Review Article

The expanding role of nuclear medicine in therapeutic strategies

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Introduction

The concept of carrying a cytotoxic radionuclide directly to cancerous cells is an attractive alternative to conventional forms of radiation treatment. The very close contact between the radionuclide and the cell to be destroyed enables the absorbed radiation to be concentrated at the site of abnormality with the minimal injury to healthy tissue.[1] The concept is not new. After a stalemate period in which radiometabolic treatment seemed to be unfashionable, not only has the already-existing radionuclide therapy returned to be appreciated and widely applied, but novel radionuclide therapies have also come about in recent years. In fact, the European Association of Nuclear Medicine (EANM) has published guidelines for the planning and actuating of most of these therapies. Prospects are excellent and they will revolutionise treatment of some common diseases as their use has been proven in studies and an increasing number centres are applying these treatments all over Europe, even as first-line. This article is a representative overview regarding the current common radionuclide therapy applications and the new radionuclide treatments available.

Key words

Nuclear medicine, radiometabolic therapy, novel radionuclide treatment

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Basic principles and considerations

Several factors affect uptake of radiopharmaceuticals into diseased tissue, e.g. variations in interstitial pressure and in blood perfusion. The cumulative absorbed radiation close to tissue undergoing radionuclide therapy is a function of both the quantity of radiopharmaceutical taken up at a cellular site and its subsequent retention at that site.[2] The physical half-life must not be too short since the radionuclide irradiates diseased tissue insufficiently. A long half-life gives unnecessary protracted doses to normal tissue. No radiopharmaceutical is entirely selective. Radiation toxicity assessments are required. Radionuclides may be classified into five groups according to the range of principal radiation emitted: alpha, beta with a mean range less than 200 μm, beta with a mean range of more than 200 μm, beta with a range greater than 1 mm, and radionuclides which decay by processes called electron capture and/or internal conversion.[3] Size of tumour masses, potential inhomogeneity of uptake of the radiopharmaceuticals, availability and costs all affect the choice of a radionuclide label.

Thyroid radionuclide therapy

Perhaps the best-known application of radionuclide therapy is the use of radioiodine (^{131}I) in malignant and benign thyroid disease. The Royal College of Physicians has recently updated guidelines issued in 1995 with the latest recommendations for the management of hyperthyroidism. Radioiodine therapy is the treatment of choice in patients with Plummer's disease provided there is no sign of malignancy. Surgery is being used less frequently in Graves' disease and the preferred treatment is now ^{131}I. Age is not a limit in such cases because low doses are administered, and considered quite safe. Radio-iodine therapy or surgery are indicated when a goitre causes local symptoms (dyspnoea, dysphagia) but therapy is preferred in elderly patients with concomitant diseases or patients with recurrence post-surgery.[4]

For more than 50 years, radioiodine has also been used in treatment of thyroid malignancy. Good results with respect to overall and recurrence-free survival in patients with well-differentiated thyroid carcinoma confirm the efficiency of their safe treatment as follows:[4]

1. Allows detection of metastases not detectable by standard imaging
2. Prophylactic ablation of thyroid remnants after near-total thyroidectomy
3. Successfully indicated in local recurrences, lymph nodes or distant metastases where tumour burden is low.

Myeloproliferative disease

Phosphorous-32 (^{32}P) was the first therapeutic radioisotope used in leukaemia about 70 years ago. Today there remains a distinct subgroup of elderly patients with polycythaemia vera and essential thrombocythaemia who can be treated with oral or intravenous ^{32}P. Since the range of beta emissions is at most a few millimetres, and since ^{32}P emits no other types of radiation, no hospital admission is required. It has been an accepted treatment for myeloproliferative disease for more than 30 years.[5] ^{32}P is incorporated into the nucleic acids of rapidly proliferating cells and suppresses hyperproliferative cell lines rather than eradicate them. It is perfectly well tolerated in the elderly (>65 years) and induces a long survival with an excellent quality of life.[5] Patients should be pre-treated with venesection to reduce haematocrit to 42-47%. One must note that ^{32}P in young and middle-aged increases risk of leukaemia several years after therapy, therefore other alternatives are considered such as hydroxyurea and anagrelide since they are considered a safer first-line treatment and can be administered on a long term basis too.[6,7]

Palliation of metastatic bone disease

Pain associated with bone metastases is a clinical problem contributing to patient morbidity, reducing quality of life and bringing about depression, anxiety, fear and loss of independence.[8] Symptoms are exacerbated by neurologic deficits, pathologic fractures, immobility and sequelae of hypercalcaemia.[9] Three palliative therapies for metastatic bone pain provide symptom control:

1. External beam radiotherapy
2. Narcotic and non-narcotic analgesics and
3. The introduction of radioactive bone seeking biphosphonates into the management plan.

There is now compelling data to support the use of bone-seeking radiopharmaceuticals as effective (in 90%) and cost-effective in pain palliation.[10] Almost any cancer may metastasize to bone, and may be a significant symptom in more than 50% of the most common cancers. Bone-seeking qualities of strontium (Sr) were described by Stöltzner in 1874 and the isotope ^{89}Sr was first reported in 1937. ^{89}Sr started being used in clinical practice for metastatic bone disease in 1941, but only in the 1980s was the potential of this therapy fully recognised. Beta-emitting ^{89}Sr, ^{32}P, samarium(^{153}Sm)-ethylenediaminetetramethylene-phosphate and rhenium(^{186}Re)-hydroxyethylidene are approved for use in many regulatory jurisdictions. Nuclear medicine physicians should now be involved in long term patient care and should collaborate with referring physicians in multi-disciplinary clinics. They should also be involved as early as possible for optimum results. Indications for radiopharmaceutic therapy in patients with bone metastases symptoms are listed in table 1 and contra-indications in Table 2. Distribution of these radiopharmaceuticals is predicted from ^{99}Tc-methylene-diphophonate bone scan, also a bone seeking radiopharmaceutical and routinely carried out in nuclear medicine departments. External beam techniques have the advantage of more rapid palliation, but unsealed source therapy agents offer a more sustained radiotherapy besides treating more than one metastatic site concomitantly. The most recent advancement is the use of the alpha-emitting radium-223 (Ra), which seems a promising new treatment.[11] A multi-centre trial of prostate cancer patients demonstrated that ^{223}Ra is at least as effective as currently used radiopharmaceuticals and is also considerably less toxic. By contrast to beta-emitting isotopes, alpha-emitters produce a high linear-energy-transfer radiation and increases anti-tumour effect by virtue of its densely ionizing abilities locally but with relative sparing of the bone marrow because of its short-track length.

Hepatic cell carcinoma (HCC)

HCC is one of the most common cancers worldwide and is increasing due to better healthcare of liver cirrhosis and chronic hepatitis C patients. Prognosis is extremely poor. Curative treatment (liver transplantation, surgical resection, ethanol injection, radiofrequency ablation) can only be carried out in less than 25% of patients. Systemic chemotherapy leads only to low levels of response without any improvement in survival.[12] External radiotherapy is of little use because of the high risk of hepatic toxicity. Thus, two principle therapeutic approaches may be considered: arterial chemoembolization (causes tumour ischaemia) and metabolic radiation therapy via arterial administration. HCC is a hypervascularised tumour mainly supplied by the hepatic artery. Non-tumoral liver is mostly vascularised by the portal vein. Hence intra-arterial injection of radioactive therapeutic agent and its trapping in tumour micro-vessels enables a high tumour:non-tumour liver ratio to be attained, with maximum delivery of high dose to tumour. Beta-emitting ^{131}I-lipiodol (ethiolised oil, a naturally iodinated fatty acid ethyl ester of poppy seed oil), rhenium(^{188}Re)-lipiodol and yttrium(^{90}Y)-labelled microspheres are applied. The first attempts to use ^{131}I-lipiodol therapy in HCC dates back to 1986. A partial or incomplete response rate (i.e. reduction of more than 50% in tumour size or tumour marker amount) is observed in an average of 40%,[13] even up to 71% in some studies. ^{131}I-lipiodol has proven effectiveness in the treatment of HCC with portal thrombosis, and as adjunct treatment for operated HCC in which it reduces the risk of recurrence. This treatment is at least as

effective as chemoembolisation but is much better tolerated. This treatment involves the nuclear physician and radiologists who intervene under fluoroscopic control.

Radiosynovectomy

An overview of most studies investigating therapeutic radionuclides and their direct injection into joints affected by synovitis do not show a considerable therapeutic gain when administered alone, but combining long-acting steroids with them has synergistic effects.[14] Benefits are observed in 60-80% of patients with a large range of refractory and painful arthropathies (e.g. rheumatoid arthritis, spondyloarthropathies such as psoriatic arthritis, persistent synovial effusions, other inflammatory joint diseases such as Lyme's and Bechet's disease).[15] The beta emitters ^{90}Y-citrate/silicate (knee), ^{186}Re-sulphide (hips, shoulders, elbows wrists, ankles, subtalar joints) and erbium(^{169}Er)-citrate (metacarpophalangeal, metatarsophalangeal, digital interphalangeal joints) are all approved in Europe.[15] Collaboration between rheumatologists, orthopaedic surgeons and nuclear physicians is required. Together they must weigh risks against benefits. Radiation in non-malignant conditions should be resorted to when all other treatments are unsuccessful. Patients must fail at least one intra-articular injection of long-term glucocorticoids. The mechanism of action of these radionuclides is probably coagulation necrosis of superficial synovial cells due to beta irradiation, and their consequent sloughing. Contra-indications include patients with symptoms due exclusively to cartilage damage and ruptured Baker's cyst. Treatment can be repeated after 6 months. Response is unlikely before 14 days, and may be delayed even up to 1 month.

Metaiodobenzylguanidine (MIBG) therapy

Since 1981 radioiodinated MIBG has established its place in diagnosis and treatment of tumours derived from the neural crest, and which uptake and retain this radiopharmaceutical. The higher sensitivities and specificity of MIBG scintigraphy in phaeochromocytoma and neuroblastoma led to its therapeutic use in these conditions.[16] Over 95% of phaeochromocytomas concentrate MIBG and this therapy has proven to reduce tumour function, allow symptom palliation, tumour arrest and regression. ^{131}I-MIBG also has a proven value in the treatment of stage III or IV neuroblastomas and paragangliomas. Studies demonstrate that this therapy should be incorporated earlier and at a more favourable moment in treatment protocols, even instead of combination chemotherapy to obtain operability.[16] Several new applications are being investigated with the aim of improving the therapeutic index. ^{131}I-MIBG is probably the best palliative treatment for patients with advanced disease, as the invasiveness and toxicity of this therapy compare favourably with that of chemotherapy, external beam radiotherapy and immunotherapy.[17] In carcinoid tumour and medullary thyroid carcinoma the sensitivities are slightly lower and fewer patients with these conditions undergo this therapy successfully.

Radioimmunotherapy (RIT) in non-Hodgkin's lymphoma (NHL) treatment

RIT represents an exciting new therapeutic option for the treatment of B-cell NHL. Targeted radiotherapy is advantageous compared to other systemic therapies because chemotherapeutic agents have low selectivity whereas ligand-targeted radiotherapy is based on over-expression or potentially unique expression of target molecules on tumour cells.

With the approval of two radiolabelled immunoconjugates, ^{90}Y-ibritumomab-tiuxetan and ^{131}I-tositumomab, RIT is emerging as a safe and effective treatment strategy. RIT provides a novel approach in which monoclonal antibodies directed against tumour-specific antigens are used to target therapeutic radioisotopes to sites of disseminated disease.[18] Toxicity to uninvolved tissues is minimised. NHL is inherently radiosensitive. Radiolysis is induced in both the target cell and adjacent tumour cells, because of radiation crossfire effect.

Most B-cell lymphomas express CD20, making it a suitable target antigen for therapeutic radioactive monoclonal antibodies. CD20 is not present on stem cells and its expression

Table 1: *Most common indications for radionuclide therapy in patients with bone metastases (McEwen AJ, 1996)*

- Metastatic bone disease
- Positive bone scan irrespective of x-rays
- Bone pain
- Recurrent bone pain in previously irradiated site
- Pain in more than one site requiring analgesia
- Bone pain requiring radiotherapy to most painful site
- Radiotherapy to one site with multiple abnormalities on bone scan but no pain outside radiotherapy field

Table 2: *Contraindications to radiopharmaceutical therapy in cancer patients with bone metastases (McEwan AJ, 1996)*

- Platelet Count < 100,000 (relative)
- Platelet count < 60,000 (absolute)
- White count < 2.5 x 106/L
- Rapidly falling blood counts
- Evidence of disseminated intravascular coagulopathy
- Impeding pathologic fracture (treat acute symptoms and reconsider)
- Impeding cord compression (treat acute symptoms and reconsider)
- < 2 months projected survival
- Prior myelosuppressive chemotherapy
- Extensive soft tissue metastases

does not vary at different stages of the cell cycle. Moreover, it does not internalise or shed from the cell surface in response to antibody binding. By linking anti-CD20 monoclonal antibodies to an appropriate therapeutic isotope (beta-emitters ^{131}I and ^{90}Y), sites of disseminated disease can effectively be targeted. ^{90}Y-ibritumomab tiuxetan is a murine anti-CD20 monoclonal antibody linked via 'tiuxetan' to ^{90}Y. The principle toxicity is reversible myelosuppression but is generally very well tolerated. The development of human anti-murine antibody (HAMA) reactions could potentially preclude re-treatment upon relapse but extensive studies have shown that incidence of HAMA reactions is only 1%.[18] A ^{90}Y-ibritumomab-tiuxetan regimen is completed in 1 week with 2 hospital visits. An initial intravenous infusion of rituximab monoclonal antibody is given (250mg/m^2). One week later, patients receive a second infusion of rituximab followed 4 hours later by a single injection of ^{90}Y. Doses of radiation absorbed by uninvolved organs and marrow are well below acceptable safety levels.[19] As the path-length of beta particles is very short, treated patients pose a negligible risk of irradiating other individuals (hospital workers, family members) and may be administered on an outpatient basis. RIT approach allows multiple sites of disseminated disease to be targeted simultaneously without having to identify the location of individual tumours. Major clinical studies have shown that RIT as second line therapy in NHL gives high response rates, increasing survival rate and reducing relapse rates or increasing time intervals between relapses. Today these encouraging results are pushing researchers to investigate the possibility of including ^{90}Y-ibritumomab-tiuxetan earlier in NHL therapy, i.e. first-line.

Receptor-targeted radiopeptide therapy

Peptides are important regulators of various biological processes. Radioactive neuropeptides like somatostatin analogues are widely used for symptomatic treatment of malignant hormone-secreting neuroendocrine tumours and their metastases. They act via high-affinity G-protein coupled receptors. The basis of somatostatin receptor-targeted radiotherapy is the over-expression of some of these receptor subtypes on neuroendocrine tumours and even some non-neuroendocrine tumours. They inhibit hormone secretion and improve quality of life, with little effect on tumour size or growth. Neuroendocrine tumours often cause symptoms from excess hormone secretion rather than from growth, invasion or local anatomic effects. Frequently slow growing, they may still be life threatening. Many gastroenteropancreatic tumours including insulinomas, gastrinomas, vipomas, glucagonomas, somatostatinomas, and non-functioning pancreatic tumours are treated by these methods.

In diagnosis, the prototypic radioligand and the gold-standard for somatostatin receptors scintigraphy,[20] a routine scan in many nuclear medicine units, is 111-indium (^{111}In)-octreotide (somatostatin analogue). It is very sensitive and a preferred method in staging and follow-up of neuroendocrine tumours. Moreover, radiopeptides show rapid diffusion and localisation, rapid clearance, efficient laboratory synthesis and lack of immunogenicity. A remarkable response rate (stabilization and improved quality of life) in different cancers has been observed in major studies in many centres.[20] In therapy, beta-emitter ^{90}Y is most commonly used. Recently lutetium-177 (^{177}Lu) has been introduced, allowing formation of a radiopharmaceutical with a sevenfold higher affinity to somatostatin type 2 receptors. ^{177}Lu allows concomitant imaging and therapy. Chemical combination of a radionuclide with selective radiopharmaceutical is often complex since direct labelling is rarely possible. A large conjugating molecule (chelator) needs to be attached to the radiopharmaceutical to form kinetically and thermodynamically stable radiometal complexes.

A sufficiently high expression of somatostatin receptors (by ^{111}In-octreotide scan) of all lesions demonstrated anatomically by conventional radiological techniques is required. The radiopharmaceutical concentration on scintigraphy should be at least as high as the non-specific uptake within the liver. Studies are underway to determine maximum doses that may be administered, and time intervals between repeated treatments. Although in it infancy, the concept of this therapy has been proven and is now being practiced in many European centres. Renal toxicity has been the main dose-limiting toxicity. Infusion of cationic amino acids reduces the uptake of peptides in tubular cells. Structural modifications of peptides will lead to new radiopeptides with much lower renal uptake. Somatostatin-based radiopeptides with a more suitable receptor subtype profile will allow the targeting of a broader spectrum of tumours. Several new radiopeptides are under development.

Conclusion

Nuclear medicine is an ever-expanding speciality and this is not only true for diagnostic procedures, but also for radionuclide therapy. The aim of radionuclide therapy is to reach maximal radiation dose to the tumour or target-pathology, but only minimal dose to normal tissue. It may be tailored to the lesion or patient to be treated. Use of radiopharmaceuticals is becoming more widespread and popular since costs are decreasing rapidly and the implementation of such treatment is quite simple and straightforward. Today radionuclide therapy is mainly an integral part of nuclear medicine. In the future it will be part of a multi-disciplinary therapy.

References

1. Sisson JC. Radionulide therapy for malignanacy: influences of physical characteristics of radionuclides and experience with meta-iodobenzylguanidine. Clin Oncol 5: 1-21
2. Ackery D. Principles of radionuclide therapy. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell PJ, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 358-62
3. Humm JL. Dosimetric aspects of radiolabeled antibodies for tumour therapy. J Nucl Med 1986; 27: 1490-7
4. EANM procedure guidelines for therapy with Iodine-131 therapy: www.eanm.org/publications (accessed September 20, 2007)

5. Tennvall J, Boudewijn B. EANM procedure guideline for ^{32}P phosphate treatment of myeloproliferative diseases. Eur J Nucl Med 2007; 34: 1324-7
6. Polycythaemia Vera: The Merck Manuals Online Medical Library http://www.merck.com/mmhe/sec14/ch178/ch178b.html accessed March 1, 2008
7. Gunnar Enkström K, Löfvenberg E. Treatment of Myeloproliferative Disorders with hydroxyurea: effects on Red Blood Cells geometry and deformability. Blood 1998;91:3986-91
8. Duat RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer 1982; 50: 1913-8
9. Stoll BA. Natural history, prognosis, and staging of bone metastases in Stroll BA, Parboos S Bone metastates: Monitoring and Treatment. Raven, NY, 1983, pp 1-20
10. McEwan AJ Palliation of bone pain. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell P J, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 407-21
11. Nillson S, Franzen L, Parker C, Tyrell C, Sokal M *et al.* Bone-targeted radium-223 in symptomatic hormone refractory prostate cancer: a randomised multi-centre, placebo-controlled phase II study. Lancet Oncol 2007; 8: 587-94
12. Badvie S. Hepatocellular carcinoma. Postgrad Med J 2000; 76: 4-11
13. Garin E, Bourguet P Use of labelled lipiodol in the treatment of hepatic tumours. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell PJ, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 473-82
14. Lovegrove FT, Clunie GP. Radiation synovectomy. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell PJ, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 771-80
15. EANM procedure guidelines for radiosynovectomy: www.eanm.org/publications accessed September 21, 2007
16. Hoefnagel CA, de Hraker J, Valdes Olmos RA, Voute PA 1994 ^{131}I-MIBG as first-line treatment in high risk neuroblastoma patients. Nucl Med Comm 15: 712-7
17. Hoefnagel CA, Lewington VJ. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell PJ, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 445-57
18. Hagenbeek A, Delaloye B Editorial perspective – Advances in B-cell non-Hodgkin's lymphoma Leukaemia and Lymphoma, 2003 Vol. 44: (supp 4) S1-S4
19. Witzig TE, White CA, Gordon LI, Murray JL, et al. Safety of yttrium-90 ibritumomab-tiuxetan radioimmunotherapy for relapsed low-grade, follicular or transformed non-Hodgkin's lymphoma J Clin Oncol, 2003; 21: 1263-70
20. Macke HR, Muller-Brand J. Receptor-targeted radiopeptide therapy. Nuclear Medicine in Clinical Diagnosis and Treatment edited by Ell PJ, Gambhir SS (3rd Ed). Churchill Livingstone 2004. pp 460-71