck cancer, NSCLC, triple-negative breast cancer, and bladder cancers.

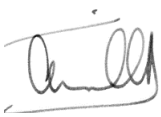
Supportive care is also well presented in this edition with papers reviewing anaemia and thrombocytopaenia, as well as the recent advances in radiotherapy for prostate cancer, a major therapeutic approach in combating this prevalent disease.

> "Molecular-targeted therapies that emerged years ago continue to steadily increase our armamentarium in the treatment of solid and haematological malignancies."

The next edition of *EMJ Oncology* will be published later in the year, and will provide comprehensive coverage of the intriguing events that will take place during the highly anticipated European Cancer Congress in Vienna, Austria on 25th-29th September. Here, the latest findings in cancer prevention, diagnosis, and treatment of patients throughout the world will be presented in full, so it is surely not to be missed!

I hope that you enjoy reading this latest issue, and that you are looking forward to what promises to be an important year for oncologists and haematologists everywhere.

Yours sincerely,



Ahmad Awada

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

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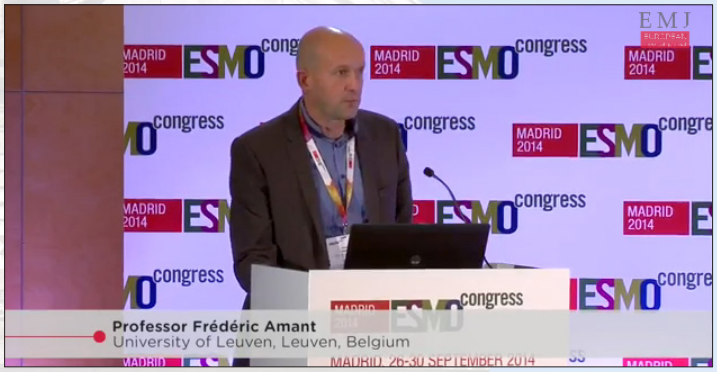

Study Shows Chemotherapy and Radiotherapy are Safe for Babies *in Utero*

Prof Frédéric Amant

The 'National Lung Matrix' Trial – a New Strategy for Cancer Drug Research

Dr Susan Galbraith

The Anti-PD-L1 Monoclonal Antibody, MEDI4736, in Treating Solid Tumours

Dr Rachel Humphrey

Rolapitant Reduces Nausea and Vomiting Associated with Cisplatin-Based Chemotherapy

Dr Bernardo Leon Rapoport

The Effects of Pertuzumab & Trastuzumab on Patients with HER2-Positive Metastatic Breast Cancer

Prof Sandra Swain

Second-Line Afatinib Increases Progression-Free Survival (PFS) in Metastatic Head and Neck Cancer

Dr Jean-Pascal Machiels

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EDITOR'S PICK

My paper selection is 'Paradigm shift in the management of gynaecological cancers' by Sap and Van Trappen. This paper is of interest because it summarises the advances in the management of gynaecological cancers. More importantly it emphasises a multidisciplinary approach to these tumours, which not only improves the outcome but also increases the diagnostic accuracy and decreases morbidity.

Prof Ahmad Awada

PARADIGM SHIFT IN THE MANAGEMENT OF GYNAECOLOGICAL CANCERS

Katelijn Sap, *Philippe Van Trappen

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ABSTRACT

In this review we highlight novel aspects of diagnostic imaging in gynaecological cancers, the paradigm shift in the surgical management of certain female pelvic cancers, as well as potential new molecular targeted therapies. In the last decade, ultra-radical surgery has been shown to increase survival in advanced ovarian cancer (OVC) when extended surgical procedures are included during primary cytoreductive surgery or at interval debulking procedures after neoadjuvant chemotherapy. In cervical cancer (CVC) and endometrial cancer (EMC) endoscopic (laparoscopic or robotic) operations have been shown to significantly reduce the morbidity without altering the cancer-related survival. Although the sentinel lymph node concept is already established in early-stage vulvar cancer, its diagnostic accuracy in EMC and CVC is still under debate. Novel molecular targeted therapies including blocking agents against new blood vessel formation (anti-angiogenesis) and polyadenosine diphosphate ribose polymerase inhibitors have been shown to prolong the progression-free survival in advanced OVC. Other molecular therapies, single or combined, are under investigation in OVC and EMC.

Keywords: Ovarian cancer, endometrial cancer, cervical cancer, positron emission tomography (PET), magnetic resonance imaging (MRI), ultra-radical surgery, robot, sentinel lymph node, molecular therapy.

INTRODUCTION

Pelvic gynaecological cancers (GYC) include cancer of the vulva, vagina, cervix, uterine corpus, fallopian tubes, and ovaries. The primary treatment depends mainly on the tumour type (e.g. carcinoma versus sarcoma) and stage of disease, but usually involves surgery in early-stage disease and surgery combined with (neo) adjuvant chemotherapy and/or radiotherapy in high-risk early-stage or advanced stage of disease. Worldwide, cervical cancer (CVC) is the fourth most common cancer in women, with an estimated 528,000 new cases in 2012. The majority of new CVC cases and CVC mortality occurs in the developing world.[1] In developed countries, the most commonly diagnosed GYC is uterine cancer with 320,000 new cases in 2012 worldwide, of which 52.5% were in the more developed world. Endometrial cancer (EMC) has an incidence rate of 26.5 per 100,000 women per

year in the United States. However, ovarian cancer (OVC) has the highest mortality rate and claims more lives than the other gynaecological malignancies combined: 7.8 per 100,000 in 2009 in the United States.[2]

New diagnostic imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) and diffusion-weighted or dynamic contrast-enhanced magnetic resonance imaging (DWI-MRI or DCE-MRI) are focusing more on potential local tumour activity besides structural changes.[3-5] Molecular imaging, mainly PET and MRI, plays an important role in the management of gynaecological malignancies, and has an impact in different clinical settings.

The surgical management of pelvic GYC has undergone a paradigm shift, especially in the past decade. It has evolved from open surgery to less invasive endoscopic procedures (i.e. laparoscopic or robotic) for EMC and CVC on one hand, and to more ultra-radical surgery (URS), especially in the upper abdomen, for the treatment of advanced OVC on the other hand. In addition, the concept of the sentinel lymph node (SLN) is now being explored in early-stage EMC and CVC, despite being already established in vulvar cancer (VUC). Molecular therapies, often targeting/blocking growth factor receptors on tumour cells or vascular endothelial cells, have recently been introduced in the management of GYCs, and this has opened up new horizons for individualised treatment. In this review we discuss the current and potential future novel strategies in the management of different pelvic female cancers.

MATERIALS AND METHODS

A search of the PubMed and MEDLINE databases for articles published before January 2015 was performed. Only English language articles were considered. Search terms included 'cervical cancer', 'endometrial cancer', 'uterine cancer', 'ovarian cancer', 'fallopian tube cancer', and 'vulvar cancer', in association with 'surgery', 'laparoscopic surgery', 'robotic surgery', 'ultra-radical surgery', 'sentinel lymph node', 'staging', 'molecular imaging', 'PET', 'CT', 'PET/CT', 'PET/MRI', 'MRI', or 'molecular therapies'. With the selection criteria used 78,926 papers were found. For this review, recent papers were selected in case they reported results from prospective (randomised) trials, (observational) cohort studies, comparative studies, case-matched controlled studies, systematic reviews, or meta-analyses.

NEW CANCER IMAGING MODALITIES

MRI and PET, often combined with computed tomography (PET/CT), have become increasingly important in the management of gynaecologic malignancies. MRI has become the mainstay of imaging modalities in staging and follow-up of EMC and CVC.[6] In EMC, MRI is used for assessing the depth of myometrial invasion and cervical extension, hence selecting patients for lymphadenectomy. In CVC, MRI is used in initial staging, assessing local tumour infiltration in surrounding tissues, monitoring response to primary (chemo) radiotherapy, and detecting local recurrence. It is also important in determining the feasibility of fertility-preserving surgery, i.e. radical amputation (radical trachelectomy), or conisation of the cervix in young women, by assessing proximal extension of the tumour. PET/CT appears to be valuable for initial staging in CVC and for detection of recurrent disease. In OVC, PET/CT can be useful in detecting recurrent disease in the setting of a rising CA-125 level without remarkable anatomical imaging findings.[3]

In a recent study, whole-body DWI-MRI has been shown to help assess operability of OVC, for example it improves detection of mesenteric and serosal metastatic spread when compared with CT.[7] The focus of imaging in gynaecological malignancies has shifted recently from visualising morphological/structural changes to detecting local tumour activity. PET/CT and new applications of MRI have been shown to be especially useful in providing this kind of functional information. PET/MRI has been shown to offer higher diagnostic confidence in the discrimination of benign and malignant lesions in gynaecological malignancies compared with PET/CT.[8] In another study PET/MRI correctly identified 98.9% of malignant lesions, whereas MRI alone correctly identified 88.8% of malignant lesions.[9] Considering the reduced radiation dose and superior lesion discrimination, PET/MRI may replace PET/CT in the future. Another MRI application is the DCE-MRI, which makes use of intravenous gadolinium-based contrast in providing information on angiogenesis. Especially in CVC, it may be useful in detecting small tumours and may also help distinguish between recurrent tumours and radiation fibrosis.[10]

ULTRA-RADICAL SURGERY FOR ADVANCED OVARIAN CANCER

Approximately 70% of OVC patients have advanced-stage disease. For several decades the inverse relationship between residual tumour after debulking surgery and overall survival (OS) has been the cornerstone of OVC treatment. Residual disease after primary debulking surgery (PDS) has been shown to be the single most important prognostic factor in advanced OVC. Hence, optimal cytoreductive surgery (CRS), combined with platinum-based chemotherapy, i.e. carboplatin/paclitaxel, remains the standard of care (SoC).

Primary URS in advanced OVC, as advocated by Chi et al.,[11] includes extensive upper abdominal surgery, such as diaphragm peritonectomy, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and resection of tumour from the porta hepatis when necessary.[12,13] Their study showed an increase in 5-year OS from 34-47% when diaphragmatic surgery was included in the CRS. This effect has also been shown by Aletti et al.[14] By aggressive intestinal surgery optimal cytoreduction can be achieved in more than 70% of cases.[15] Cai et al.[16] showed that in patients where bowel resection was considered, 67% had optimal cytoreduction with a median survival of 50 months, compared to 45% optimal debulking in patients where no bowel resection was performed with a median survival of 44 months. However, URS comes with a significant complication rate and post-operative morbidity, such as digestive fistula, lymphocysts, and septic and pulmonary complications.[13,17] Wright et al.[18] showed that the number of extended radical procedures (e.g. diaphragmatic surgery, bowel resection) was directly related to the percentage of complications, with 20%, 34%, and 44% complications when zero, one or two radical procedures were performed, respectively.

Another approach to achieve optimal cytoreduction in advanced-stage OVC is to perform an interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC). This approach appears to improve short-term morbidity, while retaining a similar survival rate (SR).[19] Despite recent randomised controlled trials addressing this issue and demonstrating non-inferiority of the NAC-IDS concept, the debate on PDS versus NAC-IDS continues.[20] Significant efforts have been made to further define subgroups of patients who would benefit most from NAC, such as patients with small volume disease widespread on peritoneal surfaces and bowel serosa, but no consensus has been reached. A possible role for an explorative laparoscopy to help triage patients towards PDS or NAC has been demonstrated.[21,22]

LAPAROSCOPIC AND ROBOTIC SURGERY IN ENDOMETRIAL AND CERVICAL CANCER

Since the introduction of laparoscopic surgery in benign gynaecology in the 1980s and in gynaecological oncology in the 1990s, two large prospective randomised trials (the LACE001 trial and the total laparoscopic hysterectomy [TLH] study) showed in 2010 less morbidity (less blood loss, less pain, shorter hospital stay, and faster recovery) for TLH as compared to total abdominal hysterectomy (TAH) in early-stage EMC.[23,24] The Gynecologic Oncology Group (GOG) LAP2 study in EMC showed an almost identical 5-year OS in both arms (TLH and TAH) at 89.8%.[25] In addition, laparoscopic procedures in CVC, such as laparoscopically assisted radical (vaginal) hysterectomy, have been shown to be feasible and safe with regards to mortality combined with low morbidity.[26]

Since FDA approval in 2005 for the use of the Da Vinci Robotic surgical system there has been a paradigm shift towards more minimally invasive surgery, not previously achieved with traditional laparoscopy. This resulted in more than 50% of endometrial staging procedures being performed by robotic-assisted surgery in 2010 in the United States.[27] This may be due to its shorter learning curve for performing complex gynaecological oncological procedures compared to laparoscopy. There might also be particular advantages of robotic surgery over traditional laparoscopy in obese patients.[28] Technical advantages for the surgeon are the improved three-dimensional stereoscopic vision, the wristed instruments, and improved surgical precision with tremor-cancelling software. The main limitation of robotic-assisted procedures is the higher cost; however, this may decrease with increased utilisation.

Several research groups have reported outcomes (e.g. complications, survival) of robotic-assisted hysterectomy or radical hysterectomy with pelvic lymph node dissection in EMC and CVC, respectively, proving the feasibility and safety in gynaecological oncology.[29-35] Compared to

laparoscopic procedures, the robotic approach is associated with less blood loss and shorter hospital stay.[36] There is no significant difference in the yield of lymph nodes and the percentage of peri or post-operative complications for robotic-assisted versus laparoscopic procedures (see Table 1). Several Phase III trials are ongoing, such as the LACC001 trial, which compares total laparoscopic radical hysterectomy or total robotic radical hysterectomy with total abdominal radical hysterectomy for the treatment of early-stage CVC.

SENTINEL LYMPH NODES IN GYNAECOLOGICAL CANCERS

The SLN concept was introduced by Giuliano et al.[37] in 1994 in breast cancer (BrC) and since the 1990s it has become the SoC for early-stage BrC and malignant melanoma, resulting in a significant decrease in morbidity whilst retaining a similar SR.[38] In VUC, the SLN concept has been widely accepted as the SoC for unifocal, unilateral squamous cell cancer lesions of less than 4 cm, since the published data of the multicentre observational study by Van der Zee et al.[39,40] They showed a low groin recurrence rate of 2.3% and an excellent disease-specific SR of 97% at 3 years in sentinel node-negative patients, combined with a decreased short and long-term morbidity (less wound breakdown, cellulitis, recurrent erysipelas, and lymphoedema of the legs) compared to inguinofemoral lymphadenectomy.

Recent trials on SLN biopsy in EMC showed a large range of detection and false negative rates, but also used different SLN techniques: injectant (isosulfan blue, radioisotope, indocyanine green), injection site (uterine subserosa, cervix, or hysteroscopic injection into the endometrium) and pathologic technique are all of importance. To date, there is no standardised method for SLN biopsy in EMC. A recent prospective multicentre study[41] investigated the detection rate and diagnostic accuracy of the SLN by cervical dual injection (with technetium and patent blue) in early-stage EMC. They included 133 patients from 9 centres. They found a sensitivity of 84% and negative predictive value (NPV) of 97% for the SLN. A thorough review by Levinson and Escobar[42] reported detection rates range from 62-100%, with false negative rates between 0-50% and NPVs from 95-100%. It is clear that larger trials are needed to more accurately determine the efficacy of the SLN concept in EMC.

Table 1: Overview of selected papers on robotic surgery in endometrial cancer (EMC) and cervical cancer (CVC).

Author	Year	Procedure: (radical) hysterectomy + pelvic LNN	Total number of patients	Operating time (min)	Blood loss (ml)	LNN	Hospital stay (days)	Intra-operative complications (%)	Post-operative complications (%)
Lowe et al.[29]	2009	Robotic (EMC)	405	170.5	87.5	15.5	1.8	3.5	14.6
Lim et al.[30]	2011	Robotic vs. LSK (EMC)	122 122	147.5 186.8	81.1 207.5	19.2 24.7	1.5 3.2		
Cardenas-Goicoechea et al.[31]	2010	Robotic vs. LSK (EMC)	102 173	237 178	109 187	22 23	1.88 2.31	2 6	15 33
Lowe et al.[34]	2009	Robotic (CVC)	42	215	50	25	1	4.8	12
Chong et al.[32]	2013	Robotic vs. LSK (CVC)	50 50	230 211	55 202	25 23.1		0 8	
Hoogendam et al.[33]	2014	Robotic (CVC)	100	319	185	24	4		
Reynisson et al.[35]	2013	Robotic vs. open (EMC+CVC)	180 51	185-314 233	100 700		2.4-5.5 7.3	2 6	15 33

LNN: average number of prelevated lymph nodes per surgical procedure; vs.: versus.

Deep injection into the cervix has a clear technical advantage compared to injection into the uterine subserosa or hysteroscopic injection into the endometrium, as it is the easiest site to reach pre-operatively. Furthermore, this injection site has been proven to reach the proper areas of drainage.[43]

A recent systematic review and meta-analysis[44] assessed the accuracy of the SLN procedure in patients with early-stage CVC. The authors identified 49 eligible studies, which included 2,476 SLN procedures. The overall detection rate was 93% and pooled sensitivity was 88%. It was concluded that the SLN procedure performed well diagnostically in patients with early-stage CVC. However, larger prospective trials are needed to elucidate its value in the standard surgical management of early-stage CVC. Finally, the importance of ultra-staging and the use of immunohistochemistry in addition to standard haematoxylin and eosin staining has proven to be vital in the validity of the SLN concept.[42,45]

MOLECULAR TARGETED THERAPIES

Since the 1990s, the standard (neo) adjuvant chemotherapeutic treatment in most OVCs has been carboplatin and paclitaxel. More recently, the addition of molecular targeted agents such as molecules that block new vessel formation (anti-angiogenesis) has demonstrated a prolonged progression-free survival (PFS) in Stage 3 OVC. In addition, the value of polyadenosine diphosphate ribose polymerase (PARP) inhibitors as second or third-line therapy has been shown in the treatment of recurrent OVC. Bevacizumab, the anti-VEGF (vascular endothelial growth factor) monoclonal antibody, has been shown to improve PFS in newly diagnosed OVC, and in both platinum-sensitive and platinum-resistant recurrent OVC in several trials, most importantly the ICON7, GOG218, OCEANS, and AURELIA trials.[46-49] In the ICON7 trial, including 1,528 patients with newly diagnosed OVC, the benefits (PFS and OS) of bevacizumab were greater in those patients at high risk for progression of disease. In the OCEANS trial, including 484 patients with platinum-sensitive recurrent OVC, the PFS was in favour of the bevacizumab group: 12.4 months versus 8.4 months. In the AURELIA trial, including 361 patients with platinum-resistant recurrent OVC, the PFS was 6.7 months in the bevacizumab arm versus 3.4 months in the placebo arm.

More recently, oral alternatives (pazopanib, nintedanib, cediranib) to the intravenous administered bevacizumab have been studied in trial settings, showing often concordant findings with the use of bevacizumab. Prolonged PFS was seen when for example pazopanib was given as maintenance treatment, nintedanib concomitant to chemotherapy and further as maintenance treatment, and cediranib as maintenance treatment.[50,51]

Olaparib is a potent oral PARP inhibitor that has shown antitumour activity in patients with high-grade serous OVC. The PARP enzyme plays an essential role in repair of single-stranded DNA breaks. In tumours with homologous recombination deficiency (HRD), PARP inhibition leads to the formation of double stranded DNA breaks that cannot be accurately repaired, and thus to cell death. HRD can be found in approximately 50% of serous OVCs. This is not only due to a germline or somatic mutation of *BRCA1* or *BRCA2*, but also due to epigenetic silencing of the *BRCA* genes or to the mutation of other genes involved in HRD.

In a randomised controlled Phase II study by Ledermann et al.,[52] olaparib has been shown to improve PFS in patients with platinum-sensitive relapsed high-grade serous OVC (PFS in the overall study group: 8.4 versus 4.8 months; PFS in the subgroup of *BRCA*-mutated patients: 11.2 versus 4.3 months). However, at the interim analysis this did not translate into an OS benefit. Currently, there are four ongoing randomised placebo-controlled trials of maintenance therapy with a PARP inhibitor. The latest trials in OVC focus on detecting subgroups that are especially sensitive to a certain form of targeted therapy (e.g. the SOLO trials, evaluating olaparib in *BRCA*-positive ovarian cancer) or combinations of targeted therapy that are possibly more potent (e.g. combining olaparib and cediranib in OVC).[53]

The chemotherapy of choice in advanced EMC is the combination of carboplatin and paclitaxel, as in OVC.[54,55] However, OS in patients with advanced EMC is poor. Hence, better therapy is needed and targeted molecular therapies are emerging as possible treatment candidates. These include molecules that target VEGF (bevacizumab), mammalian target of rapamycin (mTOR; temsirolimus and everolimus), tyrosine kinase receptors (sorafenib), human epidermal growth factor (EGF) receptors (erlotinib), and human EGF Receptor-2 (HER-2; trastuzumab).[56] With these

targeted therapies partial response was seen in up to 12.5% of cases and stable disease in up to 48% of cases, lasting for at least 4 months. Patients with metastatic and/or inoperable locally advanced recurrent CVC who have been treated before with chemoradiotherapy constitute a high-risk population with a difficult therapeutic challenge. For these patients, the FDA has recently (August 2014) approved the anti-angiogenesis drug bevacizumab.[57]

CONCLUSION

Imaging in pelvic GYCs has evolved from standard CT scan and MRI to the combination of PET with CT and whole-body DWI or DCE-MRI, focusing on potential local tumour activity besides structural changes. Given the superior lesion discrimination of MRI compared to CT, whole-body DWI-MRI combined with PET may replace PET/CT in the future. URS with extended surgical procedures such as diaphragmatic stripping and bowel resection is associated with longer PFS and OS in advanced OVC. Hence, randomised trials are needed to consolidate this. Laparoscopic procedures in CVC and EMC have been shown to be safe in terms of survival, with similar SRs as in open surgery, but with a decreased morbidity for the patients. Robotic surgery is recently emerging in the management of early-stage EMC and CVC with less blood loss and shorter hospital stay. The concept of the SLN procedure performed diagnostically well in patients with early-stage CVC and EMC in recent trials, but larger prospective studies are needed.

Molecular targeted therapies such as blocking new blood vessel formation (anti-angiogenesis) and PARP inhibitors have been shown to increase PFS in advanced/relapsed OVC. Other targeted therapies such as mTOR or tyrosine kinase inhibitors have been shown to induce stable disease for several months in advanced/relapsed EMC. Recently, the FDA and European Medicines Agency have approved the anti-angiogenesis drug bevacizumab for women with advanced CVC. Results from single or combined molecular targeted therapies in trial settings in GYCs are awaited.

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FIELD CANCERISATION OF THE UPPER AERODIGESTIVE TRACT: SCREENING FOR SECOND PRIMARY CANCERS OF THE OESOPHAGUS IN CANCER SURVIVORS

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ABSTRACT

Tobacco, alcohol, and betel quid are the main causes of squamous cell cancers of the upper aerodigestive tract. These substances can cause multifocal carcinogenesis leading to multiple synchronous or metachronous cancers of the oesophagus, head and neck region, and lungs ('field cancerisation'). Globally there are several million people who have survived either head and neck squamous cell cancer (HNSCC) or lung cancer (LC). HNSCC and LC survivors are at increased risk of developing second primary malignancies, including second primary cancers of the oesophagus. The risk of second primary oesophageal squamous cell cancer (OSCC) ranges from 8-30% in HNSCC patients. LC and HNSCC survivors should be offered endoscopic surveillance of the oesophagus. Lugol chromoendoscopy is the traditional and best evaluated screening method to detect early squamous cell neoplasias of the oesophagus. More recently, narrow band imaging combined with magnifying endoscopy has been established as an alternative screening method in Asia. Low-dose chest computed tomography (CT) is the best evidence-based screening technique to detect (second primary) LC and to reduce LC-related mortality. Low-dose chest CT screening is therefore recommended in OSCC, HNSCC, and LC survivors. In addition, OSCC survivors should undergo periodic pharyngolaryngoscopy for early detection of second primary HNSCC. Secondary prevention aims at quitting smoking, betel quid chewing, and alcohol consumption. As field cancerisation involves the oesophagus, the bronchi, and the head and neck region, the patients at risk are best surveilled and managed by an interdisciplinary team.

Keywords: Squamous cell carcinoma, second malignancy, lung, head and neck, endoscopy, surveillance, tobacco, alcohol, betel, neoplasm, tumour, computed tomography.

EPIDEMIOLOGY AND INCREASED CANCER SURVIVORSHIP

Oesophageal cancer (OEC) is the eighth-most common cancer globally with approximately 456,000 new cases per year. Globally the incidence of oesophageal squamous cell cancer (OSCC) clearly outweighs that of oesophageal adenocarcinoma but there are marked epidemiological differences between Western countries and Central Asia and China. Head and neck squamous cell cancer (HNSCC) accounts for approximately 600,000 new cases annually worldwide. With almost 1,825,000 new cases annually, lung cancer (LC) is the most common cancer in the world.[1] The topic of cancer survivorship is becoming increasingly important in current cancer management. Both HNSCC and LC survivors are at risk of developing second primary cancers, including OSCC.[2-5] Long-term survivors of HNSCC or LC are increasing and may amount to 3-5 million persons globally. OSCC survivors

are increasing too; they are at increased risk of second primary HNSCC or LC.[6-8] This review addresses the OSCC risk of people who survived either head and neck cancer (HNC) or LC and gives recommendations for surveillance.

RISK FACTORS: TOBACCO, ALCOHOL, AND BETEL QUID

Tobacco and Alcohol

Smoking and alcohol are well-known risk factors not only of OSCC but also of HNC;[4,8-11] tobacco being the main culprit of LC. Tobacco and alcohol use can cause 'field cancerisation' of the upper aerodigestive tract (UADT) and the lungs.[12] The development of multiple primary squamous cell cancers and widespread epithelial oncogenic alterations, including carcinoma *in situ,* dysplasia, and hyperkeratosis, have long been recognised as the field cancerisation phenomenon.[8,12] Field cancerisation can lead to multiple synchronous and/or metachronous cancers of the oesophagus, lungs, and head and neck region (i.e. oral cavity, oropharynx, hypopharynx, or larynx). 90% of the tumours in head and neck are squamous cell carcinomas, and at least 75% of them are attributable to the combination of tobacco and alcohol consumption. The odds ratio of OSCC may be as high as 50.1 for those who are both heavy smokers and heavy drinkers in comparison to people who neither drink nor smoke.[13] It has been estimated that a history of smoking, alcohol consumption, and diets low in fruits and vegetables account for almost 90% of OSCC cases in the USA. Tobacco and alcohol synergistically increase OSCC risk.[8]

Betel Quid

In Central, Southern, and Southeastern Asia chewing of areca nut or betel quid is prevalent. Unfortunately, the use of areca nut or betel quid (areca nuts wrapped in betel leaves) is associated with an increased risk of oral and oropharyngeal cancer (ORC) as well as of OSCC. The combination of betel nut chewing with tobacco smoking synergistically potentiates the risks of oral, oropharyngeal, or oesophageal squamous cell cancers.[14-16]

Interestingly, the cancer risk from mouth, pharynx, oesophagus, to larynx increases with alcohol and cigarette consumption, but decreases with betel consumption. Tobacco, alcohol, and betel quid act synergistically in OSCC tumourigenesis and are independent risk factors for distinct cancers of the UADT.[9] In Taiwanese men the lifetime risk of UADT cancer was calculated to be 9.42% versus 1.65% for betel chewers versus non-chewers, 3.22% versus 1.21% for cigarette smokers versus non-smokers, and 4.77% versus 1.85% for alcohol drinkers versus non-drinkers. The lifetime UADT cancer risk reached 17.2% in men who chewed more than 20 betel quids a day.[9]

Mutations of the Enzyme Aldehyde Dehydrogenase (ALDH)

Alcohol drinking results in exposure to acetaldehyde, derived from the beverage itself and formed endogenously. Acetaldehyde is a genotoxic compound that is detoxified by ALDH. The presence of the *ALDH2-2* allele encodes ALDH2, an inactive enzyme. Carriers of the *ALDH2-2* allele accumulate acetaldehyde and have higher relative risks of alcohol-related OEC and HNCs as compared with individuals with wild-type alleles. The International Agency for Research of Cancer stated in 2009 that acetaldehyde derived from alcoholic beverages could cause cancer and that alcohol consumption, i.e. ethanol in alcoholic beverages, was classified as a group 1 carcinogen.[17] A strong linkage of inactive ALDH2 to increased susceptibility to multiple cancers was reported in male Japanese drinkers with OEC or ORC. A similar association between inactive ALDH2 and the risk of multiple intraoesophageal and OEC accompanied by oropharyngolaryngeal or stomach cancers (or all) was described in Japanese male alcoholics. These reports indicate that inactive ALDH2 plays an important role in susceptibility of the UADT to multiple cancers.[18-20]

INFECTION WITH HUMAN PAPILLOMA VIRUS (HPV)

The aetiologic factors of HNSCC in patients who have never used tobacco or consumed alcohol are not yet well understood. Multiple lines of evidence indicate that nowadays HPV infection contributes to tumourigenesis in up to 70% of ORC in North America and Europe.[21] Approximately 30% of all HNSCC patients are infected with HPV, mostly with high-risk type HPV-16. Interestingly, oropharyngeal HNSCC patients with HPV infection show fewer synchronous second primary tumours

compared with HPV-negative HNSCC.[22] The reason appears to be the absence of carcinogen-induced early genetic changes in the epithelium and the development of multifocal tumours as known for heavy smokers and alcohol abusers. About 25% of OSCC cases are HPV-positive. It is unclear if having HPV alone is sufficient to cause OEC or if other factors such as tobacco and alcohol interact with HPV to trigger carcinogenesis. At present the role of HPV infection in OSCC carcinogenesis is not well understood.[23,24] A recent study suggests that HPV-16 infection may be involved in OSCC tumourigenesis in Xinjiang Kazakh patients in China.[25]

RISK OF SECOND PRIMARY OEC

12-19% of LCs are diagnosed at tumour Stage 1.[4] When screening for LC is done by using low-dose computed tomography (CT), the percentage of LC being detected at early stages rises to 47.5%.[26] Thanks to curative treatment options the majority of Stage 1 (non-small-cell) LC patients become long-term LC survivors. LC survivors carry a significantly increased risk of developing second primary OEC (odds ratio 2.29).[4] Endoscopic surveillance of the oesophagus should be considered in these patients.[4,27]

HNSCC patients have quite a good outlook: 5-year disease-specific survival of HNSCC patients now reaches 66% in the USA[5] and steps up to 80% or even 90% in patients with Stage 2 or Stage 1 HNSCC. Second primary malignancies (SPM) have been recognised as the leading long-term cause of death in patients surviving HNC.[2,3,5,28] SPM in HNSCC survivors mainly develop in the lungs and oesophagus but also in the head and neck region itself.[28-30] In Western literature, the overall incidence of SPM in HNSCC patients has been reported to range from 9.1-19.0%, with an annual incidence ranging from 3.2-4.0%.[5] Globally HNSCC patients carry a risk of second primary oesophageal squamous cell neoplasias (OSCN) of 8.9-30.4%; the odds ratios or excess absolute risks may be as high as 240.96 or 72.5.[28,31-36] Unfortunately, the OSCC prognosis is generally dismal, with a 5-year survival rate of approximately 10-16% in Western countries.[8] Quitting smoking reduces the risk of SPM.[37]

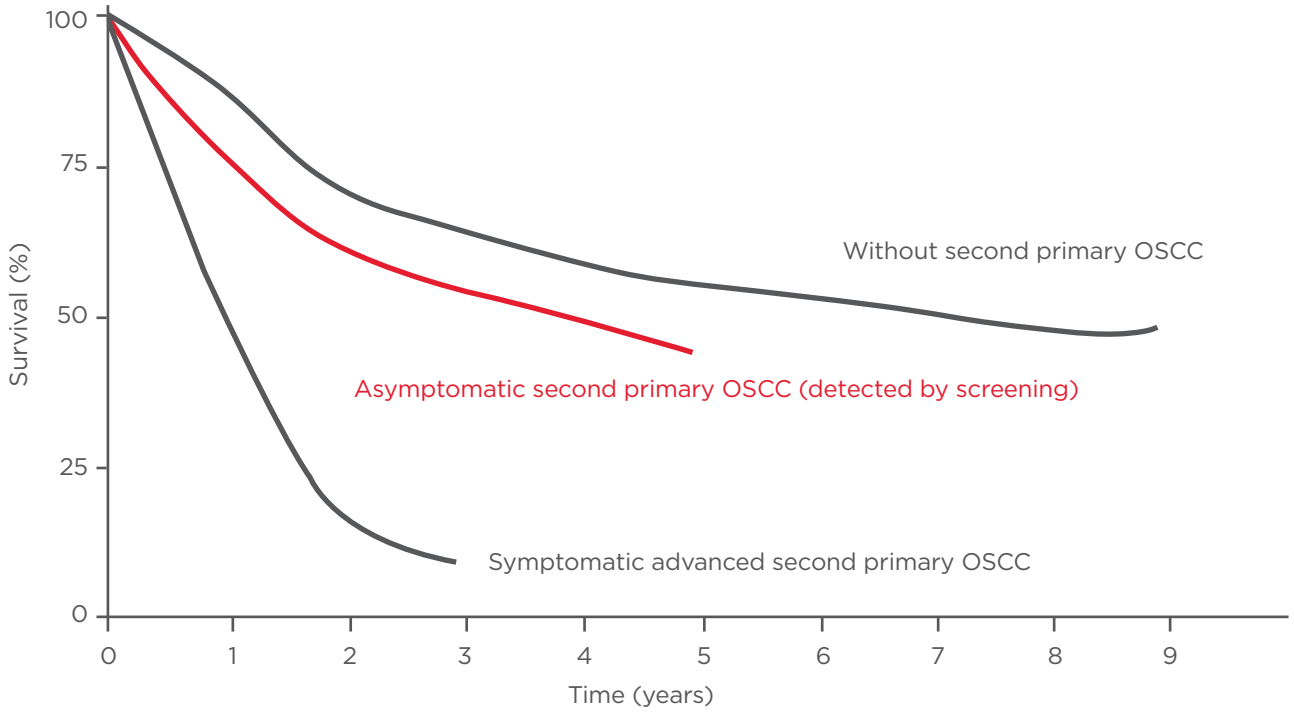

Figure 1: Perspective relative survival of HNSCC patients with and without second primary oesophageal squamous cell cancer (OSCC).
Asymptomatic oesophageal squamous cell neoplasias are detected by screening at an early stage (red line). Symptomatic second primary OSCC is generally diagnosed at advanced stages.
HNSCC: head and neck squamous cell cancer.
With permission from Scherübl et al.[38]

ENDOSCOPIC SCREENING FOR EARLY OSCN

The aim of surveillance is to detect asymptomatic OSCC at very early stages, where both endoscopic and surgical resection generally result in long-term survival. However, when symptomatic OSCC is diagnosed in HNSCC or LC survivors, advanced OSCC stages are prevalent and the outlook is very poor. Overall survival of HNSCC or LC survivors with second primary cancer, in particular second primary OSCC, is significantly lower (5-year survival rate of only 6%) than the overall survival of those without SPM.[2,3,5,38] (Figure 1).

The recommendation that HNSCC and LC survivors undergo periodic endoscopic surveillance is based upon the assumption that on the one hand OSCC adversely affects survival and on the other, surveillance can reduce mortality by detecting OSCN at a very early stage.[38-41] Several lines of evidence suggest that OSCC is diagnosed in routinely screened HNSCC patients more commonly than in those not screened.[29,31-36,39-41] In routinely screened HNSCC patients, OSCC cases are detected at earlier cancer stages.[35,38] Nowadays, OSCC limited to the upper layers of the mucosa (T1a: m1, m2) can be treated effectively by endoscopic resection and thereby with low morbidity and very low mortality. OSCC invading the lamina muscularis mucosae (m3) or the upper layer of the submucosa (<500 μm: sm1) has a higher risk of lymph node metastases and in Europe is generally only chosen for endoscopic resection if no further risk factors are present, such as poor grade of differentiation, angioinvasion, or a higher grade of tumour cell dissociation.[27] OSCC invading the deeper layers of submucosa (sm2, sm3) should be managed surgically and/or by chemoradiotherapy. In elderly patients with very significant comorbidities an endoscopic approach may be considered even in sm2 or sm3 cancers. Therefore, the aim of surveillance is to detect second primary oesophageal neoplasias at (very) early stages, i.e. intraepithelial neoplasias or m1/m2 intramucosal cancers.

LUGOL CHROMOENDOSCOPY OF EARLY OSCC

Chromoendoscopy with Lugol's solution (1-2%) used to be the traditional and reference procedure to screen for early OSCC in high-risk patients. Multicentric squamous neoplasias of the oesophagus can be visualised by Lugol chromoendoscopy as Lugol-voiding lesions (LVL), because dysplastic or hyperkeratotic epithelium does not stain with Lugol iodine solution and appears white or pink, whereas normal epithelium is stained brown. Multiple LVL have been associated with a very high risk of multiple cancers arising in the oesophagus, as well as in the head and neck region.[7,38,39] The sensitivity and specificity of Lugol chromoendoscopy to detect OSCC in high-risk groups amounts to about 80-96% and 63-72%, respectively.[29] The French Ear, Nose and Throat (ENT) Society suggests using flexible white-light, high-resolution video oesophagoscopy combined with targeted biopsies of any suspected oesophageal lesion. In addition, it recommends applying Lugol chromoendoscopy as this technique diagnoses more early-stage preneoplastic and neoplastic lesions with better definition of local extension of more advanced OECs.[42] (Figure 2).

NARROW-BAND IMAGING (NBI) AND MAGNIFYING ENDOSCOPY (ME)

NBI is a novel optical technique that enhances the diagnostic capability of gastrointestinal endoscopy by highlighting the intraepithelial papillary capillary loops of the squamous mucosa by means of light passed through filters that narrow the spectral bandwidths, incorporated into a red-green-blue sequential illumination system. NBI combined with ME has been demonstrated to further improve the detection rate and accuracy of early OSCC in HNSCC patients.[33] In a recent study NBI endoscopy with ME was reported to be the ideal screening tool to search for early oesophageal squamous neoplasias; the respective sensitivity, specificity, and accuracy amounted to 97.3%, 94.1%, and 96.3%.[29] These observations go in line with an Asian-Pacific consensus conference on early-stage oesophagogastric cancer in 2011; that consensus conference stated that NBI could replace chromoendoscopy in routine examination because it is easy to use and adds much information to conventional white light imaging, but it cannot eliminate chromoendoscopy when we make a final diagnosis for treatment decision making (Figure 3).[43] Both due to unpleasant side-effects and low specificity of Lugol chromoendoscopy, high-resolution flexible video oesophagoscopy with NBI may well become the

preferred routine screening technique for second primary OSCN in the near future. In most countries of Western Europe NBI endoscopy is generally available and widely used.

SCREENING RECOMMENDATIONS OF NATIONAL HEALTHCARE SOCIETIES

Risks of second primary malignancies differ among LC or HNSCC survivors of different countries and regions. Therefore, there are no generally and worldwide accepted recommendations of screening for second primary OSCC. The recent guidelines of the French ENT Society recommend upper-gastrointestinal endoscopy in the initial workup of hypopharyngeal squamous cell cancer and in all chronic alcoholics with HNSCC,[42] corresponding to the great majority of HNSCC patients in France. Similarly, healthcare specialists in Taiwan pointed out that the odds ratios for second primary OSCC were 18.41, 40.49, and 240.96 in patients suffering from malignancy of the oral cavity, oropharynx, and hypopharynx, respectively.[34] They recommend periodic OSCC screening according to the individual risk stratification.[35] Still, most national ENT, gastroenterology, and cancer societies have yet to make up their minds and have to balance possible survival benefits resulting from screening against economic restraints. Efforts to reduce heavy alcohol and tobacco consumption as well as betel quid chewing are generally recommended and often supported by national campaigns.

OSCC SURVIVORS: SURVEILLANCE FOR SECOND PRIMARY CANCERS OF THE HEAD AND NECK, AND THE LUNGS

Risk of developing a second malignancy should be anticipated after curative treatment of OSCC. Common risk factors including lifestyle and genetic alterations may explain both the pattern and the increased incidence of second primary cancers in OSCC survivors. Because of the high mortality of OEC itself, not much attention was previously paid to the development of SPM. Due to promising results of a recent prospective study of the National Lung Screening Trial research team, today LC screening has become the focus of increasing interest in high-risk groups.[26]

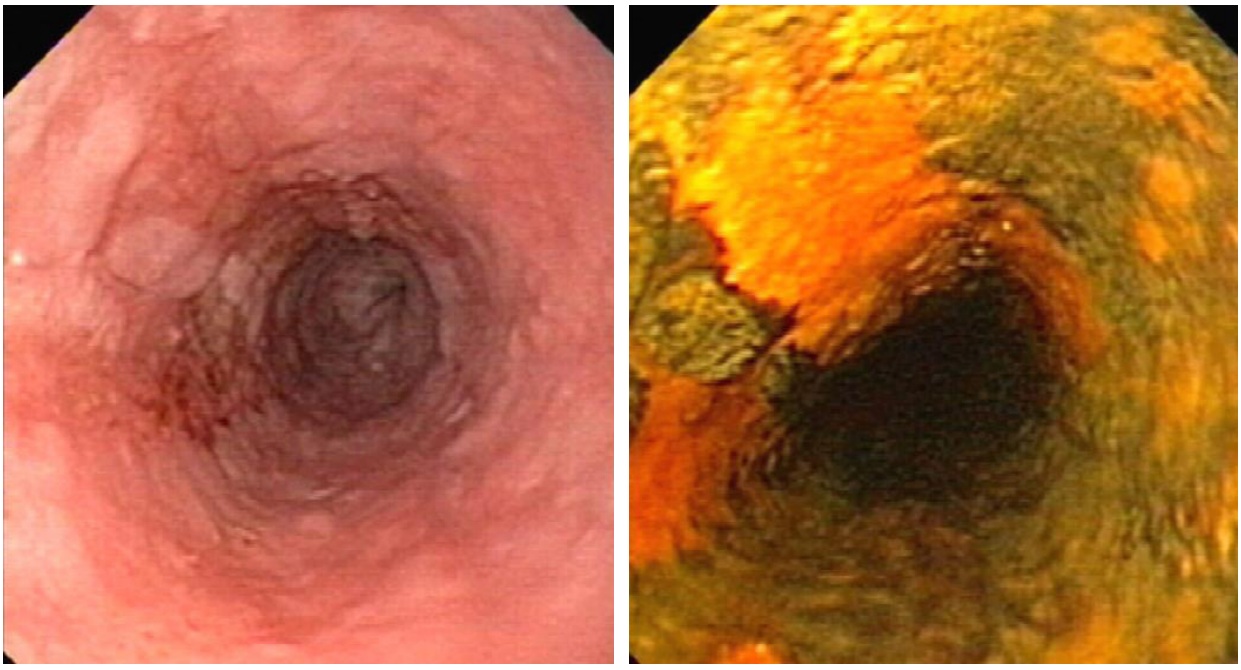

Figure 2: Oesophageal squamous cell cancer (OSCC) in a HNSCC patient.
Left panel: Videoendoscopic image of an OSCC (Stage T1aN0M0) at 25 cm from the incisors. 29 months ago the patient had been treated for a squamous cell cancer of the oral cavity. Right panel: The same tumour after staining with Lugol dye solution to delineate the tumour margins.
HNSCC: head and neck squamous cell cancer.
With permission from Scherübl et al.[40]

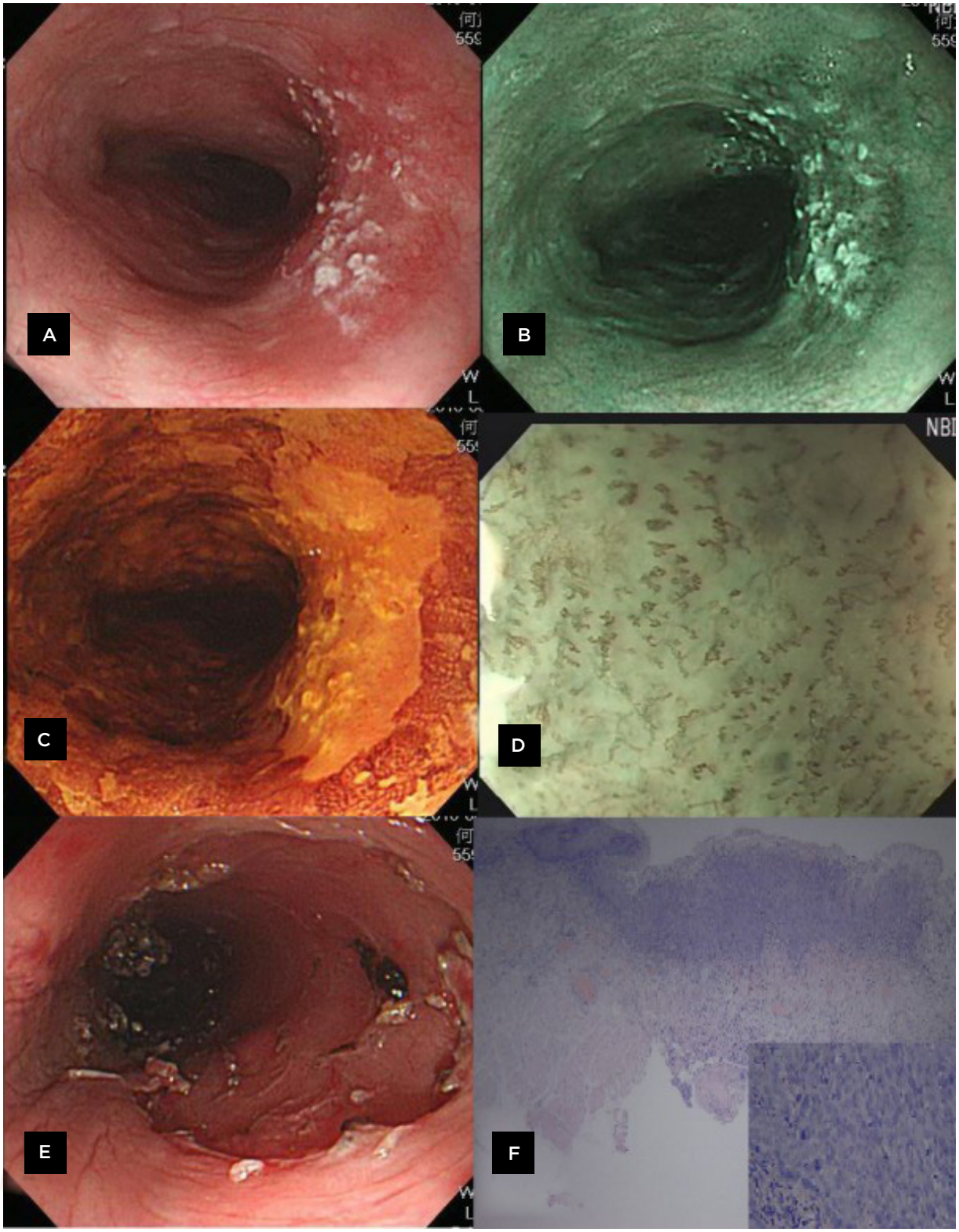

Figure 3: Endoscopic surveillance and management of synchronous high-grade intraepithelial neoplasia of oesophagus in a laryngeal cancer patient.

A: A flat superficial neoplasia with hyperaemia in white-light imaging system. B: A superficial neoplasia with brownish discolouration under narrow-band imaging system. C: Lugol-voiding of the neoplasia after spraying a 1.5% Lugol's solution. D: Abnormal intraepithelial capillary loops under narrow-band imaging system with magnifying endoscopy. E: Endoscopic submucosal dissection of the superficial neoplasia. F: Mucosal cancer invading the lamina propria (main picture: H&E stain, 40x; right bottom: H&E stain, 100x). H&E: haematoxylin and eosin.

With permission from Chung et al.[29]

Superficial HNCs

OSCC patients have a risk of 8.3-27.1% of developing SPM.[8] Due to common risk factors such as tobacco and alcohol, OSCC shows a particularly high association with LC and HNC. Matsubara et al.[44] reported that OSCC patients are at very high risk for the development of both HNC and LC after oesophagectomy and that the early detection of second cancers allowed less invasive treatment with favourable outcomes.

Patients with OSCC, particularly alcohol drinkers, current smokers, and those with the *ALDH-2* allele and multiple LVL of the oesophageal mucosa, have an increased risk of superficial squamous cell cancer within the head and neck region. As Lugol chromoendoscopy is not applicable to the head and neck region, NBI in combination with ME is the preferred technique to search for early (i.e. superficial) HNSCC in OSCC patients.[7,8] The ability to detect a second primary cancer at a (very) early stage is of benefit for patients at high risk of superficial HNSCC. However, controlled prospective studies that provide evidence for a survival benefit of endoscopic surveillance in OSCC survivors have yet to be performed.[6]

Lung Cancer

LC is the largest single cause of death from cancer in the world. As the number of long-term OEC survivors continues to increase worldwide, the incidence of second primary cancers including LC will increase. Detecting and treating SPM appear to be effective in OSCC patients. Thus, recent evidence suggests similar overall survival rates in OEC patients with or without SPM.[8] Both early asymptomatic LC and superficial HNSCC are amenable to curative treatment.[4,7] Detection of early LC is best achieved by low-dose chest CT. Periodic, low-dose CT screening leads to a shift to detection of earlier-stage non-small-cell LC and thereby reduces LC mortality.[26] Nowadays, both HNSCC and OSCC survivors should be considered for regular screening for early LC by low-dose chest CT.

CONCLUSION

As field cancerisation involves the oesophagus, the bronchi, and the head and neck region, the patients at risk are best surveilled and managed by an interdisciplinary team.

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PERSPECTIVES IN SURGERY OF OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER

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ABSTRACT

20-50% of patients with newly diagnosed non-small-cell lung cancer (NSCLC) have synchronous metastases. This dramatically affects survival and traditionally excludes patients from the spectrum of curative therapies. Nonetheless, studies have been performed to assess the role of surgery in Stage 4 NSCLC with metastases circumscribed to a single or limited number of organs, proposing the definition of oligometastatic NSCLC to enlarge the possibility of curative resection. Aggressive treatments have shown promising results; however, the great heterogeneity of survival outcomes implies the bias of selection of patients who can benefit from surgery. The new molecular-targeted systemic therapies, cytotoxic regimens, and radiant treatments can complement surgery in metastatic NSCLC, leading to optimal control of the disease. Retrospective series can help us to design prospective trials, selecting patients with positive prognostic determinants to undergo intensive resective and pharmacologic treatments. Molecular and gene profiling will probably be the most accurate method to elect candidates to sanative therapy in Stage 4 NSCLC.

Keywords: Oligometastatic non-small-cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), Stage 4 NSCLC, thoracic surgery.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) remains one of the primary causes of cancer-related death, and accounts for approximately 80% of all lung cancer (LC) histotypes. 20-50% of patients have metastatic disease at presentation, according to the findings of current imaging methods. Stage 4 NSCLC has an overall median survival time of 7-11 months from time of diagnosis, and it is not traditionally considered suitable for curative therapies.[1] In this context, surgery has always had a marginal role. Nonetheless, the advent of systemic targeted agents and the amelioration of local control of metastases impose the re-evaluation of the pointlessness of surgical treatment in Stage 4 LC. A number of studies have shown promising results for an aggressive approach, including surgery and combined systemic treatments for patients suffering from NSCLC with distant secondarisms; however, the heterogeneity of outcomes points out the lack of election of patients. Pursuant to the characteristics of the patient and the disease, several authors proposed criteria to select candidates for intensive sanative therapy. Weak evidence prevents the ordinary inclusion of the encouraging paradigms described to attempt the cure of Stage 4 NSCLC.

DEFINING OLIGOMETASTATIC NSCLC

Hellman and Weichselbaum[2] in 1995 proposed the consideration for Stage 4 cancers with metastases circumscribed to a single or limited number of organs. The definition of oligometastatic disease aims for the election of candidates to aggressive curative treatments, on the basis of the conception of an intermediate disseminated tumour stage characterised by the confined involvement of organs. In the aforementioned editorial, the metastatic potential is supposed to be correlated to the macroscopic and histological features of the tumour, with special regard to size

and grade, as well as the 'seed and soil' crosstalk of aberrant cells. Furthermore, 5-year survival rates (5SRs) of NSCLC remain unsatisfactory after surgery with curative intent, and disease recurrences, including distant metastases, are frequent.[3] These findings suggest a common subtle micrometastatic pattern in patients undergoing restorative resection. In effect, the definition of Stage 4 disease, subtending the presence of secondarisms, is based upon imaging features with recognised sensitivity and detection limits.

The definition of oligometastatic NSCLC, according to prognostic and therapeutic implications, is challenging, even though the majority of authors include patients with 1-5 metastases in this category. Oligometastases are distinct from oligo-recurrences, which envisage a metachronous pattern. The increase in sensitivity of diagnostic tools and the perspective of local control of tumour masses lead to the augmentation of diagnosis of occult Stage 4 NSCLC while simultaneously inciting new therapeutic solutions for patients. In addition, it is evident that there is a lack of prognostic accuracy of the actual staging criteria based upon macroscopic characteristics. Gene expression and molecular profiling could represent the leading indicators in the future, as well as in selecting patients with Stage 4 NSCLC who are amenable for curative surgery. The importance of microRNA expression in oligometastatic patients treated with high-dose radiotherapy has been assessed, revealing that microRNA-200c enhancement in an oligometastatic cell line can predict the polymetastatic progression. These findings suggest the biological, genetic, and molecular bases of the oligometastatic stage.[4]

THE ROLE OF SURGERY

Surgery has been performed with success for Stage 4 NSCLC. Resection of synchronous brain metastases improves the outcome in patients with an adenocarcinoma and small lung tumour, without abnormal mediastinal lymph nodes seen on the computed tomography (CT) scan or during mediastinoscopy.[5-7] Prognostic factors also include controlled primary tumour site, the absence of extracranial disease, a good performance status, and an age of <60 years. Surgical resection of the brain masses or stereotactic radiosurgery combined with adjuvant whole-brain radiotherapy prolongs survival by approximately 8-11 months. Radiosurgery can be used for the local control of metastases, avoiding the postponement of resection of the primitivity. Surgery is the best treatment to reduce intracranial pressure, therefore it is privileged in case of mass effect. Palliative radiosurgery can be performed in patients with NSCLC with poor prognosis to improve neurological deficits.[8]

Concerning isolated suprarenal gland secondarisms from NSCLC, adrenalectomy is the treatment of choice, significantly improving long-term survival in both synchronous and metachronous patterns.[9] A 2013 review emphasises the heterogeneity of survival outcomes, discussing the definition of the oligometastatic stage.[10] The authors argue the need for randomised trials. The series included 49 studies, with 2,176 patients with 1-5 metastases treated with surgical metastatectomy, stereotactic ablative radiotherapy, or stereotactic radiosurgery, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only one study reported randomised data, referring to patients with brain metastases as comprising 60% of the articles. 82% of patients had a controlled primary tumour. 1-year overall survival (OS) was 15-100%, 2-year OS was 18-90%, and 5-year OS was 8.3-86%. This variability among survival outcomes implies a fragmentary knowledge of prognostic determinants in patients included in the diagnosis of Stage 4 NSCLC, underlining the lack of patients who can benefit from aggressive treatments.

Pfannschmidt and Dienemann[11] emphasise the difficulty in evaluating the effectiveness of surgical resection, mainly due to the selection bias. The reported overall 5SR is about 28% for patients with satellite nodules and 21% for patients with ipsilateral nodules. In the case of resected brain metastasis, the 5SR is 11-30%, similar to the benefit observed in the case of adrenalectomy, in which the 5SR is 26%.[11] In a series of 84 newly diagnosed NSCLC patients presenting with a solitary brain metastasis, the survival outcome was found to be comparable to Stage 1 NSCLC. The median survival was 25.6 months for Stage 1, 9.5 months for Stage 2, and 9.9 months for Stage 3. Primary LC was treated in half of the cases by thoracic radiation therapy, chemotherapy, or both. 53 patients underwent craniotomy and 31 stereotactic radiosurgery. 1-year OS was 49.8%, 2-year OS was 16.3%, and 5-year OS was 7.6%. The authors concluded that intensive treatment during the early stages is justified for a thoracic

Stage 1 NSCLC with a solitary brain metastasis, contrary to locally advanced cancers.[12]

PROGNOSTIC FACTORS

The number of metastatic sites is a potential predictor of survival. The Southwest Oncology Group published the data collected from 1974-1988 of 2,531 patients with extensive stage NSCLC, indicating a sole metastatic site as a favourable determinant.[13] A retrospective series of 1,284 patients with a diagnosis of Stage 4 NSCLC at presentation revealed that OS without brain secondarisms is significantly correlated with the number of metastatic sites. Brain metastases conferred a worse prognosis (median OS of 7 months versus 9 months; 95% confidence interval, 7-8 months versus 8-10 months), with an inverse correlation with the volume of all metastases or the largest lesion.[14]

Ashworth et al.[10] reported that definitive treatment of the primary tumour, N-stage, and a disease-free interval of at least 6-12 months are significant prognostic factors for surgery in Stage 4 NSCLC on multivariate analyses. The median OS range was 5.9-52 months (overall median 14.8 months; for patients with a controlled primary tumour 19 months). The median time to any progression was 4.5-23.7 months (overall median 12 months). The statistical dispersion observed in 1-year, 2-year, and 5-year OS was confirmed. In a retrospective series of 53 patients with oligometastatic NSCLC, mainly with a single metastatic brain lesion, treated with curative intent in the period from January 1997 to May 2010, weight loss and the use of a positron emission tomography-CT scan in pre-operative staging had an independent positive prognostic value. The need for radical pulmonary resection was confirmed.[15]

SYSTEMIC THERAPIES

The current guidelines from the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario[16] recommend adjuvant cisplatin-based regimens for patients with Stage 2 or 3A NSCLC who have undergone radical resection. Neoadjuvant therapy has demonstrated effectiveness in the case of satisfactory pathological response and negative surgical resection margins,[17] but exclusively cytotoxic drugs have been used in the majority of trials. Patients with Stage 3 NSCLC obtain benefit in terms of progression-free survival and OS by neoadjuvant and adjuvant treatment; on the other hand, the need for complementary systemic therapies for patients with Stage 2 NSCLC is still debated. Concerning Stage 4 NSCLC, early surgery and the local control of metastases, in addition to the aspecific cytotoxic regimen, could act in synergy with biological agents. These compounds could represent a cancer signalling-targeted strategy to control masses' overgrowth,[18] regulated by the crosstalk with macro and microenvironment. Molecular-targeted agents could reduce the prolonged dissemination of secondarisms and the 'seed and soil' reciprocity between aberrant cells and the destination tissues. Indeed epidermal growth factor receptor (EGFR) is involved in the haematogenous and lymphatic spread of malignant cells, in their pro-metastatic interdependence with stromal tissue[19] as well as in the evasion of tumour immunosurveillance.[20]

EGFR inhibitors have shown efficacy in selected non-surgical patients with a disseminated disease characterised by a mutated gene, in spite of the heterogeneity of survival outcomes. The variability of mutations among cancer cell lines, acquired resistances, and the mitogenic pathways' redundancy are probable reasons for the inter and intra-individual differences in response.[18] The solution to the development of resistance is one of the major therapeutic objectives of modern pharmacology, and could be reduced by three new third-generation compounds presented at the 2014 ASCO meeting.[21] Preoperative anti-EGFR molecules have been administered with weak benefits. In these trials the study population was not selected for EGFR mutations, but retrospectively analysed; the genetic alteration was the strongest predictor of response,[22,23] as expected. However, mutations affect a minority of patients with specific epidemiologic characteristics: non-smokers, adenocarcinoma histologies, and Asian ethnicities. A few authors have developed randomised trials in a selected population. Adjuvant administration of anti-EGFR designed for mutated receptors seem to have promising applications.[24-26] Furthermore, studies demonstrate that EGFR inhibitors are safe and active on brain metastases of NSCLC.[27]

Several trials have investigated the role of cetuximab in an unselected population reporting weak advantages, as seen for bevacizumab, the anti-vascular endothelial growth factor compound which could contraindicate resection for the risk

of bleeding.[28] Nevertheless, the monoclonal antibody has demonstrated a high safety profile as well as an anti-proliferative action on NSCLC and its active brain metastases.[29] In addition, crizotinib has been used for echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase translocation and *ROS1*-rearranged NSCLC with success.[30,31] In these terms it is legitimate to apply the concept of neoadjuvant or adjuvant systemic treatment to oligometastatic stages amenable to surgery. Molecular-targeted agents could have a synergistic activity to surgery, as argued for radiotherapy.[32] Cytotoxic and biological drugs could strengthen surgery in selected patients before and after, with an acceptable toxicity.

CONCLUSION

LC is the most lethal tumoural disease in the world. The cause of the poor survival is that the vast majority of LCs are diagnosed at an advanced stage, owing to the limited role of screening programmes and the absence of early symptoms in most cases. In spite of the fact that low-dose tomographic screening has demonstrated efficacy for reducing mortality in persons at high risk for LC,[33] this practice is not routinely performed yet. The current tumour, node, metastasis (TNM) classification, based upon macroscopic features, defines prognosis and permits the election for curative or palliative treatments. Limitations of the TNM staging are pointed out by the great heterogeneity existing among survival outcomes in patients included in specific staging categories. The most important variability is observed in Stage 4 NSCLC, which regrettably comprises a large component of all newly diagnosed LCs. Several efforts have been accomplished for these patients with questionable results. Nonetheless, a non-negligible aspect of Stage 4 NSCLCs is their positive response to aggressive treatments, including surgery.

Controversy exists regarding the selection of Stage 4 candidates for sanative therapies; the definition of oligometastatic has been proposed on the grounds that a limited number of secondarisms involving a confined number of organs could represent a prognostic advantage, therefore a spur to indicate aggressive treatments. Surgery has already been performed with success in several Stage 4 cancers, and this success was attributed to systemic therapies and the local control of metastases.[34,35] Nowadays it is legitimate to attempt surgery of Stage 4 NSCLC with curative intent if the initial lesion is radically resectable, as well as the single site metastasis, in a patient with a good performance status. The benefit of surgery for patients having a locally advanced lesion or an oligometastatic disease (generally defined by a number of 1-5 metastases) is debatable. Also in this nosographic category, survival outcomes are heterogeneous; the need for prospective trials based upon the retrospective findings will help to select the patients most likely to benefit from intensive therapy. Furthermore, molecular and gene profiling could summate sensitivity to the election criteria, in consideration of the prognostic value of genetic or proteomic alterations and also the available molecular-targeted agents which can strengthen surgical resection.

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SYMPTOMS AND QUALITY OF LIFE IN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have the ability to induce symptoms either by their direct mass effect on local tissues (symptoms such as pain, bowel obstruction, obstructive jaundice, and bleeding), or by the ectopic secretion of bioactive compounds. GEP-NETs are frequently associated with significant diagnostic delays, and metastatic disease is often a feature at initial presentation. Quality of life (QoL) research in GEP-NETs is a comparatively new field, with a disease-specific QoL questionnaire, the QLQ-GINET21, having been fully validated only as recently as 2013. It has been reliably demonstrated to date that diarrhoea, fatigue, and flushing are the symptoms provoking the greatest decline in patient QoL. Furthermore, depression is highly prevalent in the GEP-NET population. This paper reviews current understanding and potential future developments in this field.

Keywords: Quality of life, patient-reported outcome measures (PROMs), gastroenteropancreatic neuroendocrine tumours (GEP-NETs), symptoms, GINET21, QLQ-C30, syndromes, neuroendocrine tumours (NETs).

INTRODUCTION: SYMPTOM SCORES, PATIENT-REPORTED OUTCOMES, AND QUALITY OF LIFE

Patient-reported outcomes are fundamentally important measures of clinical intervention, both in clinical practice and as trial endpoints. The term PROM (patient-reported outcome measure) refers to any symptom or feeling that the patient can describe. Quality of life (QoL) is (usually) a patient-reported measure which is designed to include symptoms as well as emotional domains such as anxiety and depression. Measuring symptoms and emotional domains is not easy, but there is extensive research on these measures in other cancers (http://groups.eortc.be/qol). With the advent of new therapies for gastroenteropancreatic neuroendocrine tumours (GEP-NETs), it is essential that these measures are used to test PROMs before and after any novel intervention in order to inform future practice of their impact.

Gastroenteropancreatic Neuroendocrine Tumours

GEP-NETs are a rare, heterogeneous group of neoplasms that arise from neuroendocrine tissue in the digestive tract. Whilst the overall majority of GEP-NETs are non-functional (NF), in a significant proportion the neoplasm secretes bioactive peptides congruent with the cell type of tumour origin, giving rise to a diverse array of distinct clinical syndromes. The most common of these is the carcinoid syndrome.[1] Despite their heterogeneous origins, most GEP-NETs share a number of biochemical markers, chromogranin A being the most diagnostically significant.[2] The majority occur as sporadic tumours, and some are found as part of defined familial cancer

syndromes.[3] Incidence in industrialised nations ranges from 2 to 4.4 per 100,000 per year, with marginally higher prevalence in women and persons of African-American descent.[4-6] The surveillance, epidemiology, and end results program (SEER) data suggest that GEP-NETs are generally slow-growing neoplasms with overall 5-year survival rates of 60-65%. Prognostic factors include tumour site, type, degree of differentiation, and degree of spread. Thus, well-differentiated locally invasive tumours may yield a 5-year survival of up to 82%, whilst poorly differentiated metastatic neoplasms a 5-year survival as low as 4%. The best outcomes are seen in benign insulinomas and rectal NETs with 95% and 88% 5-year survival, respectively.[4,6,7]

Disease-Specific Symptoms

i) Universal symptoms

All GEP-NETs may present with features unrelated to their source of origin, functionality, or location within the gastrointestinal (GI) tract. These include pain, nausea, diarrhoea, vomiting, iron deficiency anaemia arising from occult blood loss, bowel obstruction, obstructive jaundice, ascites, and rarely frank rectal bleeding. NF GEP-NETs may only manifest with these signs and symptoms once distant metastatic spread generates mass effects in other tissues. The commonest presenting symptoms of non-functional pancreatic NETs (NF-pNETs), which are over twice as common as functional pNETs,[8] are abdominal pain (40-60%), jaundice (30-40%), and weight loss (25-50%). Due to the absence of a distinct hormonal syndrome, NF-pNETs are often detected as an incidental finding,[9] and at diagnosis 60% of NF-pNETs will have metastasised, the liver being the commonest site.[10]

ii) Carcinoid tumours

Carcinoid tumours are neoplasms that arise from enterochromaffin cells, a class of secretory neuroendocrine cells widely distributed in the enteral epithelium. Functional carcinoid tumours are most commonly found in the jejunum and ileum,[11] secreting 5-hydroxytryptamine (serotonin, 5-HT) as well as histamine, bradykinin, and kallikrein. It is secretion of these vasoactive peptides into the systemic circulation that generates the carcinoid syndrome, classically a triad of dry flushing (flushing without sweating, occurs in 70% of patients), diarrhoea (occurs in 50% of patients), and dyspnoea (triggered by histamine-mediated bronchospasm, seen in 50% of patients).[12,13] Approximately 10% of patients with a secretory carcinoid will exhibit all three symptoms concurrently. Abdominal pain, related to mesenteric desmoplasia, necrosis of hepatic metastases, or capsular stretch is found in up to 50% of patients.

The commonest carcinoid syndrome symptom is fatigue (69% of patients), appearing more commonly than in many other cancers, and may be a specific effect of hormone secretion. Other common features are nausea (seen in 39%), loss of appetite (39%), myalgia (up to 42%), insomnia (36%), and dry skin (39%).[14] Bowel obstruction arises in up to 20% of cases at presentation.[15] Lacrimation, rhinorrhoea, and a pellagra-like syndrome resulting from depletion of niacin due to a high 5-HT turnover may also be seen in rare cases.[16] Therefore all patients experiencing psychological effects in carcinoid disease should be considered for intravenous or oral vitamin B replacement.[1,17]

Up to 20% of patients exhibit features of carcinoid heart disease (CHD) at presentation,[18] a secondary restrictive cardiomyopathy resulting from fibrosis of the tricuspid and pulmonary valves. Left-sided heart disease may be seen in up to 15% of patients with CHD. The presence of CHD has been shown to dramatically worsen outcomes, with 3-year survival as low as 31% (versus 68% in patients without CHD).[19] Initially presenting with murmurs, CHD will eventually progress to peripheral oedema, pulsatile hepatomegaly, and ascites if left untreated. A rare complication of carcinoid syndrome is the carcinoid crisis, most commonly precipitated by induction of anaesthesia or direct handling of the tumour. Caused by the sudden release of large amounts of vasoactive mediators into the systemic circulation, it is characterised by tachycardia, labile blood pressure, profound flushing, and bronchospasm.[1]

Timely diagnosis in carcinoid tumours is an ongoing problem.[20] The commonest misdiagnoses are irritable bowel syndrome (leading to a mean diagnostic delay of 68 months), food allergies or intolerance (leading to a mean diagnostic delay of 168 months), depression (mean diagnostic delay of 205 months), other psychiatric disorders (mean diagnostic delay of 86 months), and lactose intolerance (mean diagnostic delay of 180 months). A survey of 154 patients undertaken by the United Kingdom's NET Patient Foundation found that 19% had waited for more than 5 years for a diagnosis.

iii) Insulinomas

Insulinomas are rare neoplasms derived from pancreatic β-cells. Overall incidence was up to 4 per million per year in one case series,[21] making insulinomas the commonest functional pNET. Approximately 5% of cases can be attributed to multiple endocrine neoplasia Type 1 (MEN1).[22] Up to 10% of cases metastasise.[23] Insulinomas become symptomatic due to ectopic hypersecretion of insulin into the systemic circulation triggering episodes of hypoglycaemia, with symptoms classically worsening during periods of exercise, fasting, or intercurrent illness, and improving on eating. Symptoms[24-29] can be grouped into three categories:

a) Neuroglycopaenic symptoms (overall seen in 90% of patients) such as slurred speech, confusion (80%), blurred vision (59%), drowsiness or coma (38% and 47%, respectively), inattention, overeating (15-50%), and eventually a hypoglycaemic neuropathy in rare cases.
b) Adrenergic symptoms (seen in 60-70% of cases) such as anxiety, palpitations (seen in around 12%), sweating (up to 69%), xerostomia, and tremor (up to 24%).
c) Cholinergic symptoms such as hunger and paraesthesia.
The mean delay in diagnosis for insulinomas is around 4 years.[25]

iv) Gastrinomas

Gastrinomas are rare tumours of the pancreas and duodenum characterised by the hypersecretion of gastrin. Overall incidence is around 1-2 per million per year. Gastrinomas show approximately equal preponderance for the duodenum or pancreas. It is thought that up to 70% occur within a triangle defined inferiorly by the 2nd and 3rd portion of the duodenum, medially by the pancreatic neck and body, and superiorly by the confluence of the common bile and cystic ducts.[30] Up to 10% will occur elsewhere in the abdomen (stomach, spleen, omentum, liver, ovary). Up to 60% will metastasise, and up to 25% are associated with MEN1.[22,23]

Hypersecretion of gastrin triggers both parietal cell hypersecretion of hydrochloric acid into the stomach and parietal cell hyperplasia.[31] The resulting combination of severe peptic ulceration and diarrhoea is termed Zollinger-Ellison Syndrome. In 35% of cases diarrhoea is the sole feature. Commonest presenting symptoms are epigastric and abdominal pain (up to 100% of patients),[32] diarrhoea (up to 73% of patients, often with steatorrhoea due to inactivation of lipase), gastro-oesophageal reflux disease (up to 64% of cases), upper GI bleeding (up to 17% of patients), perforation (up to 5% of presenting cases), and obstruction (up to 5% of cases). On endoscopy, up to 91% of patients with a gastrinoma will show duodenal or pyloric ulcers.[33] The mean delay in diagnosis is 6.1 years.

v) Glucagonomas

Glucagonomas arise from pancreatic α-cells with an incidence of around 0.1 per million per year. 50-80% of cases metastasise, and 10% of cases are associated with MEN1.[22,23] Symptoms are triggered by ectopic hypersecretion of glucagon, leading to persistent gluconeogenesis and lipolysis. The pathogenomic feature of hyperglucagonaemia is migratory necrolytic erythaema (MNE), a cutaneous eruption seen in 70-90% of cases. MNE presents as a maculopapular rash that becomes vesicular and necrotic, eventually healing with pigmented scarring. MNE is most commonly seen on the limbs and perioral skin, and appears to be triggered at sites of skin pressure, friction, or trauma.[34,35] Other common symptoms are weight loss (seen in up to 80%), insulin resistance or frank Type 2 diabetes mellitus (40-90%), anaemia (up to 90%), hypoaminoacidaemia (up to 80%), and diarrhoea (around 25% of cases). The mean delay in diagnosis is 7 years.

vi) VIPomas

VIPomas secrete vasoactive intestinal peptide (VIP) and are amongst the rarest GEP-NETs with an incidence of 0.1 per million per year. Up to 70% will metastasise and up to 5% occur in conjunction with MEN1.[22,23] Ectopic hypersecretion of VIP leads to VIPoma, characterised by profuse watery diarrhoea and electrolyte disturbances. Diarrhoea output above 700 ml per day is seen in all patients, with up to 70% exceeding 3,000 ml per day. Hypokalaemia, often severe, and dehydration are universal. Hypercalcaemia and hyperglycaemia occur in up to 50% of cases and hypochlorhydria in up to 76%. One-third of patients may also experience intermittent flushing.[36-39]

vii) Somatostatinomas

Somatostatinomas are neoplasms of δ-cells that secrete somatostatin. Overall incidence is thought to be <1 per 10 million per year. Up to 45% are associated with MEN1, and up to 70% of tumours

will metastasise.[22,23] They are most commonly found in the pancreatic head and duodenum (ampulla and periampullar), although only 20% of duodenal tumours secrete clinically significant quantities of somatostatin (versus over 90% of pancreatic neoplasms). Duodenal somatostatinomas are sometimes associated with neurofibromatosis Type 1. Classically, hypersecretion of somatostatin results in the triad of diabetes mellitus (due to inhibition of insulin secretion), cholelithiasis (due to inhibition of cholecystokinin-mediated gall bladder emptying), and diarrhoea with steatorrhoea. Gastric hypochlorhydria, weight loss, and hypoglycaemia have also been reported.[40-42]

Quality of Life

GEP-NETs are frequently diagnosed at a late stage, when metastatic disease is already present, and maximising QoL is therefore increasingly supplanting a curative approach. Prior to 2013, the European Organisation for Research and Treatment of Cancer (EORTC) generic cancer QLQ-C30 questionnaire was the only widely used tool to assess QoL.

i) QLQ-GINET21

The GINET21 module was first conceived in 2006[43] and underwent final Phase IV psychometric validation in 2013.[44] It focuses on flushing, GI symptoms, weight, anxiety, communication with patients, and treatment side-effects. Whilst the GINET21 has been validated for all types of GEP-NET, data on the rarer functional pNETs have been difficult to generate in statistically significant quantities. Only a limited number of insulinoma patients were included in the original development of the GINET21 and there is to date no separate QoL measure available for use for these patients. As the majority of patients will be curatively treated by surgery and the number of metastatic insulinoma patients is so small, developing a questionnaire would be very challenging. A small number of patients with secretory gastrinomas were included in the early stages of the development of the GINET21, but it was felt that there were not enough to make GINET21 a valid measure for this particular patient subgroup. As they have very specific symptoms, developing a QoL measurement tool for these patients may be feasible. The functional pNETs in iv-vii above are so rare that very little is known about patients' QoL. Despite the GINET21 having been validated for their use, the specificity of the syndromes generated by pNETs as a group gives rise to the question as to whether a separate QoL questionnaire, or an amended GINET21 is required in future to fully capture the issues experienced by patients in these circumstances. To date there are no published data to support this, a reflection on the difficulty of acquiring statistically significant data quantities.

ii) Norfolk QoL NET

The Norfolk QoL NET was developed in 2009 with a focus on symptom frequency, duration, and severity, impact on activities of daily living (ADLs), and effects of treatment with somatostatin analogues.[45] A comparative study published in 2011 suggests that there is strong correlation between the final scores for both the QLQ-GINET21 and the Norfolk QoL NET. Furthermore, serum 5-HT levels and, significantly, overall tumour burden appear to correlate strongly with final QoL scores in both QLQ-GINET21 and Norfolk QoL NET.[46]

There is some evidence that overall QoL is perceived as good by patients, as suggested by a 1999 study of 119 patients (carcinoid: n=64 and pNETs: n=55) using the QLQ-C30.[47] However, a 2009 study in Norway using the SF-36 short form health survey comparing 196 NET patients with a healthy sample of 5,258 found significantly lower scores across all domains, in particular, the ability to complete ADLs and mental health.[48] Poor mental health in particular appears to be prevalent in patients with pNETs, as demonstrated by a 2009 study of 55 pNET patients using the SF-12, BDIII, GHQ-12, and state-trait anxiety inventory (STAI) questionnaires found an overall prevalence of mild to-moderate depression of 40%.[49]

Symptoms appearing to have the greatest impact on patient QoL have been identified as fatigue and diarrhoea (flushing to a lesser extent) in a study of 36 consecutive patients with carcinoid tumours in Sweden using the QLQ-C30.[14] Fatigue and diarrhoea were the reason for patients scoring poorly in their ability to complete ADLs, work, and social activities. The same study identified that the worst aspect of emotional distress was anxiety related to disease progression. Diarrhoea and flushing were identified as the most significant factors in determining QoL in an American study of 663 patients using online SF-36 and PROMIS-29 questionnaires.[50]

QoL changes during treatment are poorly understood at present, and research focus has

been overwhelmingly on medical therapies. A 2014 randomised, double-blind controlled trial (CLARINET)[51] in patients with metastatic GEP-NETs comparing lanreotide (n=101) to placebo (n=103) found no significant difference in overall QoL or overall survival (OS), although the primary endpoint of the study, progression-free survival (PFS), was significantly improved, with an estimated 24-month PFS of 65.1% in the lanreotide arm versus 33% in the placebo arm. Due to the high rate of crossover from placebo to lanreotide of over 50%, differences in OS and QoL may not be expected. Diarrhoea was the most frequently reported adverse effect, found in 26% of patients in the lanreotide arm of the trial (versus 9% in the placebo group). Similarly, a 2011 randomised, double-blind, placebo-controlled trial in patients with advanced pNETs compared sunitinib (n=86) to placebo (n=85) and demonstrated no appreciable difference in QoL as measured by the QLQ-C30 between study groups, with the exception of diarrhoea, which worsened in the sunitinib group.[52]

An earlier study[53] following 50 patients with metastatic GEP-NETs being treated with ^{177}Lu-octreotate showed significant improvements in global QoL as measured by the QLQ-C30, with particular improvements in fatigue, insomnia, and pain. Improvements in QoL were seen irrespective of tumour progression or regression. A similar trial in the palliative setting[54] with ^{131}I-metaiodobenzylguanidine (n=13) showed symptomatic improvement in 92% and 55% with ^{111}In-octreotide (n=11). A larger 2011 trial[55] of ^{177}Lu-octreotate in 256 patients with metastasised neuroendocrine tumours measuring QLQ-C30 and Karnofsky Performance Status found significant global improvements in appetite, diarrhoea (67% showed improvement), social functioning, and fatigue (improved in 49%) regardless of treatment outcome. Pain improved in 53% of patients.

DISCUSSION

QoL research in the field of GEP-NETs has been impeded by a lack of consistent measurement tools and a paucity of data relating to the individual GEP-NET subtypes. The availability of the GINET21 is anticipated to generate better quality and more relevant data.[56] Most trials and studies that have examined QoL in GEP-NETs to date have made use of general cancer QoL questionnaires such as the QLQ-C30. However, one must take into account that in those patients with disseminated or high-grade GEP-NETs, the majority of symptoms may relate to disseminated malignant disease in general rather than to a specific hormonal syndrome. In these instances a general cancer QoL questionnaire may be more applicable. There is also a strong argument to suggest a separate QoL assessment tool for NF GEP-NETs, as most development has focused on functional syndromes. The question persists as to whether separate QoL questionnaires are required for the functional pNETs in order to accurately quantify the issues faced by these patients. At present, there are no available data to settle this issue.

A novel, rapid, and comparatively resource-sparing method of data collection could be found in internet-based online questionnaires, using them to validate, update, and generate QoL questionnaires. This method is of particular interest in the study of the vanishingly rare secretory pNETs, as generating statistically significant amounts of data is exceedingly challenging. This is an issue that could be overcome by allowing patients from around the globe to contribute data, thus dramatically increasing yield. Research into the feasibility of this strategy for data collection is currently in its infancy, with the first studies due for publication in the coming months.

The availability of the GINET21 is anticipated to greatly facilitate the acquisition of QoL data as a routine aspect of clinical trials, if not as their primary outcome. Collection of patient-reported outcome data is already being integrated into routine clinical care in at least one UK centre, with patients completing a GINET21 as part of clinic visits. Adapting QoL measurement tools to routine clinical practice still faces a number of challenges. The length of the combined QLQ-C30 and GINET21 (51 questions) makes it comparatively cumbersome to administer in a clinical setting, and a shortened version, or computer-adaptive questionnaire may be a desirable tool. IT provisions will undoubtedly be key in facilitating adoption in clinical practice, with the ability to present changes in QoL to the clinician in graph form, potentially proving decisive.

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RECENT ADVANCES IN DEFINITIVE RADIOTHERAPY FOR PROSTATE CANCER

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ABSTRACT

Definitive radiation therapy is a well-recognised curative treatment option for localised prostate cancer. A suitable technique, dose, target volume, and the option of a combination with androgen deprivation therapy needs to be considered. An optimal standard external beam radiotherapy includes currently the intensity-modulated and image-guided radiotherapy techniques with total doses of ≥76-78 Gy in conventional fractionation. Data from several randomised studies increasingly support the rationale for hypofractionated radiotherapy. A simultaneous integrated boost with dose escalation focused on a computed tomography/positron emission tomography or magnetic resonance imaging/magnetic resonance spectroscopy detected malignant lesion is an option to increase tumour control with potentially no additional toxicity. The application of a spacer is a promising concept for optimal protection of the rectal wall.

Keywords: Prostate cancer, positron emission tomography, magnetic resonance imaging, external-beam radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, simultaneous integrated boost, hypofractionation, dose escalation.

INTRODUCTION

Standard curative treatment options for localised prostate cancer (PrC) are radical prostectomy (RP) or definitive radiation therapy. Equivalent biochemical recurrence rates have been frequently reported in the past.[1] Patients undergoing RP are more likely to have urinary incontinence and erectile dysfunction, while patients undergoing radiotherapy are more likely to have bowel problems.[2,3] Treatment decision is usually based on specific risk groups[4] (Table 1, including the author's suggestion for a radiotherapy treatment concept). Very low/low-risk patients and very high/high-risk patients are combined in low and high-risk groups, respectively, in most studies. A very low-risk group defines a group particularly well suited to active surveillance. The decision for a radiotherapy dose and target concept, and the decision for additional androgen deprivation therapy (ADT), are based on individual risk factors. Modern radiotherapy concepts result in favourable and improved results in comparison to older concepts,[5] even for high-risk patients, with 10-year prostate-specific survival rates of about 95% applying doses ≥75.6 Gy.[6,7]

RADIOTHERAPY TECHNIQUES

This review focuses on external beam radiotherapy (EBRT) for PrC, commonly administered as fractionated linear accelerator photon treatment. Conventional fractions are generally used, with 1.8-2.0 Gy daily fractions up to a total dose of 74-80 Gy. EBRT is based on a single treatment planning computed tomography (CT) with a specific prostate position, predominantly dependent on rectum volume (three-dimensional conformal radiotherapy [3D-RT]).[8] As a result of daily positioning uncertainties, inter and intrafraction prostate motion, safety margins need to be added around the prostate in the treatment planning process. Prostate (+/- seminal vesicles; +/- pelvic nodes) is defined as clinical target volume (CTV) with safety margins as planning target volume (PTV).

Image-guided radiotherapy (IGRT) techniques are a prerequisite for a precise prostate localisation

for every EBRT fraction and reduction of safety margins. Biochemical tumour control has been shown to be significantly lower for patients with larger rectum volumes in the treatment planning CT scans even if a posterior safety margin of 1 cm is considered without IGRT techniques.[9] Cone beam CT, ultrasound localisation with dedicated ultrasound imaging system, fiducial markers (intraprostatic gold markers, fiducial catheters) in combination with MV/kV portal imaging are used to correct patient set-up.[10,11] Higher technology fiducials include electromagnetic transponders, which transmit radiofrequency waves and require special localisation and tracking systems that track prostate motion during an EBRT fraction.[12] According to an evaluation of inter and intrafraction prostate displacements, safety margins of 9 mm/15 mm/10 mm versus 4 mm/4 mm/4 mm are required in the superior-inferior/anterior-posterior/lateral directions without versus with daily image guidance to assure treatment of PrC with an adequate precision.[13]

Intensity-modulated radiotherapy (IMRT) is an advanced 3D-RT technique, often regarded as the current standard technique for primary PrC EBRT, improving dose conformity and reducing the dose to organs at risk in comparison to conventional 3D-RT.[5] A multileaf collimator is required for IMRT. Leafs are either on constant positions (step-and-shoot IMRT) or they are moving during irradiation (dynamic IMRT). Terms such as VMAT (volumetric modulated arc therapy) or Rapid Arc are used for specific dynamic IMRT technologies with simultaneous rotation of the gantry and leafs, allowing the delivery of a treatment fraction within 1-2 minutes. Tomo Therapy®, Vero®, or CyberKnife® are specific linear accelerator technologies. A CyberKnife® (linear accelerator mounted on a robotic arm) is exclusively used for hypofractionated (high dose per fraction) or single dose (also known as radiosurgery) treatments.

Table 1: Prostate cancer recurrence risk definitions and corresponding radiotherapy concept.

Risk Group	Risk group definition	External beam radiotherapy concept	
Very low risk	Stage T1c Gleason score ≤6 PSA <10 ng/ml fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core PSA density <0.15 ng/ml/g	dose	≥72-74 Gy
		target volume	prostate +/- base of semi-nal vesicles
Low risk	Stage T1-T2a Gleason score ≤6 PSA <10 ng/ml	ADT	no indication
Intermediate risk	Stage T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml*	dose	≥76-78 Gy
		target volume	prostate + (base of) semi-nal vesicles
		ADT	+/- neoadjuvant/adjuvant ADT for 4-6 monts
High risk	Stage T3a or Gleason score 8-10 or PSA >20 ng/ml	dose	≥76-78 Gy
		target volume	prostate + (base of) semi-nal vesicles, risk adapted treatment of pelvic lmph nodes
Very high risk (locally advanced)	Stage T3b-T4	ADT	+ 2-3 years adjuvant ADT

*Patients with multiple adverse factors may be shifted into the next higher risk group.
PSA: prostate-specific antigen; ADT: androgen deprivation therapy.

DOSE ESCALATION

Several randomised EBRT dose escalation studies have been performed in the last few decades, demonstrating a biochemical and clinical recurrence free survival benefit for total doses of 74-78 Gy in comparison to doses of 64-70 Gy.[14,15] As the majority of patients were recruited in the 1990's, treatment consisted of conformal radiotherapy without IGRT. Dose escalation has been shown to significantly prevent biochemical failure in all risk groups in meta-analyses of randomised trials.[14,15] A meta-regression analysis demonstrates an advantage of 14% (82% versus 96%), 18% (71% versus 89%), and 19% (51% versus 70%) in low, intermediate, and high-risk patients, respectively, for the biochemical control after 5 years for doses of 80 Gy in comparison to 70 Gy.[14] However, high dose radiotherapy was associated with a significantly greater risk of late >Grade 2 gastrointestinal (GI) toxicity (hazard ratio 1.58 [1.24-2]; p<0.001[14] or 1.72 [1.42-2.08]; p<0.001[15]). No difference resulted in overall mortality rates (MRs) and PrC MRs. The 10-year-PrC specific MRs were 8.4% in the high dose versus 9.3% in the conventional dose arms.[15] Taking into account a usually slow progression of PrC, a longer followup will probably be required to demonstrate differences in survival rates in dose escalation trials. In an international salvage ADT trial, the time from salvage ADT to death was estimated at about 9 years, with only 17% of patients dying of PrC after 7 years.[16]

After a median follow-up period of 9 years, the MD Anderson dose escalation trial reported a significant disease-free survival benefit was reported in the group of patients with an initial prostate-specific antigen (PSA) >10 ng/ml (2% versus 15%; p=0.03) as well as in the group of high-risk patients (4% versus 16%; p=0.05).[6] As dose escalation increases biochemical tumour control, high doses of ≥76-78 Gy can be applied for all risk groups. The time to long-term salvage ADT is significantly delayed.[17] Higher toxicity rates must be weighed up against this benefit, so that modern radiotherapy techniques are particularly important in dose escalated treatment concepts. For older patients, especially low-risk patients or intermediate-risk patients with a PSA <10 ng/ml, lower doses of 70-74 Gy might be sufficient, as biochemical recurrence leads to a clinical recurrence in only a small percentage of patients. Dose escalation to ≥76-78 Gy can be generally recommended for intermediate and high-risk patients who are at greater risk of developing a metastatic disease.

TARGET VOLUME

CTV always includes the whole prostate. Focusing irradiation only on parts of the prostate is not useful as PrC is known to occur multifocally.[18] As only the proximal 2 cm are involved in >90% of patients,[19] the base of seminal vesicles should be included in the CTV in intermediate and high-risk patients. The elective irradiation of pelvic lymph nodes (PLNs) is discussed controversially. Whole pelvic radiotherapy (WPR) might improve outcomes of patients with PLN involvement by sterilising microscopic disease. An advantage in respect of biochemical recurrence-free survival in comparison to irradiation of the prostate only could be shown in a retrospective study after lymphadenectomy and histologically proven lymph node invasion in 415 patients[20] and in a large prospective randomised study with a total of 1,323 patients (radiation therapy oncology group [RTOG] 9,413, primary EBRT), particularly with neoadjuvant antiandrogen therapy.[21] PLNs were included for patients with an invasion risk of at least 15%. Smaller EBRT volumes encompassing only the true pelvis (or mini-pelvis) appear to be inadequate. Whole pelvic EBRT up to the level of the L5-S1 interspace was associated with improved progression-free survival rates in comparison to mini-pelvis EBRT or prostate only EBRT.[22] The studies that failed to show the benefit of PLN irradiation, RTOG 7,707 and GETUG-01,[23,24] did not use WPR as defined on the RTOG 9,413 study, did not consistently use antiandrogen therapy (AAT), and included relatively favourable patients. In large randomised studies demonstrating the benefit of long-term AAT for locally advanced PrC, PLNs were included in the target volume up to doses of 44-50 Gy.[25,26] Treatment concepts in these studies should be the basis for generally accepted standards.

ANDROGEN DEPRIVATION THERAPY (ADT)

EBRT with ADT has been shown to be associated with a survival benefit in comparison to ADT alone in randomised Phase III studies in patients with locally advanced PrC.[27,28] After a 10 year follow-up period, Widmark et al.[27] report an improvement of biochemical recurrence-free survival from 26% to 76%, disease-specific survival from 76% to 88%, and overall survival (OS) from 61% to 70%. Prospective

randomised studies have shown an OS advantage for EBRT with ADT in comparison to EBRT alone for patients with locally advanced or high-risk PrC. In the EORTC 22,863 study patients received a treatment with an LHRH (luteinising hormone releasing hormone) agonist for 3 years,[25] and in the RTOG 85-31 study indefinitely or until signs of progression.[26] Adjuvant AAT with bicalutamide (for a median time of 2 years) also resulted in an OS benefit in locally advanced PrC.[29] A short-term neoadjuvant ADT for 4 months was associated with a survival benefit for patients with larger local tumours (>25 cm^3) and a Gleason score 2-6 in the RTOG 86-10 study,[30] in another study for patients with a PSA >10 ng/ml and a Gleason Score ≥7.[31] High-risk patients benefit from longer ADT duration (3 and 2 years) in comparison to a shorter duration (4 and 6 months).[32,33]

RTOG 94-08 randomised patients with T1b-T2b tumours and a PSA <20 ng/ml to a short-term ADT of 4 months starting 2 months before EBRT versus EBRT alone. The largest overall and disease-specific survival benefit resulted in the group of intermediate-risk patients, with significant increase of 10-year OS from 54% to 61%. No benefit resulted for low-risk patients.[34] Thus, high-risk patients benefit from a longer ADT of at least 2-3 years. Intermediate-risk patients might benefit from short-term ADT of 3-6 months. Randomised studies must evaluate if this benefit still exists when higher doses of ≥76 Gy are used.[35] As ADT toxicity profile is well-known (hot flashes, impotence, osteoporosis, anaemia, weight gain, gynaecomastia, cardiotoxicity),[36] patients with comorbidities should be individually assessed in respect of ADT, especially long-term ADT.

HYPOFRACTIONATION CONCEPTS

Hypofractionated radiotherapy is defined by fraction doses of more than 2 Gy. Radiobiological PrC data and new advanced radiation therapy techniques with improved dose conformity are leading to an increasing number of hypofractionated treatments. Toxicity and tumour control after radiotherapy can be described by the linear-quadratic equation. An important parameter in this equation is the α/β ratio, which describes the sensitivity of normal tissues or tumours to fractionation in radiotherapy. Tumours with high α/β values are less able to repair injury between fractions than normal tissues with low α/β values, so small fractions allow recovery of normal tissues while killing tumour cells. The lower α/β ratio of PrC compared to the surrounding late-responding normal tissues (e.g. the rectal wall) lays the potential foundation for hypofractionation to improve tumour control without increasing the risk of late effects in normal tissues.[37]

Currently available Phase III studies indicate similar biochemical outcomes for the hypofractionated in comparison to conventionally fractionated treatment concepts (Table 2).[37-42] Toxicity results were also without statistically significant differences, particularly regarding long term toxicity,[37-42] though Pollack et al.[40] found worse urinary function after hypofractionated radiotherapy in the subgroup of patients with compromised urinary function before treatment.[40] Older studies, using doses below the current standard (60-64 Gy in 2 Gy fractions in the conventional arms) reported higher biochemical failure rates in the hypofractionated arms.[41,42] Several Phase I and II studies with extreme hypofractionation have been published, using fractions of 6-10 Gy up to total doses of 36-50 Gy.[43] Katz et al.[44] treated 477 patients. The majority received a total dose of 36.25 Gy in 7.25 Gy fractions. Biochemical control rates of ≥90% in low and intermediate-risk patients were reported after a median follow-up of 6 years. Phase III studies are currently recruiting. Extreme hypofractionation usually requires stereotactic techniques, including unique beam arrangements, stable immobilisation, motion control, and daily image guidance.

SIMULTANEOUS INTEGRATED BOOST TO INTRAPROSTATIC LESION

Focusing the dose escalation on the actual tumour has the potential to increase tumour control without increasing toxicity. Local PrC recurrence after primary EBRT usually originates in the location of the primary tumour, as demonstrated in studies comparing magnetic resonance imaging (MRI) before EBRT and at the time of recurrence.[45] MRI, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) with choline, acetate, or prostate-specific membrane antigen (PSMA) are suitable methods to localise intraprostatic lesions with an adequate sensitivity and specificity.[46,47] T2 weighted, diffusion-weighted, and contrast-enhanced sequences are the recommended key sequences for PrC detection and localisation in multiparametric MRI. MRS indicates the metabolism within the tissue.

Table 2: Randomised Phase III hypofractionation trials.

Reference	Patient number	Patient population	Median follow-up	Fractionation	Biochemical recurrence free survival
Lukka et al.[41]	936	Stage T1-T2 PSA <40 ng/ml	6 years	60 Gy/2 Gy	60%
				52.5 Gy/2.63 Gy	53%
Pollack et al.[40]	303	Intermediate and high risk	6 years	78 Gy/2 Gy	79%
				70.2 Gy/2.7 Gy	77%
Yeoh et al.[42]	217	Stage T1-T2	7 years	64 Gy/2 Gy	34%
				55 Gy/2.75 Gy	53%
Arcangeli et al.[38]	168	High risk	6 years	80 Gy/2 Gy	79%
				62 Gy/3.1 Gy	85%
Dearnaley et al.[39]	457	Stage T1-T3a, PSA <30 ng/ml	4 years	70 Gy/2 Gy	-
				60 Gy/3 Gy	-
				57 Gy/3 Gy	-
Hoffman et al.[37]	203	Stage T1-T3b PSA <20 ng/ml, Gleason score <10	6 years	75.6 Gy/1.8 Gy	-
				72 Gy/2.4 Gy	-

PSA: prostate-specific antigen.

High choline peaks indicate malignant areas, correlating to a higher ratio of cellular membranes per volume and a higher turnover of phospholipid membranes within the carcinoma.[46]

Molecular imaging by means of PET provides another method to study metabolic activity of tumours *in vivo*. PSMA has been used increasingly in recent years, tending to show a higher proportion of patients with suspected disease in comparison to other tracers.[47] The hybrid technology PET/CT reduces image fusion mismatches significantly. Studies comparing PET results with histological PrC specimens reported a specificity and positive predictive value between 80-90%.[48] Treatment planning studies applying ^{18}F-choline PET/CT, MRI/MRS, or angiotensin-converting enzyme PET-CT demonstrated a considerable potential for dose escalation to the macroscopic tumour with only minor changes of the dose to the organs at risk and normal tissue complication probability.[49,50] The opportunity for an improved adaptation of treatment plans for the individual patient results.

Clinical data on acute toxicity in a group of 118 PrC patients after dose escalation with a simultaneous integrated boost (SIB) technique to an MRI/MRS detected tumour (76 Gy median dose to PTV and 80 Gy median dose to gross target volume [GTV] prescribed) did not find an increase of severity or incidence of acute toxicity.[51] The additional SIB did not increase quality of life (QoL) changes in the acute phase or >1 year after radiotherapy in a QoL study.[52] Long-term results, including biochemical and clinical tumour control, have not been reported yet. Phase III studies are examining focal dose escalation up to 95.5 Gy, with doses of 76 Gy in 2 Gy fractions or 77 Gy in 2.2 Gy fractions to the whole prostate.[53]

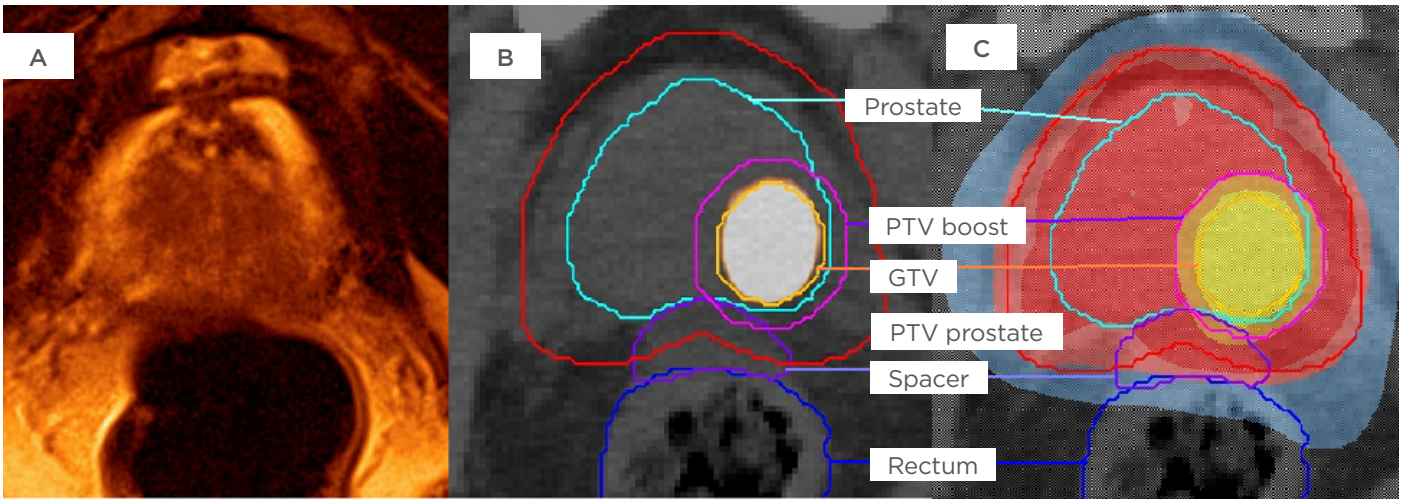

Figure 1: Simultaneous integrated boost to intraprostatic lesion with hydrogel spacer.
Tesla-2 weighted magnetic resonance imaging (A), prostate-specific membrane antigen positron emission tomography–computed tomography with spacer (B), isodose distribution with spacer and contours for treatment planning (C) in axial slices.
PTV: planning target volume; GTV: gross target volume.

SPACER APPLICATION

Rectum toxicity is the dose-limiting toxicity. Dose-volume correlations have been reported in many studies. Hyaluronic acid, human collagen, an inflatable balloon, or hydrogel are potential materials that have been used in clinical studies to create a prostate-rectum separation effectively.[54] The injection or implantation is performed under transrectal ultrasound guidance via the transperineal approach under local, spinal, or light general anaesthesia.[54] Spacer insertion is facilitated by a prior hydrodissection, helping to place the spacer between Denonvilliers' fascia and anterior rectal wall, using the same 18-gauge spinal needle. The implantation of a biodegradable balloon implies an incision of 3-5 mm and 1.5 cm depth.[55] A distance of about 1 cm results after spacer injection or placement, leading to significantly lower rectal doses. Injections of up to 20 ml of spacer volume usually created a space of 1-1.5 cm between the prostate and rectal wall.[56,57] Studies have shown stable spacer volumes during the radiotherapy period.[55,58]

Well-tolerated injection or implantation techniques and low rectal treatment-related toxicity have been demonstrated in prospective studies.[59,60] GI toxicity was evaluated in a group of 48 patients in a multi-institutional study. Only 12% of patients experienced Grade 2 acute GI toxicity (no patients with Grade 3 or higher toxicity) and 7% (two patients, one of them with Grade 1 at baseline already) experienced Grade 1 late GI toxicity within 12 months after treatment (no patients with Grade 2 or higher toxicity).[60] Long-term clinical results and the results of randomised studies are needed to better define the beneficial effect for the patient. Nevertheless, randomised trials are needed to define the benefit on the best level of evidence. The first randomised trial, evaluating the hydrogel spacer injection, has already closed patient accrual. An example for hypofractionated dose escalation to a simultaneous integrated boost with a hydrogel spacer is demonstrated in Figure 1. PrC was diagnosed in the left peripheral lobe in MRI and PSMA PET. A plan was calculated with a total dose of 78 Gy to the prostate in 2 Gy fractions, simultaneously 93.6 Gy in 2.4 Gy fractions to the intraprostatic lesion (GTV). Only 0.5% of the rectum volume was included within the 70 Gy isodose, so that extremely high doses can be delivered even to peripheral lesions without the risk of relevant rectal toxicity.

CONCLUSION

Radiobiological PrC data, technical advances in imaging techniques, treatment planning, and treatment delivery changed external beam radiotherapy standard concepts and led to new concepts that need to be evaluated in the near

future. The current standard implicates the delivery of a high conformal dose to the prostate with small safety margins, resulting from the application of daily image guidance. Hypofractionated radiotherapy is used increasingly, as data of prospective randomised trials are available with follow-up periods of several years. Extreme hypofractionation, definition of a simultaneous integrated boost with a focused dose escalation, and the application of a spacer to protect the rectal wall are promising concepts that need to be evaluated in randomised Phase III trials. They might develop to new standards, making radiotherapy a convenient treatment with low toxicity and high tumour control rates.

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DEVELOPMENT OF DRUGS TARGETING THE PI3K SIGNALLING PATHWAY IN LEUKAEMIAS AND LYMPHOMAS

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ABSTRACT

The phosphoinositide 3-kinase (PI3K) family of signalling enzymes play a key role in the transduction of signals from activated cell surface receptors controlling cell growth and proliferation, survival, metabolism, and migration. The intracellular signalling pathway from activated receptors to PI3K and its downstream targets v-akt murine thymoma viral oncogene homolog (Akt) and mechanistic target of rapamycin (mTOR) is very frequently deregulated by genetic and epigenetic mechanisms in human cancer, including leukaemia and lymphoma. In the past decade, an arsenal of small molecule inhibitors of key enzymes in this pathway has been developed and evaluated in pre-clinical studies and clinical trials in cancer patients. These include pharmacological inhibitors of Akt, mTOR, and PI3K, some of which are approved for the treatment of leukaemia and lymphoma. The PI3K family comprises eight different catalytic isoforms in humans, which have been subdivided into three classes. Class I PI3K isoforms have been extensively studied in the context of human cancer, and the isoforms p110α and p110δ are validated drug targets. The recent approval of a p110δ-specific PI3K inhibitor (idelalisib/Zydelig®) for the treatment of selected B cell malignancies represents the first success in developing these molecules into anti-cancer drugs. In addition to PI3K inhibitors, mTOR inhibitors are intensively studied in leukaemia and lymphoma, and temsirolimus (Torisel®) is approved for the treatment of a type of lymphoma. Based on these promising results it is hoped that additional novel PI3K pathway inhibitors will in the near future be further developed into new drugs for leukaemia and lymphoma.

Keywords: Akt, B cell receptor, leukaemia, lymphoma, mTOR, phosphoinositide 3-kinase, PTEN.

INTRODUCTION

Leukaemia and Lymphoma

Leukaemia represents 3% of new cancer cases in males and females, while lymphoma represents 5% and 4% of new cases in males and females, respectively.[1] In terms of deaths, leukaemia accounts for 4% and 3% of total cancer deaths in males and females, respectively, while lymphoma accounts for 3% in both sexes.[1] Leukaemia is subdivided into acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), and chronic myeloid leukaemia (CML), for which different therapies are used and outcomes vary.[2] Two main categories of lymphoma are Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), the latter making up around 90% of cases.[3] However, lymphomas are currently classified depending on cell type, of which several types exist.[4,5] The 2008 World Health Organization classification categorises the tumours of the haematopoietic and lymphoid tissues into: (i) mature B cell neoplasms; (ii) mature T cell and natural killer cell neoplasms; (iii) HL; (iv) histiocytic and dendritic cell neoplasms; and (v) post-transplant lymphoproliferative disorders.[4,5] The management of haematological malignancies such as leukaemia and lymphoma has greatly benefited from the development of targeted anti-cancer therapies in the past decade.[6,7] Successful

examples of targeted therapies include anti-CD20 monoclonal antibodies (rituximab) in ALL and B cell lymphoma.[7] Small molecule inhibitors (imatinib, Glivec®/Gleevec®) of the BCR-ABL kinase (breakpoint cluster region-Abelson murine leukaemia viral oncogene homolog) have been successfully applied to the treatment of CML. The hyper-activation of the phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene homolog/mechanistic target of rapamycin (PI3K/Akt/mTOR) pathway has been linked to increased cell growth and proliferation, survival, and chemoresistance in leukaemia and lymphoma, and thus also represents an attractive target for the development of anti-cancer drugs in these malignancies.[8-12]

The PI3K Signalling Pathway

PI3Ks are a family of lipid kinases that catalyse the phosphorylation of plasma membrane phosphoinositides on the D-3 position of the inositol ring, resulting in the production of three distinct second messengers: phosphatidylinositol 3-monophosphate (PI(3)P), phosphatidylinositol 3,4-bisphosphate (PI(3,4)P_2), and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P_3/PIP_3).[13] PIP_3 is the key second messenger in the activation of the PI3K downstream targets Akt and mTOR. In short, PIP_3 binding to the pleckstrin homology domains of Akt and phosphoinositide-dependent protein kinase-1 (PDK1) results in full activation of Akt, through phosphorylation at Thr308 by PDK1 and at Ser473 by the mechanistic target of rapamycin complex 2 (mTORC2) (Figure 1).[8,9,12] Active Akt then phosphorylates an array of proteins that control cell survival, growth, and cell cycle progression.[8,9,12] These include glycogen synthase kinase-3, forkhead box, subgroup O transcription factors, apoptosis-modulating proteins of the Bcl-2 family, and the murine double minute-2 E3 ubiquitin protein ligase (Figure 1).[8,9,12] Akt-mediated phosphorylation of the tuberous sclerosis-2 (TSC2) protein impairs the GTPase-activating activity of the TSC1/TSC2 complex towards the rat sarcoma (Ras) homologue enriched in the brain (Rheb). Rheb activates the mechanistic target of rapamycin complex 1 (mTORC1), which in turn controls cell growth via the ribosomal protein S6 kinase and eukaryotic translation initiation factor 4E binding protein (Figure 1).[8,9,12] Based on primary sequence homology, regulation, and *in vitro* substrate specificity, PI3Ks are subdivided into three classes (I-III).[12,14] Class I PI3Ks are further subdivided into Class I_A and I_B, based on the type of cell surface receptor that activates PI3Ks: Class I_A PI3Ks (comprising the catalytic isoforms p110α, p110β, and p110δ) are activated by receptor tyrosine kinases (*RTKs*), while the Class I_B PI3Ks (comprising the catalytic isoform p110γ) are activated by G protein-coupled receptors. Class I PI3Ks can also be activated by direct binding of Ras to the p110 catalytic isoforms.[8,9,12]

Deregulation of PI3K/Akt/mTOR Signalling in Cancer

Constitutive activation of the PI3K/Akt/mTOR pathway has been reported in many different human cancers and has been linked to different types of molecular alterations.[15] Somatic mutations can target the genes encoding catalytic PI3K isoforms (mostly *PIK3CA*-encoding p110α) or regulatory isoforms (mostly *PIK3R1*-encoding p85α). *PIK3CA* mutations are clustered in two 'hot spots' located in the helical (exon 9) and kinase (exon 20) domains and are associated with increased kinase activity and oncogenic potential.[16,17] Intriguingly, somatic mutations that activate catalytic Class I PI3K isoforms are mostly restricted to *PIK3CA*, and the genes encoding the other Class I catalytic isoforms, such as *PIK3CB*, *PIK3CD*, and *PIK3CG* have not been found to be targeted by the same 'hot spot' mutations in cancer.[16] However, it should be noted that p110β, p110δ, and p110γ have the ability to induce oncogenic transformation as wild-type proteins.[18] Somatic mutations found in cancer can also target the genes encoding Akt isoforms and mTOR. Another type of genetic alteration targeting components and regulators of the PI3K/Akt/mTOR pathway are mutations in the phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*).[15] PTEN is a phosphatase that de-phosphorylates PIP_3 to produce phosphatidylinositol 4,5-bisphosphate (PI(4,5)P_2), thus antagonising PI3K activity. *PTEN* regulation is complex and involves a variety of transcriptional and post-transcriptional events that can impact on its expression and activity.[19] In addition, the PI3K/Akt/mTOR pathway can be activated in cancer by mutations in *RTK* or *RAS* genes, *RTK* hyperactivation driven by receptor over-expression/amplification, or the establishment of autocrine loops involving RTKs and their cognate ligand.

PI3K/Akt/mTOR Signalling in Leukaemia and Lymphoma

Similarly to the situation in other cancers, deregulated activation of the PI3K/Akt/mTOR pathway has been reported in leukaemia and lymphoma.[9,11,12,20] In general, *PIK3CA* mutations are not believed to be the major cause of PI3K/Akt/mTOR pathway activation in leukaemia and lymphoma.[21] In contrast, *PTEN* inactivation has been reported in AML and NHL.[22,23] In addition, mutations and hyperactivation of tyrosine kinases (BCR-ABL), Feline McDonough Sarcoma-like tyrosine kinase 3, mast/stem cell growth factor receptor, platelet-derived growth factor receptor-β, or Ras (NRAS and KRAS), as well as increased expression/activity of components of the pathway can be the underlying factors.[8,9,24,25]

PI3K/Akt/mTOR Pathway Inhibitors as Anti-Cancer Drugs

Over 20 years after the discovery of the first pharmacological inhibitors of PI3K and mTOR, a wide array of small molecules has been developed by the pharmaceutical industry.[13,14,26,27] These can be broadly subdivided into different classes: pan-PI3K inhibitors (BKM-120), isoform-specific PI3K inhibitors (idelalisib, IPI-145), PI3K/mTOR inhibitors (BEZ-235, VS-5584), Akt inhibitors (MK-2206, perifosine), allosteric mTOR inhibitors (rapamycin analogs, rapalogs: sirolimus, everolimus, temsirolimus, ridaforolimus), and mTOR kinase inhibitors (OSI-027, CC-223) (Figure 1 and Figure 2). Generally, single agent PI3K/Akt/mTOR pathway inhibitor treatment has been reported to produce only incomplete responses in different cancers[27] and the genetic background of the tumours, in particular the *PIK3CA* mutational status, is believed to play a major role in the response to these agents.[28] However, combining these agents with standard chemotherapy or other targeted agents may represent a more promising approach to successful use of these agents in human cancer patients.[27]

PI3K/Akt/mTOR Pathway Inhibitors in Leukaemia and Lymphoma

In contrast to the situation in other cancers, B cell malignancies appear to be uniquely responsive to PI3K inhibitors, in particular to isoform-specific PI3K inhibitors targeting the Class I_A isoform p110δ.[14,27,29-31] This PI3K isoform is hallmarked by its tissue specificity, since it is mostly expressed in leukocytes and plays a crucial role in intracellular signalling by the B and T cell receptors.[32-34] Although it is not targeted by somatic mutations in cancer, its expression and activity was reported to be increased in leukaemia and linked to cell proliferation and chemoresistance.[14,35-37] Accordingly, small molecule inhibitors of p110δ (Figure 1 and Figure 2), in particular CAL-101 (idelalisib, Zydelig®) were shown to be active in several pre-clinical models of leukaemia and lymphoma.[14,36,38-41] The pre-clinical data for CAL-101 in leukaemia and lymphoma and the early phase clinical studies have been recently reviewed.[14,41] Pre-clinical studies of CAL-101 in CLL showed that the p110δ inhibitor induced apoptosis in primary cells *ex vivo*.[40] CAL-101 was also reported to induce apoptosis in lymphoma cell lines and primary cells.[38] The subsequent clinical trials with idelalisib led to its approval by the FDA in July 2014 for relapsed CLL (in combination with rituximab), for relapsed follicular B cell NHL, and for relapsed small lymphocytic leukaemia.[29,30,42] In a Phase I trial in relapsed/refractory CLL, idelalisib showed a favourable safety profile, while inducing an overall response rate (ORR) of 72%.[43] The Phase III study of idelalisib and rituximab in CLL patients demonstrated improved rates of overall response and overall survival at 12 months, compared to rituximab and placebo.[29] In a Phase I study in relapsed indolent NHL, idelalisib was reported to have a favourable safety profile and achieved an ORR of 47%.[44] Another Phase I study in relapsed/refractory mantle cell lymphoma also reported a favourable safety profile and an ORR of 40% for idelalisib.[45] The Phase II study of idelalisib in patients with NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinaemia), showed a response rate of 57%, with 6% of patients having complete responses.[30] Idelalisib also showed an acceptable safety profile in NHL patients in this study.[30] Idelalisib is currently undergoing further clinical testing in additional indications, as single agent or in combination with other drugs (Table 1).

In addition to CAL-101, other PI3K inhibitors are currently under study in leukaemia and lymphoma. IPI-145, a dual specificity p110δ and p110γ inhibitor, was shown to be active in pre-clinical studies in CLL.[46] This compound is currently being evaluated in clinical trials in lymphoma (Phase III in combination with rituximab) and CLL (Phase III in combination with the anti-CD20 monoclonal

antibody ofatumumab) (Table 1). BKM-120 is a pan-class I PI3K inhibitor which is currently undergoing clinical testing in different cancers. This inhibitor was reported to be active in pre-clinical studies in B cell lymphoma and CLL.[47-49] BKM-120 is currently undergoing Phase I and Phase II clinical testing in leukaemia and lymphoma (Table 1).

Another approach to target the PI3K/Akt/mTOR pathway in haematological cancers is to use dual specificity PI3K/mTOR inhibitors, such as BEZ-235 and VS-5584 (Figure 1 and Figure 2). BEZ-235 was reported to have pre-clinical activity in AML and lymphoma.[50-52] BEZ235 and VS-5584 are currently undergoing Phase I clinical testing in leukaemia (Table 1). The rapamycin analogs ('rapalogs') are allosteric inhibitors of mTOR and only inhibit mTORC1, while mTORC2 is resistant to these compounds. Rapalogs represent the class of inhibitors of the PI3K/Akt/mTOR pathway which are the subject of the greatest number of clinical trials at present (Table 1). The clinical studies underway in leukaemia and lymphoma are investigating rapalogs (sirolimus, everolimus, temsirolimus, ridaforolimus) as single agents, or in combination with standard chemotherapeutic agents, or other targeted agents (Table 1).

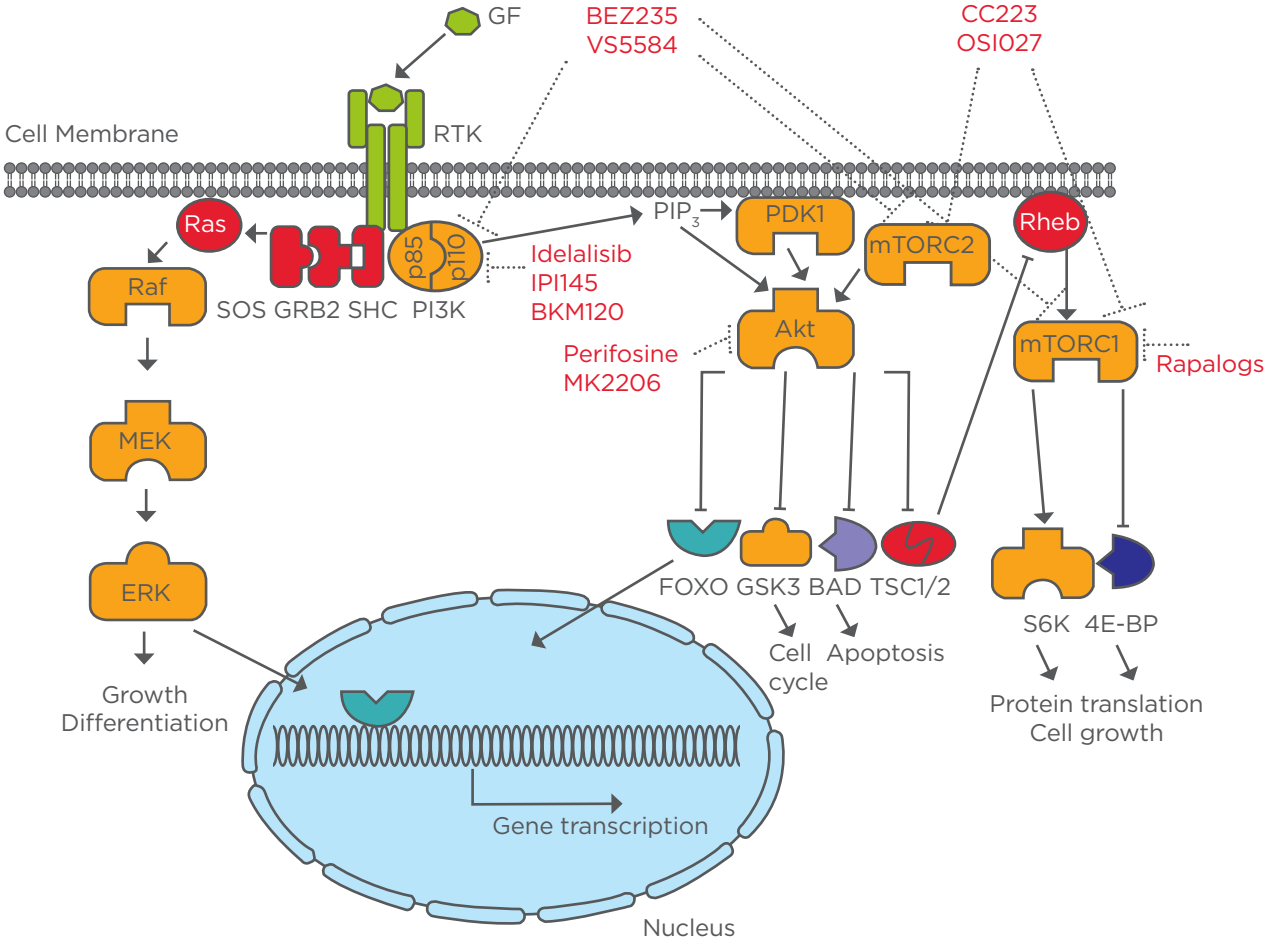

Figure 1: Schematic representation of the PI3K pathway, its regulation by growth factor (GF) binding to receptor tyrosine kinases (RTKs) and the main downstream mediators activated.

The main classes of targeted drugs (Akt inhibitors, PI3K inhibitors, PI3K/mTOR inhibitors, mTOR kinase inhibitors, and allosteric mTOR inhibitors/rapalogs) are also depicted.

PI3K: phosphoinositide 3-kinase; mTOR: mechanistic target of rapamycin; Akt: murine thymoma viral oncogene homolog; mTORC1: rapamycin complex 1; mTORC2: rapamycin complex 2; Rheb: Ras homologue enriched in the brain; 4E-BP: 4E binding protein; S6K: S6 kinase; SOS: son of sevenless; GRB2: growth factor receptor-bound protein 2; SHC: SH2-containing proteins; ERK: extracellular-signal-regulated kinase; Ras: rat sarcoma; MEK: mitogen-activated protein kinase; FOXO: forkhead box subgroup O; GSK3: glycogen synthase kinase 3; BAD: Bcl-2-associated death promoter; TSC1/2: tuberous sclerosis complex Type 1/2; PDK1: phosphoinositide-dependent kinase-1.

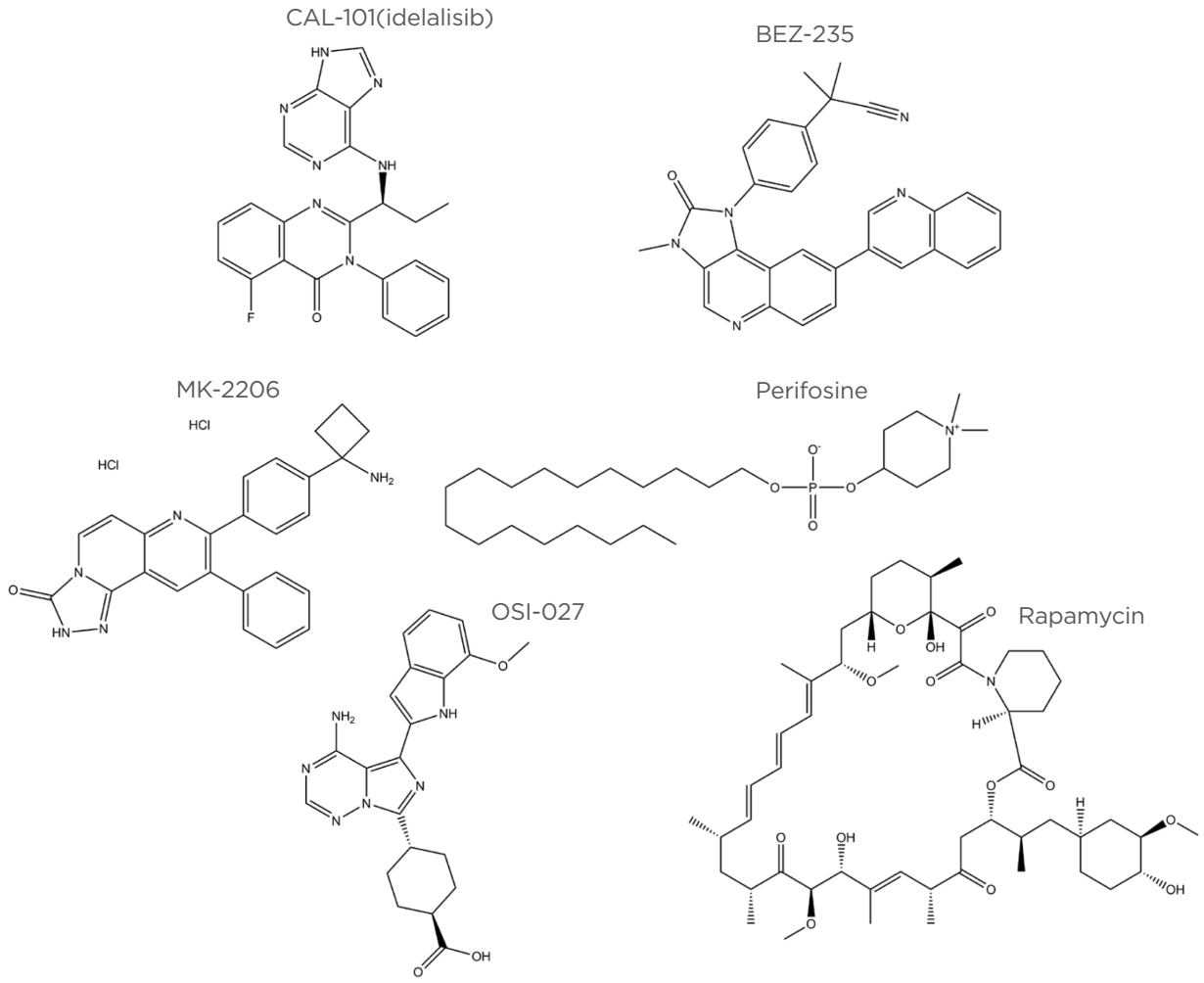

Figure 2: Chemical structures of selected PI3K/Akt/mTOR pathway inhibitors.
The p110δ inhibitor CAL-101 (idelalisib), the PI3K/mTOR inhibitor BEZ-235, the Akt inhibitors MK-2206 and perifosine, as well as the mTOR inhibitors OSI-027 and rapamycin are presented.
PI3K: phosphoinositide 3-kinase; Akt: v-akt murine thymoma viral oncogene homolog; mTOR: mechanistic target of rapamycin.

Temsirolimus (Torisel®) is approved for the treatment of relapsed and/or refractory mantle cell lymphoma (MCL) in the European Union and several other countries outside the USA. In a Phase III trial, temsirolimus significantly improved progression-free survival and objective response rate compared with other therapeutic regimens in patients with relapsed or refractory MCL.[53] In a Phase II trial in relapsed or refractory MCL, the combination of temsirolimus and rituximab produced an ORR of 59%.[54] Everolimus was also found to be active in relapsed or refractory MCL in a Phase II clinical trial.[55]

In addition to rapalogs, mTOR can be targeted by kinase inhibitors that have the advantage of inhibiting both mTORC1 and mTORC2. The mTOR kinase inhibitor OSI-027 was reported to be active in pre-clinical studies in BCR-ABL-expressing CML cells, AML, ALL, and lymphoma.[56-58] OSI-027 and CC223 are currently undergoing Phase I clinical testing in lymphoma, together with other solid tumours (Table 1). The Akt inhibitor MK-2206 was evaluated in a Phase II clinical trial in AML, but had only limited activity as a single agent, although it displayed anti-leukemic activity in a pre-clinical setting.[59] Further clinical trials are ongoing with this agent in lymphoma and leukaemia (Table 1). Perifosine is another Akt inhibitor that has been evaluated in pre-clinical and clinical studies in leukaemia and lymphoma.[60-62] A Phase II study in CLL found limited responses, but these did not correlate with impaired Akt phosphorylation, suggesting Akt-independent effects of perifosine.[63] Feedback and feedforward loops are known to occur between PI3K, mTORC1, mTORC2, and Akt.

Table 1: Overview of current clinical trials with selected PI3K/Akt/mTOR pathway inhibitors in leukaemia and lymphoma (data from http://clinicaltrials.gov/).

ID ClinicalTrials.gov	Phase	Drug(s)	Target(s)	Disease
NCT01756118	I	BEZ-235 single agent	PI3K + mTOR	acute leukaemia
NCT01991938	I	VS-5584 single agent	PI3K + mTOR	lymphoma
NCT01396499	I	BKM-120 single agent	Class I PI3K	leukaemia
NCT02049541	I	BKM-120 + rituximab	Class I PI3K	B cell lymphoma
NCT01719250	pilot study	BKM-120 single agent	Class I PI3K	NHL
NCT01693614	II	BKM-120 single agent	Class I PI3K	lymphoma
NCT01476657	I	IPI-145 single agent	p110δ + p110γ	HM
NCT01871675	I	IPI-145 + bendamustine/rituximab	p110δ + p110γ	lymphoma, CLL
NCT02158091	Ib/II	IPI-145 + fludarabine/cyclophosphamide/rituximab	p110δ + p110γ	CLL
NCT01882803	II	IPI-145 single agent	p110δ + p110γ	NHL
NCT02049515	III	IPI-145 + ofatumumab	p110δ + p110γ	CLL, SLL
NCT02004522	III	IPI-145 + ofatumumab	p110δ + p110γ	CLL, SLL
NCT02204982	III	IPI-145 + rituximab	p110δ + p110γ	lymphoma
NCT01088048	I	idelalisib + chemotherapy/immunomodulatory/anti-CD20	p110δ	lymphoma, CLL
NCT01090414	I	idelalisib single agent	p110δ	CLL, NHL
NCT01644799	I	idelalisib + lenalidomide	p110δ	follicular lymphoma
NCT01306643	I/II	idelalisib single agent	p110δ	NHL
NCT01838434	I/II	idelalisib + lenalidomide	p110δ	lymphoma (MCL)
NCT01393106	II	idelalisib single agent	p110δ	HL
NCT01203930	II	idelalisib + rituximab	p110δ	CLL, SLL
NCT01796470	II	idelalisib + GS-9973	p110δ	lymphoma, CLL
NCT02135133	II	idelalisib + ofatumumab	p110δ	CLL, SLL
NCT02044822	II	idelalisib + rituximab	p110δ	CLL (17p del)
NCT01569295	III	idelalisib + bendamustine/rituximab	p110δ	CLL
NCT01539291	III	idelalisib single agent	p110δ	CLL
NCT01732926	III	idelalisib + bendamustine/rituximab	p110δ	NHL
NCT01732913	III	idelalisib + rituximab	p110δ	NHL
NCT01659021	III	idelalisib + ofatumumab	p110δ	CLL
NCT01980888	III	idelalisib + bendamustine/rituximab	p110δ	CLL
NCT01658007	pilot study	sirolimus + multiagent chemotherapy	mTOR	leukaemia, lymphoma
NCT00874562		rapamycin + corticosteroid	mTOR	ALL
NCT01154439	I	everolimus + multiagent chemotherapy	mTOR	leukaemia
NCT01403415	I	temsirolimus + dexamethasone/ mitoxantrone/vinc/pegaspargase	mTOR	leukaemia/lymphoma
NCT01523977	I	everolimus + chemotherapy	mTOR	paediatric ALL
NCT00671112	I	everolimus + bortezomib	mTOR	lymphoma
NCT02240719	I	everolimus + bendamustine	mTOR	leukaemia, lymphoma
NCT00819546	I	everolimus + PKC412	mTOR	AML, MDS
NCT01902160	I	temsirolimus + brentuximab vedotin	mTOR	HL
NCT01535989	I	temsirolimus + inotuzumab ozogamicin	mTOR	B cell lymphoma
NCT01169532	I	ridaforolimus + vorinostat	mTOR	lymphoma

Table 1 continued.

ID ClinicalTrials.gov	Phase	Drug(s)	Target(s)	Disease
NCT00968253	I,II	everolimus + chemotherapy	mTOR	ALL
NCT00935792	I,II	everolimus + alemtuzumab	mTOR	lymphocytic leukaemia
NCT00918333	I,II	everolimus + panobinostat	mTOR	leukaemia, lymphoma
NCT02109744	I,II	rapamycin + decitabine	mTOR	AML
NCT01075321	I,II	everolimus + lenalidomide	mTOR	lymphoma
NCT01076543	I,II	temsirolimus + lenalidomide	mTOR	lymphoma
NCT01381692	I,II	temsirolimus + bortezomib/rituximab/ dexamethasone	mTOR	lymphoma
NCT01389427	I,II	temsirolimus + rituximab/chemotherapy	mTOR	MCL
NCT01198665	I,II	everolimus + chemotherapy	mTOR	lymphoma
NCT01567475	I,II	everolimus + rituximab	mTOR	NHL
NCT01078142	I,II	temsirolimus + rituximab, bendamustine	mTOR	lymphoma
NCT00474929	I,II	everolimus + sorafenib	mTOR	lymphoma
NCT01453504	I,II	everolimus + DHAP	mTOR	HL
NCT01854606	Ib/II	everolimus + AEB071	mTOR	B cell lymphoma
NCT00634244	II	sirolimus + combination chemotherapy	mTOR	AML
NCT01611116	II	temsirolimus + standard therapy	mTOR	AML
NCT01869114	II	sirolimus + azacitidine	mTOR	AML, MDS
NCT00838955	II	temsirolimus single agent	mTOR	HL
NCT01022996	II	everolimus single agent	mTOR	HL
NCT01843998	II	sirolimus single agent	mTOR	cut T cell lymphoma
NCT01665768	II	everolimus + rituximab	mTOR	lymphoma
NCT01653067	II	temsirolimus + rituximab, DHAP	mTOR	B cell lymphoma
NCT00942747	II	temsirolimus single agent	mTOR	lymphoma (CNS)
NCT01637090	II	everolimus single agent	mTOR	cut T cell lymphoma
NCT01281917	II	temsirolimus + velcade	mTOR	NHL
NCT00978432	II	everolimus + LBH589	mTOR	B cell lymphoma
NCT00790036	III	everolimus single agent	mTOR	B cell lymphoma
NCT01646021	III	temsirolimus (versus ibrutinib) single agent	mTOR	MCL
NCT00700258	IV	temsirolimus + sunitinib	mTOR	MCL
NCT01180049	IV	temsirolimus single agent	mTOR	NHL
NCT00698243	I	OSI-027 single agent	mTOR	lymphoma (+ other)
NCT01177397	I,II	CC-223 single agent	mTOR	B cell lymphoma
NCT01369849	I/II	MK-2206 + bendamustine/rituximab	Akt	CLL, SLL
NCT01258998	II	MK-2206 single agent	Akt	lymphoma
NCT01253447	II	MK-2206 single agent	Akt	AML
NCT01481129	II	MK-2206 single agent	Akt	B cell lymphoma

mTOR: mechanistic target of rapamycin; PI3K: phosphoinositide 3-kinase; NHL: non-Hodgkin's lymphoma; CLL: chronic lymphocytic leukaemia; MCL: mantle cell lymphoma; ALL: acute lymphocytic leukaemia; HL: Hodgkin's lymphoma; Akt: v-akt murine thymoma viral oncogene homolog; SLL: small lymphocytic leukaemia; MDS: myelodysplastic syndrome; HM: haematological malignancy; CNS: central nervous system; AML: acute myeloid leukaemia.

These loops explain that synergy between selected kinase inhibitors (such as JAK2 inhibitors) and PI3K inhibitors, especially pan-class I PI3K inhibitors, has been reported in myeloid malignancies, including myeloproliferative neoplasms.[64,65] These combinations may be further studied in other haematological malignancies, where these regulatory loops are relevant.

CONCLUSION AND OUTLOOK

The approval of the first PI3K inhibitor for CLL and B cell NHL in 2014 strongly supports the further development of PI3K pathway inhibitors in leukaemia and lymphoma. The most advanced drugs are p110δ PI3K inhibitors (idelalisib) and rapalogs (temsirolimus). Multiple clinical trials are underway with these agents in haematological malignancies and it is likely that further drugs will be approved in different indications in the near future. There are different possible ways to optimise the use of these agents in the future, including the development of predictive biomarkers for patient selection, the design of additional combinatorial approaches involving PI3K inhibitors and other drugs (targeted agents or standard chemotherapy), and the elucidation of potential mechanisms of resistance.

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ALLOIMMUNE THROMBOCYTOPAENIC DISORDERS: A REVIEW

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ABSTRACT

Alloimmune thrombocytopaenia (AIT) is caused by alloantibodies against specific platelet glycoproteins. Alloimmune thrombocytopaenic disorders include alloimmune neonatal thrombocytopaenia, post-transfusion purpura, refractoriness to platelet transfusions, passive AIT, and transplantation-associated AIT. In this review we have summarised five thrombocytopaenic syndromes caused by platelet-reactive alloantibodies. Increased awareness of these syndromes, together with the greater availability of highly specialised laboratory methods to detect and to characterise platelet-reactive alloantibodies, will lead to their more frequent diagnosis.

Keywords: Thrombocytopaenia, alloimmune, alloantigens.

INTRODUCTION

Thrombocytopaenia defined as a platelet count below 150,000/mm^3 is a common cause of abnormal bleeding. A low platelet count can result from decreased production or increased destruction of platelets. Decreased platelet production can result from suppression or failure of the bone marrow. Thrombocytopaenia is also caused by shortened platelet survival and this is much more common than thrombocytopaenia caused by inadequate production. Platelet destruction is most commonly immune-mediated. Platelets perform innate and adaptive immunity functions through ligand receptor interactions involving the many glycoproteins expressed on their surface membranes. It is known that 33 human platelet alloantigens (HPAs) are expressed on six different platelet glycoproteins: GPIIb, GPIIIa, GPIa, GPIb, GPIa, and CD109. Twelve antigens are clustered into six biallelic groups (HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, HPA-16). These are numbered in order of their discovery. This review specifically discusses the diagnosis and management of benign alloimmune disorders of platelets.

HUMAN PLATELET ALLOANTIGENS (HPAs)

Antibody formation against alloantigens[1] of the human platelet membrane is responsible for clinical syndromes and transfusion-related conditions such as neonatal alloimmune thrombocytopaenia (NAIT), post-transfusion purpura (PTP), platelet transfusion refractoriness, and passive alloimmune thrombocytopaenia (PAIT).

PLATELET-SPECIFIC ALLOANTIGENS

Platelet-specific alloantigens (PSAs[2,3]) are antigens which are unique to the platelet membrane. These antigens cause the two well-characterised thrombocytopaenic disorders PTP and NAIT. Although not yet established as a frequent cause of refractoriness to platelet transfusions in multi-transfused thrombocytopaenic patients, the platelet-specific antigens may potentially be an important factor in refractoriness. The study of the immunochemistry of the platelet-specific antigens has been important because of their locations on functionally important platelet surface glycoproteins. They play an important role in

platelet function: they serve as receptors for the physiological stimulators thrombin, adenosine diphosphate, and collagen. Furthermore, the receptors for von Willebrand factor and fibrinogen are glycoproteins. Associated with these glycoproteins are the platelet-specific antigens (Table 1).

HPAs[4] are located in receptors in the platelet membrane and are frequently involved in alloimmunisation. The Class I human leukocyte antigens (HLAs) HPA-1, -2, -3, -4, -5, and -15 are present in the GPIIIa, GPIba, GPIIb, GPIIIa, GPIa, and CD109 glycoproteins, respectively. According to Ghevaert et al.[5] 95% of the antiplatelet antibodies are specific for HPA-1a or 5b; 5% of the cases involve allele antibodies for HPA-2, -3, and -15. To date 33 HPAs have been described and their molecular basis has been defined. 24 PSAs have been defined by immune sera, of which 12 have been grouped into 6 biallelic systems (HPA- 1, -2, -3, -4, -5, and -16). DNA-typing methods[6] based on polymerase chain reaction (PCR) restriction fragment length polymorphism or the use of allele-specific oligonucleotide hybridisation and single specific primer PCR enables rapid typing for HPA systems, which makes these techniques feasible in most clinical settings where urgent HPA typing is required.

NAIT

NAIT refers to a disorder[7] in which foetal platelets contain an antigen that the mother lacks, and is inherited from the father. These antibodies cross the placenta and bind to the foetal platelets. Clearance of the antibody coated platelets results in foetal/neonatal thrombocytopaenia, a condition that is responsible for severe life-threatening bleeding of the newborn.[8,9] Early diagnosis or suspicion of NAIT is essential for effective therapy even if the identity of the offending platelet antibody is unknown. The passively transmitted maternal antibodies can affect either a foetus or neonate, and failure to recognise this condition results in low platelet counts that can cause intracranial haemorrhage of an otherwise healthy infant either *in utero* or at birth. Major platelet antigens are fully expressed as early as the 19th week of gestation.[10] The severity of clinical symptoms of the disorder can vary from no observable indication of disease (whereby the thrombocytopaenia is discovered incidentally) to severe intracranial bleeding. Intracranial haemorrhage in NAIT has been estimated to cause neurologic impairment in 20% of affected infants and death in 10%.[11] HPA-1a is the most common platelet antigen implicated in NAIT, causing ~78% of proven cases. The other specific platelet antibodies implicated are anti-HPA-5b (~19%), and anti-HPA-2, -3, and -4 (~3%). Less common platelet antigens have also been reported to cause infrequent cases of NAIT.[12]

Although platelet-specific antigens and antibodies are known to cause NAIT, it is important to differentiate between HPA and HLA antigen-antibody reactions. HLA Class II determinants may be associated with HPA-1a alloimmunisation. Because many HPA-1a-negative women who have become sensitised to the HPA-1a antigen have HLA-B8, HLA-DR3, and DR52a antigens, it is speculated that these markers may increase the risk of alloimmunisation.[12] Routine typing to determine an HLA phenotype is not feasible because immunisation may not occur even if the markers are present, or severe alloimmunisation may occur when they are absent.[10]

Table 1: Alloimmune thrombocytopaenic syndromes (ATSs) caused by platelet-specific alloantibodies.

Classic ATSs	Platelet antigen system	Protein antigen	Antigen frequency
Neonatal alloimmune thrombocytopaenia	HPA-1a	GPIIIa	>80%
Post-transfusion purpura	HPA-4	GPIIa	>99%
Passive alloimmune thrombocytopaenia	HPA-1a	GPIIIa	>80%
Platelet transfusion refractoriness	HPA-5b HPA-1b	GPIa GPIIIa	20-90%
Transplatation-associated thrombocytopaenia	HPA-1a and HPA-5b	GPIIIa GPIa	20-99%

HPA: human platelet alloantigen; GP: glycoprotein.

NAIT should be considered when a thrombocytopaenic neonate does not respond to transfusion of random platelets or intravenous immunoglobulin (IVIg), but demonstrates and sustains an adequate platelet count shortly after transfusion (i.e. 1 h post transfusion of maternal platelets). The incidence[5,11-13] of NAIT has been estimated to be 1 in 1,500-5,000 live births, and as 60% of identified cases occur in first pregnancies that are otherwise uneventful, it is difficult to predict who may be at risk. The first indication of NAIT may be the presence of unexplained petechiae and/or purpura in a newborn with a platelet count of <100,000/mm^3. A diagnosis of NAIT should only be made after exclusion of maternal history of an autoimmune disorder, thrombocytopaenia, or drug abuse. Cordocentesis to determine the foetal platelet count has been used in managing pregnancies complicated by NAIT, but this approach is being minimised or avoided due to the significant procedure-related risks. The earlier the intracranial haemorrhage occurred in the previous sibling, the greater the risk for intracranial haemorrhage in the currently affected foetus.

We perform[5,11,14,15] maternal and paternal platelet antigen typing, as well as maternal human anti-platelet antibody evaluation when the woman or her sister has an obstetrical history suggestive of this diagnosis (e.g. foetal death due to intracranial haemorrhage, neonatal thrombocytopaenia of undetermined aetiology). We perform paternal platelet antigen genotyping if the foetus is at risk of NAIT. If the father is heterozygous HPA-1a/1b, the foetal HPA status should be determined by typing foetal DNA for platelet antigens by PCR. The most widely accepted prevention strategy in the USA is weekly maternal antenatal administration of intravenous gamma globulin, ranging between 1-2 g/kg/week and/or prednisone 0.5-1 mg/kg/day. Therapy has been initiated as early as at 12 weeks of gestation in pregnancies in which a previous intracranial haemorrhage occurred, with good perinatal outcomes. Although use of glucocorticoids in pregnant women has been associated with an increased risk of pre-term premature rupture of membranes, this has not been described in the literature of pregnancies complicated by NAIT. Experts suggest cesarean delivery with consideration of vaginal birth only if the foetal platelet count is greater than 100,000/mm^3 prior to delivery.

POST-TRANSFUSION PURPURA (PTP)

PTP[16] is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. The antibody against HPA-1a is responsible for most cases. Patients[17] with PTP can present with severe thrombocytopaenia (e.g. platelet count ≤20,000/mm^3) that develops approximately 5-10 days following transfusion. The thrombocytopaenia often lasts from days to weeks. This condition appears in patients pre-exposed to foreign platelet-specific antigens by pregnancy or blood transfusion, and develops following a booster of incompatible platelets by producing high titre anti-HPA antibodies. These antibodies paradoxically destroy recipient platelets.[17] Several mechanisms have been proposed to explain the destruction of the patients' own platelets along with transfused platelets: adsorption of antigen-antibody complexes, cross-reactive antibodies, or autoantibody production. The majority of PTP[17] cases occur in patients with HPA-1b/b genotype producing anti-HPA-1a antibodies after transfusion of HPA-1a antigen; occasionally exposure to other platelet antigens induces the disease. More than one species of platelet-specific antibody may be implicated in rare cases of PTP. However, specific tests to determine the platelet antigenic composition and/or the presence of anti-platelet antibodies may not be readily available.

PTP[17-19] is an immunologically mediated thrombocytopaenia and may be confused with drug-induced or immune thrombocytopaenia (ITP), since the blood and bone marrow smears are consistent with immune platelet destruction in all of these disorders (i.e. thrombocytopaenia, occasional large platelets on the blood smear, increased megakaryocytes in the bone marrow). Since drug-induced thrombocytopaenia is relatively rare, and *de novo* ITP developing in someone who has recently been transfused rarer still, the possibility of a provisional diagnosis of PTP in someone with a history of a recent transfusion is reasonable. The preferred therapy for PTP is IVIg in high doses (400-500 mg/kg per day, usually for 5 days); alternatively, 1 g/kg per day for 2 days can be given for severe thrombocytopaenia. It usually takes about 4 days for the platelet count to exceed 100,000/mm^3.

REFRACTORINESS TO PLATELET TRANSFUSIONS

Platelet refractoriness[20,21] is a complication of platelet transfusion that affects variable proportions of patients, mostly depending on their diagnosis, previous immunologic stimuli, and type of blood products used for transfusion. Refractoriness to platelet transfusion can be separated into immune and non-immune causes. Immune causes include alloimmunisation to HLA and/or platelet-specific antigens due to prior exposure from pregnancy, transfusions, and/or transplantation. Non-immune causes, based on studies in patients with acute myeloid leukaemia or haematopoietic progenitor cell transplants, include fever, sepsis, splenomegaly, disseminated intravascular coagulation, bleeding, veno-occlusive disease, graft-versus-host disease, and medications. A large recent[20,22] study showed that platelet refractoriness develops in 13% of patients with acute leukaemia transfused with traditional blood products and in 3-4% of recipients of white-cell-reduced blood components. Alloimmunisation should be suspected when patients fail to have adequate platelet count increments following transfusion.

In general, poor increments following at least two ABO compatible transfusions stored for less than 72 hours should be documented prior to searching for histocompatible transfusions because, for reasons that are sometimes elusive, patients can have poor increments to a single transfusion with excellent responses to subsequent transfusions. Immune causes of platelet consumption include HLA Class I or HPA antibodies, major and minor ABO incompatibility, drug-induced antibodies, and antibodies to plasma proteins. Different[21,23] serological tests were developed to distinguish immune from non-immune causes of platelet refractoriness. In each assay, patient serum is incubated with a source of donor target antigen to demonstrate the presence of alloantibodies. There is no consensus regarding which test (lymphocytotoxicity test, platelet immunofluorescence test, lymphocyte immunofluorescence test, enzyme-linked immunosorbent assay [ELISA], antigen capture ELISA, monoclonal antibody-specific immobilisation of platelet antigens, solid-phase red cell agglutination test) yields optimum results. Multiplex flow cytometric bead assays are ideal for diagnosing refractoriness. Although studies have compared different testing strategies, there is no clear gold standard.

Once it is determined that a patient is alloimmunised to HLA antigens, compatible platelets are required for transfusion.[24] The large number of polymorphisms in the HLA system complicates the provision of HLA-matched platelets. With approximately 70 antigens to consider, the probability of finding matched donors for recipients with fewer common HLA phenotypes is low, even if a large number of HLA-typed plateletpheresis donors are available. Because of this, different strategies of donor selection are used, such as platelet cross-matching. Alternative methods for treating patients who are refractory to platelets and have thrombocytopaenic bleeding include the use of IVIg or anti-D immunoglobulin in patients who are Rh-positive.

PAIT

PAIT[23,25,26,27] is characterised by abrupt onset of thrombocytopaenia within a few hours of transfusing a blood product (usually plasma) that contains high-titre platelet-specific antibodies. In this syndrome, in contrast with PTP, the thrombocytopaenia immediately follows the transfusion and the duration is shorter, from several hours to a few days. Although the PSA can be detected in the donor's plasma and on the recipients platelets, it is not detectable in the recipient's plasma, suggesting that virtually 100% of the transfused alloantibodies bind soon after transfusion.[22,28] It is very important to investigate these cases because of the potential for multiple recipients to develop this syndrome, the responsible blood donor must be excluded from future blood donation. In comparison with PAIT caused by anti-HPA-1a, the severity of the thrombocytopaenia is consistent with other alloimmune syndromes (NAIT, PTP), and is consistent with the concept that the alloimmune thrombocytopaenic syndromes differ in severity largely on the basis of the number of antigen sites per platelet.

TRANSPLANTATION-ASSOCIATED ALLOIMMUNE THROMBOCYTOPAENIA (TAIT)

This syndrome[25,29,30] can occur as a severe complication either with a solid organ

transplantation, or an allogeneic bone marrow transplant. Both anti-HPA-1a and anti-HPA-5b alloantibodies can cause thrombocytopaenia that may develop immediately after or a long time after transplantation. An immune mechanism[27,28,31] was suggested by the repeated platelet count increase after treatment with high dose γ-globulin. Thrombocytopaenia by an alloimmune mechanism has been reported in patients after autologous peripheral blood stem cell transplantation. Solid organ transplants can rarely lead to AIT.[32] Reduced platelet levels are commonly seen after liver transplantation. In one reported series of 76 such procedures, a minimal mean platelet count of 86,000/mm^3 was measured on the third postoperative day and sequestration of platelets in the liver was demonstrated by the use of radio-labelled platelets. In another recently reported series of 43 liver transplantations, however, the nadir platelet count occurred about 1 week after transplantation and averaged 65,000/mm^3.

CONCLUSION

Alloimmune thrombocytopaenia is not the commonest cause of thrombocytopaenia, which has a wide variety of underlying causes. It is important to consider the clinical context of the thrombocytopaenia to guide rational investigation. The best practice guidelines for treatment aim to reduce the risk of severe haemorrhage in thrombocytopaenic patients. The outcome of ongoing and future studies will be crucial for determining the precise role of alloantibodies in the pathophysiology of disease. In the clinical setting it is also important to consider unusual alloimmune thrombocytopaenic disorders in which alloantigens that could be limited to just one family could cause important disease (i.e. NAIT caused by a private alloantigen; theoretically, PAIT or TAIT related to directed donations of blood or bone marrow). These considerations underscore the need for serological investigation to involve the family members rather than to rely on standard platelet-typing donor pools.

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MULTIPLE MYELOMA AND RENAL FAILURE

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ABSTRACT

Renal failure (RF) occurs in approximately 20-30% of multiple myeloma (MM) patients at diagnosis and in more than 50% of patients with advanced disease. The pathogenesis of RF is related to the production of monoclonal light chains that can damage either the tubule (myeloma kidney) or the glomeruli (light chain deposition disease or amyloid light-chain amyloidosis). In the past, the prognosis of patients with MM and RF was considered poor due to the limited number of effective and non-nephrotoxic drugs that were available. At present, novel drugs acting both on MM clone and on bone marrow microenvironment have been introduced into clinical practice; among them, bortezomib-containing regimens have proved to be the most effective. High-dose myeloablative therapy followed by autologous stem cell rescue can also be proposed in younger patients with no other relevant comorbidities.

Keywords: Myeloma, renal failure, light chains.

EPIDEMIOLOGY AND PATHOGENESIS OF RENAL FAILURE (RF) IN MULTIPLE MYELOMA (MM)

MM is a clonal B cell neoplasm characterised by proliferation and accumulation of B lymphocytes and plasma cells in the bone marrow and, more rarely, at extramedullary sites. Its annual incidence is 6/100,000 in Western countries, thus representing the second most common haematological malignancy after non-Hodgkin's lymphomas.[1] RF occurs in approximately 20-30% of MM patients at diagnosis and in more than 50% of patients with advanced disease.[2] The incidence of this complication in the different reports varies depending on its definition, either serum creatinine above 2 mg/dl or reduced glomerular filtration rate (GFR). Recently, the International Myeloma Working Group has provided recommendations on the definition of renal impairment, using the estimated GFR (eGFR) using the modification of diet in renal disease as the guiding parameter.[3] Stages of renal impairment can thus be classified upon the degree of eGFR, which can be mildly (60-89 ml/min), moderately (30-59 ml/min), or severely (15-29 ml/min) reduced, with end-stage renal disease defined as eGFR <15 ml/min. RF occurs by various mechanisms, the most frequent of which is tubular damage caused by cast formation.[4] Light chains are filtered through the glomeruli and then endocytosed and catabolised by the cells of the proximal tubule. When a large number of light chains are produced, the catabolic capacity of the proximal tubule is overwhelmed and an excess of light chains reaches the distal nephron, where they complex with Tamm-Horsfall protein, forming tubular casts that finally cause tubular obstruction. Light chains can also damage proximal tubular cells, leading to Fanconi syndrome, and induce interstitial fibrosis due to the production of pro-inflammatory cytokines (interleukin-6, tumour necrosis factor alpha).[5]

At the glomerular level, light chain deposition can result in amyloidosis (mostly lambda chains) or light chain deposition disease (LCDD) (kappa chains); glomerular damage, either caused by vascular deposition of amyloid fibrils, or granular deposits in the mesangium, finally results in nephrotic syndrome.[6] All the conditions described above can be worsened by comorbidities such as

diabetic nephropathy or nephroangiosclerosis, or by extrarenal factors such as dehydration, hypercalcaemia, hyperuricaemia, and concomitant use of contrast media or nephrotoxic drugs such as non-steroidal anti-inflammatory drugs. Bence Jones MM is more frequently associated with RF than other MM isotypes except immunoglobulin D MM, in this rare condition renal insufficiency is observed in 100% of cases.[2] In the case of RF in a patient with monoclonal gammopathy of unknown significance (MGUS), differential diagnosis between all the conditions mentioned above must be carried out. In the presence of albuminuria or non-selective proteinuria, subcutaneous abdominal fat aspiration should be performed in order to confirm the presence of amyloidosis; if this is excluded the patient should undergo renal biopsy in order to diagnose the presence of LCDD or non-MGUS related nephropathies. In the case of MM secreting only light chains (Bence Jones), or in oligosecretory MM, serum free light chains should be evaluated, as a greater correspondence to tumour load as compared to Bence Jones proteinuria has been demonstrated.[7]

ANTIMYELOMA THERAPY (AMT)

AMT is of crucial relevance for MM patients with RF, since a prompt reduction of tumour burden combined with adequate supportive care can lead to improvement of renal function in a significant percentage of cases,[8,9] although reversal of RF can potentially be observed even after the completion of an agitated saline contrast test (ASCT).[10] To achieve this important goal, rapidly effective non-nephrotoxic induction regimens should be selected. In the majority of the studies performed in the past, induction therapy consisted either of vincristine-doxorubicin-dexamethasone, eventually modified by replacing doxorubicin with another anthracycline, or of high-dose dexamethasone.[8,9,11,12] In recent years, both immunomodulatory drugs and bortezomib have been routinely used in various combinations in induction therapy prior to ASCT and have subsequently been employed as induction regimens in patients with MM and RF. Thalidomide-dexamethasone is active in relapsed/refractory MM patients with RF[13] with an acceptable toxicity profile. Pharmacokinetic studies have demonstrated that the kidney is apparently not involved in thalidomide metabolism, as the drug undergoes spontaneous hydrolysis in plasma, and only a small amount of thalidomide is excreted unchanged in the urine.[14] Furthermore, no correlation between thalidomide clearance and renal function has been observed.[15] Although two small studies have shown an unexplained incidence of hyperkalaemia in MM patients with RF treated with thalidomide,[16,17] the data were not confirmed in a larger case series[13] or in patients with newly diagnosed MM.[18]

Major concerns arose regarding the use of lenalidomide in patients with RF. Although direct damage to the kidney has not been demonstrated in MM, worsening of renal function has been described in patients with amyloid light-chain amyloidosis.[19] Lenalidomide is excreted by the kidney, so that its clearance decreases in patients with RF, with a consequent 6-12 hour increase in plasma half-life and area under the curve.[20] Retrospective evaluation of relapsed refractory MM patients with some degree of renal impairment treated with full dose lenalidomide in the context of clinical trials including mainly patients with normal renal function[21,22] confirmed the efficacy of the drug but also the occurrence of haematological toxicity, mainly thrombocytopaenia, which can potentially lead to more frequent treatment discontinuations. Later reports[23,24] that were mainly focused on patients with RF showed that a proper dose reduction can limit haematological toxicity. These data were confirmed also by the FIRST clinical trial[25] aimed at evaluating the efficacy of long-term lenalidomide-dexamethasone in MM patients ineligible for transplant.

Treatment of patients with MM and RF with bortezomib-containing regimens has shown interesting results in terms of both efficacy and improvement of renal function.[26,27] Sub-analyses of the data of a large randomised trial conducted in newly diagnosed MM patients[28,29] have shown that response rate and toxicity in the bortezomib-melphalan-prednisone arm (VMP) was not affected by RF; moreover, as compared to the melphalan-prednisone arm, treatment with VMP resulted in a higher percentage of patients achieving a normal renal function in a shorter period of time. Several studies[29-31] pointed out that reversal of RF after bortezomib-containing regimens is related to the response to therapy. Furthermore, these regimens warrant rapid responses, and this could be crucial in increasing the chances of reverting RF. Bortezomib seems to act specifically on the pathogenesis of myeloma-related RF, as inhibition of nuclear factor kappa-B could potentially prevent cytokine-mediated inflammatory damage to the interstitium that is observed in myeloma kidney[5,32] or mesangial alterations that can be detected in

light-chain deposition disease.[6,33] A recent report aimed at retrospectively comparing the role of novel agents in reverting RF in newly diagnosed MM confirmed a greater efficacy of bortezomib-containing regimens.[34]

Other novel drugs have shown efficacy in MM patients with RF in the relapsed/refractory setting, and will probably be proposed as induction therapy at disease onset in the near future. Among them, carfilzomib, a novel proteasome inhibitor, was initially demonstrated to be effective even in dialysis-dependent patients without necessity of dose reductions;[35] recent results of a multicentre European trial,[36] however, seem to suggest that the drug should be administered with caution in patients with renal insufficiency. Bendamustine, a unique bifunctional alkylating agent, has been used both in combination with steroids and with bortezomib in newly diagnosed or relapsed-refractory MM; interesting results were also reported in patients with RF so that its use could be proposed in the context of induction therapy for MM patients with RF.[37]

Renal insufficiency has long been considered an exclusion criterion for major trials aimed at evaluating the efficacy of ASCT in MM.[38,39] Antineoplastic drugs have a narrow therapeutic index so that major toxic events can occur in patients with reduced excretory organ function due to an increase in dose intensity that is frequently difficult to predict. An early animal study[40] has reported, in the case of RF, an increased toxicity of melphalan related to a longer terminal half-life of the drug. Conversely, more recent reports have pointed out that MM patients with RF can be treated with high-dose melphalan showing a spectrum of toxicity similar to that reported in patients with normal renal function.[41,42] Other reports have demonstrated the feasibility of autologous haematopoietic stem cell (SC) transplant in a small series of patients with MM and chronic RF using different conditioning regimens,[11,12,43-45] but data concerning toxicity were more controversial. These initial studies were important as they allowed for depiction of the problem of SC priming and transplant conditioning. In fact, both SC priming and conditioning regimens should include drugs that do not undergo renal excretion, for this purpose cyclophosphamide, busulfan, and melphalan have been used in the different studies. Cyclophosphamide, both as a parent compound and as an alkylating moiety, is excreted through the kidney in percentages ranging from 1-30%,[46] and this seems to be independent from renal function; however, when used for SC priming, a dose reduction could be reasonable in patients with RF.

SC mobilisation performed using granulocyte-colony stimulating factor (G-CSF) alone has been proposed by several groups in order to avoid cyclophosphamide-related toxicity;[11-13] an alternative strategy could also be represented by plerixafor, which has been successfully used as an adjunct to G-CSF for SC priming in a small series of patients with MM and RF.[47] Busulfan has been employed in preparative regimens for SC transplant in MM patients;[38,39] only negligible amounts of the compound are eliminated through the kidney, as the liver is the major site of drug metabolism. In the case of melphalan, initial data were more controversial, as several studies suggested that the pharmacokinetic parameters are related to creatinine clearance,[48,49] while other authors demonstrated that the main route of melphalan elimination is spontaneous degradation;[50] most reports, however, agree on the wide interindividual differences in drug metabolism.[41,50] Despite these contrasting findings it is well known that, at present, high-dose melphalan is the most effective preparative regimen for ASCT in MM,[51] and it is thus correct to include it in high-dose programmes for patients in RF; most authors agree on the fact that a dose reduction (80-140 mg/m^2) should be made in order to avoid excessive mucosal toxicity. Several recent reports have addressed the issue of the combination of bortezomib and busulfan as a preparative regimen for ASCT in MM;[52,53] these data, however, should be confirmed in large clinical trials.

SUPPORTIVE THERAPY

Nephrologic consultation is mandatory when taking care of MM patients with RF. Dehydration and hypercalcaemia must be carefully avoided and infections must be promptly treated. Nephrotoxic drugs should not be administered; in particular, non-steroidal anti-inflammatory drugs should be replaced with morphine derivatives for pain control. All the pharmacokinetic properties of each drug must be evaluated prior to administration in order to perform dose reduction with respect to creatinine clearance. For dialysis-dependent patients, the timing of administration of each drug must be evaluated prior to the dialytic procedure in order to avoid under or over-exposition of the patient to the drug. Bisphosphonates can be used in patients with RF, provided it is accompanied by an

appropriate dose reduction schedule as per the manufacturer's recommendations.[54] As the management of the myeloma kidney relies on the rapid removal of nephrotoxic light chains from the serum, plasma exchange was proposed several years ago as a possible method to achieve this goal. Initial studies showed a beneficial effect of plasma exchange in improving renal function;[55] this was not confirmed by later trials.[56] Recently, mechanical removal of serum light chains by high cut-off haemodialysis has been evaluated, and encouraging results were obtained when this method was used in combination with dexamethasone ± bortezomib-based regimens.[57]

FINAL REMARKS

Although different mechanisms can be responsible for or contribute to the occurrence of RF in MM patients, prompt reduction of tumour load can lead to an improvement in renal function in a significant percentage of patients, and in general, an appropriate antimyeloma therapy can result in prolonged patient survival.

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CHECKPOINT BLOCKADE IN CANCER IMMUNOTHERAPY: SQUARING THE CIRCLE

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ABSTRACT

Manipulating the complex interaction between the immune system and tumour cells has been the focus of cancer research for many years, but it is only in the past decade that significant progress has been made in the field of cancer immunotherapy resulting in clinically effective treatments. The blockade of co-inhibitory immune checkpoints, essential for maintaining lymphocyte homeostasis and self-tolerance, by immunomodulatory monoclonal antibodies has resulted in the augmentation of anti-tumour responses. The greatest successes so far have been seen with the blockade of cytotoxic T lymphocyte associated antigen-4, which has resulted in the first Phase III clinical trial showing an overall survival benefit in metastatic melanoma, and in the blockade of the programmed cell death protein-1 axis. This concise review will focus on the clinical advances made by the blockade of these two pathways and their role in current cancer treatment strategies.

Keywords: Cancer immunotherapy, cytotoxic T lymphocyte associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), programmed death ligand-1 (PD-L1).

INTRODUCTION

There were an estimated 14.1 million new cases of cancer diagnosed in 2012 worldwide[1] and, coupled with an increasingly ageing population, the significant global health burden of cancer has led to the search for additional anti-tumour therapeutic strategies to be undertaken. The ability to harness and amplify the immune system's response towards tumour cells has appeared an attractive option in the development of cancer therapies. The principle of the immune surveillance hypothesis, first suggested by Burnet and Thomas[2-4] in the 1950s, proposes that the host's immune system can identify nascent tumour cells and act to eradicate them. The ability of the immune system to recognise cells as tumour cells is essential to preventing the eradication of healthy cells, and is dependent on the cell expressing an identification marker or 'tumour-specific antigen' which elicits an immune response (IR). Lymphocytes were proposed to be the principle cell mediating the immune surveillance mechanism. Without this protective mechanism, the rates of carcinogenesis would be expected to be much higher than experienced. Although an attractive hypothesis, experimental evidence to support the theory was lacking until the late 1990s when, amongst other advances, research showed that lymphocytes and interferon-gamma work together to prevent the development of tumours in immunodeficient mice.[5]

The concept of cancer immunoediting developed from these initial theories and was proposed to describe the interaction between the immune system and cancer, whereby malignant cells become less immunogenic leading to immune escape by the tumour.[6] The cancer immunoediting theory has three phases: elimination, equilibrium, and escape. The stage of tumour elimination reflects the traditional immune surveillance concept whereby the immune system recognises and eliminates tumour cells. The second stage of equilibrium describes the process by which tumour cells can adapt and become progressively less immunogenic and resistant to the actions of effector cells whilst some tumour cells continue to be eliminated. Therefore, the tumour is not completely eradicated

and is kept in check by the immune system. The final escape phase occurs when tumour cells can adapt to develop strategies for evading or subverting a host's IR, for example by expressing ligands that can inhibit T cell activation and proliferation, thereby escaping from the immune system's effector mechanisms and enhancing their ability to proliferate in an unrestricted manner. The aim of immunotherapy is to alter the balance from tumour escape to tumour elimination.

Following the formation of these hypotheses, cancer immunotherapy was a theoretical possibility but over the subsequent decades it failed to translate into effective clinical therapies and therefore appeared to be an impossible feat. The failure of therapies was principally due to a lack of understanding of the immunosuppressive features of the local tumour microenvironment and the need for T cells to infiltrate the tumour to exert their anti-tumour effect. However, in recent years, major breakthroughs in both the understanding of the IR and in the generation of specific monoclonal antibodies (mAbs) aimed at immune checkpoints have led to effective cancer immunotherapies and the achievement of a metaphorical 'squaring of the circle'.

The field of cancer immunotherapy has expanded in recent years, including adoptive cellular therapy, vaccine approaches, and T cell gene therapy. In this concise review, the focus will be on one major branch of cancer immunotherapy, namely the generation of immunomodulatory antibodies designed to manipulate the immune system's co-inhibitory receptors to augment T cell effector function and the anti-tumour response. In contrast to traditional cancer therapies, which have direct cytotoxic effects on the malignant cells, this branch of cancer immunotherapy relies on indirect methods of tumour attack by manipulating the IR in the tumour microenvironment. This indirect method has been postulated to reset the immune memory with potentially more durable responses.

CO-INHIBITORY RECEPTORS

Cytotoxic T Lymphocyte-Associated Antigen-4 (CTLA-4)

The major breakthrough in translational cancer immunotherapy, resulting in successful Phase III clinical trials, followed the development of mAbs against CTLA-4. CTLA-4 is a co-inhibitory receptor that is expressed on activated T lymphocytes and is constitutively expressed on regulatory T lymphocytes. It acts as an inhibitory checkpoint to restrict the magnitude and duration of the IR generated after antigen engagement with the T cell receptor. The immune system has inherent inhibitory checkpoints to limit the degree of immune system activation, thereby preventing collateral damage of surrounding normal tissue and the sequela of autoimmunity. Both CTLA-4 and CD28, a co-stimulatory receptor, are members of the immunoglobulin (Ig) superfamily of receptors. Following the presentation of antigen by major histocompatibility complex molecules on antigen-presenting cells (APCs), the second signal for T cell activation is provided by CD28, which resides on the T cell surface, as it interacts with its respective ligands. CTLA-4's function appears to counteract that of CD28, as they share the same ligands, CD80 (B7-1), and CD86 (B7-2), which are expressed on APCs. CTLA-4 has a higher affinity for these ligands, leading to the theory that CTLA-4 may out-compete CD28 for ligand engagement, resulting in the restriction of the co-stimulatory function of CD28.[7]

The essential role played by CTLA-4 in limiting the IR and maintaining lymphocyte homeostasis was aptly demonstrated by the observations that CTLA-4 knockout mice develop fatal lymphoproliferative disorders within 3-4 weeks of birth.[8,9] The blockade of CTLA-4 with an antagonistic antibody was postulated to increase immune stimulation by releasing the inhibitory brakes on the effector IR in the presence of tumour. Initial preclinical models confirmed this theory by showing that anti-CTLA-4 antibodies could reject tumours and also that this rejection resulted in persistent immunity when challenged for a second time with tumour cells.[10] Whilst the mechanism of action of anti-CTLA-4 antibodies is still being investigated, evidence derived from murine models has shown the blockade of CTLA-4 on both effector and regulatory T cells contributes to its anti-tumour effect. Anti-CTLA-4 antibodies act to deplete the number of regulatory T cells within tumours and the composition of the tumour microenvironment, in particular the presence of Fcγ receptor–expressing macrophages, is essential in enabling this depletion to occur.[11,12] The initial success in anti-CTLA-4 antibody therapy was shown in the treatment of advanced melanoma. The increasing incidence of melanoma and the poor prognosis of patients with metastatic melanoma (MM), with median overall survival (OS) rates of less than 1 year, had indicated that new effective therapies were greatly needed.[13]

There have been two mAbs to CTLA-4 which have been examined in Phase III clinical trials in patients with advanced melanoma, ipilimumab and tremelimumab. Ipilimumab is a fully human immunoglobin G1 (IgG1) mAb to CTLA-4. The landmark Phase III randomised controlled trial (RCT) by Hodi et al.[14] was the first to show an OS benefit for any therapy in the treatment of MM. The study compared ipilimumab with and without glycoprotein 100 (gp100) vaccine with a gp100-alone group in patients with previously treated advanced melanoma. Gp100 is a peptide vaccine originating from a melanosomal protein, and has shown enhanced anti-tumour activity in combination therapy, for example with interleukin 2.[15] There was a significant difference in OS between the ipilimumab/vaccine group when compared with the vaccine-alone group (10 months versus 6.4 months). There was no significant difference noted between either of the ipilimumab groups. The second Phase III trial, which demonstrated a survival advantage for ipilimumab therapy in patients with melanoma, was performed by Robert et al.[16] They compared patients, who had no previous treatment for melanoma, receiving ipilimumab plus dacarbazine with a group receiving dacarbazine plus placebo. Dacarbazine is an alkylating agent and is the most commonly used chemotherapy in the treatment of melanoma. There was a significant increase in median OS for those receiving ipilimumab with dacarbazine rather than dacarbazine and placebo (11.2 months versus 9.1 months). In contrast to ipilimumab, tremelimumab is a humanised IgG2 mAb to CTLA-4 and was studied in treatment-naïve patients with melanoma in a Phase III trial by Ribas et al.[17] Unlike the aforementioned ipilimumab trials, no significant difference in median OS was shown between tremelimumab-treated patients and those receiving standard chemotherapy despite the induction of initially durable responses in a subset of patients.

The objective responses reported with ipilimumab were durable, with 60% of patients, in a study by Hodi et al.,[14] maintaining their response for more than 2 years. Furthermore, in the ipilimumab/dacarbazine study, the median duration of response was 19.3 months (for those achieving a complete or partial response).[16] However, despite these durable responses, the clinical trials have shown that only a relatively small subset of patients derive benefit from ipilimumab therapy, with a reported overall response rate (RR) of 10.9–15.2%, irrespective of whether they were treatment naïve prior to receiving ipilimumab.[14,16] The ability to identify the group of patients who would benefit from ipilimumab therapy would limit the number of patients exposed to potentially harmful adverse events (AEs) and also would enable treatment to be tailored to those with the highest chance of success. The search for a predictive biomarker of ipilimumab response is currently ongoing but provisional studies have suggested that an initial high expression of FoxP3 may be a predictor of success.[18]

In this new era of immunotherapy agents, it has become apparent that the traditional disease response criteria, either using Response Evaluation Criteria in Solid Tumors or World Health Organization standards, may not be sufficient to assess disease responsiveness. Durable responses have been reported in patients who have initially developed new lesions shortly after commencing ipilimumab,[16] suggesting that the response may take longer to manifest itself when compared to directly cytotoxic traditional anti-tumour agents.[19] Immune-related response criteria have been proposed whereby total tumour burden is assessed, but further evaluations of these criteria are ongoing. In view of CTLA-4's function as a 'brake' on the duration and amplitude of T cell effector functions, it could be predicted that side-effects from therapies aimed at blocking CTLA-4 would manifest as autoimmune phenomena. The initial Phase I/II studies[20-22] identified that the majority of drug-related AEs were mostly inflammatory in nature (Table 1). Predominantly, these immune-mediated AEs affect the gastrointestinal tract, skin, liver, and endocrine systems, and the frequency of Grade 3-4 treatment-related AEs with ipilimumab were recorded as 10-15%[14] but much higher, at a rate of 56.3%, when ipilimumab was combined with dacarbazine,[16] potentially due to dacarbazine's known hepatotoxicity.

The majority of immune-mediated AEs can be treated with systemic glucocorticoid therapy and, in some rare steroid-resistant cases, with anti-tumour necrosis factor antibodies. The emphasis for successful management of these AEs is on active medical surveillance and prompt initiation of treatment which may result in the cessation of ipilimumab therapy and lead to prevention of life-threatening complications. The use of prophylactic systemic steroid therapy in combination with ipilimumab therapy has not been shown to be of benefit in reducing the incidence of severe cases of treatment-related colitis.[20] Furthermore, the

use of systemic steroids to treat immune-related AEs has not been shown to affect the efficacy of ipilimumab's anti-tumour response.[14,16] The success of ipilimumab in the treatment of melanoma has resulted in an examination of its function in other tumour types. A large Phase III trial[23] randomised 799 patients to receive either ipilimumab or placebo after receiving radiotherapy for castration-resistant prostate cancer (CRPC) that had progressed after docetaxel chemotherapy. No significant difference was found in median OS between the ipilimumab and placebo groups (11.2 months versus 10 months). As expected, Grade 3-4 treatment-related AEs were higher in the ipilimumab group (26% versus 3%). Further Phase III trials are ongoing to examine the role of ipilimumab in chemotherapy-naïve patients with prostate cancer. Anti-tumour responses have been reported in patients with metastatic renal cell carcinoma (RCC), with Phase II studies reporting a tumour RR of 12.5% in patients receiving 3 mg/kg of ipilimumab[24] and also in patients with Stage 3B/4 non-small cell lung cancer (NSCLC).[25]

Programmed Cell Death Protein-1/ Programmed Death Ligand-1 (PD-1/PD-L1)

PD-1 is also a co-inhibitory member of the Ig super family of receptors. Its prime function is to restrict T cell activation and effector function in the peripheral tissues at sites of inflammation and/or infection.

Table 1: The common immune-related adverse events associated with therapeutic immunomodulatory antibodies.

Immune-related adverse event
Dermatological • Rash • Pruritus • Vitiligo • Alopecia
Gastrointestinal • Diarrhoea • Colitis
Pulmonary • Pneumonitis
Endocrine • Hypothyroidism • Hyperthyroidism • Hypophysitis • Hypopituitarism
Hepatic • Hepatitis • Abnormal liver function tests

Its expression is induced upon activation of T cells, although it can also be expressed on B cells, natural killer cells, and monocytes. PD-1 exerts its function by interacting with its two known ligands, PD-L1 (PD-L1, also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 is expressed on activated T cells, B cells, and APCs, including tissue-associated macrophages. Furthermore, PD-L1 is expressed on some tumour cells allowing the tumour to circumvent T cell effector function by providing inhibitory signals to evade immune attack. PD-L1, as well as serving as PD-1's ligand, also interacts with CD80 and therefore any blocking of PD-1 does not make PD-L1 completely redundant. PD-1's second ligand, PD-L2, has a more restricted expression profile and is expressed on dendritic cells, mast cells, and macrophages.

The function of PD-1 in the maintenance of peripheral self-tolerance and the prevention of uncontrolled immune activation was established in preclinical models where it was firstly observed that PD-1 knockout mice developed autoimmune phenomenon including arthritis, glomerulonephritis, and autoimmune dilated cardiomyopathy.[26,27] Further preclinical models demonstrated apoptosis of activated T cells when exposed to tumour-associated PD-L1[28] and also that *in vivo* injection of anti-PD-L1 antibodies inhibited growth of tumours expressing PD-L1.[29] A number of mAbs targeting PD-1 have been examined in clinical trials. Nivolumab (also known as BMS-936558), a fully human IgG4 mAb to PD-1, was initially studied in a Phase I trial of 296 patients examining its safety profile and anti-tumour activity in melanoma, NSCLC, RCC, and prostate and colorectal cancer.[30] Objective responses were reported in NSCLC, melanoma, and RCC only and the disease responses observed were durable with 65% of evaluable patients maintaining their response for >1 year. Grade 3-4 treatment-related AEs were reported in 14% of patients and, in particular, drug-related pneumonitis was reported in 3% of treated patients with three drug-related deaths attributed to pneumonitis. Interestingly, when available tumour biopsies were examined for PD-L1 expression, 36% (9/25) of patients with positive biopsies had an objective response, compared to 0% of patients with PD-L1 negative tumours, suggesting that the expression of PD-L1 could be a possible biomarker for disease response to nivolumab. Further immunohistological examination of tumour biopsies taken prior to commencing nivolumab therapy

showed a significant association between PD-1 expression on tumour-infiltrating lymphocytes and PD-L1 expression by the tumour cells.[31] Maintenance of disease response after stopping nivolumab therapy has also been shown in the treatment of melanoma, suggesting that an immune memory is established resulting in durable responses.[32]

Pembrolizumab (previously known as lambrolizumab or MK-3475) is a humanised IgG4 kappa mAb against PD-1. Two different dosing regimens have been examined in patients with advanced melanoma, with the highest confirmed RR seen in 10 mg/kg (52%) when compared with 2 mg/kg and a reported combined confirmed RR across all doses of 38%.[33] It should be noted that there was a higher RR reported in this trial than in the Phase III RCTs of ipilimumab. The inclusion of patients who had previously received other immunotherapies, namely ipilimumab, allowed the study to show no significant difference in RR between those who were ipilimumab-naïve and those who had received prior ipilimumab therapy. An overall RR of 26% has been reported with pembrolizumab in patients with advanced melanoma who were ipilimumab refractory, indicating that the failure of one immunotherapy should not preclude treatment with another.[34] Interestingly, as with the reports from the ipilimumab clinical trials, delayed responses were noted, including some as late as 36 weeks after treatment initiation.

The third mAb to PD-1, pidilizumab, is a humanised IgG1-kappa mAb to PD-1 which has been studied in combination with rituximab (an anti-CD20 mAb) in patients with relapsed follicular lymphoma in a non-randomised Phase II trial.[35] An objective RR of 66% (16/29) was achieved with no reported Grade 3-4 treatment-related AEs, but further randomised trials are required to test its efficacy. Many tumours have been found to express PD-L1 and, in patients with RCC, high intratumoural levels of PD-L1 expression have been associated with more aggressive tumours.[36] Moreover, in ovarian cancer, a significantly poorer prognosis was reported in patients with a high intratumoural level of PD-L1 expression.[37] In view of the observation that many tumour types express PD-L1 as an escape mechanism to avoid immune effector functions, mAbs to PD-L1 have also been developed in an attempt to manipulate the PD-1/PD-L1 axis. Brahmer et al.[38] performed a Phase I trial of 207 patients with a variety of solid-organ malignancies who received BMS-936559, a fully human IgG4 mAb to PD-L1. This antibody inhibits the binding of PD-L1 to both PD-1 and CD80. There were no objective responses reported in colorectal or pancreatic cancers but objective responses were seen in melanoma, RCC, NSCLC, and ovarian cancer. For those patients with at least 1 year of follow-up, 50% had a durable response lasting for a minimum of 1 year. The percentage of objective responses to this anti-PD-L1 antibody (only 17% for those patients with melanoma) appeared to be lower than for anti-PD-1 therapies. However, the frequency of treatment-related AEs of Grade 3-4 severity was reported as only 9% in those patients treated with anti-PD-L1 with no reported cases of Grade 3-4 colitis.[38] In the clinical trials examining anti-PD-1 mAbs, Grade 3-4 AEs were reported in 12-22% of patients.[30,32-34] Treatment-related pneumonitis has been identified as a severe AE in anti-PD-1 trials, with reported frequencies of 3-4%[30,32-33] and a small number of deaths reported as a consequence of pneumonitis. High clinical suspicion for pneumonitis and prompt initiation of steroid therapy has been recommended in those patients receiving anti-PD1 or anti-PD-L1 therapy.[39]

COMBINATION THERAPY

Combination therapy has appeared attractive in the study of immunomodulatory antibodies as it may potentially allow for a lower dose of each antibody to be used, thus harnessing both of their immunomodulatory functions. Preclinical studies have shown that the blockade of both CTLA-4 and PD-1 pathways resulted in a more marked anti-tumour effect than blocking either pathway alone, suggesting that combination therapy may be a more effective therapeutic approach.[40] A Phase I study examining the role of combination therapy with nivolumab and ipilimumab in patients with melanoma has reported objective responses in 53% of patients with substantial tumour reductions in excess of 80%.[41] Predictably, the frequency of treatment-related AEs of Grade 3-4 in patients receiving concurrent therapy was high at 53% but these events were generally reversible in nature. The combination of radiotherapy with immunomodulatory antibodies has also been examined, with a Phase III trial investigating patients with CRPC receiving radiotherapy followed by either ipilimumab or placebo reporting no significant difference in OS between either group.[23] Further collaborative Phase III RCTs are required but the high objective RRs initially reported with immunomodulatory antibody combination therapy are encouraging.

CONCLUSION

In conclusion, immunomodulatory mAbs, aimed at blocking immune checkpoints, have given rise to a new era of cancer immunotherapy. Their impact on the treatment of MM has resulted in durable responses and improvements in OS, and they have also demonstrated anti-tumour activity in a variety of other solid organ malignancies. The discovery of biomarkers to predict those patients who are more likely to respond to immunomodulatory therapy will allow for a more tailored approach to treatment, with a reduction in the number of patients exposed to potentially severe immune-mediated AEs. The need to redefine criteria for disease response has also been identified, as the pattern of objective responses differs when compared to conventional, directly cytotoxic cancer therapies. Future clinical studies examining the combination of immunomodulatory antibodies with conventional anti-cancer therapies (e.g. radiotherapy), their role in treatment naïve patients, and the efficacy of manipulating the PD-1/PD-L1 pathway in those patients who are ipilimumab refractory will further define the role of these agents in cancer therapy. Combinations of different immunotherapies may hold the key to maximising RRs, although this will only be determined by further collaborative clinical trials.

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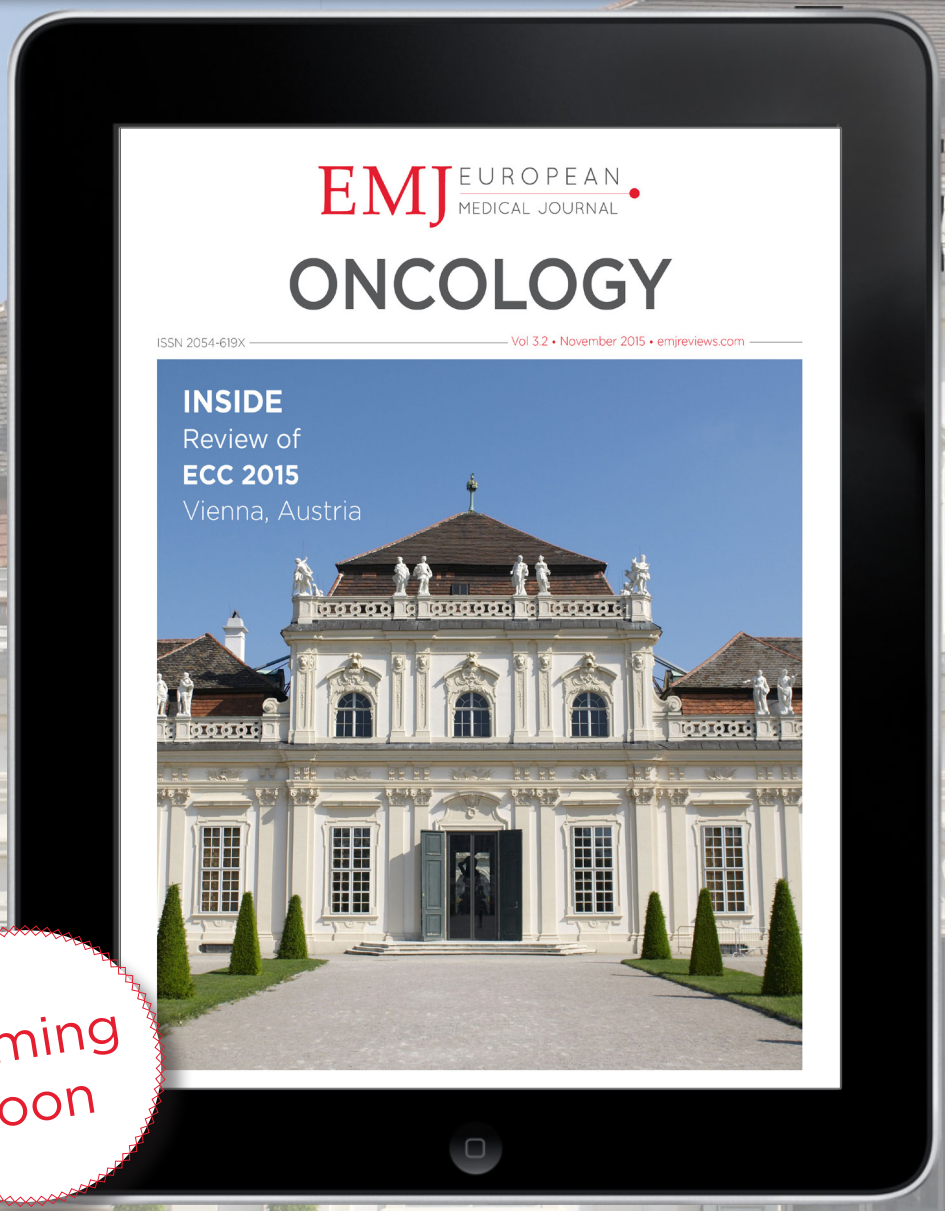

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HOW I TREAT: PROGNOSTICATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA: A GAZE INTO THE FUTURE

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Chronic lymphocytic leukaemia (CLL) is due to the relentless accumulation of monoclonal B lymphocytes with a distinct immunophenotype (i.e. surface membrane immunoglobulin [weak], CD5+, CD19+, CD23+) in bone marrow (BM), peripheral blood, and lymphoid tissues. CLL is a frequent disease with an incidence of around 5 per 100,000 in Western countries. The median age of patients at diagnosis is approximately 70 years, and the incidence of the disease dramatically increases with age, reaching >20 per 100,000 in individuals older than 70 years.

The median survival of patients with CLL has improved over the last few decades but there is not yet a curative therapy for this disorder. While the overall median survival of patients with CLL is now about 10 years, the individual prognosis ranges from a few months to a normal lifespan. Therefore, prognostication is an essential component in the management of patients with CLL.

Although somewhat overlapping, it is useful to distinguish prognostic factors (parameters that predict the likelihood of disease progression and hence the need for therapy) from predictive factors (markers that inform about the probability of response to a given therapy). For the sake of clarity, it is better to cluster these two groups of parameters under the name of outcome predictors, rather than prognostic factors (Figure 1). In this context, it is important to underscore that the correlation of a parameter with an outcome does not qualify it as a prognostic factor unless a number of criteria (e.g. harmonisation/standardisation, reproducibility, independent prognostic value, and superiority over other parameters that predict the same outcome) are fulfilled.

In CLL, prognostic factors at diagnosis foretell the clinical behaviour of the disease, particularly the likelihood of disease progression, and also provide a raw estimate of the life expectancy. They are useful to inform the patient and to advise the frequency and characteristics of the follow-up, and whether it is preferable that the patient can be controlled in a general setting or in a specialised CLL centre. Although developed 40 years ago, clinical staging systems independently devised by Rai and Binet continue to be employed. Clinical staging systems are based on the concept that CLL cells first accumulate in blood, subsequently in lymph nodes and spleen, and eventually in BM, leading to its functional failure. Patients with early, low-risk disease have a median survival of >15 years, while those with advanced, high-risk disease have a median life expectancy of <3–4 years. Importantly, assigning a clinical stage to a given patient only requires a physical examination and a complete blood cell count; such simplicity is a great advantage as it permits the use of clinical stages in any setting.

Although useful, clinical stages have some limitations. Firstly, in Western countries, approximately 80% of patients are presently diagnosed in asymptomatic, early-stage routine blood analysis, and this blurs the usefulness of clinical stages as a whole. Secondly, clinical stages do not identify patients whose disease will progress as compared to those in whom the disease will remain stable. Thirdly, patients are classified as in an advanced stage based on the presence of anaemia or thrombocytopaenia, regardless of their origin. However, patients with advanced disease because of immune cytopaenia have a better outcome than those with cytopaenia due to a heavy infiltration of the BM by lymphocytes. Fourthly, clinical stages do not predict response to treatment. Finally, current therapies are overcoming the poor prognostic significance of clinical stages. As an example, the prognosis of patients with advanced or high-risk disease is getting closer to the prognosis of patients with intermediate-risk disease thanks to more effective therapies.

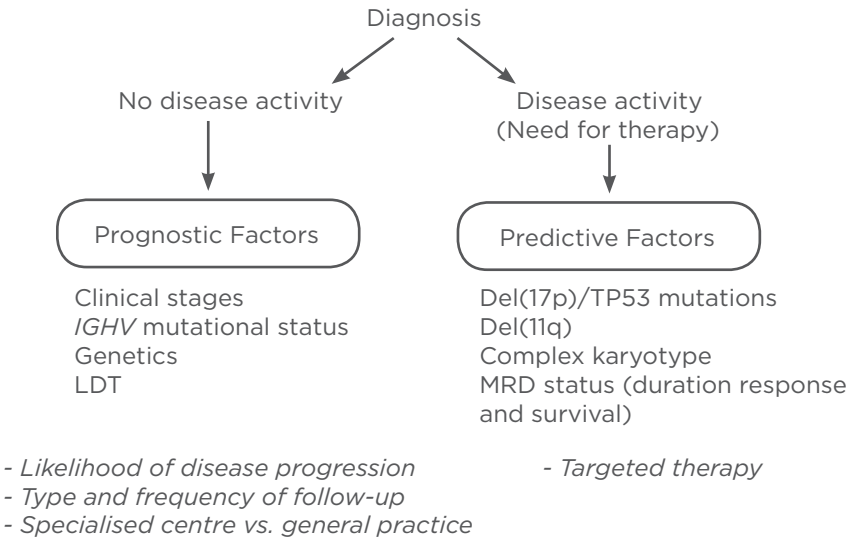

Figure 1: CLL: From prognostic factors to predictive factors.
CLL: chronic lymphocytic leukaemia; LDT: lymphocyte doubling time; MRD: minimal residual disease; vs.: versus.

There are a number of parameters that add prognostic power to clinical stages, including *IGHV* mutational status, ZAP70, and CD38 expression, genetic lesions, lymphocyte doubling time, and serum beta-2 microglobulin level. Among them, *IGHV* gene mutational status is the most important prognostic factor. In landmark studies conducted at the end of the last century it was demonstrated that in CLL the *IGHV* gene can either be mutated (50-70% of cases) or unmutated (30-50% of cases), and that *IGHV* mutational status correlates with biological and clinical features. Thus, while patients with mutated *IGHV* usually have indolent disease not needing therapy and good prognosis, those with unmutated *IGHV* tend to have a rapidly progressive disease, require early intervention, respond poorly to therapy, and have short survival. Notably, many adverse prognostic features, such as advanced clinical stage, del(11q), del(17p), *TP53, NOTCH1,* and *SF3B1* mutations predominate in unmutated cases, whereas the opposite is true for patients with mutated *IGHV. IGHV* mutational status is thus not only the backbone for two different forms of CLL but also a central feature around which revolve many other prognostic factors.

As for the future, clinical stages should continue to be used since they give valuable information about the tumour burden and allow the comparison of series of patients seen over decades. However, clinical stages should be complemented by biomarkers, particularly *IGHV* mutational status. Other valuable prognostic parameters are genetic lesions; del(13q) as sole abnormality identifies patients with an excellent prognosis, whereas del(11q), del(17p)/*TP53* mutations, or complex karyotype (≥2 lesions) are associated with poor outcome, mainly because patients harbouring these lesions respond poorly to therapy.

As in many other tumours, CLL prognostication is rapidly shifting from prognostic to predictive factors. Response to therapy and degree of response are the most important predictors of life expectancy in cancer patients. CLL is not an exception to that rule. Although it could be argued that new treatments such as BCR inhibitors (ibrutinib), the PI3K inhibitor IPI-145 (duvelisib), or the BCL2 antagonist ABT-199 that result in long-term survival with no need of complete response may eventually challenge the 'response-survival' paradigm, a longer follow-up of clinical trials investigating these agents is necessary to draw firm conclusions.

Unfortunately, the number of response predictors in CLL is limited. The presence of del(11q) is associated with poor response to fludarabine alone and demands the use of chemoimmunotherapy as treatment. More importantly, del(17p)/*TP53* mutations convey resistance to fludarabine-based treatment, including chemoimmunotherapy, and a very short survival (median <2 years). Patients with the latter lesions should be treated with new agents, active across all genetic subgroups

or, in selected cases, allogeneic stem cell transplantation. There is also some notion that patients with *NOTCH1* mutations might gain no benefit from anti-CD20 monoclonal antibodies (rituximab, ofatumumab).

Now, next generation sequencing platforms are making it possible to investigate the correlation of genetic lesions, even at subclonal level, with clinical outcomes. There is evidence, for instance, that subclonal *TP53* mutations detected at diagnosis result in refractoriness to chemoimmunotherapy (as in clonal mutations) and short survival. In contrast, the same does not seem to be true for *NOTCH1, SF3B1,* and *BIRC3* mutations.

Importantly, outcome predictors can change as a result of better therapies. In line with this, there is not a unique 'one size fits all' set of predictive markers; for example, response predictors to ibrutinib may differ from those of chemoimmunotherapy. On the other hand, novel agents may trigger mechanisms of resistance to therapy, as it occurs with ibrutinib and *BTK* and *PLCγ2* mutations that induce (and become markers of) treatment failure. Finally, although not yet incorporated into the routine evaluation of response to treatment, patients with undetectable minimal residual disease (MRD) after therapy have a longer progression-free and overall survival; this opens the door to MRD-guided clinical trials and management.

In summary, profound changes in our understanding of CLL are taking place, including the way prognosis is assessed. A number of biomarkers are being incorporated to already existing outcome predictors. Nevertheless, applying all available and claimed 'new' prognostic factors to every single patient with CLL would be not only unrealistic but also more confusing than informative. Therefore, only robust predictors identified with strict methodology and considered more informative than other markers for the same event should be taken into consideration. Building up prognostic models for CLL is on the agenda of many groups of investigators, the important challenge being to construct reproducible, reliable, and easy-to-apply tools.

FURTHER READING

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