

Targeted radionuclide therapy for neuroendocrine tumours

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Abstract

Evidence supporting the potential contribution of targeted radiotherapy to the management of neuroendocrine tumours is now strong. Acting systemically, this is an effective option for patients with inoperable or multi-site disease. Toxicity is generally low, being limited to reversible myelosuppression and theoretical nephrotoxicity. Prerequisites for treatment success include demonstration of high tumour uptake relative to non-target tissues on quantitative diagnostic radionuclide imaging and stable haematological and biochemical function. In addition to ¹³¹I metaiodobenzylguanidine therapy, which is now well established, there is growing interest in radiolabelled peptide therapy using a range of somatostatin receptor analogues such as ⁹⁰Y DOTATOC and ⁹⁰Y lanreotide. The results of clinical experience are summarised and the direction for future research is discussed.

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Introduction

There is growing consensus that the future of cancer treatment for solid tumours lies in a multi-modality approach. Targeted radionuclide therapy offers several advantages compared with conventional management options for neuroendocrine tumours (NETs). Selective tumour localisation allows treatment to be administered systemically while minimising potential toxicity to non-target, healthy tissues. Targeted therapies are usually better tolerated than other, systemic treatments and deliver higher absorbed radiation doses to the tumour than can be achieved by external beam irradiation. This is particularly important in the context of NETs which are relatively radioresistant compared with other solid cancers.

tumours of neuroectodermal origin, including pheochromocytoma, carcinoid tumours and medullary thyroid carcinoma (Sisson *et al.* 1981). More recently, interest has focused on somatostatin receptor (SSR) targeting, which exploits the over-expression of SSRs on the cell surfaces of a range of NETs (Kwekkeboom *et al.* 1993). Diagnostic radiopharmaceuticals can be modified for therapeutic use by substituting a therapeutic radioisotope for the γ -emitting, imaging radiolabel. Thus ¹²³I mIBG can be replaced by ¹³¹I mIBG. SSR analogues used for diagnostic scintigraphy are labelled using Indium-111 (¹¹¹In). For therapy, ¹¹¹In is replaced by the radiometal label, yttrium-90 (⁹⁰Y).

Examples of tracer ¹²³I mIBG and ¹¹¹In octreotide images are given in Figs 1, 2 and 3.

Targeting mechanisms

Targeted therapy has evolved from diagnostic radionuclide imaging. Treatment success depends upon the specificity of the targeting, carrier molecule and upon the choice of an appropriate radioisotope label. Two targeting pharmaceuticals are routinely used to diagnose and stage neuroendocrine tumours. Metaiodobenzylguanidine (mIBG) is a guanethidine analogue which is selectively concentrated by the neuroadrenergic system and by

Radionuclide selection

Several factors influence the selection of an appropriate therapy radioisotope. For practical purposes, choice is limited to β -particle emitters. It is important that the physical half-life of the selected radionuclide matches the biological turnover of the carrier–radiolabel complex *in vivo*. Physical half-life directly relates to the rate at which an absorbed radiation dose is delivered. Whereas a high

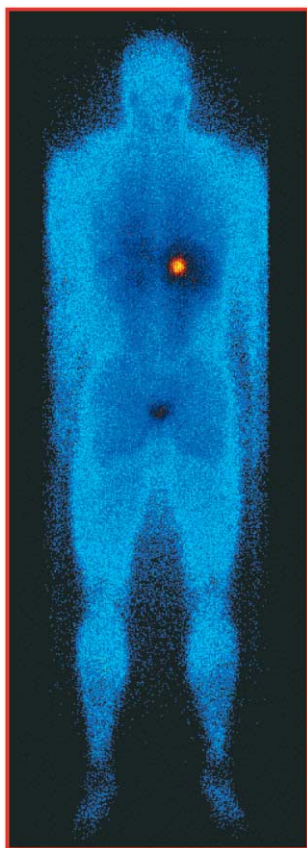


Figure 1 ^{123}I -MIBG whole body imaging: solitary intra-adrenal phaeochromocytoma.

dose rate is particularly suited to rapidly dividing tumours, a longer physical half-life and low dose rate may be more effective for relatively indolent malignancies such as NETs. The ultimate target to achieve cell death is the nucleus. The β emitter selected must therefore have an appropriate path length to reach the nucleus, depending upon the site of cellular radiopharmaceutical concentration. mIBG, for example, is stored in cytoplasmic vesicles, so that the nucleus is well within range of medium energy β particles such as ^{131}I . Carrier molecules that target the cell surface, such as SSRs, require a longer particle path length to achieve nuclear damage and are ideally labelled with high energy β emitters such as ^{90}Y . The characteristics of radiopharmaceuticals used to treat NETs are summarised in Table 1.

Treatment delivery

Radionuclide therapy for NETs is usually administered by intravenous infusion. Radiopharmaceutical uptake is heterogeneous, reflecting a combination of poor tumour vascularity, high interstitial pressure and central necrosis

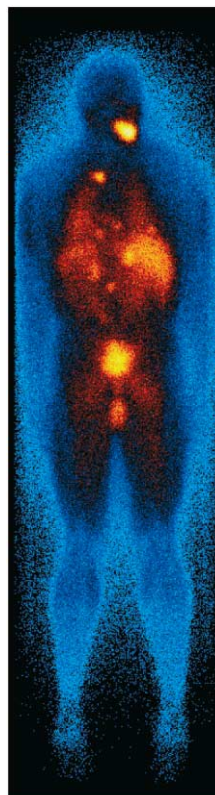


Figure 2 ^{123}I -MIBG whole body imaging: malignant phaeochromocytoma.

in larger lesions. The resulting non-uniform radiation dose distribution is mitigated by the long particle range of medium and high energy β -particle emitters, which allows crossfire between adjacent cells. The particle range of ^{90}Y , for example, extends across 50 to 70 cell diameters. Direct intra-arterial injection achieves higher intra-tumoural concentrations and may be of value in treating isolated hepatic or cerebral lesions, but is less helpful in managing disseminated disease (Buscombe *et al.* 2003).

Patient selection

The only curative treatment for NETs is complete surgical excision, although debulking may also prolong survival. Targeted therapy is generally reserved for patients with inoperable or multi-site disease. Several criteria govern patient eligibility for this approach.

The prerequisite for treatment is confirmation of selective tumour targeting at all known sites on diagnostic tracer imaging. It is essential that the same tracer is used for imaging and treatment – this is particularly important for SSR therapy, where individual peptides target different receptor populations. Detailed image quantification is required to measure the intensity of uptake by

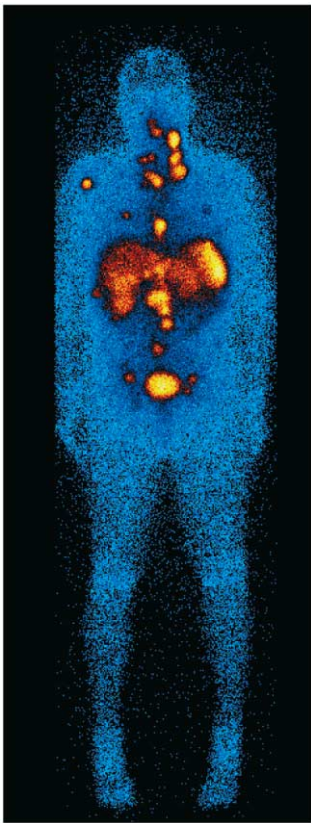


Figure 3 ¹¹¹In Octreotide whole body imaging: medullary thyroid cancer.

tumour compared with normal tissues – the therapeutic ratio, although, for practical purposes, this can be assessed visually in the majority of cases. The therapeutic ratio reliably predicts the radiation absorbed dose that will be delivered to the tumour and likely toxicity resulting from ‘bystander’ irradiation of non-target tissues such as the bone marrow. Ideally, patients should undergo both quantitative ¹²³I mIBG and ¹¹¹In peptide tracer imaging to establish which pharmaceutical offers the optimal therapeutic ratio for treatment.

Second, patients must be haematologically and biochemically stable. All high activity radionuclide therapies result in a degree of reversible myelosuppres-

Table 1 Physical characteristics of radioisotopes used to treat NETs (adapted from Flower (10))

Radionuclide	Half life (days)	β energy (mean) (MeV)	Mean particle range (mm)
¹⁷⁷ Lu	6.7	0.15	0.27
¹³¹ I	8	0.2	0.45
⁹⁰ Y	2.7	0.94	4.2

¹⁷⁷Lu, lutetium-177.

sion. The rate of recovery is partly dose-related but depends more on underlying bone marrow reserve. Increased toxicity is likely in patients who have extensive bone marrow infiltration by the tumour at the time of treatment and in subjects who have been heavily pretreated with chemotherapy or external beam radiotherapy. Concurrent chemotherapy or interferon therapy are avoided to minimise the risk of additive, unpredictable myelosuppression. As both mIBG and radiolabelled SSRs are renally excreted, impaired renal function will result in slow radiopharmaceutical clearance and increased toxicity.

Lastly, patients must be co-operative and reasonably independent to minimise the radiation risk to staff and carers. Specific radiation protection requirements will depend on the radioisotope used.

Contra-indications to treatment include pregnancy, lactation, unmanageable urinary incontinence, which might lead to radioactive urine contamination, myelosuppression and renal failure. These criteria are summarised in Table 2.

Treatment administration

Unsealed source therapies are administered in designated facilities incorporating appropriate lead shielding, en suite washing facilities and radiation monitoring equipment. Treatment should be delivered by a specialist multi-disciplinary team with appropriate training and experience in managing unsealed source therapy. ¹³¹I mIBG is administered by slow intravenous infusion with monitoring of vital signs. The high energy photon emitted by ¹³¹I

Table 2 Patient selection criteria for targeted radionuclide therapy

Indications

- Inoperable/metastatic NET
- Increased uptake at all known tumour sites
- Stable haematology
 - Hb>100 g/l
 - WBC>3.0×10⁹/l
 - Platelets>100×10⁹/l
- Stable biochemistry
 - Urea<10 mmol/l
 - Creatinine<160 μmol/l
 - GFR>40 ml/min
- Co-operative

Contraindications

- Pregnancy/lactation
- Haemodynamic instability precluding isolation
- Unmanageable urinary incontinence
- Myelosuppression
- Renal failure

WBC, white blood cell count; GFR, glomerular filtration rate.

necessitates a period of isolation post-therapy, depending on national regulations. As a pure β -particle emitter, ^{90}Y peptide therapy is generally simpler to administer and treatment can theoretically be undertaken on an out-patient basis, again according to national legislation. Co-administration of amino acids reduces renal tubular peptide binding and significantly lowers the risk of acute and delayed radiation nephritis due to thrombotic microangiopathy (Moll *et al.* 2001).

Treatment efficacy

^{131}I mIBG and radiolabelled peptide therapy have been introduced cautiously in Europe. Development has been largely investigator led and no randomised clinical trials have been undertaken. Although a number of small series have been published, wide variations in practice are reported, making comparison of results between centres difficult.

^{131}I mIBG

A survey of mIBG practice in Europe was undertaken in 1999 (Lewington *et al.* 2003). Data were collated from 14 institutions undertaking ^{131}I mIBG therapy for a range of NETs. Pancreatic NETs are rarely mIBG avid and were not included in the survey. Over 99% of 537 treated patients had refractory, stage III/IV disease. Excluding childhood neuroblastoma, overall objective response (complete and partial tumour response) was 30%. This was associated with reduction in measurable tumour markers (complete and partial response) in 38% of patients and subjective response in 52%. Toxicity was virtually confined to temporary myelosuppression – 14% World Health Organization grades I and II; 3% grades III and IV. Mean response duration was 18.4 months (range 1–144 months). The combination of high symptom benefit with low toxicity suggests that ^{131}I mIBG therapy is a valuable palliative treatment option for patients with advanced NETs. Preliminary data suggest an activity–response relationship, with superior responses at higher cumulative administered activities, but formal phase II studies are required to investigate this further.

^{90}Y peptide therapy

The greatest clinical experience using radiolabelled SSR therapy is reported using ^{90}Y DOTATOC. Paganelli *et al.* (2002) reported 28% overall responses in 87 patients treated using repeated infusions of ^{90}Y DOTATOC. Cumulative activities of 7.4–20.2 GBq were administered, the maximum tolerated activity per cycle being 5.18 GBq. Waldherr *et al.* (2002) reported 23% overall response rates in 39 patients treated using cumulative activities of

7.4 GBq/m² delivered in four treatment cycles. Subjective response was high – reduced diarrhoea (83%), flushing (46%) and wheeze (63%).

Toxicity is limited to temporary myelosuppression, particularly lymphopaenia, although this is rarely dose limiting. The potential risk of nephrotoxicity, reported previously, is reduced by co-administration of amino acids.

Experience using ^{90}Y lanreotide has also been reported in 154 patients with a range of NETS (Virgolini *et al.* 2002). Overall response was 14% with 41% tumour stabilisation. ^{90}Y DOTATOC uptake is superior to ^{90}Y lanreotide in approximately 66% of NET patients but lanreotide may have a role in managing iodine-negative thyroid cancer, hepatocellular carcinoma and lung cancer.

Conclusions

Targeted therapy can make a major contribution to the management of NETs. Given the range of therapy options for advanced disease, a major challenge for the future will be to optimise treatment sequencing to ensure maximal benefit without compromising patients' eligibility for subsequent therapies.

Attention must focus on improving selection for targeted therapy and on adopting standardised protocols so that results in relatively rare tumour types can be compared between centres. The modest overall response rate reported is likely to reflect a combination of relative undertreatment in a patient population that tends to present late with bulky, end-stage disease. Limited ^{131}I mIBG data support further activity escalation studies, underpinned by detailed dosimetry to clarify a theoretical dose–response relationship. Tumour stabilisation may be a valid outcome in NETs but long-term follow-up is required to assess survival gain, particularly for more indolent tumour types. The potential contribution of radiosensitisers to enhance the efficacy of targeted therapy in an hypoxic environment remains unexplored.

Further research is planned to evaluate more selective SSR peptides and alternative radiolabels, such as lutetium-177 (Kwekkeboom *et al.* 2001, 2003). The way forward may lie in a combined approach, exploiting the theoretical advantages of short- and long-range radionuclides for a mixed volume, heterogeneous tumour population.

Anecdotal evidence indicates a potential role for targeted therapy in a neo-adjuvant setting. A relatively modest 20–40% reduction in tumour volume, particularly when associated with reduced tumour vascularity, may facilitate surgical resection of otherwise inoperable solitary tumours.

Access to targeted therapy in Europe is variable, constrained by a shortage of facilities, cost and limited

knowledge among referring clinicians. The trend towards multidisciplinary cancer team working and randomised clinical trials will help to raise awareness of unsealed source therapy and improve the selection of patients for treatment. In addition, a substantial infrastructure investment will be required to meet predicted demand and to ensure that the potential of this approach is realised.

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