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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Recent advances in theranostics and challenges for the future

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ABSTRACT

Theranostic nuclear oncology is on the cusp of adoption into routine clinical management of neuroendocrine tumours (NETs) following publication of the Phase 3 randomised controlled trial, NETTER-1. For the first time, level 1b evidence of efficacy and safety of 68-gallium/177-lutetium-DOTA-octreotate peptide receptor radionuclide therapy, of mid-gut neuroendocrine tumours was established. Multicentre Phase 2 studies of 68-gallium/177-lutetium-prostate specific membrane antigen theranostic approaches to management of end-stage metastatic castrate-resistant prostate cancer, are also very encouraging. However, the retrospective uncontrolled data currently available are inadmissible for formal regulatory agency evaluation. The challenge is to engage with oncologists and urologists, and to collaborate with the pharmaceutical industry, to design and perform the controlled clinical trials required for regulatory approval, and eventual reimbursement for theranostic nuclear oncology procedures. Strategies to facilitate timely establishment of an evidence base are considered in this review of theranostic advances over the past year. The prime objective is the provision of novel, effective, safe, personalised, tumour-targeted molecular theranostic management of metastatic castrate-resistant prostate cancer, and other cancers, such as non-Hodgkin lymphoma, which express the appropriate molecular receptor tumour targets. It would also be desirable to offer theranostic treatments at an earlier stage of malignant disease when the benefit is likely to be greater. The ultimate goal of theranostic nuclear oncology is to prolong survival and to improve quality of life for cancer patients worldwide. This may only be achieved through close collaboration between oncologists, nuclear physicians, radiologists, dosimetric physicists, Pharma, and, above all, with the patients themselves, in ways which are explored in this review.

THERANOSTIC NUCLEAR ONCOLOGY DEFINED

Theranostic nuclear oncology integrates diagnostic and therapeutic functions within the same radiopharmaceutical molecular targeting platform, termed a theranostic pair. It is predicated upon the radiolabelling of cancer type-specific biomarkers, which allow precise molecular imaging to reflect the unique molecular pathology of tumour cells. This strategy identifies individual patients who may then benefit from tumour molecular phenotype-targeted radionuclide therapy. Selection of patients for any radionuclide therapy is thus performed by the demonstration of sufficient uptake in all active tumour sites in order to deliver a radiation absorbed dose adequate to achieve therapeutic goals of symptom or disease control. "We see what we treat, and we treat what we see". (Richard Baum). Physicists are more precise; they employ the term theranostics to describe the use of tracers to predict the radiation absorbed dose

in molecular radiotherapy, and hence the safety and likely efficacy of a treatment in an individual patient.¹

Professor Johannes Czernin, Editor-in-Chief of the *Journal of Nuclear Medicine*, envisions that, during the next decade, nuclear medicine will experience a remarkable renaissance as diagnostic, predictive, and prognostic biomarkers become integrated with novel theranostic approaches.² The realisation of the dream of precision medicine will require the ability to determine whole body target expression and inhibition, and accurately to assess treatment response early. Such is the promise of theranostic nuclear oncology.

HISTORICAL DEVELOPMENT UP TO NOVEMBER 2016

The concept of nuclear theranostics was developed over 75 years ago, when Sam Seidlin used iodine-131 for diagnostic imaging, confirmation of target expression, and radionuclide therapy of thyroid cancer.³ The history of the

evolution of targeted radionuclide therapy, up to and including its state-of-the-art as presented at the Theranostics World Congress held November 2016, has been comprehensively reviewed by Professor Katherine Vallis (CRUK and MRC Oxford University Institute of Oncology).⁴

SNAPSHOT OF CURRENT STATUS

The present review of recent advances in theranostics will be confined to those reported in the 12-month period up to, and including, the World Association of Radiopharmaceutical and Molecular Therapy (WARMTH) Congress at IAEA, and the European Association of Nuclear Medicine meeting in Vienna October 2017. This snapshot of the current status of theranostic nuclear oncology will then act as a point of reference to define the challenges to our rapidly evolving molecular specialty, as we seek to realise its potential to revolutionise the clinical care of cancer patients worldwide.

PEPTIDE RECEPTOR RADIONUCLIDE THERANOSTICS OF NEUROENDOCRINE TUMOURS

The pioneer of the modern theranostic radionuclide approach to neuroendocrine tumours (NETs), Professor Eric Krenning at the Erasmus Medical Centre Rotterdam, recounted, in 2017, his epic saga, and cautionary tale, of over 17 years of clinical development, which was required eventually to achieve regulatory approval and oncologist acceptance of 177-lutetium-DOTA-octreotate for peptide receptor radionuclide therapy (PRRT) of gastroenteropancreatic (GEP) NETs.⁵ Prospective clinical trial data on patients treated with 177-lutetium-DOTA-octreotate in Rotterdam have been collected since 2000 and later, much later, formed the basis of a multinational Phase 3 randomised controlled clinical study in mid-gut NETs. This NETTER-1 Study enrolled 229 patients with advanced progressive somatostatin-receptor positive, well-differentiated mid-gut NETs. A landmark study, it represented the first randomised controlled clinical trial (RCT) performed in PRRT and was published in January 2017 in the *New England Journal of Medicine*.⁶ The primary end point was progression-free survival (PFS), which was estimated at month 20 as 65.2%, compared with 10.8% of controls treated with standard somatostatin receptor analogues.⁶ In a letter to the Editor, Hofman et al point out that the reported rate of vomiting in the trial is almost never seen after standard premedication with a setron 5-HT-receptor antagonist and dexamethasone prior to infusion of 25 g of lysine and 25 g of arginine. They also remark that other agents used to treat this disease, such as everolimus, have generally been compared with placebo rather than the potentially efficacious antiproliferative therapy of augmented-dose octreotide used in the NETTER-1 trial.⁷

The NETTER-1 Study was conducted by Advanced Accelerator Applications, according to Pharma industry criteria, in order to obtain formal regulatory approval, and eventual reimbursement, to ensure adoption of PRRT of GEP-NETs into mainstream oncologist practice. Patient selection on NETTER-1 did not require 68-gallium PET/CT, but with the recent wider availability of this modality, the theranostic

pair 68-gallium/177 lutetium is likely to become universally adopted for PRRT.

The favourable results and minimal toxicity profile seen in the NETTER-1 Study were hardly surprising given that clinical experience in multiple centres across Europe and Australia over the previous 10 years had demonstrated comparable, if not greater, improvement in patient outcomes in Phase 2 studies. The Rotterdam group very recently published long-term follow-up of 443 GEP-NET patients and compared their results in 177-lutetium-octreotate therapy of 94 patients with progressive mid-gut NET. These patients with progressive disease (PD) at baseline were comparable with those on the NETTER-1 Study and showed partial response (PR) 30%, PD 10%, PFS 24 months [95% confidence interval (18–30 months)], with overall survival (OS) 46 months [95% confidence interval (32–60 months)].⁸

In fact, median PFS more than double that reported in the NETTER-1 Study has been achieved using combination chemoradiopeptide therapy regimens such as capecitabine-177-lutetium DOTATATE.⁹ This combination has also been trialled prospectively in Rotterdam over the past 10 years and is scheduled for reporting in 2017. Meanwhile, in view of the success of capecitabine-temozolomide chemotherapy reported by Jonathan Strosberg,¹⁰ this regimen was combined with standard activity-dose 177-lutetium-DOTA-octreotate PRRT of advanced progressive GEP-NETs with very encouraging results.¹¹ In a single centre Phase 1/2 study of patients with advanced progressive pancreatic NETs overall response rate (ORR) was 83%, complete remission (CR) 13%, PR 70% and no patient manifested PD on treatment. Median PFS was 48 months. Median OS had not been reached at a median follow-up of 33 months.¹²

A multicentre Phase 2 RCT investigator-initiated study CONTROL-NETS, (CTC0120/AGO14 NET), is currently being performed, under the aegis of the Australasian Gastro-Intestinal Trials Group, to define toxicity and efficacy of this capecitabine/temozolomide/PRRT combination treatment of GEP-NETS.

Notwithstanding the excellent results of 177-lutetium-DOTA-octreotate PRRT monotherapy in thousands of patients with advanced progressive metastatic GEP-NETs throughout Europe and Australia, the European Neuroendocrine Tumor Society rated the evidence for PRRT only as Level 3, and found no place for such radionuclide treatment in its guidelines—except perhaps for consideration as a last line salvage therapy of pancreatic NETs when all the standard chemotherapy and biological therapy regimens had failed, or been stopped by unacceptable toxic side effects. Publication of NETTER-1 has elevated PRRT to level 1b evidence and the latest European Neuroendocrine Tumor Society guidelines have admitted that PRRT may be contemplated earlier in the treatment algorithm.¹³ Significantly, the NETTER-1 Study has achieved FDA regulatory approval of 177-lutetium-DOTA-octreotate PRRT of GEP-NETs as of September 2017, and, in Europe, European Medicines Agency approval is anticipated in early 2018.

Even more noteworthy, the sponsor of the NETTER-1 Study, (Advanced Accelerator Applications), has just been acquired by Novartis for a purchase price of USD 3.9 billion. (cnbc.com 30 October 2017). This major commitment by Big Pharma to theranostic nuclear oncology is a welcome vote of confidence in our future.

However, whilst the very costly drug regulatory approval process grinds ever-so-slowly, the pace of radiopharmaceutical development is increasing exponentially. The classic drug evaluation methodology of Phase 3 RCT multicentre studies with ORR, PFS and OS end points, designed for chemotherapy, will be unable to cope with the array of new small molecules, each radiolabelled with positron, gamma, beta, or alpha emitters, emerging on the horizon.

It is now becoming apparent that ¹⁷⁷-lutetium-somatostatin receptor antagonists may deliver a higher tumour radiation-absorbed dose than that of ¹⁷⁷-lutetium-DOTA-octreotate agonists, despite their lack of internalisation.¹⁴ The theranostic pair ⁶⁸-gallium-JR11 and ¹⁷⁷-lutetium-DOTA-JR11 (¹⁷⁷-lutetium-OPS-201) is currently in Phase 1/2 international multicentre open-label clinical trial in patients with GEP-NETs, and other tumours with neuroendocrine characteristics such as bronchial carcinoid and pheochromocytoma. This prospective study is being run by Ipsen Pharma (NCT02592707) and investigators are already contemplating possible evaluation of radiolabelled somatostatin receptor antagonists in patients with breast cancer, small cell lung cancer, renal cell cancer, medullary thyroid cancer and non-Hodgkin lymphoma (NHL).¹⁵ Other receptor systems, such as the gastrin-releasing peptide receptor and cholecystokinin receptor subtype 2, are alternative targets for radiolabelled antagonists.

Jean-Claude Reubi has been working with somatostatin analogues since 1982, and, together with another pioneer of theranostics, Professor Helmut Maecke, recently published a set of strategies to mitigate cancer targeting heterogeneity, changes in phenotype during disease progression and resistance. They remark that in NETs, up to three receptors can be coexpressed at relatively high density. NETs, such as breast, prostate, and brain tumours, concomitantly express several G protein-coupled receptors at a high density. They propose three strategies for multireceptor targeting in tumours: the use of heteromultivalent ligands which may bind simultaneously or monovalently to their different molecular targets, coinjection of a cocktail of radioligands, and sequential injection of different radioligands.¹⁶

In the foreseeable future, this constellation of receptor ligands may be radiolabelled with a variety of theranostic radiometals apart from ⁶⁸-gallium and ¹⁷⁷-lutetium. New alpha, beta, gamma, and Auger electron emitting radionuclides, such as ⁶⁷-gallium, ⁴⁷-scandium, ¹⁶⁶-holmium, ¹⁶¹-terbium, ¹⁴⁹-terbium, ²¹²-lead/²¹² bismuth, ²²⁵-actinium, and ²¹³-bismuth, are all in preclinical trial, some even in the clinic, although supply is currently very limited.¹⁷

The multiplicity of radionuclide choice leads to contemplation of cocktails of different therapeutic isotopes in the same patient. Combination radionuclide treatment of GEP-NETs with both ¹⁷⁷-lutetium and ⁹⁰-yttrium has been reported by several groups, most recently from Australia, where patients with progressive bulky NETs treated first with ⁹⁰-yttrium-DOTA-octreotate then subsequent cycles of ¹⁷⁷-lutetium-DOTA-octreotate achieved median PFS of 33 months in a relatively poor prognostic cohort.¹⁸

PROSTATE SPECIFIC MEMBRANE ANTIGEN THERANOSTICS OF PROSTATE CANCER

Whilst, at present, contemplation of optimal choices of molecule and radiolabel may be conjectural, the breaking news story of 2017 is beyond conjecture. Prostate cancer is the most common cancer and second-most frequent cause of cancer-related death in the USA.¹⁹ Recent advances in theranostic nuclear oncology management of metastatic castrate-resistant prostate cancer (mCRPC) herald an impending worldwide explosion in clinical demand. The dramatic impact of ⁶⁸-gallium-prostate specific membrane antigen (PSMA) PET/CT imaging upon diagnosis and treatment of prostate cancer has been documented in a recently-published, prospective, multicentre Australian study of 431 patients imaged for primary staging (25%), or for restaging/biochemical recurrence (75%).²⁰ On the basis of the ⁶⁸-gallium-PSMA PET/CT diagnostic imaging, the previously intended management was changed in over half the patients.²⁰ An international retrospective study of 100 patients demonstrated that ⁶⁸-gallium-PSMA PET/CT had altered management in 39% of patients with biochemically-recurrent prostate cancer.²¹ Present state-of-the-art of ⁶⁸-gallium-PSMA PET/CT imaging has been comprehensively reviewed as the gold standard for restaging recurrent prostate cancer.²² Simple kit formulations for bench-top preparation of ⁶⁸-gallium-PSMA are becoming available and are under preclinical and early clinical evaluation. They can provide high-yield, high-purity, rapid labelling at room temperature, without a requirement for a hot-cell environment, or expensive automated synthetic modules and consumables. Such kits are currently in routine clinical use in some Australian centres,²² and this simple technology will potentially allow all nuclear medicine facilities with PET/CT capability, to offer ⁶⁸-gallium-PSMA theranostic imaging worldwide.

From a urologist viewpoint, when disease progression occurs on androgen-depletion therapy, despite castrate levels of serum testosterone, first-line treatments for mCRPC comprise abiraterone plus prednisone, enzalutamide or sipuleucel-T.²³ Second-line treatment with abiraterone or enzalutamide, in patients unwilling to face the toxicity of chemotherapy, is often limited and responses are short-lived because of cross-resistance caused by, *e.g.* alternative splicing of the androgen receptor (AR). The opinion expressed by this urologist, "PSMA PET/CT or PET/MRI should be considered the new gold standard for imaging of males with biochemical recurrence," would recommend referral for PSMA-targeted endoradiotherapy of mCRPC. This enlightened view is not shared by his American urological

colleagues who omit any mention of 177-lutetium-PSMA in their 2017 “up-to-date comprehensive review of the current clinical practise guidelines in the treatment of CRPC”.²⁴ In Europe, urologists have remarked the great potential for theranostic 177-lutetium-PSMA applied under compassionate use provisions in end-stage mCRPC.²³ The multicentre study of 145 mCRPC patients treated in 12 centres across Germany since 2013 reported an ORR 45%, indicated by a prostate specific antigen (PSA) decline of greater than 50%.²⁵ Clemens Kratochwil, in a presentation to the annual congress of the EANM October 2017, documented this surrogate marker of response in seven reported studies of PSMA-radionuclide theranostic treatment of advanced mCRPC and compared them with published response data for approved, and non-approved, non-radionuclide molecular therapies. The pooled cohort of 160 patients treated with 177-lutetium-PSMA-617 achieved a mean decline in PSA greater than 50% in 42%, compared with 46% of the 92 patients who received 177-lutetium-PSMA-I&T. Theranostic alpha radionuclide treatment with 225-actinium-PSMA achieved the highest surrogate response of 63% in 38 patients. Comparison with standard approved regimens in mCRPC showed comparable PSA decline of greater than 50% with abiraterone (29%), enzalutamide (54%), and cabazitaxel (39%). Agents which failed to meet their clinical trial end points showed minimal responses; cabozantinib (11%), and tasquinimod (4%).

However, correlation between survival and PSA levels is complex in advanced mCRPC characterised by increasing heterogeneity and the various mechanisms associated with development of castration resistance. In addition, PSA response can be compromised by flare phenomena or visceral metastases not producing PSA. Consequently, the Prostate Cancer Clinical Trials Working Group 3 has proposed imaging methods to assess response.²⁶ This correlation is likely to be even greater with the recent advent of wide availability, in Europe and Australia at least, of 68-gallium-PSMA PET/CT, which shows superior early detection rates of recurrence and metastases.²⁰ Follow-up 68-gallium-PSMA PET/CT imaging is routinely performed between the second and third cycles of 177-lutetium-PSMA therapy to monitor response to the molecular-targeted treatment. In the German multicentre study ORR determined by imaging demonstrated PR 45% and stable disease 28%.²⁵

The outcome parameter of most significance for the patient is, however, survival benefit. Professor Richard Baum presented updated long term follow-up data at the WARMTH meeting in Vienna October 2017 updating his publication of 2015.²⁷ In his single centre study, 224 patients with mCRPC were analysed up to 55 months following 177-lutetium-PSMA therapy which achieved median OS 27 months.

After numerous encouraging retrospective reports of a favourable response of advanced mCRPC to 177-lutetium-PSMA, it is time for a reality check. These uncontrolled retrospective, single-centre Phase 2 studies of heterogeneous populations, using different treatment protocols, have yielded only Level 3 evidence of efficacy. In 10–15% of patients, 68-gallium-PSMA PET/CT fails to demonstrate the molecular target receptor, and

they are thus ineligible for treatment. 30% of those treated with 177-lutetium-PSMA fail to respond to the first cycle, although up to half these patients may respond to subsequent cycles.²⁸ In patients refractory to 177-lutetium-PSMA therapy, or for those who relapse early, dramatic response in end-stage mCRPC has been achieved with alpha radionuclide therapy with 225-actinium-PSMA.²⁹ Professor Mike Sathekge's group in Pretoria achieved complete imaging and biochemical response in almost all of 25 end-stage salvage prostate cancer patients treated with 225-actinium-PSMA. (Personal communication December 2017).

Whilst these single centre outcome data will not be admissible for formal assessment by regulatory agencies, Verburg and Luster, both consultants to major pharmaceutical companies, remark that “PSMA targeted imaging and therapy have become part of routine clinical care in an almost unprecedented rapid adoption process, and has replaced the previous clinical standard management of mCRPC wherever the necessary facilities are available and regulations for compassionate usage allow it.”³⁰ They also add a cautionary note; “If PSMA is really to remain in clinical practice, or for that matter even enter clinical practice in many countries, nuclear medicine as a whole will need to step up its act, bridge differences, and carry out the tedious work of performing proper, outcome-based, randomised, double-blind trials.”³⁰ However, just as in the case of 68-gallium/177-lutetium-DOTA-octreotate theranostic management of NETs, all the R&D and early phase clinical studies of 68-gallium/177-lutetium-PSMA in mCRPC have been performed in university hospitals. Without involvement of Pharma, the logistics and expense of mounting multicentre international RCTs is beyond the capability of the nuclear medicine community.

In a press release of 2 October 2017, Endocyte, Inc announced the purchase of an exclusive worldwide license of PSMA-617 from ABX GmbH, as a Phase 3 ready PSMA-targeted radioligand therapy for development in prostate cancer. The clinical trial is scheduled to commence mid-2018. However, the long lead-time for trial design, initiation, recruitment, follow up and evaluation will require several years for attainment of the desired goals of regulatory approval and reimbursement. Meanwhile, an interim measure may be to attempt to harmonise current 68-gallium/177-lutetium-PSMA theranostic clinical management of mCRPC by adhering to a single, simple protocol, using the same PSMA molecule with standardised eligibility and response evaluation criteria in respect of PSA, ORR, PFS, OS, and QOL. Whilst these non-randomised data would remain unlikely to satisfy Pharma standards or the requirements of regulatory agencies, they would provide essential *prima facie* evidence of efficacy and toxicity in a very large patient population.

WARMTH, in conjunction with the World Federation of Nuclear Medicine and Biology, has proposed such a harmonisation program in 25 centres worldwide, contemplating co-ordinated treatment of over 1000 patients within 2 years. The WARMTH NIGHTCAP National Investigators Global Harmonisation Theranostics of Cancer of Prostate) Study program will also train

and mentor personnel at new sites around the world for safe effective practice of 68-gallium/177-lutetium-PSMA theranostic management.

In the real world, the Editor-in-Chief of the *Journal of Nuclear Medicine* pointed out “That the exceptionally high demand for PSMA-targeted theranostics is providing the strongest evidence of its usefulness...its adoption is driven by the market, that is patients and their treating physicians, because it successfully addresses an unmet need.”³¹ An editorial in the *Journal of Clinical Oncology* in October 2017 agreed that there is an unmet need and concluded; “Finally, the poor outcomes overall in these trials with taxane therapy underscore the major unmet need for novel approaches to extend the survival of patients in this treatment refractory mCRPC setting.”³²

Toxicity of 177-lutetium-PSMA therapy of mCRPC is mild, even in this characteristically heavily pre-treated elderly population. Myelotoxicity in 10% is largely attributable to tumour infiltration of red marrow. Salivary gland toxicity, which may result in mild to moderate xerostomia is most prevalent with 225-actinium-PSMA. Prior botox injection has been reported anecdotally to mitigate salivary gland toxicity but not concomitant ice cooling (Richard Baum EANM 2017). In his report of 4 years of personal experience of administering up to 11 cycles of 177-lutetium-PSMA therapy, Professor Baum had encountered no renal toxicity. However, other investigators have regarded the kidney as representing the critical organ and in dosimetry studies report the radiation dose to kidneys as 0.72 ± 0.21 Gy GBq⁻¹.³³ Salivary gland doses were relatively high; parotid 0.55 ± 0.14 Gy GBq⁻¹, submandibular 0.64 ± 0.40 Gy GBq⁻¹ and lachrymal glands 3.8 ± 1.4 Gy GBq⁻¹.²⁹ Xerostomia is more severe after 225-actinium-PSMA therapy with estimated radiation absorbed dose to salivary glands 2.33 Sv RBE MBq⁻¹.²⁹

DOSIMETRY

Accurate measurement of dosimetry is time-consuming and difficult, and to date the need for, and added value of, dosimetry to optimise the therapeutic activity-dose in the individual patient has been far from self-evident. Dose estimations are confounded by radiobiological effects of radionuclide therapy at the cellular and molecular levels and any extrapolation from external beam radiotherapy will be erroneous, given the fundamental differences in dose rate and mechanisms of DNA damage. Nevertheless, the European Council Directive 2013/59, to be translated into national legislations before 6 February 2018, stipulates that in medical exposures for radiotherapeutic purposes, including radionuclide therapy, exposures of target volumes shall be individually planned and their delivery appropriately verified.³⁴

Even if we could, should we incorporate complex unproven dosimetric methodology to treatment of each patient in clinical practice? It may, in fact, be better to regard radionuclide therapy as being characterised as a tumour-selective treatment modality with more similarities to systemic chemotherapy, especially given that efficacy may often be determined by pharmacokinetics and repair mechanisms, and also perhaps by obscure immunologic and local inflammatory reactions. Other confounding factors for

dosimetric analysis include the prospect of combination chemimmunoradionuclide therapy with radiation sensitizers, or the use of polyADP ribose polymerase inhibitors to interfere with DNA repair.

Any estimate of dosimetry requires quantitative imaging at several time intervals in order to generate time/activity data. The short half-life of 68-gallium is challenging for serial collection of dosimetric data in individual patients over the required time period. The time-dependent biodistribution of 177-lutetium-PSMA was determined by SPECT/CT at a minimum of 5 time points, starting immediately after therapy, for at least 3 days post-treatment for each of three cycles in nine patients, by Kulkarni et al³⁵. The dosimetric findings in this study are very important and will significantly influence the prescribed administered activity of 177-lutetium-PSMA at each cycle. The tumour uptake by the prostate cancer metastases declined by 57% between Cycle 1 and Cycle 2, the residence time was 62% less and tumour radiation absorbed dose was reduced by 64% in the second cycle. There was a concomitant increase of 62% in kidney activity between Cycle 1 and Cycle 2, with 34% longer residence time and mean renal radiation absorbed dose increase of 34% during the second cycle. Subsequent tumour and renal uptake remained stable over the third cycle.³⁵

Such rigorous serial post-therapy dosimetric quantitative imaging is impractical for routine clinical use, but the recent advent of simplified single-shot quantitative imaging after PRRT may allow contemplation of measurement of dosimetry in every patient. A three-dimensional approximation of the dose distribution of 177-lutetium-DOTATATE can be made by a single quantitative SPECT image at 4 days, with acceptable accuracy,³⁶ and, with modification, may perhaps be extrapolatable to 177-lutetium-PSMA therapy. Fluorine-18 has a more convenient half-life and 18-fluorine-PSMA-1007 PET/CT is currently under evaluation to provide the capability for repeated quantitative dosimetric imaging.³⁷ Given that diagnostic accuracy is comparable with that of 68-gallium-PSMA PET/CT, the newly-developed 18-fluorine-PSMA ligands will potentially offer advantages in cost and availability over 68-gallium, in addition to facilitation of dosimetry.

REFINEMENT OF TRACER MOLECULES

Professor Hans-Jürgen Wester presented his unpublished innovative concept of radiohybrid twin tracers at the WARMTH and EANM meetings in October 2017. Radiohybrid tracers are chemical twins that inherently comprise two moieties suitable for labelling with 18-fluorine or a radiometal, e.g. 68-gallium or 177-lutetium. When labelled with 18-fluorine, the second site is complexed with cold metal; when labelled with a radiometal, the other site is occupied by cold 19-fluorine. Because these radiohybrids are chemical twins they are likely to manifest identical *in vivo* properties in respect of pharmacokinetics, affinity etc. and allow extrapolation of toxicity, selectivity and specificity data. First-in-man clinical 18-fluorine, natural gallium radiohybrid PSMA PET/CT imaging studies demonstrated excellent tumour uptake at 1 h in prostate cancer, with the advantage of very minimal bladder activity. Radiolabelling at room temperature

gives high yield at 15 min using a simple in-house procedure, without the requirement for an automated synthetic module.

What does the theranostic approach offer to the 10–15% of patients whose mCRPC tumours fail to take up 68-gallium-PSMA? Alternative receptors may be available for tumour targeting, such as the gastrin-releasing peptide antagonist Neo BOMB1. Preclinical studies showed superiority of the antagonist over the agonist, in much the same way as for GEP-NET somatostatin receptor targets. Preliminary clinical studies of 68-gallium-Neo BOMB1 PET/CT show excellent prostate cancer uptake, albeit with quite high pancreatic activity, and translation to 177-lutetium-Neo BOMB1 is planned.³⁸

Meanwhile, given that 68-gallium or 18-fluorine labelled PSMA ligand, PET/CT imaging detects sites of recurrence in more than 80% of all patients, and even in 90% of patients after external beam radiotherapy or brachytherapy,³¹ prostate cancer patients may not wish to undergo the currently mandated prior treatment with at least two lines of approved and endorsed strategies according to standard multidisciplinary guidelines. Indeed, urologists are now listening to the “clear desire of prostatic cancer patients, and patient organisations, that this effective theranostic option, with such an excellent toxicity profile, be made available now to patients with earlier stages of the disease; in these stages patients might receive a superior benefit, a longer PFS and an improved quality of life, as they exhibit a better performance status and lower tumour burden.”²³

The Advanced Prostate Cancer Consensus Conference 2017 recommended third-line treatment of advanced disease with cabazitaxel and with AR and AR signalling inhibitors.³⁸ A systematic review of 1338 patients receiving third-line treatment showed 21% achieved PSA decline of greater than 50% but toxicity caused discontinuation of treatment in 10–23%. By comparison 43% of 669 patients receiving 177-lutetium-PSMA as third-line treatment had PSA decline greater than 50%, and no patient experienced toxicity which stopped therapy. OS was marginally better in the 177-lutetium-PSMA group. (14 vs 12 months).³⁹

RADIOIMMUNOTHERAPY OF NON-HODGKIN LYMPHOMA

The desire for early, non-toxic, efficacious theranostic management is not limited to sufferers of prostate cancer. NHL is another very common malignancy which has been effectively treated with 131-iodine-antiCD20 radioimmunotherapy (RIT) in relapsed/refractory disease following traditional R-CHOP chemotherapy.⁴⁰ First-line 131-iodine-rituximab RIT of advanced follicular NHL on the INITIAL Phase 2 Study,⁴¹ achieved CR in 88% and partial response (PR) in 10% according to Deauville criteria on the 3 month 18-fluorine-FDG PET/CT scan. Follow-up at 10 years was reported in 2017,⁴² at which time neither median time-to-next-treatment, nor median PFS or median OS had been reached. Only 16% experienced disease progression within 10 years of a single outpatient

treatment with a prescribed activity of 131-iodine-rituximab predicated upon a radiation absorbed dose of 2 Gy to red marrow. There was no significant toxicity and no patient required admission to hospital as a consequence of the RIT. The long-term durability of CR in this single-shot theranostic study, which used prospective individualised dosimetry in every patient to obviate toxicity, is manifestly superior to all standard therapies for follicular NHL, and is much less costly. The recent substitution of 177-lutetium-rituximab, in place of 131-iodine radiolabelling will facilitate outpatient therapy by minimising radiation exposure of carers, whilst retaining the ability to perform individual prospective dosimetry.⁴³ A recent industry-sponsored Phase 1/2 clinical study of 177-lutetium-lilotomab satetraxan anti-CD37 monoclonal antibody RIT in eight patients with NHL, demonstrated that tumour radiation absorbed doses comparable with those achieved with 131-iodine-tositumomab anti-CD20 Mab were attained, at red marrow doses below the 2 Gy threshold for myelotoxicity.⁴⁴

Whilst these developments are encouraging, we must learn from our previous failure to persuade oncologists to incorporate RIT into their routine management of NHL; witness the inability of 131-iodine-tositumomab (Bexxar, Brentford, UK) to find clinical acceptance, and its subsequent withdrawal by GSK from the market in 2014. Similarly, 90-yttrium-ibritumomab-tiuxetan (Zevalin, Cambridge, MA) RIT of NHL has failed to become incorporated into mainstream oncologist practice.

ONCOLOGIST ENGAGEMENT IN THERANOSTICS

The challenge to those of us wishing to practise theranostic nuclear oncology is to become more physicianly in the care of our patients, and to engage with our medical oncologist colleagues in a close collaboration for personalised management of cancer. Nuclear physicians also need to learn molecular oncology and become fluent in the new language of genomics and proteomics by attending intensive courses such as that conducted at the University of Ulm as a 2 year European Society for Medical Oncology accredited online course supplemented by 6 periods of 1-week of personalised onsite instruction. We must also understand the pharmacokinetics of the new radio-nuclide targeting agents and the radiobiology of their effector mechanisms, in order to work with our physicist colleagues to design practical dosimetric theranostic protocols for each of our patients.

More and more advanced trainees entering our specialty are becoming dual-trained as nuclear physicians and medical, or radiation, oncologists. They will, more than ever, look to their radiologist colleagues for collaboration in the integration of molecular targeting with CT and MRI anatomical and functional parameters in dual-reading sessions and other collegiate activities. But, by itself, this team-building will not be enough. Theranostic nuclear oncology needs exposure on mainstream oncology websites, such as CIVIC ONCOLOGY, and publications in the oncology literature. Whilst almost every issue of the *Journal of Nuclear Medicine* in the 12-month period under review, contained at least one theranostic paper, the *Journal of*

Clinical Oncology, official organ of the American Society of Clinical Oncology, contained none.

Perhaps, now is the time to change the paradigm. Mainstream oncology appears to show signs of disenchantment with their precision approaches to cancer therapy by such agents as immune-checkpoint inhibitors, which have largely failed to provide durable response or survival gain, at a high cost in degradation of quality of life due to toxicity, both systemic and fiscal.

The concept underlying personalised medicine is that molecular analysis of a tumour in an individual patient will allow the selection of effective drugs to control that tumour and thereby prolong survival. This philosophy was subjected to scrutiny in a Sounding Board of the *New England Journal of Medicine* by two Canadian oncologists.⁴⁵ They remark two significant limitations in the increasing number of anticancer drugs targeting different signalling pathways. Most molecular-targeted agents provide only partial inhibition and many are too toxic to be used in combination. Pathways that signal cancer cell proliferation or cell survival are highly plastic and adaptable, whereas pathways that stimulate cell death may be suppressed. Normal cells depend upon related signalling pathways, and their inhibition leads to toxicity. In the Darwinian model of tumour evolution, intratumour heterogeneity is present early in cancer development and resistant subclones are selected by cancer treatment, leading to rapid relapse with refractory disease. Their stark conclusion that there should “be a clear message to patients that personalised cancer medicine has not led to gains in survival or its quality” was contested in a subsequent letter to the Editor, but those correspondents concluded “However imperfect the present status of ‘precision medicine’ it remains an important aspect of current therapy and provides directions for future advances.”⁴⁶

Maybe the way forward lies in our direction. Perhaps, the unique attributes of molecular targeted theranostic nuclear oncology might help to realise the potential of precision medicine. Demonstration of the specific molecular tumour receptor by biomarker imaging in the individual patient does not require biopsy, with its attendant problems of sampling error and tumour heterogeneity. Given receptor expression, the targeted endoradiotherapy exerts its tumoricidal action through direct DNA strand breaks and bystander effects on both tumour and its supporting stroma, which may be enhanced through concomitant radiosensitizers and by locally induced immune stimulation. It remains to be demonstrated to the satisfaction of oncologists, whether theranostic nuclear oncology can achieve tumour control with prolonged survival, minimal toxicity and actual enhancement of quality of life. It is probable, however, these potential therapeutic advantages may well become apparent to cancer patients long before wide acceptance by their treating doctors.

PATIENT REPORTED OUTCOMES (PROS) AND UNMET NEEDS

We live in a global village, connected by the all-embracing internet, by virtue of which our patients learn of the most

recently developed treatments for their cancer. Prolonged survival and improvement of quality of life are of paramount importance, and these concerns are reflected in the all-important patient reported outcomes (PROs) of novel cancer therapies. Josh Mailman, Chief Operating Officer of WARMTH, reported his own perspective as a patient with progressive GEP-NET in an invited editorial in the *Journal of Nuclear Medicine*, September 2017. Within 2 months, it had become the most accessed article in that journal over the previous 2 years.⁴⁷ His disease has been controlled for the past 10 years by theranostic 68-gallium/177-lutetium-octreotate treatment at Bad Berka, and, like him, many of his countrymen have chosen to fly to Europe over the past decade to receive theranostic management of their cancer, unavailable in the USA.

Unlike NETs, prostate cancer is not a rare disease, and (im) patients are unlikely to resign themselves to waiting another 10 years for access to 177-lutetium-PSMA whilst regulators and reimbursement agencies procrastinate. Perhaps, the newly-established non-stop flights from Europe, and from North America, to Australia might be filled with prostate cancer patients seeking theranostic 68-gallium/177-lutetium/225-actinium-PSMA management in the antipodes. Even closer, Southern hemisphere centres in South Africa and Chile also currently provide state-of-the-art theranostic nuclear oncology as an outpatient procedure.

RESPONSE TO GLOBAL DEMAND

It is already apparent that the public hospital system will not be able to cope with the anticipated demand, especially if inpatient radionuclide treatment continues to be mandated in Europe. The private sector is currently responding to market projections by building new comprehensive cancer centres which will incorporate theranostic nuclear oncology as core business.

How may these global market forces be reconciled with regulatory agency exigencies in the quest to provide timely, safe, efficacious, cost-effective, quality theranostic nuclear oncology services worldwide? One approach may be to perform pragmatic, prospective, harmonised studies, using an adaptive clinical trial design, supplemented by continued observation in large patient populations treated on standard protocols in the real world. The dual focus of such large-scale studies would be enhanced patient access to provide timely treatment and rigorous data collection within a learning continuum, which would then inform subsequent formal controlled clinical trial design. Such controlled data will be necessary to satisfy drug regulatory agencies and persuade the pharmaceutical industry to invest in theranostic nuclear oncology to ensure a sustainable future.

Perhaps the currently perceived need for Phase 3 RCTs may be modified in the event that dramatic improvement in survival and quality of life is unequivocally demonstrated in large populations of mCRPC patients worldwide. If it thus becomes

self-evident to patients, and their oncologists, that theranostic nuclear oncology can add years to life, and life to years, it will inevitably lead to adoption of personalised molecular-targeted radionuclide therapy within mainstream routine oncology clinical practice throughout the world.

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