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Radionuclide cancer therapy

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Therapeutic nuclear medicine is rapidly developing as an additional treatment modality in oncology. Its unique characteristics are the systemic, yet selective delivery of radiation doses in target tissues, its non-invasiveness, the relative lack of immediate and late side effects, and the advantage that uptake and retention in the tumor can be pre-assessed by tracer studies. Many different tumor seeking radiopharmaceuticals are being used for therapy by different routes and a variety of targeting mechanisms.

The current clinical role of radionuclide therapy is briefly reviewed, as well as more general aspects and considerations, such as mechanisms for tumor targeting, the choice of radionuclide labels, radiopharmacy, drug delivery, radiation protection, dosimetry and toxicity.

Key words: radionuclide therapy, tumor targeting, therapeutic nuclear medicine, radiopharmaceuticals for cancer treatment

INTRODUCTION

IN THE PAST DECADE the role of nuclear medicine in oncology has changed and expanded, in particular in the field of tumor detection, quantitative function analysis of organs at risk during oncological therapy, *in vivo* pharmacokinetic studies of drugs and formulations, as well as therapy.

In diagnostic tumor imaging more or less specific tumor seeking radiopharmaceuticals depict the tumor as a "hot spot." Specific metabolic characteristics and biological properties of tumors are being exploited not only for the diagnosis, staging and follow-up, but also for characterization of the tumor and to target radionuclides at tumors for therapy. In addition some benign disorders, e.g. thyrotoxicosis and rheumatoid arthritis, may also be treated with radioactive open sources.

Radionuclide therapy is a unique cancer treatment modality, which can selectively deliver radiation doses in target tissues, is systemic and non-invasive, is associated with few immediate and late side effects, and has the advantage that the uptake and retention in the tumor can be assessed with a tracer study prior to administering a therapeutic dose.

The basis for successful radionuclide therapy is a good and selective concentration and prolonged retention of the radiopharmaceutical by the tumor. The effect depends on the total absorbed radiation dose and the sensitivity of the lesion to radiation. The radiation effect is only maximally exploited if the radioactivity remains in the tumor for total decay. In practice this is almost never the case because of biologic turnover.

TARGETING MECHANISMS/ RADIOPHARMACEUTICALS

There is a steadily expanding list of tumor seeking radiopharmaceuticals with different targeting mechanisms, which are currently being used or can potentially be used in humans for therapy. A good knowledge of the site of the deposition of the radiopharmaceutical in relation to the cell's nucleus is essential for the proper choice of the label by the effective range of the alpha- or beta-particles. It is possible to incorporate radionuclides into the DNA of the cell nucleus or into the cytoplasm via the metabolism (e.g. by ^{131}I as iodide and ^{131}I-MIBG), to attach radioisotopes to the cell surface (e.g. via antibodies and receptor binding agents) or to bring radioactivity into close vicinity of the tumor cell, e.g. by targeting at the extracellular osteoid or by local or regional administration, such as the intraarterial

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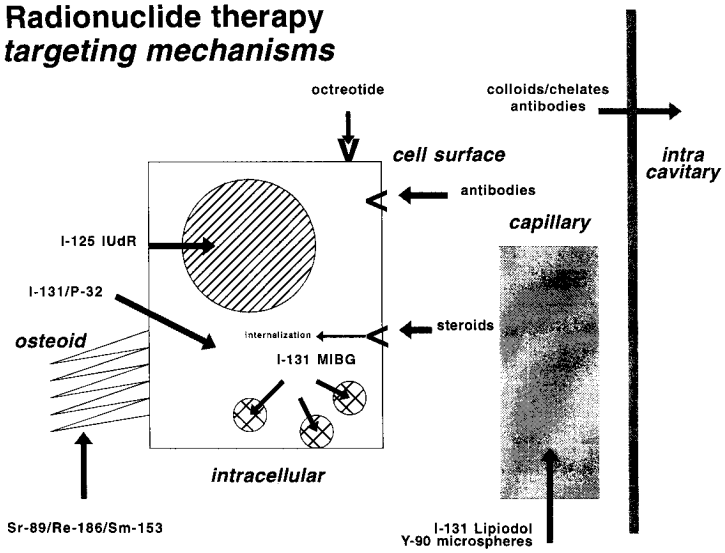


Fig. 1 Schematic representation of the various targeting mechanisms for radionuclide therapy, showing the site of deposition in relation to the cell's nucleus.

use of radiolabeled microspheres and the intracavitary application of radiocolloids and monoclonal antibodies (Fig. 1).

To achieve meaningful radiation doses it is essential that the tumor cells have sufficient and accessible binding sites and that the radiopharmaceutical is "carrier-free," i.e. not containing nonlabeled molecules, which also bind to the target thereby reducing the number of binding sites available for the radioactive compound.[1]

RADIONUCLIDE LABELS

The choice of the radionuclide by its physical characteristics plays an important role in the delivery of an adequate radiation dose. Table 1 shows the range of major radionuclides available for therapeutic application.[2,3] Most often low-energy beta-emitters are used to attain intense irradiation of the target while sparing the surrounding tissues. The range of the beta-rays must be in accordance with the distance between the site of the radiolabeled molecule and the structure in which the radiation effect is intended to take place (the nucleus). Most of the radionuclides currently used for therapy deliver so-called "low-LET" radiation. Specific pharmaceuticals labeled with "high-LET" beta- or alpha-particle emitters, which produce intense ionization over an ultrashort path length, may deliver higher radiation doses, provided that the uptake of the radionuclide is highly selective. In this respect also the tumor size is important, as for isotopes with different physical characteristics the optimal tumor size varies.[4] Auger electron emitting radionuclides also have a high relative biological effectiveness (RBE), but, due to the range being much less than a cell's diameter, require a carrier which brings the source into or close to the nucleus.[5]

QUALITY CONTROL/DRUG DELIVERY/ LOGISTICS

For most of the used radiopharmaceuticals it is essential that, just prior to the administration of therapeutic amounts to patients, quality control, checking both the radionuclide and radiochemical purity takes place, as impurities will not contribute to the tumor targeting, but may add to the side effects of such a treatment. Relatively high doses of radioiodinated pharmaceuticals (e.g. MIBG, antibodies, lipiodol) with a high specific activity undergo autoradiolysis, which is dependent on the temperature, the volume and the presence of stabilizers and scavengers in the formulation.[6] Although blocking the thyroid with potassium iodide is an important aid to reduce the radiation dose to the thyroid, too much free ^{131}I (e.g. > 5%) will nevertheless result in uptake of some radioiodine in the thyroid.

Several routes of administration prevail, depending on the indication, e.g. oral, intravenous by either bolus injection or infusion, intraarterial, intracavitary, and intratumoral. In the case of i.v. or i.a. infusion of radioactive material over hours, dedicated systems with lead shielded vials, infusion pump and monitoring equipment exist or may be developed for specific purposes. For most applications, however, it has not yet been well established, which is the optimal route, dose, speed and frequency of administration, and which specific activity will result in the greatest possible tumor uptake.

Other logistical factors are the availability and licensing of radiation protected isolation facilities, and the necessity of guidelines for radiation protection to ensure

that the treatment is safe both for the patient and for relatives/friends, personnel and the environment. Results of a European survey by the E.A.N.M. Task Group Radionuclide Therapy demonstrate that there is considerable variation between countries in radionuclide therapeutic practice, dependent on local legislation and the requirement and availability of isolation facilities.[7]

Finally, as many of the new therapeutic radiopharmaceuticals are relatively expensive, the financing of these treatments is also an issue.

Table 1 Physical characteristics of radionuclides used for therapy in order of maximum range

nuclide	half life	emission	maximum range
^{80m}Br	4.42 h	Auger	< 10 nm
^{125}I	60.0 d	Auger	→ 10 nm
^{211}At	7.2 h	alpha	→ 65 nm
^{169}Er	9.5 d	beta	→ 1 mm
^{67}Cu	2.58 d	beta/gamma	→ 2.2 mm
^{131}I	8.04 d	beta/gamma	→ 2.4 mm
^{153}Sm	1.95 d	beta/gamma	→ 3.0 mm
^{198}Au	2.7 d	beta/gamma	→ 4.4 mm
^{186}Re	3.77 d	beta/gamma	→ 5.0 mm
^{165}Dy	2.33 h	beta/gamma	→ 6.4 mm
^{89}Sr	50.5 d	beta	→ 8.0 mm
^{32}P	14.3 d	beta	→ 8.7 mm
^{90}Y	2.67 d	beta	→ 12 mm

AVAILABLE THERAPIES AND CLINICAL RESULTS

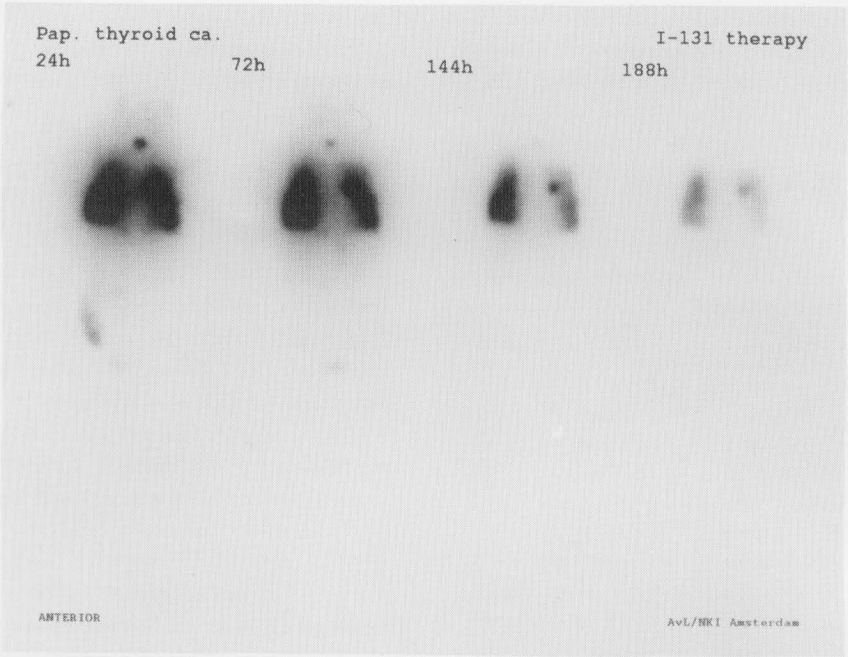
A summary of the types of radionuclide therapy which are currently available or undergoing clinical trial, as well as their indications and principle targeting mechanism are shown in Table 2. Contraindications for radionuclide therapy are pregnancy, continued breast feeding, severe myelosuppression and renal failure. In addition, a relative contraindication is any unstable condition of the patient, that does not allow isolation therapy. In this section current applications for cancer treatment will be briefly reviewed.[8]

I-131 therapy of differentiated thyroid carcinoma

Iodine-131 as iodide has been used with success to treat thyrotoxicosis and for follow up and therapy of differentiated thyroid carcinoma for nearly half a century and this experience forms the background for other forms of

Table 2 Therapeutic applications of nuclear medicine in oncology

Treatment	targeting mechanism	indications
I-131 as iodide	thyroid hormone synthesis	papillary/follicular thyroid carcinoma
P-32 phosphate	incorporation into DNA of rapidly proliferating cells	polycythemia vera essential thrombocythemia
I-131 MIBG	active uptake-l granular storage	neuroblastoma pheochromocytoma paraganglioma symptomatic carcinoid medullary thyroid ca.
In-111/Y-90 octreotide	somatostatin receptor binding	neuroendocrine tumors
I-131 anti-CD20 I-131 bispecific Moabs	antigen binding	lymphoma medullary thyroid ca. NSCLC
Sr-89 chloride Re-186 HEDP Sm-153 EDTMP Sn-117m DTPA	increased bone metabolism surrounding metastases	palliation of painful skeletal metastases (prostate/breast ca.)
i.a. Y-90 glass microspheres I-131 lipiodol	intravascular trapping	hepatocellular ca. liver metastases
intracavitary Moabs/colloids/ chelates	antigen binding/ serosal fixation	malignant effusions cystic craniopharyngioma
intratumoral I-131 Moabs P-32 colloids	direct intratumoral injection	glioma pancreatic and liver tumors



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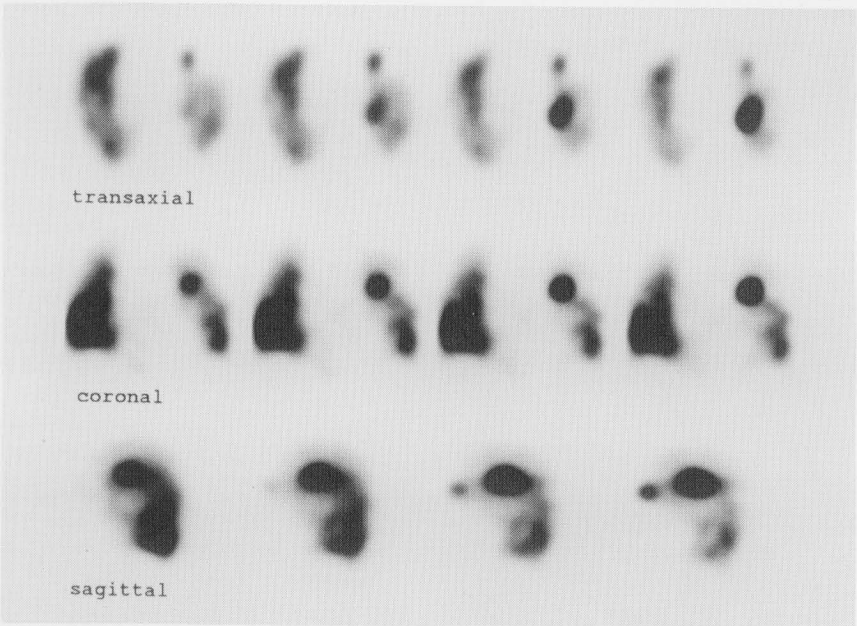

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Fig. 2 Total body scintigrams of a patient with papillary thyroid carcinoma metastatic to lymph nodes and both lungs, at 24, 72, 144 and 188 hours after 7.4 GBq (200 mCi) I-131. Although on planar scintigraphy (above) the pulmonary uptake appears to be diffuse, single photon emission tomography (below) indicates more inhomogeneous distribution of the radioactivity.

targeted radionuclide therapy.[9] More than a million patients worldwide have safely and effectively been treated for hyperthyroidism with ^{131}I-doses usually ranging 110–370 MBq (3–10 mCi). Similar doses are used for tracer studies in postoperative follow up of thyroid carcinoma.

After total or near-total thyroidectomy for thyroid carcinoma higher doses of ^{131}I ranging 1.1–5.5 GBq (29.9–150 mCi) are used to ablate residual normal thyroid tissue in order to enable scintigraphic detection and eventually radionuclide treatment of local or distant metastases, which may not sufficiently concentrate ^{131}I in the presence of thyroid remnants.

Doses up to 7.4 GBq (200 mCi) are applied for ^{131}I

Table 3 Cumulative results of ^{131}I-MIBG in neural crest tumors (Workshop, Rome, September 1991[14])

Disease	Patients	Centers	Objective response (CR/PR and rate)	Palliation
Pheochromocytoma	116	12	3/23/31 hr → 56%	most patients
Paraganglioma	8	7	1/6	all patients
Neuroblastoma	276	13	17/70 → 35%	most patients
Medullary thyroid ca.	22	5	1/6 → 32%	50%
Carcinoid tumors	52	5	2/6 → 15%	65%

CR = complete remission, PR = partial remission (> 50% decrease in tumor volume), hr = hormonal response (>50% decrease in catecholamine excretion).

Table 4 Radionuclide bone therapy: physical and clinical characteristics

Radionuclide:	**^{32}P**	**^{89}Sr**	**^{186}Re**	**^{153}Sm**
Physical properties:				
Half life	14.3 d	50.5 d	3.77 d	1.95 d
E beta max.	1.71 MeV	1.46 MeV	1.07 MeV	0.805 MeV
Maximum range	8.7 mm	8.0 mm	5.0 mm	3.0 mm
Gamma emission	none	none	137 keV	103 keV
Imaging	Brems	Brems	+ + +	+ +
Isolation	no	no	yes	yes
Clinical aspects:				
Adm. dose	370 MBq	150 MBq	1.4 GBq	37 MBq/kg
Chemical form	phosphate	chloride	HEDP	EDTMP
Response rate	74–87%	75–80%	79%	> 65%
Side effects	significant	minimal	minimal	minimal
Advantage	cost	outpatient	imaging dosimetry	imaging dosimetry
Disadvantage	BM-dose	cost	availability cost	availability cost

treatment of metastatic differentiated thyroid carcinoma, with great efficacy of in terms of objective remission and survival, without too many side effects and late effects (Fig. 2).[10] In contrast, in Ukraine and Bellarus, where, following the Chernobyl accident, a significantly increased incidence of differentiated thyroid carcinoma in children has been observed, the response of lung metastases to ^{131}I therapy has been less favorable.[11]

P-32 therapy of myeloproliferative disease

Since its introduction in 1936, radiophosphorus as ^{32}P-orthophosphate has been used in the treatment of myeloproliferative disease, particularly in polycythemia vera and essential thrombocythemia. Incorporation of ^{32}P-orthophosphate into the nucleic acids of rapidly proliferating cells was considered to be the targeting mechanism. Polycythemia vera is characterized by an autonomous proliferation of marrow cells and can be treated by repeated phlebotomies, radioactive phosphorus and chemotherapy. If untreated, the prognosis is poor (median survival 1.5 years). Both chemotherapy (Chlorambucil or Busulphan) and ^{32}P treatment yield better results than phlebotomy alone, attaining objective remissions and prolonged survival.[12]

I-131 MIBG therapy of neural crest tumors

Radioiodinated meta-iodobenzylguanidine (MIBG) has established its place in the diagnosis and treatment of tumors which are derived from the neural crest and present the characteristic features of an active uptake-1 mechanism at the cell membrane and storage granules in the cytoplasm, responsible for the uptake and retention of this radiopharmaceutical.[13] Table 3 shows the cumulative results of major centers treating neural crest tumors with ^{131}I-MIBG, as compiled in 1991.[14]

In a total of 276 **neuroblastoma** patients (predomi-

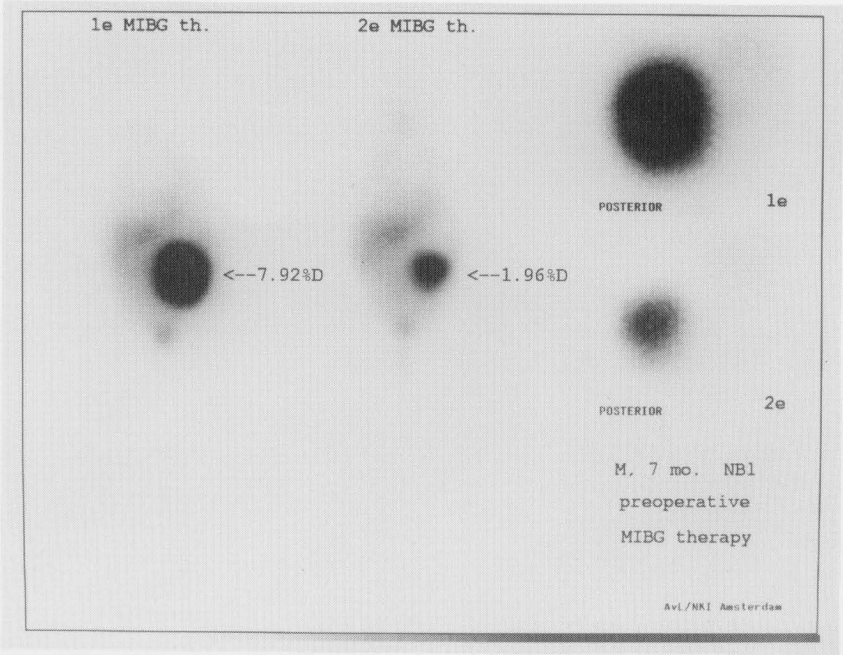

Fig. 3 ^{131}I-MIBG therapy at diagnosis of a 7-month-old baby presenting with an inoperable neuroblastoma stage III: 4 weeks after a therapeutic dose of 3.7 GBq (100 mCi) the tumor had decreased 75% in size and, following a 2nd dose, could be radically resected without further need of chemotherapy.

nantly children) the overall objective response rate was 35%. Most of these patients had stage IV, progressive and intensely pretreated disease, and were only treated with ^{131}I-MIBG after other treatment modalities had failed. In addition MIBG therapy provided valuable palliation and improved quality of life to many children as its non-invasiveness is in contrast with that of chemotherapy. ^{131}I-MIBG therapy is now being used with success preoperatively instead of combination chemotherapy in children with inoperable neuroblastoma, in order to obtain resectability of the tumor and reserve chemotherapy to treat minimal residual disease (Fig. 3).[15] Alternatively ^{125}I-MIBG may be used for therapy of micrometastases and bone marrow infiltration.

In 116 patients with **malignant pheochromocytoma** the cumulative objective response rate (including hormonal response) was 56%, and in more than 60% of the patients subjective improvement of symptoms, lowering of blood pressure, as well as pain relief were achieved.

There are few reports in the literature of successful ^{131}I-MIBG therapy of **paraganglioma**, showing objective partial remission, pain relief and a dramatic improvement in the quality of life. In 22 reported cases of **medullary thyroid carcinoma** treated with ^{131}I-MIBG, a 38% objective response rate and palliation in 50% of the patients was observed, and results in 52 patients with metastatic **carcinoid** revealed objective response in only 19%, but palliation, which may be very meaningful and long lasting, in 65% of these patients. A more recent study of palliative therapy of 50 patients with carcinoid tumors using either ^{131}I-MIBG or high doses of unlabeled ("cold") MIBG demonstrated no objective remissions but palliation in 60% of the patients with either modality.[16]

Radiolabeled peptides

At present only few radiolabeled peptides are available for use in nuclear medicine.[17] The long acting analogue of somatostatin, octreotide, has been labeled with ^{125}I for autoradiography and with ^{123}I, ^{111}In and ^{99m}Tc for scintigraphy of neuroendocrine and other tumors. ^{123}I-labeled Vasoactive intestinal peptide (VIP) has also used with success for tumor imaging. Reubi found VIP-receptors much more frequently present on the cell surface of most tumors than somatostatin-receptors. Approaches to radionuclide therapy include the use of somatostatin analogs labeled with β-emitting radioisotopes, such as ^{131}I (not optimal), ^{90}Y, ^{188}Re and ^{161}Tb, and the administration of cold octreotide or sodium maleate to diminish the dose-limiting renal accumulation of the radiopharmaceutical.

Attempts have been made to treat tumors with high doses of ^{111}In-DTPA-octreotide, despite its unfavorable characteristics for therapy (halflife 2.8 days, pure gamma emissions at 174 and 247 keV and biodistribution).

Radioimmunotherapy

Since the development of the hybridoma technique in 1975, a great variety of radiolabeled monoclonal antibodies or fragments are used for diagnostic scintigraphy of tumors. Although the experience and image quality varies, in many cases the accumulation of radiolabeled mono-

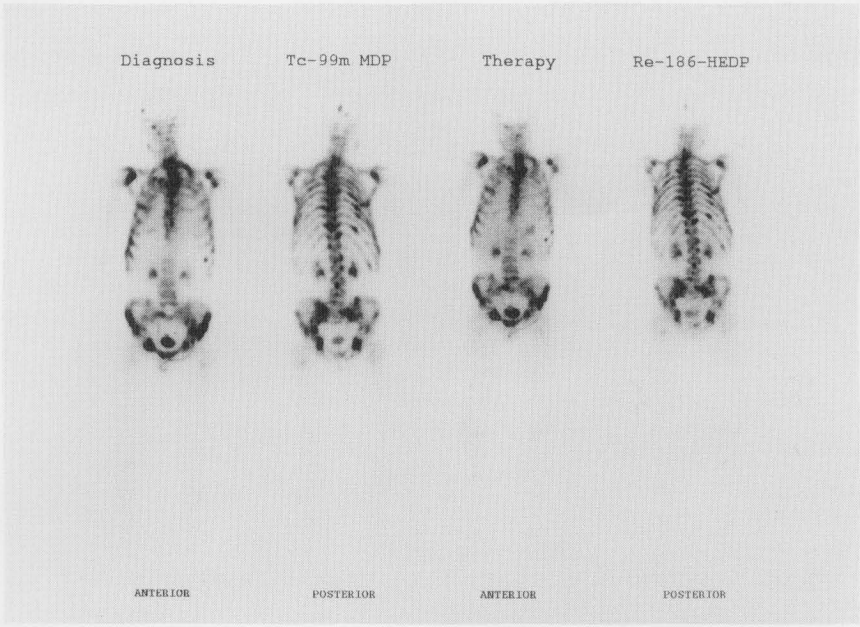

Fig. 4 Palliative therapy of painful bone metastases using ^{186}Re-HEDP in a patient with prostatic carcinoma. Note the excellent correlation of the diagnostic bone scintigram (left) and the post-therapy scintigrams (right).

clonal antibodies (in % dose) was not very high, the retention not very long, and the volumes of tumors which could be imaged relatively large, i.o.w. the dosimetric parameters unfavorable. This has limited their therapeutic application till recently. Particularly for solid tumors the cumulative reported results[18] are poor (objective response rate of 1.2%). For some indications regional or intracavitary application avoided some of the problems in selective targeting of antibodies (cumulative objective response rate 17.4%).

More recently, however, considerably better results have been reported in the treatment of leukemia and lymphoma, particularly using ^{131}I-anti-CD20 monoclonal antibodies (objective response rates up to 70% with a relatively high number of patients attaining a complete remission).

Other developments of radioimmunotherapy include the production of chimeric, "humanized" and bispecific antibodies, multistep targeting technology such as Avidin-Biotin pretargeting, the use of other labels (^{67}Cu, ^{186}Re and ^{211}At), neutron capture therapy using ^{10}B, the combination of modalities, the conjugation of antibodies with drugs and toxins, and the use of biologic response modifiers.[18]

Bone therapy

Although it has been 50 years since the use of radioactive strontium for the treatment of bone metastases was first described by Pecher, a revival of radionuclide bone therapy is seen in recent years, partly due to the fact that more suitable agents become available, partly due to a greater appreciation of radionuclide therapy in general.

Bone therapy may be the treatment of primary bone tumors, such as osteosarcoma, which produce osteoid and in which bone seeking radiopharmaceuticals are in fact tumor seeking, also targeting lung- and soft tissue metastases. Bone therapy may also be the treatment of painful skeletal metastases, which may be palliated due to the absorbed radiation dose in the zone of reactive bone surrounding the tumor. Bone metastases of some tumors may also be treated by specific tumor seeking radiopharmaceuticals, e.g. ^{131}I in thyroid carcinoma or ^{131}I-MIBG in neuroblastoma.

Radiotherapists are used to give 8 Gray by external beam to the hemi or total body with success: around 80% of patients respond. However all other tissues in the body receive a similar radiation dose, which may cause considerable side effects. Radionuclide therapy is less invasive, better tolerated and produces a similar response, limiting the radiation dose to the site of the metastases and sparing the normal tissues.[19]

Table 4 summarizes the major physical and clinical characteristics of 4 available beta-emitters for bone therapy: Phosphorus-32, Strontium-89, Rhenium-186 and Samarium-153. The first two are relatively long living beta-emitters, the latter are beta/gamma emitters with shorter physical half lives and good imaging properties (Fig. 4). Reported results so far indicate response rates similar to radiotherapy and minimal side effects, except for ^{32}P. More recently, ^{117m}Sn-DTPA is undergoing clinical investigation as a therapeutic bone seeking agent.

Table 5 Principal drug interactions for radionuclide therapy

Treatment	Drug interference	Drug intervention
I-131 as iodide	anti-thyroid medication T4/T3 hormones contrast agents excess iodine (drugs, food, topical applications)	Lithium carbonate TSH
I-131 MIBG	Labetalol, Reserpine Calcium-channel blockers Tricyclic antidepressants Ephedrine, Cocaine Adrenergic blocking agents Sympathicomimetic agents Phenothiazines, a.o.	Nifedipine "cold" MIBG hyperbaric oxygen
Sr-89 chloride	Calcium supplements	
Intra-arterial therapy		epinephrine
Radiosynoviorthesis	chelates (e.g. EDTA)	

Alternative approaches: intraarterial/intracavitary/intratumoral targeting

Tumors, which are localized or regional, may be targeted via the **intraarterial** route using formulations which preferentially lodge in arterioles and capillaries of the tumor.[20] Tumors are usually rich in vasculature and liver metastases, for instance, are almost exclusively dependent on arterial blood supply in contrast to the normal liver which receives most of its blood from the portal vein.

As oil contrast is selectively retained in tumor vessels, as well as in tumor cells, **^{131}I-Lipiodol** is used with success for i.a. therapy of liver tumors. Another intraarterial approach was the production of ^{32}P and ^{90}Y **glass microspheres**. Hepatic artery scintigraphy using ^{99m}Tc-MAA has become an essential aid to verify the correct positioning of the arterial catheter, to quantify the arteriovenous shunting to the lungs and to assess tumor-to-normal-liver ratios just prior to radioactive particle therapy. The selectivity of intraarterial radioactivity to the tumor may be further increased by modern arteriographic techniques and the use of vasoactive drugs, which cause vasoconstriction of the normal liver arterioles, but to which tumor vessels, lacking smooth muscle, are insensitive.

An alternative route to bring radioactivity into close contact with tumors which have spread over the serosal linings of cavities and to tumor cells present in the malignant effusions, is by **intracavitary** administration of radiolabeled **colloids, chelates or monoclonal antibodies**. Intracavitary radionuclide therapy can be applied to the pleural, pericardial and peritoneal cavities, intrathecally into the cerebrospinal fluid, and into cystic tumors, e.g. cystic craniopharyngioma.[20]

Another example of intracavitary use of radionuclide therapy is the treatment of benign joint diseases, such as rheumatoid arthritis and other forms of synovitis, by ^{90}Y-citrate/silicate, ^{186}Re-sulphide colloid and ^{169}Er-citrate ("radiosynovectomy").

Some tumors may be treated by direct intratumoral injection of radioisotopes, e.g. the use of ^{131}I-labeled antitenascin antibodies in glioma[21] and ^{32}P-colloids for palliation of inoperable pancreatic and hepatic tumors.[22]

SIDE EFFECTS AND LONGTERM EFFECTS

Major series, in which patients treated with ^{131}I have been followed up for decades, show that side effects and long-term complications of this treatment do not constitute a real problem.

Possible acute side effects are nausea and vomiting, sialadenitis, radiation sickness, temporary painful swelling of metastases, thyroid storm and bone marrow suppression.[23]

Possible long-term effects of ^{131}I-therapy are hematologic effects, pneumonitis and lung fibrosis, fertility disorders, induction of leukemia and other second neoplasms. In practice these late effects are hardly ever seen and long-term (20–40 year) follow up studies of patients treated with ^{131}I or ^{32}P show that radionuclide therapy has in fact a much lower risk of leukemia and second cancers than chemotherapy and external beam radiotherapy.[24,25]

Toxicity may also be due to the targeting agent rather than to the radiation effect. E.g., in the case of radioimmunotherapy, apart from radiation-induced bone marrow toxicity, additional limiting factors may be acute toxicity (which can present with symptoms like fever, chills, flushing, urticaria, rash, headache, nausea, vomiting, dyspnea, hypotension, tachycardia, anaphylaxis, serum sickness, bronchospasm) and the human antimouse antibody (HAMA) response limiting repeated application.

In order to promote the safety of radionuclide therapy, it is essential that the relative lack of side effects and long-

term effects in comparison to chemotherapy and external beam radiotherapy is substantiated by registration of ill effects.

DRUG INTERACTIONS

As many of the mechanisms exploited for radionuclide tumor targeting are related to delicate and complex tumor cell functions, one must be aware that drugs and other factors may interact with these mechanisms, either in a positive (i.e. increased uptake/prolonged retention) or, more often, in a negative way (no uptake/early release of the radiopharmaceutical). Table 5 shows the principal drug interactions with radionuclide therapy.

Drugs interfering with the uptake and/or retention of the radiopharmaceutical may be the cause of false negative results in diagnostic tumor imaging; however, in radionuclide therapy such drug interactions are far more serious, as the altered biodistribution of the therapeutic agent may lead to an increased radiation burden to normal tissues and render the absorbed dose to the tumor insufficient for tumor response.

Use of some other drugs may have a positive effect on the therapeutic index of a radiopharmaceutical (drug intervention).

DOSIMETRY

A simplified equation used to calculate the absorbed radiation dose delivered by a beta-emitting radionuclide which is uniformly distributed and decays within water equivalent tissue (e.g. a tumor) is: D_{beta} (Gy) = $19.9 \times C \times E \times T1/2_{eff}$, in which C is the concentration in MBq per gram tissue, E is the average beta-energy in MeV and $T1/2_{eff}$ the effective halflife in days, which accounts for the fixed physical decay of the radionuclide and an approximation of the biologic turnover of the compound, which is variable and may be different for diagnostic and therapeutic doses as a result of cell damage.

The specific activity in the target tissue tumor can be estimated by adding volumetric information obtained by palpation, x-rays, ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI) to the uptake measurements. As the volumetry does not always reflect the actual volume of viable tumor to be treated and as the inhomogeneity of distribution of the radiopharmaceutical (Fig. 2) is not accounted for, the formulation can not be but an approximation of the dose.

Dosimetry in clinical practice remains difficult, with calculated absorbed radiation doses to the tumor not always matching the observed response. Animal models, such as the xenografted MIBG-concentrating neuroblastoma in the nude mouse, enable the study of the pharmacokinetics, dose-scheduling, dose-response relations and pharmacologic intervention.

EDUCATION

Apart from creating suitable conditions and facilities for radionuclide therapy, it is essential that the level of specific training and expertise of all personnel involved in this form of treatment is adequate. Standardization of therapeutic nuclear medicine procedures will improve the overall quality and will enable better comparison and pooling of reported results. Clinicians making use of radionuclide therapy should be informed more widely about this modality.

CONCLUSION

Taking into account that for most indications radionuclide therapy still finds itself in a last position among other treatment modalities, the response reported to date can certainly be considered as promising. By moving radionuclide therapy forward in treatment protocols, as is now being explored in neuroblastoma, the efficacy of this modality in view of the overall management of oncological disease can be optimized, appreciating that the invasiveness and toxicity compare favorably with that of chemotherapy, immunotherapy and external beam radiotherapy.

Many aspects require further investigation. The mechanisms of uptake and retention, the dose-scheduling as well as pharmacological intervention to enhance the radiation dose delivered to the tumor and to minimize toxicity to non-target tissues are being further investigated. Dosimetry requires more attention to allow a better assessment of the tumor dose and to account for the exposure of the normal tissues and the environment. Animal model studies, microdosimetry using intratumoral thermoluminescence measurements and autoradiography, as well as pharmacokinetic computer modeling may all be helpful in this respect. More pathways into the tumor cell are to be explored and more agents will be identified to selectively target radioactivity. For some of these agents high-LET labels, such as ^{125}I, ^{90}Y and ^{211}At, may increase the radiotoxicity to these cells.

Lastly, nuclear medicine therapy requires a multidisciplinary approach and should not be regarded to be in competition with any of the other treatment modalities in finding its optimal place in the overall management of every individual indication. Successful therapeutic nuclear medicine requires responsible action of both specialists in designing and carrying out these treatments, of hospital directors and health authorities to create the proper environment for such treatment and of legislators to see to it that safety regulations on the one hand protect the environment but on the other ensure that treatment of cancer patients remains feasible.

REFERENCES

1. Spencer RP. An update on therapeutic uses of radiotracers in neoplastic disease. *Semin Nucl Med* 15: 21–27, 1985.
2. Adelstein SJ, Kassis AI. Radiobiologic implications of the microscopic distribution of energy from radionuclides. *Int*

J Rad Appl Istrum [B] 14: 165–169, 1987.
3. Volkert WA, Goeckeler WF, Ehrhardt GJ, Ketring AR. Therapeutic radionuclides: production and decay property considerations. *J Nucl Med* 32: 174–185, 1991.
4. Wheldon TE, O'Donoghue JA, Barrett A, Michalowski AS. The curability of tumours of differing size by targeted radiotherapy using ^{131}I or ^{90}Y. *Radiother Oncol* 21: 91–99, 1991.
5. Humm JL, Charlton DE. A new calculational method to assess the therapeutic potential of Auger electron emission. *Int J Radiat Oncol Biol Phys* 17: 351–360, 1989.
6. Wafelman AR, Suchi R, Hoefnagel CA, Beijnen JH. Radiochemical purity of iodine-131 labelled metaiodobenzylguanidine infusion fluids: a report from clinical practice. *Eur J Nucl Med* 20: 614–616, 1993.
7. Clarke SEM, Hoefnagel CA, Fischer M, Chatal JF, Lewington V, Troncone L, et al. EANM survey of radionuclide therapy practice in Europe. *Eur J Nucl Med* 24: 907, 1997. (abstract)
8. Hoefnagel CA. Radionuclide therapy revisited. *Eur J Nucl Med* 18: 408–431, 1991.
9. Clarke SEM. Radioiodine therapy of the thyroid. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh: Churchill Livingstone, pp. 833–845, 1994.
10. Hundeshagen H. Postoperative diagnosis and therapy of thyroid carcinoma by nuclear medicine. *Eur J Nucl Med* 8: 541–545, 1983.
11. Reiners Chr, Biko J, Bauer W, Wuttke K, Streffer C, Voigt G, et al. Radioiodine treatment of advanced thyroid cancer in children from Belarus living in highly contaminated areas. *Eur J Nucl Med* 21: 743, 1994. (abstract)
12. Nilsson S. Phosphorus-32 therapy in myeloproliferative diseases. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh: Churchill Livingstone, pp. 847–849, 1994.
13. Hoefnagel CA, Lewington VJ. MIBG therapy. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh: Churchill Livingstone, pp. 851–864, 1994.
14. Troncone L, Galli G, eds. Proceedings of the International Workshop on The Role of [^{131}I]Metaiodobenzylguanidine in the Treatment of Neural Crest Tumors. *J Nucl Biol Med* 35: 177–362, 1991.
15. Hoefnagel CA, de Kraker J, Valdés Olmos RA, Voûte PA. ^{131}I-MIBG as a first-line treatment in high risk neuroblastoma patients. *Nucl Med Commun* 15: 712–717, 1994.
16. Taal BG, Hoefnagel CA, Valdés Olmos RA, Boot H, Beijnen JH. Palliative effect of metaiodobenzylguanidine in metastatic carcinoid tumors. *J Clin Oncol* 14: 1829–1838, 1996.
17. Hoefnagel CA. Possibilités thérapeutiques au moyen de la MIBG, l'Octréotide et les autres peptides. *Revue de l'ACOMEN* 2: 71–77, 1996.
18. Chatal JF, Mahé M. Therapeutic use of radiolabelled antibodies. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*, 2nd edition, Edinburgh: Churchill Livingstone, 1998.
19. McEwan AJ. Palliation of bone pain. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh: Churchill Livingstone, pp. 877–892, 1994.
20. Fischer M. Alternative approaches to targeting therapy. *In*: Murray IPC, Ell PJ, eds.: *Nuclear Medicine in Clinical Diagnosis and Treatment*. Edinburgh: Churchill Livingstone, pp. 893–896, 1994.
21 Riva P, Arista A, Tison V, Sturiale C, Franceschi G, Spinelli A, et al. Intralesional radioimmunotherapy of malignant gliomas. An effective treatment in recurrent tumors. *Cancer* 73 (Suppl 3): 1076–1082, 1994.
22. Order SE, Siegel JA, Principato R, Zeiger LE, Johnson E, Lang P, et al. Selective tumor irradiation by infusional brachytherapy in nonresectable pancreatic cancer: a phase I study. *Int J Radiat Oncol* 36: 1117–1126, 1996.
23. Van Nostrand D, Neutze J, Atkins F. Side effects of "rational dose" Iodine-131 therapy for metastatic well-differentiated thyroid carcinoma. *J Nucl Med* 27: 1519–1527, 1986.
24. Schober O, Günter H-H, Schwarzrock R, Hundeshagen H. Hematologic long-term hazards after radioiodine therapy of thyroid cancer. *J Nucl Med* 28: 581–582, 1987.
25. Beierwaltes WH. Horizons in radionuclide therapy: 1985 update. *J Nucl Med* 26: 421–427, 1985.