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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Theranostic radiopharmaceuticals: established agents in current use

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ABSTRACT

Although use of the term “theranostic” is relatively recent, the concept goes back to the earliest days of nuclear medicine, with the use of radioiodine for diagnosis and therapy of benign and malignant thyroid disease being arguably the most successful molecular radiotherapy in history. A diagnostic scan with ^{123}I -, ^{124}I -, or a low activity of ^{131}I -iodide is followed by therapy with high activity ^{131}I -iodide. Similarly, adrenergic tumours such as pheochromocytoma and neuroblastoma can be imaged with ^{123}I -metaiodobenzylguanidine and treated with ^{131}I -metaiodobenzylguanidine. Bone scintigraphy can be used to select patients with painful bone metastases from prostate cancer who may benefit from treatment with beta- or alpha-particle emitting bone seeking agents, the most recent and successful of which is ^{223}Ra radium chloride. Anti-CD20 monoclonal antibodies can be used to image and treat non-Hodgkins lymphoma, though this has not been as commercially successful as initially predicted. More recently established theranostics include somatostatin receptor targeting peptides for diagnosis and treatment of neuroendocrine tumours with agents such as ^{68}Ga -DOTATATE and ^{177}Lu -DOTATATE, respectively. Finally, agents which target prostate-specific membrane antigen are becoming increasingly widely available, despite the current lack of a commercial product. With the recent licensing of the somatostatin peptides and the rapid adoption of ^{68}Ga - and ^{177}Lu -labelled prostate-specific membrane antigen targeting agents, we have built upon the experience of radioiodine and are already seeing a great expansion in the availability of widely accepted theranostic radiopharmaceuticals.

INTRODUCTION

Although use of the term “theranostic” is relatively recent, and also applies to therapies which do not involve radionuclides, the concept goes back to the earliest days of nuclear medicine, with the use of radioiodine for diagnosis and therapy of benign and malignant thyroid disease being arguably the most successful molecular radiotherapy in history. A definition of theranostic involves the administration of a diagnostic agent:

- (1) to determine localisation in the site or disease state under study as a surrogate for a potential therapeutic agent with similar chemical properties;
- (2) to examine its biodistribution as predictive of off-target (adverse) effects of the potential therapeutic agent;
- (3) as an aid in determining the optimal therapeutic dosage or activity to be administered, based on the anticipated tumoricidal doses measured in the tumour site (*i.e.* dosimetry); and/or
- (4) to monitor the response to this treatment.¹

Molecular radiotherapy or radionuclide therapy can be highly effective in treatment of tumours, but it is not without its dangers, making it important to select patients who are most likely to benefit from the administration of the therapeutic agent. Indeed, it can be argued that some chemotherapeutic and radiotherapeutic agents have failed in clinical trials due to inadequate patient selection; *e.g.* the patient does not express the target of the drug and/or the systemically administered drug does not reach the target in sufficient quantities.

Although common sense (and regulations in some countries) suggests that the quantity of a radiotherapeutic agent to be administered should be optimised for an individual patient, in practice this rarely happens.^{2,3} However, in many cases it is possible to do this with a theranostic agent. Just as chemotherapeutic agents are administered to the maximum tolerated dose in terms of normal tissue toxicity, molecular radiotherapy is often administered in an activity chosen to

result in the highest acceptable whole body dose or critical tissue radiation dose.

Theranostics is an active area of radiopharmaceutical research, as evidenced by other papers in this issue of the journal. However, we will review some long established examples of the theranostic concept which provide the underpinning for current research. Before discussing specific agents we must first address several general issues.

CHALLENGES IN THERANOSTICS

Chemical or biological equivalence?

How similar must the diagnostic and therapeutic agents be? In the ideal form, theranostics would involve chemically and therefore, biologically identical compounds. Radioiodine and metaiodobenzylguanidine (MIBG) meet this ideal (see below) but few others do. Although the diagnostic radiometals, ^{111}In and ^{68}Ga , and their therapeutic counterparts, ^{90}Y and ^{177}Lu , are all trivalent metals which can be attached to a targeting moiety with the same chelator, such as DOTA, there are subtle differences in their chemical structures which can affect their biological properties.^{4,5} To this end, ^{86}Y has been used for diagnostic PET imaging prior to therapy with ^{90}Y labelled compounds, but there is very limited availability of ^{86}Y making its use not very widely applicable.^{6–8}

H-J Wester has used the expression “twins in spirit” for a pair of theranostic molecules which are not chemically or biologically identical but which are similar enough in biodistribution that the diagnostic moiety adequately predicts the biodistribution of the therapeutic analogue.⁹ The reasons for using these twins are mainly practical, as discussed below. The patent status of a molecule may limit its availability for clinical use. The labelling conditions may differ between, *e.g.* ^{68}Ga and ^{177}Lu ; labelling with ^{68}Ga is best performed with a chelator which labels rapidly at room temperature, such as NOTA or tris (hydropyridinone) ligands,^{10–12} whereas ^{177}Lu labelling requires a more stable chelator such as DOTA.

Use of licensed products

The licensing/registration status of the diagnostic or therapeutic agent may limit its use, though the importance of this varies between countries. For example, in the international Phase III clinical trial of ^{177}Lu -DOTATATE (Lutathera®) in neuroendocrine tumours, it could be argued that PET imaging with ^{68}Ga -DOTATATE should have been used for patient selection and monitoring of response.¹³ However, the much inferior agent ^{111}In -pentetreotide (Octreoscan®) was used with lower-resolution SPECT imaging because it was a commercially available licensed agent.¹⁴

Cost of licensing a theranostic pair

Bringing a new drug to market is an expensive proposition.¹⁵ A theranostic pair can be twice as costly as a single agent because each may require a separate licensing application. In the above example of neuroendocrine tumours, this has happened, with separate licensing applications for ^{68}Ga -DOTATATE (NETSPOT®) and ^{177}Lu -DOTATATE (Lutathera)

being submitted by the same company in the USA. However, for the European market a different agent, ^{68}Ga -DOTATOC (SomaKit-TOC®), was licensed for the diagnostic portion of the procedure prior to therapy with ^{177}Lu -DOTATATE.

ESTABLISHED CLINICAL USE

Radioiodine in thyroid disease

The use of radioiodine in benign and malignant thyroid disease has long been the standard of practice around the world.¹⁶ In benign thyroid disease, for many years a low activity of ^{131}I -iodide was administered for a diagnostic scan or determination of percentage uptake using a collimated probe. Because of the poor dosimetry and imaging characteristics of ^{131}I , ^{123}I -iodide is being used increasingly in its place, though often a $^{99\text{m}}\text{Tc}$ -pertechnetate scan will suffice. The therapeutic activity of ^{131}I -iodide to be administered is then individualised based on the size of the patient's gland and the percentage uptake of iodide in order to deliver a radiation dose of 100–150 Gy to the thyroid.¹⁷

Differentiated thyroid carcinoma is initially treated surgically, followed by a diagnostic scan using a low activity of ^{131}I -iodide or, increasingly, ^{123}I -iodide or ^{124}I -iodide.¹⁸ The purpose of the diagnostic scan is to identify residual functioning tissue in the thyroid bed and to document the extent of metastases and their avidity for iodide. However, despite 70 years' experience with radioiodine therapy, there is no generally accepted dosage regimen for individually optimised therapy.^{19,20} Although activities of 1–5 GBq are recommended, most commonly 3.7 or 5.55 GBq are administered. Indeed, the value of 3.7 GBq (100 mCi) was originally proposed for ^{130}I -iodide and translated to ^{131}I -iodide on an empirical basis.¹⁶ A few years ago, two large studies showed equivalent results with 1.1 GBq compared to the standard 3.7 GBq in low risk thyroid carcinoma.^{21,22} Thus, a therapy which has been in use for 70 years is still being optimised.

Figure 1 shows an example of serial treatment of a patient with differentiated thyroid carcinoma.

Metaiodobenzylguanidine (MIBG) in adrenergic tumours

^{131}I -MIBG (iobenguane) was developed by the Ann Arbor group for imaging adrenergic nerve terminals in the adrenal medulla.²³ Its chemical structure is an amalgam of the neuron blocking drugs bretylium and guanethidine. It was quickly shown to be useful in detection of pheochromocytoma²⁴ and soon thereafter, its first therapeutic use was reported.²⁵ Since then, it has had a chequered history because of limited availability due to lack of a commercial sponsor and a dearth of randomised controlled trials.^{26–28}

Nonetheless, ^{131}I -MIBG is an effective agent and a true theranostic in that the diagnostic and therapeutic products are chemically identical.²⁹ A diagnostic scan is performed using ^{131}I - or ^{123}I -MIBG to demonstrate “adequate uptake” in the lesion(s), though there is little agreement on a definition of this criterion. In general, for therapy with ^{131}I -MIBG fixed activities between 3.7 and 11.1 GBq are administered rather than using a dosimetric approach, though the latter has been attempted.³⁰ Patient

Figure 1. Serial whole body anterior planar gamma camera images in a 64-year-old male with differentiated thyroid carcinoma who was initially treated surgically. (a) Imaging following first ablation dose of 5940 MBq ^{131}I -iodide show multifocal tracer uptake in the neck, particularly on the left side confirmed by SPECT/CT (not shown), suggestive of residual functioning thyroid tissue. (b) Imaging following second dose of 6785 MBq ^{131}I -iodide 6 months later shows no evidence of iodine-avid disease.

preparation includes withdrawal of a long list of potentially interfering medications and provision of adequate blockade of the thyroid gland.²⁹ In recent years, a high specific activity preparation of ^{131}I -MIBG (Azedra®) has been investigated which may allow administration of higher activities with fewer side effects attributable to the cold drug;³¹ however, this is not yet commercially available.

Figure 2 shows an example of a patient with pheochromocytoma undergoing a diagnostic scan with ^{123}I -MIBG prior to therapy with ^{131}I -MIBG.

Bisphosphonate bone scintigraphy prior to palliation of painful bone metastases

Palliative treatment of painful bone metastases from prostate and breast cancer became more widely available in the 1990s

Figure 2. Images following administration of 400 MBq ^{123}I -MIBG in a 62-year-old female with suspected pheochromocytoma. (a) Anterior whole body planar gamma camera image shows an intense focus of activity in the abdomen. (b) Contrast-enhanced CT scan shows a nodule in the left adrenal gland. (c) Fused SPECT/CT image shows colocalisation of activity to the nodule in keeping with pheochromocytoma. MIBG, metaiodobenzylguanidine.

with the commercial introduction of ^{89}Sr chloride (Metas-tron®), ^{153}Sm -lexidronam (EDTMP; Quadramet®), and ^{186}Re -etidronate (HEDP).^{32–34} For all of these agents, bone scintigraphy with $^{99\text{m}}\text{Tc}$ -bisphosphonates (medronate, oxidronate) is used in patient selection by documenting sites of increased osteoblastic activity. For ^{153}Sm -lexidronam and ^{186}Re -etidronate, the targeting mechanism is the same as $^{99\text{m}}\text{Tc}$ -bisphosphonates, *i.e.* binding to hydroxyapatite. In contrast, ^{89}Sr chloride localises by a different mechanism as an analogue of calcium, though the bone scan still provides an adequate prediction of localisation. However, the diagnostic scan is not used to tailor an individual patient's dose and the standard activities administered are 150 MBq ^{89}Sr chloride, 37 MBq kg^{-1} ^{153}Sm -lexidronam, and 1295 MBq ^{186}Re -etidronate.³⁴ A recent study has highlighted the potential role of patient specific dosimetry in ^{186}Re -etidronate therapy.³⁵

In 2013, ^{223}Ra chloride (Alpharadin; Xofigo®) became available for treatment of patients with castration resistant metastatic prostate cancer; indeed, the Phase III clinical trial was terminated early due to the survival advantage of the patients who received the active drug, the first bone seeking radionuclide to produce such an effect.³⁶ Bone scintigraphy is used to select patients who may benefit from ^{223}Ra chloride; however, the activity administered is calculated based on the patient's weight, not degree of accumulation of activity on the diagnostic scan.³⁷ Recent work has shown the feasibility of imaging based dosimetry with ^{223}Ra chloride.³⁸

Targeting the CD20 antigen in non-Hodgkins lymphoma

The first commercially available radioimmunotherapeutic agents were ^{90}Y -ibritumomab tiuxetan (Zevalin®, USA and Europe) and ^{131}I -tositumomab (Bexxar®, USA, now withdrawn).^{39,40} Both targeted the CD20 antigen in non-Hodgkins lymphoma and a pre-therapy diagnostic scan was required in the USA. For ibritumomab, 185 MBq of the ^{111}In analogue was used with imaging with 2–3 scans over 3–5 days, though this was only to confirm normal biodistribution and was not used in dose adjustment. Indeed, the standard activity of 15 MBq kg⁻¹ ^{90}Y -ibritumomab is only reduced in patients with platelet counts between 100,000 and 150,000 mm⁻³ who receive 11 MBq kg⁻¹. The maximum activity to be administered is 1200 MBq. The requirement for the ^{111}In scan has been removed because of its cost, inconvenience and rare utility; it was never required in Europe.⁴¹

For tositumomab, a low activity (185 MBq) of ^{131}I -tositumomab is administered for the diagnostic scan, with three sets of images acquired over 7 days.⁴² These images are used to confirm normal distribution and to estimate the activity required to deliver a total body dose of 0.75, or 0.65 Gy in patients with platelet counts between 100,000 and 150,000 mm⁻³.^{43,44} The therapeutic activity is typically 2000–6000 MBq.

In the early days, it was posited that the difference in beta particle energy, and hence path length in tissue, might determine the choice of agent; *i.e.* ^{90}Y -ibritumomab with its higher energy and path length being suited to larger tumours and the lower energy ^{131}I -tositumomab for smaller ones.⁴² The two agents might even be used sequentially, switching from ibritumomab to tositumomab as tumours shrank. However, in the end, it was convenience and commercial issues which resulted in the continuing availability of ibritumomab, albeit with modest usage, while tositumomab has been withdrawn from the market.⁴⁵

With the expiry of the patent on ibritumomab, there is the potential for generic biosimilars to become available, though current interest centres on agents such as rituximab labelled with ^{131}I , ^{177}Lu , or even the alpha emitter ^{227}Th .^{46–49}

RECENTLY ESTABLISHED CLINICAL USE

Somatostatin peptide therapy

Probably, the greatest recent success story in theranostics is the development of radiopeptides which bind to the somatostatin receptor for diagnosis and treatment of patients with neuroendocrine tumours, culminating with the international licensing of a radiotherapeutic agent in 2017. The story started with the investigation of ^{123}I -Tyr-octreotide for proof of principle,⁵⁰ followed by the commercial introduction of ^{111}In -pentetreotide (Octreoscan).⁵¹ Because of the limitations of planar and SPECT imaging, analogues labelled with the positron emitter ^{68}Ga were developed for PET imaging (DOTATOC and DOTATATE), which in turn were the impetus for the expanded availability of $^{68}\text{Ge}/^{68}\text{Ga}$ generators.^{52,53} Despite the recent licensing of kits for use with ^{68}Ga , numerous technical, regulatory, and financial challenges limit the utilisation of these agents. In parallel with this, therapy was evaluated, first with high activities of auger

Figure 3. Serial PET images (maximum intensity projections) following administration of ~150 MBq ^{68}Ga -HA-DOTATATE in a 66-year-old male with an atypical pulmonary carcinoid with liver and bone metastases. (a) Baseline anterior projection shows multiple hepatic and bony metastases. (b) Follow-up imaging 1 year later after four cycles of 7400 MBq ^{177}Lu -DOTATATE shows reduction in size and avidity of the lesions in the liver, with some being no longer visible, and only low grade bone uptake.

electron emitting ^{111}In -pentetreotide, then the beta particle emitters ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE.^{54–57} The path of these agents to market has been a circuitous one, with various false starts due to commercial issues. Though both ^{90}Y and ^{177}Lu agents have been studied extensively, ^{177}Lu is preferred because of a more favourable side effect profile, in particular, less renal toxicity.⁵⁷ Eventually, a company used the Rotterdam data to initiate an international Phase III clinical trial of ^{177}Lu -DOTATATE (Lutathera) leading to its licensing in the USA and Europe.¹⁴ However, nothing remains the same for very long, as now there is evidence that alpha particle emitters such as ^{213}Bi - and ^{225}Ac -DOTATATE may be even more effective than ^{177}Lu .^{58,59}

Figure 3 shows an example of response in a patient with a carcinoid tumour.

Prostate specific membrane antigen

A somewhat more direct story is the development of agents to image and target the prostate-specific membrane antigen (PSMA) receptor which is overexpressed in prostate cancer,⁶⁰ though this too has faced commercial challenges. Indeed, the initial forays by Molecular Insight Pharmaceuticals were sidetracked by bankruptcy.

More than 20 years ago, a monoclonal antibody which binds to PSMA was developed, ^{111}In capromab pendetide (ProstaScint®), but it struggled commercially due to poor image quality.⁶¹ Utility was somewhat enhanced by hybrid imaging with SPECT/CT.⁶² An important problem was that capromab binds to an internal epitope of PSMA and membrane permeability is insufficient to allow adequate quantities of the tracer to accumulate. More recently, alternative antibodies such as J591 which bind to an

Table 1. Established theranostic agents in current use in the clinic

Clinical indication	Diagnostic agent	Therapeutic agent
Hyperthyroidism or thyroid cancer	^{123}I -iodide	^{131}I -iodide
Adrenergic tumours	^{123}I -iobenguane	^{131}I -iobenguane
Bone metastases from prostate cancer	$^{99\text{m}}\text{Tc}$ -MDP	^{223}Ra chloride
Non-Hodgkins lymphoma	^{111}In -ibritumomab	^{90}Y -ibritumomab
Neuroendocrine tumours	^{68}Ga -DOTATATE	^{177}Lu -DOTATATE
Prostate cancer	^{68}Ga -DKFZ-PSMA-11	^{177}Lu -DKFZ-PSMA-617

external domain of PSMA have been studied with somewhat greater success.^{63,64} However, the size of an antibody results in prolonged distribution and clearance kinetics, limiting the choice of radiolabel.^{65,66}

Molecular Insight Pharmaceuticals chose to target PSMA expression using peptide–urea small molecule inhibitors of the enzyme N-acetylaspartylglutamate peptidase, a structural and functional homologue of PSMA. These small molecules should have a more favourable pharmacokinetic profile than an intact antibody or its fragments. The purest theranostic pair would use ^{123}I (SPECT) or ^{124}I (PET) for diagnosis followed by ^{131}I for therapy, though more convenient $^{99\text{m}}\text{Tc}$ -labelled diagnostic agents were also developed.^{67–69} In parallel with this, a ^{68}Ga -labelled analogue for PET imaging was developed and popularised by the Heidelberg group and has quickly been adopted around the world. In

addition to the initial compound, DKFZ-PSMA-11, a variety of analogues are under investigation,^{70–73} and a clinical procedure guideline has been published.⁷⁴

The remarkable degree of targeting and high tissue contrast made this an ideal candidate for therapy and a variety of ^{177}Lu labelled analogues have been developed.^{72,75} Although no commercial product is available yet, investigator sponsored studies are ongoing and compassionate usage is already widespread, although the UK is lagging behind other countries.^{76,77} Promising results have also been reported with the alpha-emitter ^{225}Ac -PSMA-617.⁷⁸

FUTURE PROSPECTS

The theranostic concept goes back to the earliest days of nuclear medicine. Indeed, with a looser definition of theranostic, many nuclear medicine procedures are used to select the optimal treatment for individual patients. We have recently seen the first licensing of a companion diagnostic, $^{99\text{m}}\text{Tc}$ -etarfolatide (EC20, Folcepri®), for selection of patients for treatment of lung and ovarian cancers; both agents target the folate receptor and the therapeutic counterpart (vintafolide, EC145) is coupled to a vinca alkylid.⁷⁹ With the licensing in 2017 of ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE, and ^{177}Lu -DOTATATE and with the rapid adoption of ^{68}Ga - and ^{177}Lu -labelled PSMA targeting agents, we have built upon the experience of radioiodine and are already seeing a great expansion in the availability of widely accepted theranostic radiopharmaceuticals (Table 1).

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