Targeted radionuclide therapy

Targeted radionuclide therapy has the potential to selectively deliver radiation to diseased cells with minimal toxicity to surrounding tissues.

M Sathekge, MB ChB, MMed (Nuclear Medicine), PhD

Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Corresponding author: *M Sathekge (mike.sathekge@up.ac.za)*

The goal of targeted radionuclide therapy is to selectively deliver radiation to cancer cells and/or diseased tissue with minimal toxicity to surrounding normal tissues. The basis for successful radionuclide therapy is a theranostic approach that integrates diagnostic testing for the presence of a molecular target for which a specific treatment/drug is intended (Fig. 1). Theranostics is a revolutionary approach that promises improved therapy selection on the basis of specific molecular features of disease, greater predictive power for adverse effects due to improved patient-specific absorbed dose estimates, and new ways to objectively monitor therapy response.[1,2] Currently, radionuclide therapy remains an important treatment option because ionising radiation from radionuclides can kill cells and inhibit growth in the benign and cancerous lesions that result from proliferative diseases. Radiation kills cells by damaging the DNA in the cell nucleus, thereby inhibiting cellular reproduction. Rapidly developing studies also demonstrate the beneficial effect of combining radionuclide therapy with chemotherapy.[1]

The objective of this article is to introduce the reader to the benefits of targeted radiotherapy, also known as molecular theranostics, to improve patient management. The article highlights evidence-based radionuclide therapy, which is available in South Africa for thyroid cancer, neuro-endocrine tumours, liver tumours (primary and secondary), non-Hodgkin's lymphoma, and bone metastases, and for treating other non-cancerous diseases. A comprehensive review of the pathology and theranostic targets is beyond the scope of this article, and the reader is referred to reviews in related subjects.

Theranostics is a revolutionary approach that promises improved therapy selection on the basis of specific molecular features of disease, greater predictive power for adverse effects due to improved patient-specific absorbed dose estimates, and new ways to objectively monitor therapy response.

Targeting mechanism/radiopharmaceuticals

The process of tailoring therapy for a patient is based on selecting appropriate radiopharmaceuticals and mechanisms. The commonly employed radiopharmaceuticals and mechanisms are summarised in Table 1. Common examples of patient selection criteria for targeted radionuclide therapy are shown in Table 2.[3]

Table 1. Available radionuclide therapy in oncology

Radionuclide	Physical half-life (days)	Emission	Maximum range (mm)	Radiopharmaceutical	Targeting mechanism	Indications
I-131	8.04	Beta, gamma	4	I-131 as iodide	Thyroid hormone synthesis	Differentiated thyroid cancer
Lu-177	6.7	Beta, gamma	1	Lu-177 DOTATATE	Somatostatin-receptor binding	Neuro-endocrine tumours
Y-90	2.7	Beta	12	Y-90 DOTATATE	Somatostatin-receptor binding	Neuro-endocrine tumours
Y-90	2.7	Beta	12	Y-90 microspheres, SIR-Spheres or TheraSpheres	Intravascular trapping	Liver metastases Hepatocellular carcinoma
Y-90	2.7	Beta	12	Y-90 ibritumomab tiuxetan (Zevalin)	CD20 antigen binding	Non-Hodgkin's lymphoma
I-131	8.04	Beta, gamma	4	I-131 tositumomab (Bexxar)	CD20 antigen binding	Non-Hodgkin's lymphoma
I-131	8.04	Beta, gamma	4	I-131 MIBG	Active transport and intracellular storage	
Sm-153	1.95	Beta, gamma	3.1	Sm-153 EDTMP	Chemo-adsorption	Bone pain palliation
Sr-89	50.5	Beta	8	Sr-89 chloride	Calcium analogue	Bone pain palliation

MIBG = meta-iodobenzylguanidine; EDTMP = ethylene-diamine-tetramethylene-phosphonic acid.

Table 2. Common examples of patient selection criteria for targeted radionuclide therapy

Indications	Minimum haematological and biochemical criteria	Contraindications
Inoperable/failed conventional therapy	Hb >10 g/l	Pregnancy/lactation
Good performance status: self-caring	WCC >3x10^9/l	Inability to comply with radiation protection instructions
Confirmed histology	Platelets >100x10^9/l	Short life expectancy
Positive uptake on a diagnostic scintiscan	Urea <10 mmol/l	Renal failure
Stop/suspend interfering treatment/drugs	Creatinine <160 µmol/l	Liver failure
	GFR >40 ml/min	
	Biochemical tumour marker	

Radioactive iodine therapy: Thyroid cancer

The therapeutic use of iodine-131 (I-131) is a well-established procedure that supplements surgery in differentiated thyroid cancer (follicular and papillary).[4] The benefits of I-131 therapy include:

- facilitating the interpretation of subsequent serum thyroglobulin levels
- increasing the sensitivity of detection of locoregional and/or metastatic disease on subsequent follow-up whole-body radioactive iodine scans
- maximising the therapeutic effect of subsequent treatments
- allowing a post-ablation scan to help identify additional sites of disease that were not identified pre-ablation
- decreasing recurrence and disease-specific mortality for both known and unknown microscopic and metastatic disease.

To achieve these benefits, theranostics of thyroid cancer is performed using I-123 or I-131 for diagnostics, with single photon emission computed tomography/computed tomography (SPECT/CT) (Fig. 2), and I-131 for personalised radionuclide therapy.[5,6] Long-term follow-up confirms that patients with I-131-avid metastases have significantly better 5- and 10-year survival rates than those whose metastases do not take up I-131 and cannot be treated this way.

The process of tailoring therapy for a patient is based on selecting appropriate radiopharmaceuticals and mechanisms.

Peptide receptor radionuclide therapy: Neuro-endocrine cancer

Peptide receptor radionuclide therapy (PRRNT) is the treatment of choice in adult patients with neuro-endocrine cancer who are inoperable, who have residual disease following surgery or other ablative therapy, or who have metastases. PRRNT is based on the fact that about 70% of these tumours express somatostatin receptors (especially subtype 2) on the cell surface, which constitutes an excellent therapeutic target.[7] In PRRNT, a receptor ligand (i.e. a somatostatin analogue) is bound to a radioactive isotope (normally Lu-177 or Y-90). Commonly used radiopharmaceuticals are Lu-177-DOTATATE and Y-90-DOTATATE. The radionuclide is thereby bound to the tumour cells by these somatostatin analogues, which decay, with the resulting radiation damaging the surrounding cells.[7,8]

Positive somatostatin receptor scintigraphy with In-111 or Tc-99m-octreotide or, even better, with positron emisssion tomography/computed tomography (PET/CT) using Ga-68-DOTATATE, is an important tool for predicting the efficacy of PRRNT, and also for the assessment of the response to PRRNT (Fig. 1). PRRNT is not useful for the treatment of G3 (poorly differentiated) tumours. These tumours have high expression of Ki67 and are fluorodeoxyglucose (FDG)-PET/CT positive, but negative for a Ga-68-DOTATATE PET/CT.[7]

Accumulated evidence from clinical experience indicates that partial and complete responses may be achieved in almost 50% of patients, and that the duration of the therapy response is more than 40 months.[8] The patients' self-assessed quality of life also improves significantly after treatment with Lu-177-DOTATATE. Lastly, compared with historical controls, patients treated with Lu-177-DOTATATE show an increase in overall survival of several years from the time of diagnosis.[8] Side-effects of PRRNT are typically seen in the kidneys. These, however, are usually few and mild provided adequate protective measures such as amino acid infusion are undertaken.[3]

Selective internal radiation therapy: Liver cancer (primary and secondary)

Selective internal radiation therapy (SIRT) or trans-arterial radio-embolisation using Y-90-labelled microspheres is a treatment option for patients with unresectable primary and secondary liver malignancies.[9] This technique involves the intra-arterial injection of commercially available Y-90-labelled microspheres (SIR-Spheres and TheraSpheres) via the hepatic artery or one of its side branches. Liver metastases are primarily fed via the hepatic artery, whereas normal liver tissue is fed primarily via the portal vein. Up to 3 times more hepatic arterial vessels surround liver tumours than normal liver tissue.[10] Therefore, a

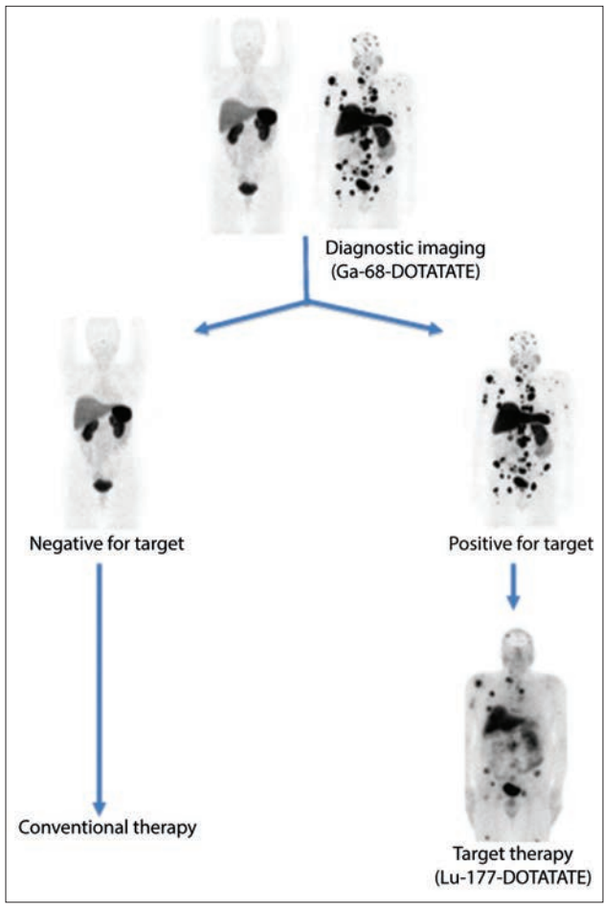

Fig. 1. Targeted radionuclide therapy demonstrating how theranostic systems combine diagnostic imaging (Ga-68-DOTATATE PET/CT) to detect the presence of a molecular target (somatostatin receptors) in each patient. A patient who is found to be positive for a molecular target is selected for therapeutic intervention, in this case Lu-177-DOTATATE.

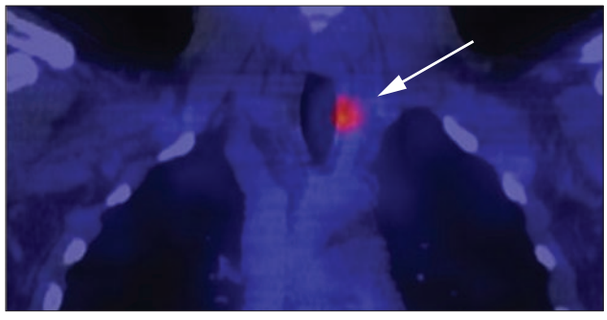

Fig. 2. SPECT/CT, showing accurate localising of pathological uptake, thus providing more accurate staging prognostic information for risk stratification, which in turn tailors management and follow-up regimens.

selective high dose (i.e. >75 Gy) to tumours can be achieved with minimal damage to normal hepatocytes, which have a tolerance to radiation doses of up to 35 Gy. Patient selection requires a meticulous work-up with an initial angiographic evaluation to maximise therapeutic response and minimise its side-effects. This is primarily to document the visceral anatomy, provide information on perfusional flow characteristics of the targeted vascular territory, identify anatomical variants, and isolate the hepatic circulation by occluding extrahepatic vessels. A pre-treatment hepatic artery Tc-99m macroaggregate of albumin (MAA) scan is performed to detect any extrahepatic shunting to the lung or gastrointestinal tract. Excessive shunting to the lungs that would result in a >30 Gy lung dose on a single administration excludes the patient from SIRT.[9]

Given the possibility of non-target deposition of microspheres, prophylactic embolisation of all extrahepatic vessels at the time of MAA assessment is performed to avoid extrahepatic deposition of microspheres. Since these vessels/organs can revascularise quickly, SIRT is performed within 2 weeks of the initial angiographic evaluation and prophylactic embolisation.

Increasing evidence confirms that early response assessment to SIRT using F-18-FDG PET/CT is superior to morphological imaging, demonstrating a correlation with tumour markers and significantly predicting progression-free survival in patients with liver malignancies (Fig. 3).

Clinical trials have shown that median survival after SIRT is about 65 weeks, and disease-control rates are 35 - 88%, depending on the criteria for response assessment.[9]

Radio-immunotherapy: Non-Hodgkin's lymphoma

Radio-immunotherapy (RIT) is well tolerated and effective in the treatment of follicular B-cell lymphomas expressing the CD20 epitope in first-line or subsequent lines of therapy.

Pain palliation with bone-seeking radiopharmaceuticals has proved to be an effective and cost-effective management tool in patients with metastatic bone pain.

RIT is a form of targeted radionuclide therapy that uses a monoclonal antibody to deliver localised radiation. RIT is given along with sufficient unlabelled antibody to saturate the non-tumour antibody binding sites, and to potentially evoke a direct antitumour effect.

Using an anti-CD20 antibody as a delivery device to target the follicular B-cell lymphomas expressing the CD20 epitope with a radionuclide (Y-90/I-131), amplifies the cytotoxic effect via a radiation cross-fire effect, whereby ionising radiation has an effect on neighbouring cells in a spherical zone surrounding the deposited radionuclide.[11] Currently, 2 radiolabelled antibodies are available for treatment of follicular non-Hodgkin's lymphoma, Y-90 ibritumomab tiuxetan (Zevalin) and I-131 tositumomab (Bexxar). Dose-limiting toxicity for both radiolabelled antibodies results in reversible bone marrow suppression. Again, 18-F-FDG PET/CT is superior to morphological imaging in demonstrating response to therapy (Fig. 4).

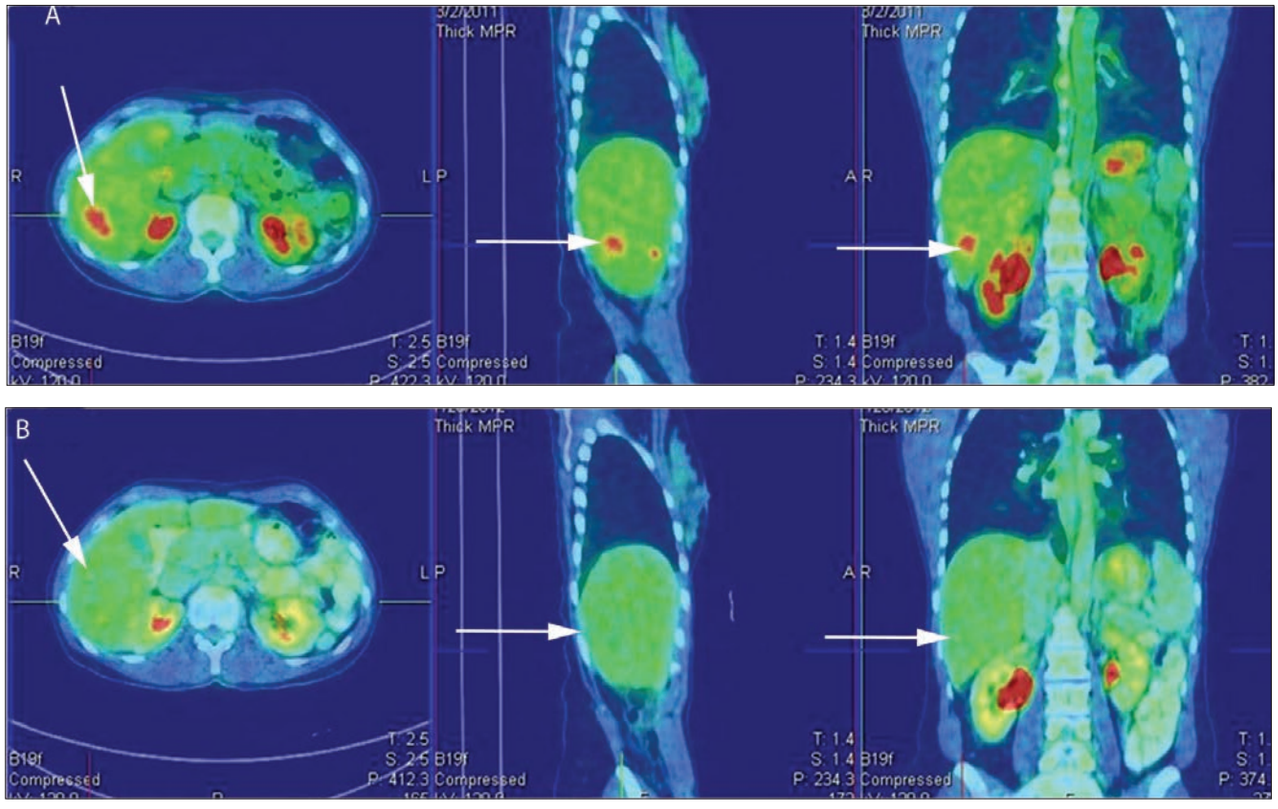

Fig. 3. The successful treatment of liver metastases from colorectal carcinoma by SIRT. A. FDG-PET/CT before treatment: well-defined foci of FDG uptake in right liver lobe due to diffuse liver metastases. B. FDG-PET/CT after 3 months post-SIRT: no abnormal liver uptake, indicating complete response.

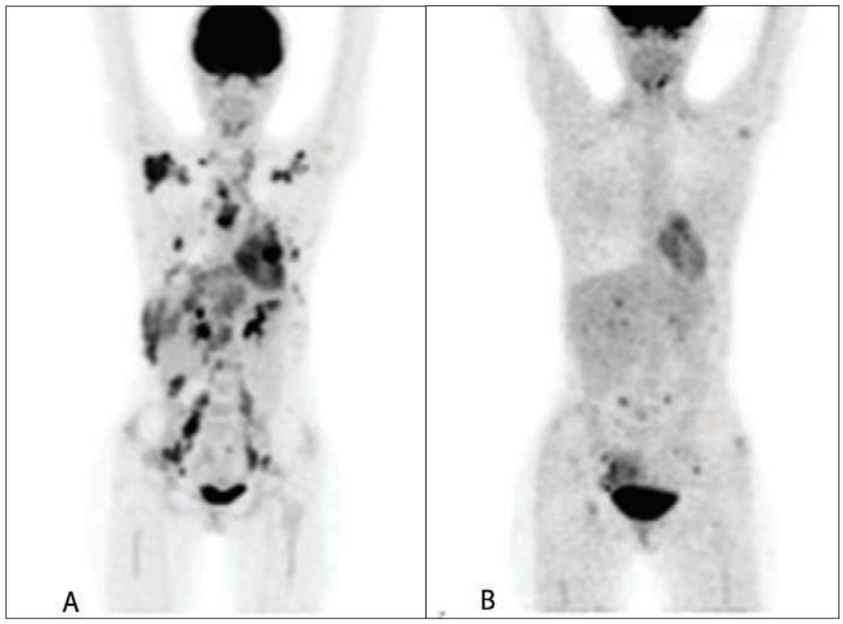

Fig. 4. Treatment of non-Hodgkin's lymphoma with radio-immunotherapy (i.e. Y-90-ibritumomab tiuxetan (Zevalin)). A. FDG- PET/CT before treatment: extensive metastases. B. FDG-PET/CT after two administrations of radio-immunotherapy (Zevalin): no evidence of disease activity. (Images courtesy of G Mariani, Pisa University Medical School, Italy.)

Data demonstrate that RIT is effective, with an overall response rate of approximately 80% and a complete response of approximately 30% in patients who are refractory to unlabelled anti-CD20 immunotherapy and chemotherapy, or have relapsed after these therapies.[11]

Despite impressive clinical trial data, these products have been underutilised because of the complexity of treatment co-ordination and concerns regarding reimbursement.

Selective internal radiation therapy (SIRT) with Y-90-labelled particles is an effective and well-tolerated treatment for non-resectable primary and secondary liver neoplasm.

I-131-meta-iodobenzylguanidine: Endocrine tumours

I-131-meta-iodobenzylguanidine (MIBG) has been shown to be effective in chromaffin tumours (neuroblastoma, phaeochromocytoma, and paraganglioma) as well as for carcinoid and medullary thyroid carcinoma. Uptake of MIBG, a norepinephrine analogue, in tissue

Table 3. Commmercially available radionuclides for radiosynoviorthesis

	Y-90	Re-186	Er-169
Physical half-life (days)	2.7	3.7	9.5
Emission	Beta	Beta, gamma	Beta
Maximum range (mm)	12	3.7	1
Compound	Citrate	Sulphide	Citrate
Joints	Large: knee	Medium: shoulder, elbow, wrist, superior hip and inferior tarsal joint	Small: MCP, PIP, DIP, MTP

MCP = metacarpophalangeal; PIP = proximal interphalangeal; DIP = distal interphalangeal; MTP = metatarsophalangeal.

reflects rich adrenergic innervation and/or catecholamine excretion. On this basis, I-131 MIBG is sensitive and specific for detecting localised and metastatic neuroblastoma, phaeochromocytoma, paraganglioma and medullary thyroid carcinoma. It can be used with precision for molecular nuclear therapy in the management of these tumours. Haematotoxicity is the primary side-effect, depending on the administered activity, degree of metastatic bone marrow infiltration, and other treatment such as chemotherapy. MIBG therapy is both safe and effective for disease palliation, with response rates varying between 30% and 75%.[12]

Bone-seeking radionuclides: Metastatic bone pain

Pain palliation with bone-seeking radiopharmaceuticals has proved to be an effective and cost-effective management tool in patients with metastatic bone pain. Radiopharmaceuticals bind to the bone matrix in areas of increased bone turnover due to a metastatic response. Beta-rays from the specific radionuclide, bound to its carrier ligand, result in the therapeutic effect. At least 7 bone-seeking radionuclides have shown evidence of both safety and efficacy in reducing pain from diffuse skeletal metastases. All have their own characteristics. The radiopharmaceuticals samarium-153-ethylene-diamine-tetramethylene-phosphonic acid (Sm-153-EDTMP) and strontium-89-chloride, which are widely approved and commercially available, are discussed briefly. Patients with a positive bone scan using technetium-99m methylene-diphosphonate (Tc-99m-MDP) are eligible for treatment if they qualify in terms of the general indications and contraindications as defined in Tables 1 and 2.

In most cases, bone marrow toxicity is limited and reversible, which makes repetitive treatment relatively safe. Several studies have shown encouraging results using bone-seeking radiopharmaceuticals, with an overall reported pain response rate of ±70 - 80% of patients.[13] This systemic form of radionuclide therapy is simple to administer and complements other treatment options. It has been associated with marked pain reduction, improved mobility, reduced dependence on analgesics, and improved performance status and quality of life.

Peptide receptor radionuclide therapy (PRRNT) is the treatment of choice in adult patients with neuro-endocrine cancer who are inoperable, who have residual disease following surgery or other ablative therapy, or who have metastases.

Radiosynoviorthesis

Radiosynoviorthesis means the restoration (orthesis) of the synovia by radionuclides.[14] Through local application of radioactive agents an attempt is made to influence the synovial process favourably as an alternative to surgical synovectomy. Intra-articular injected beta-emitting radionuclides are indicated in chronic synovitis with recurrent joint effusions in rheumatoid arthritis, seronegative spondyloarthritis, villonodular synovitis after surgery and haemarthrosis in haemophilia. The value of radiosynoviorthesis in activated osteoarthritis is variable. The technique requires appropriate selection of the radiopharmaceutical agent, which should have specific properties. The radiation energy should be sufficient to penetrate and ablate the synovial tissue, but not so great as to damage underlying articular cartilage or overlying skin (Table 3). In 40 - 80% of cases, inflammation parameters such as pain, local hyperthermia, swelling and joint effusion decrease within 3 - 4 months.[15] If a radiosynoviorthesis is not satisfactory, it can be repeated within 6 months.

Radioactive iodine therapy: Hyperthyroidism

Thyrotoxicosis can be diagnosed by high serum levels of thyroxine and tri-iodothyronine and a low serum level of thyroid-stimulating hormone. Hyperthyroidism is confirmed by high isotope (I-131 or Tc-99m) uptake by the thyroid gland, while in thyroiditis it will be

low. One of the oldest and still most widely used applications of radionuclide therapy is radio-iodine for hyperthyroidism, both the diffuse (Graves') and nodular (Plummer's) forms. The efficacy of I-131 therapy in hyperthyroidism is beyond dispute and long-term follow-up studies globally have confirmed the safety of this treatment. Hence, it is becoming the treatment of choice for hyperthyroidism. The reported incidence of induction of hypothyroidism ranges from 7% to 25% in the first year, depending on the dose.[6]

Conclusion

Targeted radionuclide therapy offers the opportunity for individualisation by tailoring the properties of the radionuclide and the targeting vehicle for each patient. Dosimetric calculations and overall good clinical tolerability favour the early application of this therapy, although currently it is commonly used in advanced stages of cancer. Clinical applications of the combination of diagnostic and therapeutic radioactive agents providing a theranostic approach have beneficial effects for patients. Currently, these products are underutilised owing to lack of information and concerns about reimbursement.

Acknowledgement. My thanks to the staff members of the Department of Nuclear Medicine at Steve Biko Academic Hospital and NTP Radioisotopes (SOC).

References

1. Lee DY, Li KCP. Molecular theranostics: A primer for the imaging professional. American Journal of Roentgenology 2011;197(2):318-324. [http://dx.doi.org/10.2214/AJR.11.6797]
2. Ersahin D, Doddamane I, Cheng D. Targeted radionuclide therapy. Cancer 2011;3(4):3838-3855. [http://dx.doi.org/10.3390/cancers3043838]
3. Druce MR, Lewington V, Grossman AB. Targeted radionuclide therapy for neuroendocrine tumours: Principles and application. Neuroendocrinology 2010;91(1):1-15. [http:dx.doi.org/10.1159/000227808]
4. Van Nostrand D. The benefits and risks of I-131 therapy in patients with well-differentiated thyroid cancer. Thyroid 2009;19(12):1381-1391. [http://dx.doi.org/10.1089/thy.2009.1611]
5. Silberstein EB. Radioiodine: The classic theranostic agent. Semin Nucl Med 2012;42(3):164-170. [http://dx.doi.org/10.1053/j.semnuclmed.2011.12.002]
6. Chatal JF, Hoefnagel CA. Radionuclide therapy. Lancet 1999;354(9182):931-935.
7. Zaknun JJ, Bodei L, Mueller-Brand J, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40(5):800-816. [http://dx.doi.org/10.1007/s00259-012-2330-]
8. Kam BLR, Teunissen JJM, Krenning EP, et al. Lutetium-labelled peptides for therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2012;39 (Suppl 1):S103-S112. [http://dx.doi.org/10.1007/s00259-011-2039-y]
9. Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Radioembolization for the treatment of liver tumors: General principles. Am J Clin Oncol 2012;35(1):91-99. [http://dx.doi.org/10.1097/COC.0b013e3181f47583]
10. Van de Wiele C, Maes A, Brugman E, et al. SIRT of liver metastases: Physiological and pathophysiological considerations. Eur J Nucl Med Mol Imaging 2012;39(10):1646-1655.
11. Goldsmith SJ. Radioimmunotherapy of lymphoma: Bexxar and Zevalin. Semin Nucl Med 2010;40(2):122-135. [http://dx.doi.org/10.1053/j.semnuclmed.2009.11.002]
12. Sisson JC, Yanik GA. Theranostics: Evolution of the radiopharmaceutical meta-iodobenzylguanidine in endocrine tumors. Semin Nucl Med 2012;42(3):171-184. [http://dx/doi.org/10.1053/j.semnuclmed.2011.11.003]
13. Fischer M, Kampen WU. Radionuclide therapy of bone metastases. Breast Care 2012;7(2):100-107. [http:dx.doi.org/10.1159/000337634]
14. Mödder G. Radiosynoviorthesis: Involvement of Nuclear Medicine in Rheumatology and Orthopedics. Meckenheim: Warlich Druck und Verlagsgesellschaft, 1995.
15. Siegel ME, Siegel HJ, Lusk JV Jr. Radiosynovectomy's clinical application and cost effectiveness – a review. Semin Nucl Med 1997;27:364-371.

Summary

- Theranostics epitomises the inseparability of diagnosis and therapy.
- Radionuclide therapy uses radioactive isotopes administered either orally or intravenously to deliver highly targeted therapy for a range of disorders, enabling the delivery of a high dose to the target, while minimising normal tissue toxicity.
- Radioactive iodine therapy for differentiated thyroid cancer and hyperthyroidism is the most commonly employed targeted radionuclide therapy.
- Peptide receptor radionuclide therapy is an effective treatment option for patients with well-differentiated somatostatin receptor-expressing neuro-endocrine tumours. Considering the mild side-effects, it may well become the first-line therapy in patients with metastatic or inoperable neuro-endocrine tumours.
- Selective internal radiation therapy (SIRT) or trans-arterial radio-embolisation using Y-90-labelled microspheres is a treatment option for patients with unresectable primary and secondary liver malignancies.
- Radiolabelled antibodies against CD20-positive cells (radio-immunotherapy) is an attractive option for the treatment of patients with non-Hodgkin's lymphoma, which can be adapted to individual prognosis and treatment needs.
- Radiolabelled MIBG is an example of theranostics and remains a useful agent for both diagnosis and therapy of endocrine tumours.
- Systemic radiopharmaceutical therapy is an important treatment option in severe, painful bone metastases that significantly lower patients' quality of life.
- Radiosynoviorthesis with the nuclides Y-90, Re-186 and Er-169 is an established option for the treatment of persistent synovitis of large, medium and small joints.
- Increasing evidence confirms targeted radionuclide therapy to be effective and safe, and shows an increase in overall survival.