Further reading

1 Murray IPC, Ell PJ. Nuclear medicine in clinical diagnosis and treatment (2nd edn). Edinburgh: Churchill Livingstone, 1998.

Nuclear medicine techniques are used to monitor the effects and side effects of therapeutic interventions, for example the effect on renal or cardiac function, to determine optimal delivery of radioactive and non-radioactive drugs, and to deliver radiation therapy to specific sites using therapeutic radionuclides.

The effectiveness of radionuclide therapy depends on several factors:

- the specificity of the localisation of the radiopharmaceutical
- the type of irradiation ($\beta$- or $\alpha$-particles, Auger electrons) in relation to the microscopic binding site localisation
- the time the radionuclide/radiopharmaceutical remains at the site of uptake (residence time)
- the time over which the radiation is delivered (the half-life of the radionuclide attached to the delivering radiopharmaceutical)
- the sensitivity of the target tissue to the radiation.

The range of available diagnostic and therapeutic procedures, some of which are illustrated in Tables 1–3, could therefore be considered by clinical group.

Endocrinology

The most commonly used agent in this group, which has been used for over 50 years, is iodine-131 ($^{131}\text{I}$) for the treatment of both benign and malignant thyroid conditions. The iodine enters the cell by the specific iodine transport mechanism and is subsequently trapped and organified. $^{131}\text{I}$ has an energetic $\beta$-emission which can penetrate several cell diameters around the cell that has taken up the iodine and cause cell death. The likelihood of response to $^{131}\text{I}$ can be demonstrated by imaging before therapy with either $^{131}\text{I}$ or $^{123}\text{I}$. The therapy is highly successful and safe for the treatment of thyrotoxicosis (toxic nodules and Graves disease) in all age groups from children to adults. More recently, its use in reducing the size of benign non-toxic goitres has been demonstrated in those patients who are unsuitable for surgical therapy.$^{1,2}$ The

| Radionuclide | Radiopharmaceutical | Emission | Disease process treated |
|--------------|----------------------|----------|-------------------------|
| $^{131}\text{I}$ | Sodium iodide | Beta | Graves disease, Toxic adenomas, Plummer's disease, Multinodular goitres |
| $^{131}\text{I}$ | Sodium iodide | Beta | Differentiated thyroid cancer, Neuroblastoma, Malignant phaeochromocytoma |
| $^{131}\text{I}$ | MIBG | Beta | Medullary carcinoma of the thyroid, Carcinoid |
| $^{32}\text{P}$ | Sodium phosphate | Beta | Polycythemia rubra vera |
| $^{90}\text{Y}$ | Yttrium citrate | Beta | Inflammatory arthropathies, Haemophilic arthropathies |
| $^{89}\text{Sr}$ | Strontium chloride | Beta | Bone metastases (prostate, breast) |

MIBG = metaiodobenzylguanidine
Table 2. Less commonly used therapeutic agents with probable benefit.

| Radionuclide | Radiopharmaceutical | Emission | Disease process treated          |
|--------------|---------------------|----------|----------------------------------|
| $^{153}$Sm  | EDTMP               | Beta     | Bone metastases                 |
| $^{186}$Re  | HEDP                | Beta     | Bone metastases                 |
| $^{131}$I   | Antibody (CD20)     | Beta     | Non-Hodgkin’s lymphoma           |
| $^{111}$In  | Octreotide          | Auger    | Carcinoid                        |
|             | Microspheres        | Beta     | Medullary thyroid                 |
|             |                     |          | Carcinoma                        |
|             |                     |          | Insulinoma                       |
|             |                     |          | Glucagonoma                      |
|             |                     |          | Neuroblastoma                    |

Table 3. Therapeutic agents of possible/likely benefit, but with insufficient published data.

| Radionuclide | Radiopharmaceutical | Emission | Disease process treated                  |
|--------------|---------------------|----------|-----------------------------------------|
| $^{188}$Re   | Perhenate           | Beta     | Coronary artery stenosis                |
| $^{90}$Y     | Wire                | Beta     | Coronary artery stenosis                |
| $^{90}$Y     | Dotatoc             | Beta     | Carcinoid                               |
|              |                     |          | Medullary thyroid carcinoma             |
|              |                     |          | Insulinoma                              |
|              |                     |          | Glucagonoma                            |
|              |                     |          | Neuroblastoma                           |

use of $^{131}$I in the treatment of differentiated thyroid cancer is also established (Fig 1).4, 5

Metaiodobenzylguanidine (MIBG) shares structural features with noradrenaline; it is taken up actively by noradrenaline transporters in sympathomedullary tissues and trapped in storage vesicles. Therefore, when labelled with $^{131}$I, MIBG can deliver therapy to malignant phaeochromocytoma cells (Fig 2). This agent will also localise in medullary carcinoma of the thyroid (mechanism unknown), neuroblastomas and carcinoid, and is used to treat tumours of these cell types. Therapy is well established for neuroblastomas and malignant phaeochromocytomas, and is less commonly used in medullary cell carcinoma and carcinoid.

Another interesting development is in the use of indium-111 ($^{111}$In)-octreotide which binds to a series of cell surface receptors expressed on a variety of tumour cells (eg carcinoid, neuroblastoma, medullary thyroid carcinoma, gastrinoma) (Fig 3). The tumour cells that have been treated are of neuroectodermal origin. The technique is still under evaluation, but it appears to have a palliative effect on these tumours.6 Modification of the molecule to the yttrium-90 ($^{90}$Y)-labelled dotatoc complex may improve the dosimetry at the tumour sites and result in improved response to therapy.7, 8

Oncology

Non-specific tracers

Therapy of bone metastases from various tumours including prostate and breast is well established with a variety of non-specific localising tracers. The radionuclide/radiopharmaceutical reaches its target predominantly by adsorption to the bone tumour interface where the bone turnover is increased. The products in use include strontium-89 ($^{89}$Sr)-chloride, rhenium-186 ($^{186}$Re)-etidronate (HEDP) and samarium-153 ($^{153}$Sm)-ethylene-diaminetetramethylene phosphonate (EDTMP). Pain is significantly reduced in patients treated with these agents. These are outpatient treatments which are simple to use but costly, though some of the cost is recouped by reducing the analgesic drug costs and morbidity of the patients. Interest is growing in the potential use of $^{188}$Re-labelled products (Fig 4); $^{188}$Re is a generator-produced radionuclide, so these agents could be manufactured on site.

Fig 1. $^{131}$I whole-body scan in a patient with differentiated thyroid cancer. There is an area of high uptake in the left pelvis corresponding to a large metastasis.
Radiolabelled antibodies

There is increasing interest in the use of radiolabelled antibodies that bind to cell surface receptors targeting specific tumour types or specific cell lines. Labelled antibodies have been in use for many years for diagnostic purposes and many have been tried as therapy, but their role in therapy is only now being established. Especially interesting results are emerging in lymphoma therapy as the anti-CD20 antibody labelled with $^{131}$I has demonstrated efficacy in non-Hodgkin's lymphoma. Injection of $^{90}$Y-labelled microspheres through cannulae inserted into the blood supply to susceptible tumours can deliver radiation therapy over a prolonged period of time.

Cardiology

Irradiation of the coronary endothelium to prevent restenosis of the vessels after angioplasty is under investigation. Restenosis following angioplasty occurs in 25–40% of patients. In animal models, transluminal irradiation of coronary vessels subjected to mechanical injury resulted in significantly less intimal proliferation than in controls. Early results suggest that this can be achieved with similar success either by the insertion of a $^{90}$Y wire (though disposal and centring of the wire can present problems) or possibly the use of $^{188}$Re (as perrhenate) instilled into the catheter balloon. Larger trials of this use are awaited.

Rheumatology

The delivery of $^{90}$Y into inflamed joints to provide relief from chronic inflammatory joint disease, although available and of proven use, is not widely used probably because clinicians looking after patients with these conditions are not aware of its place in management.

Haematology

The use of phosphorus-32 ($^{32}$P) as a phosphate for the treatment of polycythaemia rubra vera is well established.

Gastroenterology

The octreotide therapies considered above have also been used with some palliative success in carcinoid, insulinoma and glucagonomas. When the $^{90}$Y-dotatoc complex is generally available it may offer improved benefits over $^{111}$In-octreotide in these tumour groups.

Urology

The treatment of metastatic prostate cancer with $^{89}$Sr, $^{186}$Re-HEDP or $^{153}$Sm-EDTMP should almost certainly be evaluated at an earlier stage than currently practised to see if it prolongs life as well as giving symptomatic relief.
Conclusion

Radionuclide therapies can usually be targeted by using the same radio-pharmaceutical to assess whether the tumour will take up a therapy actively (eg the use of low activities of $^{111}$In) prior to the administration of the therapeutic dose. Similarly, the effect of the therapy can be monitored using either the same principle or an alternative metabolic tracer. Unlike external beam radiotherapy, radionuclide therapy has the potential advantage of delivering a high therapy dose to the target tissue and minimising the dose to normal tissue. It may also treat unrecognised metastases as well as the areas that have been identified, thus preventing the growth of further painful lesions.

These therapies are developing rapidly through the combined efforts of radiochemists, nuclear medicine specialists and oncologists. The targeting of tumour-specific biochemistry is the way forward for therapy; it allows classification of tumours by their biochemical behaviour, and will produce new therapeutic strategies using radionuclides and perhaps directing chemotherapy regimens. New therapies are undergoing evaluation, presenting opportunities for palliation and perhaps cure in the future.

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