Radiopharmaceuticals for Therapy

4

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Contents

Learning Objectives

- Understand the basic concepts on the physical and biological events underlying the radiobiological effects caused by radionuclides utilized for therapy.
- Learn the general concepts of radiobiological damage caused by radionuclides emitting β⁻ particles.
- Learn the main physical and chemical characteristics of radionuclides emitting β⁻ particles commonly employed for therapy.
- Learn the general concepts of radiobiological damage caused by radionuclides emitting α^{++} particles.

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- Learn the main physical and chemical characteristics of the radionuclide emitting α^{++} particles commonly employed for therapy—radium-223.
- Understand the potential for therapy of radionuclides emitting very low-energy β^- particles—the Auger electrons.
- Become familiar with the radiopharmaceuticals commonly used for therapy, with special attention to their in vivo pharmacokinetics and radiation dosimetry estimates to normal tissues/organs.

4.1 Introductory Background

Diagnostic radiopharmaceuticals emit γ or β^+ radiation, the former traveling at distances long enough to be detected outside the body for imaging, and the latter originating in turn high-energy photons (through the annihilation process that takes place upon interaction with β^- particles) that can similarly be detected outside the body for imaging. Instead, therapeutic radiopharmaceuticals exert their radiobiological action through the emission of electrically charged particles (α^{++} particles, β^- particles, Auger electrons) that deposit their energy within a much more limited range in tissue—from fraction of a micrometer to a few millimeters at most. This energy deposition within a restricted radius from the decay/emission point can induce radiation damage in the surrounding cells that causes the desired radiobiological effect—cell death. Depending on their energy, the β^- particles typically travel a few millimeters from their emission point, while α^{++} particles typically travel few tens of micrometers in tissues. The radionuclides emitting electrically charged particles with energy suitable for therapy are linked to carrier molecules capable of (selectively) transporting the radiotracers to the target tissues [1].

The goal of radionuclide therapy is to cause irreversible damage to tumor cell DNA, resulting in death of the tumor cell [2] (see also Chap. 11 of this book "Principles of Radiation Biology and Dosimetry for Nuclear Medicine Procedures"). Biologic response to ionizing radiation depends on many factors: cell radiosensitivity, location of radionuclide within the cell or outside, and physical properties such as absorbed dose and linear energy transfer (LET) of the emitted radiation. Linear energy transfer reflects the amount of energy deposited by radiation per unit length of travel in soft tissue, expressed in kiloelectronvolt per micrometer (keV/μm). It can also be defined as the ionization density along the track of radiation, whether electromagnetic radiation or particle radiation. Low-LET radiations produce ionizations only sparsely along their track as is typical for γ-rays or X-rays. High-LET radiations (more typical for electrically charged particles) are more destructive to biological material than low-LET radiations. In fact, with the same activity/dose, low-LET radiations induce few reactive (biochemically toxic) radicals within a cell/tissue, whereas high-LET radiation transfers most of their energy in a small region of the cell. If these ionizations are in the nucleus, the result is damage to the DNA that is more difficult to repair. Table 4.1 lists the main physical characteristics (energy, tissue path, and LET) for the particles that are (or can be) utilized for radionuclide therapy.

Table 4.1 Physical characteristics (energy, path in soft tissue, and LET) of different particle emissions utilized for radionuclide therapy

Emission	Energy (min-max)	Soft tissue path	LET (keV/μm)
α^{++} particles	5–9 MeV	40–100 μm	80
Auger electrons	450 eV–2 keV	0.002–0.5 μm	4–26
β^- particles	0.05–2.3 MeV	50–1200 μm	0.2

In addition to particle emission causing a cytocidal radiobiological effect, some radionuclides used for therapy also emit γ-rays or β^+ particles, which do not contribute to the effectiveness of therapy (and may even lead to increased irradiation to nontarget tissues), but can be used to image the distribution of the therapeutic agent. These images can be used to calculate the dose delivered to the lesion (and other tissues) by the therapeutic agent.

Therapeutic radiopharmaceuticals can be administered systemically by intravenous administration or orally, intracavitarily, or intra-arterially. The majority of radionuclide therapies are administered for treating various forms of cancer with either curative or palliation purposes. Less frequently, radionuclide therapy is utilized for benign disease, such as treatment of hyperthyroidism.

Selection of the most appropriate radionuclide for therapy must consider the type of radiation, energy, effective half-life on the target tissue, and chemistry in relation to the carrier molecule.

Key Learning Points

- Radionuclides utilized for therapy exert their radiobiological action through the emission of electrically charged particles (α^{++} particles, β^- particles, Auger electrons) that deposit their energy within a limited range in tissue—from fraction of a micrometer to a few millimeters.
- Radionuclides emitting electrically charged particles suitable for therapy are linked to carrier molecules capable of (selectively) transporting the radiotracers to the target tissues.
- Radionuclide therapy causes irreversible damage to tumor cell DNA causing death of the tumor cell.
- Biologic response to ionizing radiation depends on cell radiosensitivity, location of the radionuclide within the cell or outside, and physical properties such as absorbed dose and linear energy transfer of the emitted radiation.

- Concomitant emission of γ-rays or β^+ particles by the radionuclide used for therapy can be used to image whole-body distribution of the therapeutic radiopharmaceutical.
- Therapeutic radiopharmaceuticals can be administered systemically by intravenous administration or orally, intracavitarily, or intra-arterially.

4.2 Beta-Emitting Radionuclides

Radionuclide therapy usually employs radionuclides emitting β^- particles. These negatively charged particles have a relatively low LET (0.2 keV/μm) and a continuous spectrum of energy. After their emission, the daughter nucleus has one more proton and one less neutron than the original radionuclide. The radionuclides currently employed for therapy have maximum path lengths in soft tissues (or water-equivalent) that range from 2 to 12 mm, depending on maximum energy of the particle (Fig. 4.1). Although common terminology refers to a linear measure of path length, radioactive emission occurs always isotropically (in all directions) and must therefore be considered in terms of a "sphere" around the emission point. Furthermore, the β^- particles do not travel in a straight path (as γ-rays and X-rays do) but are continuously deviated in a random manner in all directions because of interactions with the surrounding matter (Fig. 4.2). Therefore, from a three-dimensional point of view, the path of an electron in space is similar to a tangled ball of yarn, and the maximum path range in tissues reported for each radionuclide is reached by only a few of the electrons emitted by that radionuclide. In reality, approximately 90% of the energy associated with β^- emission (as well as with β^+ emission) is deposited within about 20% of the maximum tissue range reported for each radionuclide.

The path length of β^- particles in tissues results in the so-called crossfire effect, whereby cells that have not concentrated the radionuclide are exposed to potentially lethal radiation from adjacent cells that concentrated the therapeutic agent (Fig. 4.3). This effect can enhance the effectiveness of the treatment, especially in tissues with a heterogeneous distribution in the target tissue.

The radiopharmaceuticals currently employed in clinical practice for therapy are listed in Table 4.2, while the main radionuclides emitting β^- with suitable energy for therapeutic applications are described here below.

4.2.1 Iodine-131 (^{131}I)

Iodine-131 is produced by fission of uranium-235 or by neutron bombardment of stable tellurium in a nuclear reactor. It has a half-life of 8.0 days and decays to stable xenon-131 emitting, in addition to γ-rays, β^- particles with maximum energy of 606 keV (247 keV with 1.8% abundance, 334 keV with 7.2% abundance, 606 keV with 89.7% abundance, 806 keV with 0.7% abundance). The maximum path range is 2.4 mm in tissues (mean 0.7 mm).

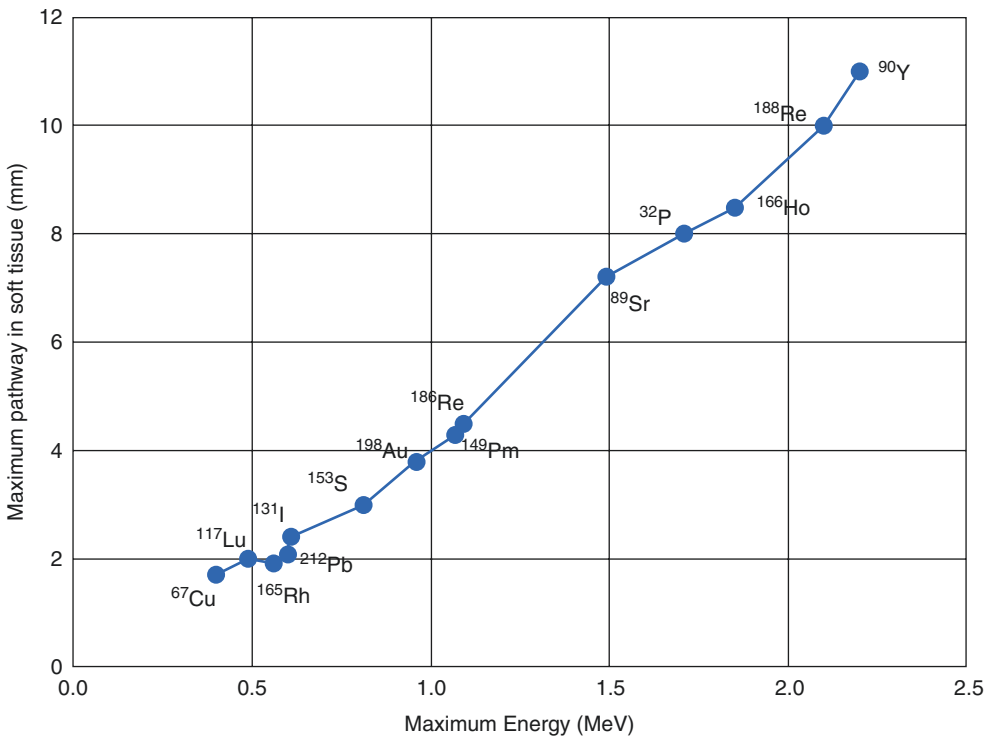

Fig. 4.1 Correlation between maximum energy (MeV) and maximum path in water/soft tissue (mm) of the main β^- particle-emitting radionuclides employed for therapy in nuclear medicine

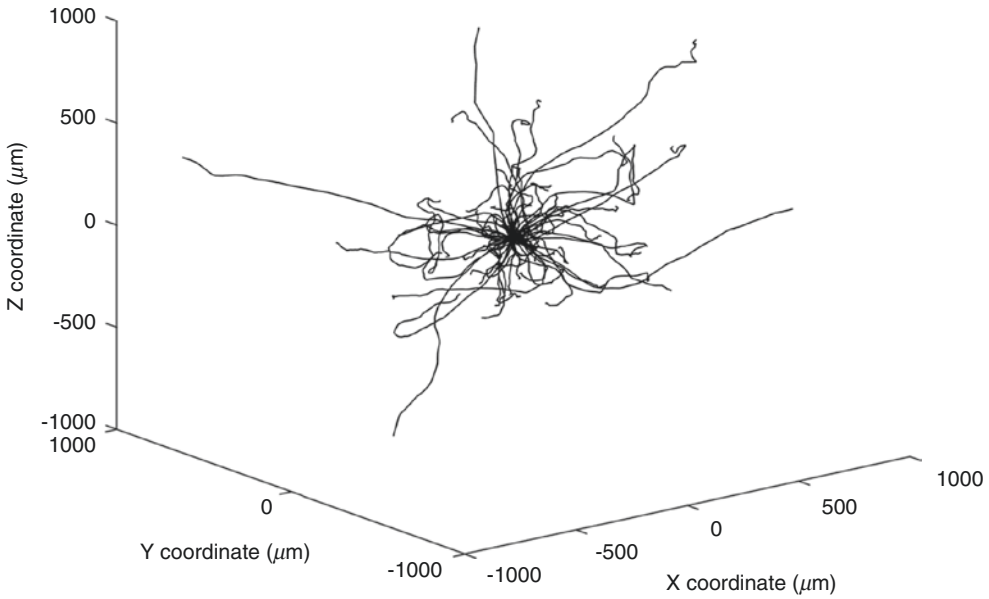

Fig. 4.2 Simulation of the tracks in water of β^- particles emitted by a point source of ^{131}I (full energy spectrum); simulation has been performed for only 100 particles, a number too limited to show the whole spectrum of possibilities (including the maximum range, which is reached only by an extremely small fraction of the particles emitted). Due to interactions with surrounding matter, the β^- particles deviate repeatedly from their initial direction. Most of the energy (about 90%) associated with the emissions is deposited within about 20% of the maximum path range reported for each radionuclide (*image provided by courtesy of Prof. Alberto Del Guerra, Department of Physics "E. Fermi", University of Pisa and National Institute of Nuclear Physics (INFN), Pisa Section, Pisa (Italy)*)

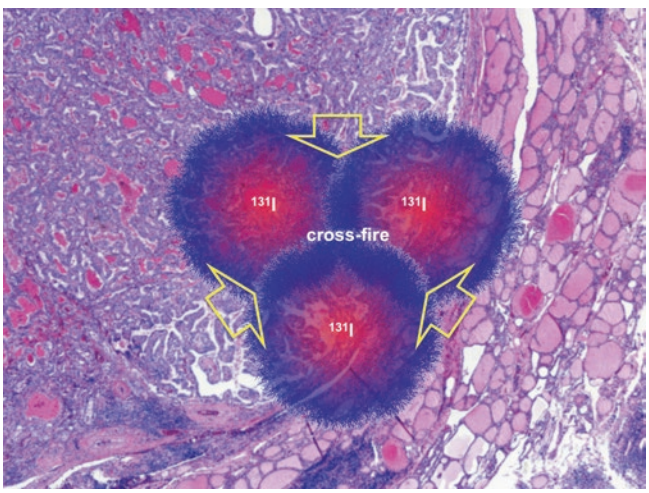

Fig. 4.3 Schematic representation of the crossfire effect for particle-emitting radionuclides employed for therapy (assumed to be β^- particles for this representation). Because of delivery of energy within a certain range from the point of emission, the radiotoxic effect is not limited to the cells that specifically accumulate the radiopharmaceutical but also involves nearby cells (either they be neoplastic or tumor cells)

In the chemical form of sodium ^{131}I-iodide, this radionuclide is extensively employed for treating benign and malignant thyroid diseases. Other therapeutic applications involve linking of ^{131}I of more complex molecules, such as meta-iodobenzylguanidine (MIBG) or monoclonal antibodies.

4.2.2 Yttrium-90 (^{90}Y)

The radio-metal ^{90}Y is produced by the generator system $^{90}Sr/^{90}Y$ and decays to stable ^{90}Zr. It has a half-life of 64 h and emits high-energy β^- particles (2.2 MeV) with a maximum path length of 11–12 mm (mean 5.3 mm). The β^- decay is associated with pair production of β^+ particles, although in a minimal proportion (32 β^+ particles per million decays); no γ-emission occurs during decay of ^{90}Y. ^{90}Yttrium is coupled to peptides and monoclonal antibodies through bifunctional chelates, such as DOTA to produce a therapeutic radiopharmaceutical.

There are currently three major clinical uses of ^{90}Y: (1) to label a monoclonal antibody for radioimmunotherapy of lymphomas, (2) to bound to resin or glass microspheres for intra-arterial radio-embolization of liver tumors, and (3) to label somatostatin analogs for peptide receptor radionuclide therapy of neuroendocrine neoplasms.

4.2.3 Rhenium-188 (^{188}Re) and Rhenium-186 (^{186}Re)

Rhenium-188 is a group VII metal with a half-life of 16.9 h that decays to stable osmium-188 with emission of β^- particles with maximum energy of 2.12 MeV having maximum range of 11 mm in tissue (mean 3.5 mm). It also emits γ-rays with energy of 155 keV (15%), favorable for gamma camera imaging.

Table 4.2 Localization mechanisms and indications for the radiopharmaceuticals most commonly used in clinical practice for radionuclide therapy

Radiopharmaceutical	Localization mechanism	Indications
^{131}I-Iodide	Transmembrane active transport: Na^+/I^- symporter (NIS)	Treatment of malignant or benign thyroid disease
[^{131}I]MIBG	Accumulation in intracellular neurosecretory vesicles	Treatment of neural crest-derived neuroendocrine tumors
	ATPase-linked energy-dependent process and pinocytosis	
^{90}Y-Ibritumomab tiuxetan	Antigen-antibody binding (anti-CD20)	RIT of NHLs
^{131}I-Tositumomab	Antigen-antibody binding (anti-CD20)	RIT of NHLs
^{90}Y- or ^{166}Ho-Microspheres	Mechanical trapping (intra-arterial micro-embolization)	Intra-arterial therapy of liver tumors
^{131}I- or ^{188}Re-Lipiodol	Mechanical trapping and pinocytosis	Intra-arterial therapy of liver tumors
^{177}Lu- or ^{90}Y-SST analogs	Receptor/ligand binding	Treatment of neuroendocrine tumors
^{32}P-Chloride	Ion exchange	Treatment of metastatic bone disease
^{89}Sr-Chloride	Ion exchange	Treatment of metastatic bone disease
^{186}Re- or ^{188}Re-HEDP	Chemisorption	Treatment of metastatic bone disease
^{153}Sm-EDTMP	Chemisorption	Treatment of metastatic bone disease
^{223}Ra-Chloride	Ion exchange	Treatment of metastatic bone disease

RIT radioimmunotherapy, *NHLs* non-Hodgkin's lymphomas, *SST* somatostatin

Rhenium-188 can be produced with relatively high specific activity by direct production in a nuclear reactor by irradiation of enriched rhenium-187. For clinical purposes it is produced in the no-carrier-added form using a generator system based on its parent radionuclide wolfram-188 (also known as tungsten-188), with a half-life of 69 days. The ^{188}W/^{188}Re generator allows local availability of ^{188}Re on demand to label kits to produce therapeutic agents [3].

Rhenium-186 can be produced in low neutron flux nuclear reactors (that are widely available throughout the world) by direct neutron activation of enriched rhenium-185; its 90-h half-life permits distribution also to sites distant from the production facility. Rhenium-186 decays to osmium-186 (^{186}Os) with the emission of β^- particles with maximum energy of 1.09 MeV and maximum path range of 4.5 mm in tissue (mean 1.1 mm); it also emits a low abundance (9%) of γ-ray suitable for gamma camera imaging (137 keV).

Both ^{186}Re and ^{188}Re have labeling chemistry properties similar to those of technetium; for this reason, these radionuclides offer the ability to utilize vast radiochemistry experience accumulated with ^{99m}Tc.

After conjugation with bone-seeking bisphosphonates, these two radionuclides are currently employed clinically for treatment of bone pain from skeletal metastases; ^{188}Re-lipiodol (a radiolabeled suspension of fatty acids) is used for treatment of hepatocellular carcinoma.

4.2.4 Lutetium-177 (^{177}Lu)

Lutetium-177 is a radionuclide emitting β^- and γ with a physical half-life of 6.7 days. It decays to stable hafnium (^{177}Hf). The β^- particles emitted by ^{177}Lu have a maximum energy of 497 keV (78.6%), 384 keV (9.1%), and 176 keV (12.2%). It also emits γ-rays with 113 keV (6.6%) and 208 keV (11%) energies, suitable for gamma camera imaging. The maximum soft tissue penetration depth is about 2 mm (mean 0.67 mm). It is produced in a nuclear reactor with "direct" or "indirect" reactor production routes based on neutron irradiation of ^{176}Lu or ^{176}Yb, respectively [4].

Currently, this radionuclide is used for labeling somatostatin analogs for peptide receptor radionuclide treatment (PRRT) of neuroendocrine tumors (NETs). However, additional possible uses of ^{177}Lu are growing, including conjugation with bisphosphonates (e.g., ^{177}Lu-EDTMP) as bone-seeking radiopharmaceuticals for treatment of bone pain from skeletal metastases and conjugation with ligands for the prostate-specific membrane antigen (PSMA) for therapy of inoperable prostate cancers.

4.2.5 Phosphorus-32 (^{32}P)

Phosphorus-32, a pure emitter of β^- particles, is produced in a nuclear reactor. It has a physical half-life of 14.3 days and a maximum energy of 1.71 MeV (100%), resulting in a maximum tissue range of 8 mm (mean 3 mm).

Treatment with ^{32}P in the chemical form of orthophosphate is indicated for palliation of bone pain from skeletal metastases, polycythemia vera, and essential thrombocythemia.

4.2.6 Strontium-89 (^{89}Sr)

Reactor-produced ^{89}Sr is an alkaline earth metal radionuclide with a half-life of 50.5 days. It is an almost pure emitter of

β⁻ particles with a maximum energy of 1.49 MeV (100% abundance) and a very low γ-ray emission (0.01% abundance) with a 0.91 MeV photopeak that precludes external imaging. The maximum path length of its β⁻ particles in soft tissues is 7.2 mm (mean 2.4 mm).

In the chemical form of $^{89}SrCl_2$ (dichloride salt), its current clinical use is for treatment of bone pain from skeletal metastases.

4.2.7 Samarium-153 (^{153}Sm)

This radionuclide is fission-produced by neutron capture using a target enriched in ^{152}Sm. It has a physical half-life of 1.9 days and emits β⁻ particles with a maximum energy of 0.81 MeV (20%), 0.71 MeV (50%), and 0.64 MeV (30%). ^{153}Sm also emits γ-rays with and energy of 103 keV (29% abundance), which are useful for gamma camera imaging. The maximum tissue range of the β⁻ particles emitted by ^{153}Sm is 3 mm (mean 0.5 mm).

The prevalent use of ^{153}Sm is in the chemical form of a radiolabeled bisphosphonate (^{153}Sm-EDTMP), employed in the clinical routine for treatment of bone pain from skeletal metastases.

4.2.8 Holmium-166 (^{166}Ho)

This radionuclide is produced by neutron capture using a target enriched in ^{165}Ho oxide. It decays with a half-life of 26.8 h to erbium-166 emitting β⁻ particles with maximum energies of 1.84 MeV (48% abundance) and 1.77 MeV (48% abundance), associated with emission of γ-rays with energies of 81 keV (5.4% abundance) and 1379 keV (1.13% abundance). The maximum tissue range of the β⁻ particles emitted by ^{166}Ho is 8.4 mm (mean 4 mm).

The prevalent use of ^{166}Ho is currently in the bound form to glass microspheres for transarterial radio-embolization of liver tumors.

Key Learning Points

- The radionuclides emitting β⁻ particles of suitable energy most commonly utilized for therapy include ^{131}I, ^{90}Y, ^{177}Lu, ^{32}P, ^{89}Sr, ^{153}Sm, and ^{166}Ho.
- The maximum path length in tissues of these radionuclides is directly correlated with their maximum energy and varies between 2 and 12 mm.
- For each radionuclide, approximately 90% of the energy associated with β⁻ emission is deposited within about 20% of the maximum tissue range.
- The path length of β⁻ particles in tissues results in the so-called crossfire effect, whereby cells that have not concentrated the radionuclide are exposed to potentially lethal radiation from adjacent cells that concentrated the therapeutic agent.
- ^{131}I has a physical half-life of 8 days and decays emitting both β⁻ particles with maximum path range of 2.4 mm in tissues and γ-rays suitable for gamma camera imaging.
- ^{90}Y has a physical half-life of 64 h and decays emitting β⁻ particles with maximum path length of 11–12 mm in tissues; there is also a very low fraction of decay associated with pair production of β⁺ particles (32 particles per million decays).
- ^{188}Re has a physical half-life of 16.9 h and decays emitting both β⁻ particles with maximum path range of 11 mm in tissues and γ-rays suitable for gamma camera imaging.
- ^{186}Re has a physical half-life of 90 h and decays emitting both β⁻ particles with maximum path range of 4.5 mm in tissues and γ-rays suitable for gamma camera imaging.
- ^{177}Lu has a physical half-life of 6.7 days and decays emitting both β⁻ particles with maximum path length of 2 mm in tissues and γ-rays suitable for gamma camera imaging.
- ^{32}P has a physical half-life of 14.3 days and emits β⁻ particles with maximum path range of 8 mm in tissues.
- ^{89}Sr has a physical half-life of 50.5 days and emits β⁻ particles with maximum path range of 7.2 mm in tissues.
- ^{153}Sm has a physical half-life of 1.9 days and decays emitting both β⁻ particles with maximum path range of 3 mm in tissues and γ-rays suitable for gamma camera imaging.
- ^{166}Ho has a physical half-life of 26.8 h and decays emitting both β⁻ particles with maximum path range of 8.4 mm in tissues and γ-rays suitable for gamma camera imaging.

4.3 Radionuclides Emitting Alpha Particles

Alpha particles are positive helium nuclei; their emission leads to a daughter nucleus with two fewer protons and two fewer neutrons than the original radionuclide. These monoenergetic particles are usually emitted with high energy (5–9 MeV) and produce a high density of ionization along their short linear tracks of 40–100 μm, corresponding to about five to ten cell diameters. The high therapeutic potential of these particles is due to their relatively large mass, based on which they have numerous interactions with nuclei of the cells they encounter along their path; this phenomenon results in high-LET values of the α particles, typically in the 80–100 keV/μm range. Their

biologic effect is independent of the oxygenation state or cell cycle phase, as their interaction with the cell nucleus results in single- and/or double-strand DNA breaks that are lethal for the cell. The tumoricidal effect is maximal if the α particles are emitted within the cell nucleus.

Despite growing investigations on several α emitter radionuclides, there is currently only one approved radiopharmaceutical available for clinical practice, radium-223 dichloride.

4.3.1 Radium-223 (^{223}Ra)

Radium-223 decays to stable lead-207 via a six-stage decay chain of short-lived daughter radionuclides, producing a number of α-, β-, and γ-emissions with different energies and emission probabilities. The fraction of energy emitted from ^{223}Ra and its daughters as α particles is 95.3% (energy range 5.0–7.5 MeV). The fraction emitted as β^- particles is 3.6% (average energies are 0.445 and 0.492 MeV), and the fraction emitted as γ-radiation is 1.1% (energy range of 0.01–1.27 MeV). It has a physical half-life of 11.4 days.

^{223}Ra can be produced efficiently in large amounts by a ^{227}Ac/^{223}Ra neutron generator (half-life 21.8 years) that guarantees availability of the radionuclide for long periods. ^{227}Ac is produced by neutron irradiation of natural ^{226}Ra.

The relatively long half-life of ^{223}Ra provides sufficient time for its preparation, distribution (including long distance shipment), and administration to patients. Its low irradiation is favorable from the point of view of handling, radiation protection, and treatment on an outpatient basis.

Administered as a chloride salt, the calcium analog ^{223}Ra has bone-seeking properties that make it useful for treating intractable bone pain from skeletal metastases.

Key Learning Points

- High-energy α^{++} particles (5–9 MeV) produce a high density of ionization along their short tracks of 40–100 μm, corresponding to about five to ten cell diameters.
- The linear energy transfer associated with emission of α^{++} particles is much higher than that associated with the emission of β^- particles of similar energy.
- The single- and/or double-strand DNA breaks caused by α^{++} particles are lethal for the cell, with a maximal tumoricidal effect when the particles are emitted within the cell nucleus.
- Although the potential for antitumor efficacy of several radionuclides emitting α^{++} particles is being explored, the only radionuclide currently used clinically is ^{223}Ra, which has a physical half-life of 11.4 days.

4.4 Radionuclides Emitting Auger Electrons

Auger electrons are low-energy orbital electrons emitted after electron capture. Electron capture causes a vacancy, which is filled by electrons moving from an outer shell and thus initiating a cascade of electron transitions that shift the vacancy toward the outermost shell.

Auger electrons have an extremely short path length in tissues (2–500 nm), due to their very low energy (0.45–2 keV), and LET ranging from 4 to 26 keV/μm. Localization of the radionuclide within the cell nucleus is a strict requirement to reach DNA (preferably within the DNA component of the nucleus) and thus achieve cell killing; mitochondrial or cell surface localization does not produce significant cytotoxic effects.

Thus, in principle the radiodosimetric burden would be maximum to the target (tumor) tissue, provided that all cells incorporate the radionuclide, and minimal in adjacent healthy tissues. Although theoretically very promising, treatment with Auger electron-emitting radionuclides remains at the moment only in a potential state, as it has not so far been possible to transfer to humans the good results obtained in experimental models (in vitro cell cultures or animal models).

Some of the radionuclides employed in diagnostic conventional nuclear medicine (^{67}Ga, ^{75}Se, ^{111}In, ^{125}I, ^{123}I, and ^{201}Tl) emit Auger electron, but no radiopharmaceutical is currently employed in clinical practice for therapeutic purposes. The only relevant clinical investigations based on emission of Auger electrons have been carried out with the use of ^{111}In-DTPA-octreotide in patients with neuroendocrine tumors. However, the pilot clinical investigations have not proceeded any further after publication of the first reports describing the superior therapeutic results obtained with ^{90}Y-labeled somatostatin analogs.

Key Learning Points

- Auger electrons are low-energy orbital electrons emitted after electron capture.
- The very low energy (0.45–2 keV) of Auger electrons results in an extremely short path length in tissues (2–500 nm).
- Localization of the radionuclide emitting Auger electrons within the cell nucleus is a strict requirement to reach DNA and thus achieve cell killing.
- Radionuclides emitting Auger electrons include ^{67}Ga, ^{75}Se, ^{111}In, ^{125}I, ^{123}I, and ^{201}Tl.
- Although potentially attractive for tumor therapy, it has not so far been possible to transfer to humans the promising results obtained with in vitro cell cultures or animal models.

4.5 Radiopharmaceutical-Based Emission of β⁻ Particles

4.5.1 Sodium ^{131}I-Iodide

Iodine-131 is commonly administered in the chemical form of sodium iodide for treating thyroid disorders. In a manner identical with that of native $^{127}I^-$ ions, the radioactive I^- ions present in the circulation and in interstitial fluid are transported into the thyroid cells against a concentration gradient by an active transport mechanism (the Na^+/I^- symporter, NIS), located on the basolateral membrane of thyroid follicular cells. This active transport process concentrates iodide 20- to 40-fold the plasma concentration under normal circumstances, a value that may in turn increase by an additional tenfold in the hyperfunctioning thyroid gland. Similarly as for other parameters of thyroid cell function and growth, the intracellular accumulation of iodine is regulated by serum TSH. Once inside the thyroid cell, iodine is oxidized by the enzyme peroxidase; this starts the organification process that enables incorporation of iodine (either native or radioactive) into tyrosine to produce molecules of monoiodotyrosine (MIT) and diiodotyrosine (DIT) that are finally combined to constitute the two chemical species of active thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Thyroid hormones stored in the colloid contained inside the thyroid follicles are finally secreted into the circulation by pinocytosis, again following stimulation by TSH under physiologic conditions.

In addition to the concentration in the thyroid gland, iodine accumulates in salivary glands, lacrimal glands, sweat glands, gastric glands, mammary gland, and the placenta. These physiological processes can induce unwanted side effects when using ^{131}I-iodide for high-dose therapy including pain in the anterior cervical region (caused by inflammation induced by the cytotoxic action of radioiodine), dysgeusia, anosmia, acute or chronic sialadenitis (sometimes with persistent xerostomia), gastritis (with nausea and vomiting), and actinic cystitis. ^{131}I uptake in the placenta and mammary gland would expose the fetus or the baby, respectively, to an unacceptable radiation dose.

^{131}I-iodide is commonly used for treating both benign thyroid diseases (hyperthyroidism caused by Graves' disease or hyperfunctioning thyroid adenomas) and malignant thyroid disease (differentiated thyroid carcinomas) [5].

^{131}I-iodide is generally administered orally (capsules or liquid solutions), while the intravenous administration is needed only in uncooperative patients or in case of uncontrolled vomiting. To facilitate and accelerate intestinal absorption, patients should fast for at least 6 h prior to and for 3 h after administration, and a low-iodine diet should be undertaken for 2–3 weeks prior to therapy.

After i.v. injection, about 20% of circulating iodide is extracted by the thyroid gland. The thyroid peak uptake/accumulation occurs within 24–48 h of administration, with about 50% of the maximum reached at 5 h. After oral administration, sodium ^{131}I-iodide is absorbed rapidly from the upper gastrointestinal tract (90% in 60 min). The main excretion route of iodine is through the kidneys, with renal clearance equal to about 2–3% of renal blood flow in subjects with normal renal function. Renal clearance of iodine is reduced in hypothyroid subjects or in patients with impaired renal function, while it is increased in hyperthyroidism. In euthyroid subjects with normal renal function, 50–75% of administered radioiodine is excreted in the urine within 48 h, while about 10% of the administered activity is excreted through the fecal route, and there is a minor fraction of excretion with sweat and through the lungs with exhaled air (the latter being almost negligible). The biological effective half-life of radioiodine in plasma is about 12 h, whereas radioiodine concentrated in the thyroid gland is released with a half-life of about 6 days. Thus, after administration of sodium ^{131}I-iodide to an individual with normal thyroid function, approximately 40% of the activity has an effective half-life of 0.4 days, whereas the remaining 60% has an affective half-life of 8 days.

Although radiation safety regulations vary from country to country, radioiodine treatment for hyperthyroidism is generally performed on an outpatient basis, after adequate preparation and dosimetric evaluation. Two methods are commonly used to select the activity of ^{131}I-iodide to be administered: (1) administration of a fixed activity based on clinical experience and (2) administration of a fixed radiation dose on the basis of dosimetric calculations. The aim of radioiodine therapy in hyperthyroid patients is to induce permanent euthyroidism or hypothyroidism.

The most common indication for therapy with ^{131}I-iodide in patients with differentiated thyroid cancer derived from the follicular epithelium (papillary and follicular carcinoma) is for ablation of postsurgical remnants after thyroidectomy in patients with intermediate- to high-risk cancer. In addition, therapy with ^{131}I-iodide is used for the treatment of locoregional recurrences and/or distant metastases, with activities varying from 1.1 to 7.4 GBq [6]. For such high-dose treatments, radiation safety regulations standing in several countries require hospitalization in specially equipped rooms for adequate handling of radioactive wastes. Patients are discharged from the hospital when measurements of their radioactivity emissions fall below certain thresholds set according to local radiation safety regulations [7].

As for all therapies with radionuclides, absolute contraindications to radioiodine treatment are pregnancy and lactation. Since the specific radioactivity of ^{131}I-iodide is very high (typically >200 MBq/μg), the amount of iodine administered for therapy with ^{131}I-Iodide is considerably lower than the recommended daily amount of iodine in a normal diet. Thus, allergy to iodine is not considered a contraindication.

Approximately 4–7 days after administration of high-dose ^{131}I-iodide for therapy, whole-body scintigraphy is performed, based on the consistent γ-ray emission of ^{131}I. The whole-body images may be supplemented by spot images

and SPECT/CT to visualize both physiologic and abnormal sites of radioiodine localization. These images provide information for staging or restaging the disease and sometimes depict previously unknown metastatic lesions.

The main radiation dosimetry estimates to patients following oral administration of ^{131}I-iodide in individuals with a normal functioning thyroid gland (without thyroid-blocking pretreatment) are reported here below, normalized to unit of administered activity:

- Effective dose 0.15 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Thyroid 2.5 mGy/MBq
  - Gastric wall 0.12 mGy/MBq
  - Urinary bladder wall 0.066 mGy/MBq

4.5.2 *Meta*-[^{131}I]Iodo-Benzyl-Guanidine (^{131}I-MIBG)

This radiopharmaceutical (also known as ^{131}I-iobenguane) was developed in the early 1980s to visualize tumors of the adrenal medulla. It is a catecholamine analog (labeled ^{123}I for diagnostic use) in which the iodinated benzyl group of bretylium is combined with the guanidine group of guanethidine (Fig. 4.4). Radioiodination is performed by the isotope exchange method.

Due to its structural analogy with catecholamines, MIBG is taken up by chromaffin cells via an active physiologic uptake mechanism, the epinephrine transporter utilized for accumulating noradrenaline in neurosecretory granules. Following depolarization induced by high transmembrane flux of calcium ions, these molecules are then secreted through an exocytosis mechanism. This uptake/accumulation process is abundantly expressed in the sympathetic ganglia, the adrenal medulla, and in all tissues with high adrenergic innervation (myocardium, salivary glands). When the drug is administered in high concentrations for therapy, passive diffusion also becomes important.

The therapeutic applications of ^{131}I-MIBG include tumors of the sympathoadrenal system originating embryologically from the neural crest, such as pheochromocytoma, paraganglioma, and neuroblastoma. Nonetheless, other neuroendocrine tumors such as medullary thyroid carcinoma, carcinoids, and gastro-entero-pancreatic (GEP) tumors can also be successfully treated, provided that diagnostic scans with ^{123}I-MIBG show satisfactory uptake in the lesions [8].

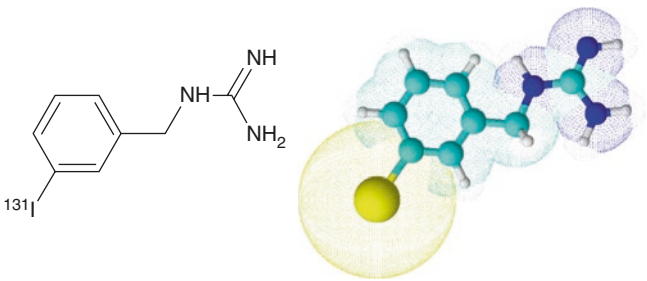

Fig. 4.4 Chemical formula (left) and 3D structure (right) of radioiodinated MIBG. Color codes: *yellow*, ^{131}I; *white*, H; *light blue*, C; *dark blue*, N

After slow i.v. infusion, the distribution pattern of ^{131}I-MIBG shows rapid initial uptake in the liver (33% of the administered activity), lungs (3%), myocardium (0.8%), spleen (0.6%), and salivary glands (0.4%). While uptake in normally functioning adrenal medulla is so low that the adrenals cannot be visualized, hyperplastic adrenals show a high uptake of ^{131}I-MIBG. About half of the administered activity is excreted in the urine within the first day, 70–90% of the activity being cumulatively excreted within 2 days; the urinary metabolic breakdown products account for approximately 5–15% of the administered activity. About 3% of MIBG excretion occurs via the gastrointestinal tract.

Absolute contraindications to therapy with ^{131}I-MIBG are pregnancy, lactation, and renal insufficiency requiring dialysis. Relative contraindications include unmanageable urinary incontinence, rapidly deteriorating renal function (GFR < 30 mL/min), progressive hematological and/or renal toxicity because of prior treatments, and myelosuppression (total white cell count $<3.0 \times 10^9$/L, platelets less than 100×10^9/L).

The most important precaution in the preparation of patients for therapy with ^{131}I-MIBG includes discontinuing drugs interfering with MIBG uptake (such as labetalol, tricyclic antidepressants, reserpine, and some sympathomimetic drugs) for an appropriate period before therapeutic administration of ^{131}I-MIBG.

Free radioiodine produced during in vivo degradation of ^{131}I-MIBG can cause accumulation of radioactivity in the thyroid and the gastrointestinal tract. Thyroid blocking using potassium or sodium iodide (KI or NaI) or Lugol's solution is necessary, generally starting 1 or 2 days prior to treatment and continuing for up to 14 days after treatment.

Administration of ^{131}I-MIBG must be performed very slowly (over 1–4 h after dilution in 50 mL of saline), because the therapy dose levels involve injecting a sizable mass amount of a catecholamine analog that may induce the sudden release into circulation of catecholamines stored in neurosecretory granules, with possible pharmacologic effects such as arterial hypertension, tachycardia, nausea, and vomiting; nevertheless, the likelihood of such an occurrence is believed to be extremely low. For the same reason, the specific radioactivity of ^{131}I-MIBG for therapy should be higher than that for diagnostic purposes (up to 1.8 GBq/mg), with the aim of reducing the incidence of pharmacologic effects; continuous monitoring of the patient's vital signs during administration is anyway recommended.

Possible side effects include nausea and vomiting within the first 24 h after administration and temporary suppression of the bone marrow (manifesting mostly with reduced platelet counts) and deterioration of renal function. Possible long-

term effects are hypothyroidism (after inadequate thyroid blockade) and persistent hematological effects (thrombocytopenia, myelosuppression). There is also sparse evidence for induction of leukemia or secondary solid tumors, but this occurrence is very rare and has been reported especially in conjunction with (long-standing) chemotherapy [9].

There is currently no consensus on the optimal dosing strategy. Even if "fixed" therapeutic activities are possible, administration of individually tailored activities based on pretherapy dosimetric estimates is to be preferred. The activity administered for each treatment and the interval(s) between possible multiple administrations (repeated treatments can be considered at 6–8-month intervals) are mainly determined by hematological radiotoxicity and by tumor biology.

The main radiation dosimetry estimates to patients following i.v. administration of ^{131}I-MIBG are reported here below, normalized to unit of administered activity:

- Effective dose 0.2 mSv/MBq
- Tissues/organs with the highest values of absorbed dose:
  - Liver 0.83 mGy/MBq
  - Urinary bladder wall 0.59 mGy/MBq
  - Spleen 0.49 mGy/MBq

Key Learning Points

- Radiopharmaceuticals labeled with ^{131}I commonly utilized for therapy include ^{131}I-iodide and ^{131}I-MIBG.
- Due to selective accumulation in normal thyroid cells and in thyroid-derived tumor cells, ^{131}I-iodide is employed for treating patients with hyperthyroidism or patients with differentiated thyroid carcinoma derived from the follicular epithelium.
- As a structural analog of catecholamines, ^{131}I-MIBG is used for therapy primarily in patients with some neuroendocrine tumors originating embryologically from the neural crest, such as pheochromocytoma, paraganglioma, and neuroblastoma.

4.5.3 Radiopharmaceuticals for Radioimmunotherapy

Radioimmunotherapy (RIT) is based on the use of radiolabeled monoclonal antibodies (or antibody fragments) targeting epitopes of antigens expressed specifically on the surface of cancer cells. The binding with tumor-specific antigens deposits ionizing radiation within the neoplastic tissue causing cytotoxicity.

The ideal tumor-associated antigen to be targeted with this form of therapy should be densely and uniformly expressed on the surface of malignant cells, but not in normal cells; furthermore, it should form a stable complex with the antibody.

Another important issue concerns the origin and structure of the antibodies employed for RIT; many monoclonal antibodies were in fact initially developed from murine cells, thus being intrinsically heterologous proteins with immunogenic activity when administered to humans. This immunogenicity is much lower for chimeric antibodies (made up of components for 60% human and 40% murine) or for the humanized proteins (with 95% of human components, while generally only the binding site for the antigen is murine) developed through genetic engineering techniques. In fact, the formation in the patient receiving these preparations of human anti-mouse antibodies (HAMA), human anti-chimeric antibodies (HACA), or human antihuman antibodies (HAHA) can alter the pharmacokinetic profiles of the radiolabeled monoclonal antibody or predispose to allergic reactions upon repeat administration. The monoclonal products currently used for the preparation of radiopharmaceuticals are characterized by greatly reduced immunogenicity compared to their predecessors.

A final important issue that is crucial for the success of RIT (especially in the case of solid tumors) has to do with molecular size/weight of the radiolabeled preparation. In this regard, intact immunoglobulin molecules are generally too large (about 150–160 kDa for IgG antibodies produced by hybridomas) to diffuse efficiently throughout a tumor mass. Such poor diffusion causes insufficient targeting of the radiolabeled antibodies to tumor cells located even a few cell diameters away from blood capillaries and constitutes a limitation to the therapeutic potential of RIT.

To overcome these limitations and reduce immunogenicity, smaller immunoglobulin fragments with much lower molecular weight have been produced. A common step in this process is enzymatic cleavage to remove the Fc fragment, which is responsible for nonspecific binding of the intact molecule with immune cells (including macrophages, dendritic cells, NK cells, B cells) causing high background uptake in the reticuloendothelial system throughout the body. Pepsin digestion results in the production of the bivalent $F(ab')_2$ fragment (molecular weight about 110 kDa), where the two antigen-binding sites are still connected by the hinge region. Two smaller monovalent Fab fragments (each about 50 kDa in molecular weight and containing only one antigen-binding site) are produced by papain digestion. Even smaller immunoreactive fragments, the single-domain binding site with molecular weight between 12 and 15 kDa, can be produced using molecular engineering techniques.

Despite several ongoing clinical investigations, no radiopharmaceuticals have been approved yet for RIT of solid tumors, whereas two radiopharmaceuticals are currently used for RIT in some hematologic diseases, as described hereinafter.

4.5.3.1 ^{90}Y-Ibritumomab Tiuxetan

^{90}Y-Ibritumomab tiuxetan is a murine monoclonal antibody that binds to lymphocytes expressing the CD20 antigen. ^{90}Y is chelated to tiuxetan, which is covalently linked to the antibody via the arginine and lysine residues contained in the antibody. This radiopharmaceutical has been approved for the treatment of low-grade or follicular B-cell NHL that has relapsed during or after treatment with other anticancer drugs and newly diagnosed follicular NHL following a response to initial anticancer therapy.

The basis for therapy with ^{90}Y-ibritumomab tiuxetan is that the CD20 antigen is expressed on the surface of normal B lymphocytes (except pre-B cells and secretory B cells) but especially on the surface of >90% of B-cell lymphomas. The CD20 antigen does not shed from the cell surface and does not internalize upon antibody binding. The β^- emission from ^{90}Y induces cellular damage through the formation of free radicals, not only in cells that have been directly targeted by the radiolabeled antibody, but also in neighboring cells—due to the crossfire effect.

^{90}Y-Ibritumomab tiuxetan administration must be preceded by unlabeled monoclonal antibody (rituximab), as part of ^{90}Y-ibritumomab tiuxetan regimen, in order to block CD20 antigens expressed on normal B cells. The unlabeled monoclonal antibody per se constitutes an approved pharmaceutical for immunotherapy regimens of NHLs, because of its intrinsic tumor cell-killing capability.

^{90}Y-Ibritumomab tiuxetan is administered as a slow i.v. infusion over 10 min; the agent has a half-life in plasma of 28–30 h. Over 7 days, a median of 7.2% of the injected activity is excreted in the urine.

The administered activity is generally 15 MBq/kg body weight with a maximum limit of 1.2 GBq (32 mCi). In patients with mild thrombocytopenia (platelet count between 100,000 and 149,000 per mm^3), the administered activity should be reduced to 11 MBq/kg. Dose-limiting toxicity for ^{90}Y-ibritumomab tiuxetan is bone marrow suppression, which is reversible; bone marrow toxicity results in possible thrombocytopenia and neutropenia, especially in patient with baseline platelet count between 100,000 and 149,000/mm^3. The median time to nadir is 7–9 weeks, and the median duration of cytopenia is 3–5 weeks. ^{90}Y-Ibritumomab tiuxetan should not be administered to patients with >25% of bone marrow involved by lymphoma and/or impaired bone marrow reserve because of, e.g., prior myeloablative therapies. Additional contraindications include platelet count <100,000/mm^3, neutrophil count <1500/mm^3, hypocellular bone marrow (<15% cellularity or marked reduction in bone marrow precursors), or history of failed stem cell collection [10].

Since ^{90}Y does not emit γ-rays and scintigraphic visualization of the secondary Bremsstrahlung X-rays is rather poor, biodistribution can be evaluated by administering a diagnostic-level activity of the surrogate radiopharmaceutical ^{111}In-ibritumomab tiuxetan. The early images (up to about 24 h) typically show activity in the blood pool, with significant accumulation in the liver and spleen, while accumulation in the lung and bone is generally low. Radiodosimetric estimates have demonstrated an up to 850-fold greater radiation dose to the tumor lesions than to normal organs.

The main radiation dosimetry estimates to patients following i.v. administration of ^{90}Y-ibritumomab tiuxetan are reported here below, normalized to unit of administered activity:

- Tissues/organs with the highest values of absorbed dose:
  - Spleen 7.35 mGy/MBq
  - Liver 4.32 mGy/MBq
  - Lungs 2.05 mGy/MBq

Key Learning Points

- Radioimmunotherapy is based on the use of radiolabeled monoclonal antibodies or antibody fragments targeting epitopes of antigens expressed on the surface of cancer cells.
- Chimeric antibodies and humanized proteins developed through genetic engineering techniques minimize the complications possibly arising in patients following repeat administration of these agents, such as the formation of human anti-mouse antibodies (HAMA), human anti-chimeric antibodies (HACA), or human antihuman antibodies (HAHA).
- ^{90}Y-Ibritumomab tiuxetan, a murine monoclonal antibody that binds to the CD20 antigen expressed on lymphocytes, is used for radioimmunotherapy of relapsed or refractory lymphomas expressing the CD20 antigen.
- ^{131}I-Tositumomab, a murine monoclonal antibody that binds to a different epitope of the CD20 antigen expressed on lymphocytes, has similar indications as ^{90}Y-ibritumomab tiuxetan for radioimmunotherapy of lymphomas expressing the CD20 antigen; however, this radiopharmaceutical is no longer commercially available.

4.5.3.2 ^{131}I-Tositumomab

^{131}I-Tositumomab is a murine monoclonal antibody labeled with ^{131}I that had been approved in the United States in 2003, with indications similar to those of ^{90}Y-ibritumomab tiuxetan in patients with non-Hodgkin's lymphomas. ^{131}I-Tositumomab is specifically directed against a different epitope of the same

CD20 surface antigen, and the reported response rate is about 70%. However, it has recently withdrawn from the market because of declining sales.

As in the case of ^{90}Y-ibritumomab, infusion of unlabeled "cold" antibody (tositumomab) was recommended before administration of the radiolabeled antibody.

Dosimetric estimations to determine the whole-body radiation-absorbed dose are possible on the basis of three sequential whole-body acquisitions after the administration of a diagnostic activity (185 MBq) of ^{131}I-tositumomab (with prior infusion of 450 mg of unlabeled tositumomab).

4.5.4 ^{131}I-Lipiodol and ^{188}Re-HDD-Lipiodol

Transarterial chemoembolization with drug-loaded lipiodol, a particulate suspension of a mixture of iodized esters of poppy seed oil fatty acid, is still employed for treatment of inoperable hepatocellular carcinoma. The rationale for using transarterial lipiodol (which is performed under angiographic monitoring) is its entrapment and embolization in the microvessels of the tumor, based on the preferential blood flow as well as retentions by pinocytosis in both the endothelial cells and tumor cells.

Most of the clinical experience with lipiodol radioembolization has been acquired with ^{131}I-lipiodol, although the most recent trials have been based on the use of ^{188}Re-lipiodol.

After transarterial administration, more than 75% of the injected ^{131}I-lipiodol remains in the liver, while the remainder distributes mainly to the lungs. Thyroidal uptake of free radioiodine released from ^{131}I-lipiodol must be prevented by thyroid-blocking medication (saturated potassium iodide or Lugol's solution) starting 2–3 days before treatment and continuing for 10–15 days. Tumor/non-tumor uptake ratios in the liver are generally >5, and more than 10% of the injected radioactivity remains within the tumor with an effective half-life of about 6 days, longer than normal liver tissue.

Administered activity can be either a fixed amount of 2.4 GBq or defined on the basis of patient-specific dosimetric estimates. Due to the long half-life of ^{131}I-lipiodol in the tumor, current legislation in some countries requires hospitalization for about 1 week, for radiation protection purposes.

Treatment is in general well tolerated and serious adverse effects are very rare, while generic asthenia is commonly reported; likewise, hematologic toxicity is exceptionally rare, although blood cell counts may be altered due to the cirrhosis-related hypersplenism. Interstitial pneumopathy due to trapping and retention of the radiolabeled particle suspension is reported as the main risk of this treatment. The highest values of absorbed dose are reported in the liver tumor, liver parenchyma, and lung.

More recently lipiodol labeled with ^{188}Re using hexadecyl-tetramethyl-diaza-decanethiol (HDD) as the chelating agent [11] has shown promising results for radio-embolization in patients with inoperable large and/or multifocal hepatocarcinomas.

^{188}Re has potentially favorable physical characteristics, such as a shorter half-life than ^{131}I (16.9 h versus 8 days), a β^- emission of high energy (2.1 MeV) with ensuing good cell-killing effect, and an associated 155 keV γ-emission favorable for gamma camera imaging (for the purpose of dosimetric estimates). The ^{188}Re-labeled agent represents therefore an excellent alternative to the older ^{131}I-labeled agent.

4.5.5 ^{90}Y- and ^{166}Ho-Microspheres

Resin or glass microspheres containing ^{90}Y or ^{166}Ho are used for transarterial radio-embolization (TARE) of liver tumors. This therapeutic procedure, also defined as selective internal radiation therapy (SIRT), is performed through selective catheterization of the main or of segmental branches of the hepatic artery under angiographic monitoring. Radioembolization is one of the several therapeutic options to treat inoperable hyper-vascular lesions in the liver due to primary hepatocellular carcinoma, cholangiocarcinoma, or metastatic tumors originating at other sites. Other therapeutic options include liver transplantation; systemic chemotherapy; locoregional treatments, such as percutaneous ablative techniques (radio-frequency ablation, laser coagulation, cryotherapy, percutaneous ethanol injection); and transarterial chemoembolization.

The rationale for SIRT relies on radio-microembolization of the hyper-vascular liver tumors, which receive their blood supply primarily from the hepatic artery, whereas the normal liver parenchyma receives blood primarily via the portal vein. Thus, microspheres injected into the hepatic artery (most commonly into the right or left hepatic artery or even more selectively into the proper segmental artery) are trapped within the tumor microvasculature and deliver radiation selectively to the tumor liver lesion. The two types of ^{90}Y-microspheres currently available commercially (resin and glass microspheres) are biocompatible but not biodegradable nor metabolized.

^{90}Y-resin microspheres are made of an acrylic polymer in which ^{90}Y is bound to the carboxylic group of the polymer after production of the microspheres. The spheres have a diameter between 20 and 60 μm and a specific radioactivity of 50 MBq per sphere. There are about 40–80 million microspheres per vial, with a total activity of 3 GBq that can be aliquoted in the radiopharmacy to select the desired amount of ^{90}Y activity. Because of their elevated number, resin microspheres used for this treatment may have a moderate

embolic effect and must be delivered at a slow rate (no more than 5 mL/min) to avoid reflux into the hepatic artery and into other organs. The shelf life of the device is 24 h, which restricts clinical flexibility and patient scheduling.

In the *^{90}Y-glass microspheres*, ^{89}Y is embedded in the glass matrix, to be subsequently activated to ^{90}Y in a nuclear reactor just before shipment to the nuclear medicine center. Their medium diameter is 20–30 μm, and the specific activity is 2500 Bq per sphere. The number of ^{90}Y-glass spheres required for treatment ranges between 1.2 and 8 million, and the preparation is supplied in six sizes of activities: 3, 5, 7, 10, 15, and 20 GBq. The embolic effect linked to treatment with the glass ^{90}Y-microspheres is limited because a lower number of microspheres is injected intra-arterially. The shelf life of the glass spheres is 15 days from the date of calibration; therefore, no physical manipulation is required to prepare the desired, patient-based activity for administration, which is obtained simply by letting a certain activity to decay to the desired level.

For both microsphere preparations, the biodistribution of ^{90}Y-microspheres is usually predicted through prior intra-arterial ^{99m}Tc-MAA administration and subsequent planar and SPECT imaging (possibly SPECT/CT). The images are analyzed to estimate extrahepatic shunting to the lungs or the gastrointestinal tract, as well as to evaluate the absorbed doses to the target and the nontarget tissues [12].

Adequacy of ^{99m}Tc-MAA scintigraphy for simulation of therapy with the ^{90}Y-microspheres is widely accepted, although not definitely proven; in fact, some discrepancies have been observed between the pretreatment ^{99m}Tc-MAA scan and posttreatment imaging obtained either with a conventional gamma camera (based on the X-ray emission linked to the Bremsstrahlung effect induced by the high-energy β^- particles emitted by ^{90}Y) or using a PET scanner (based on the extremely low—but still imageable—emission of β^+ particles, about 32 positrons per million decays). Such discrepancies are possibly due to the different nature of ^{99m}Tc-MAA versus the ^{90}Y-microspheres or to occasional alterations of the original vascular anatomy produced by angiography. Nevertheless, the acquisition of both pre- and post-therapeutic images represents a suitable source of information for risk/benefit evaluation.

Three main methods are suggested by the manufacturer to calculate the activity of resin ^{90}Y-microspheres to be administered: (1) empirical method, (2) a body surface area (BSA)-based method based on the body surface area (BSA), and (3) the partition method. A more sophisticated evaluation can be made using the voxel dosimetry approach or by Monte Carlo modeling that provides information on dose distribution and expected radiobiologic effects at the voxel level.

More recently, a new preparation of radiolabeled microspheres for TARE of liver tumors has become commercially available, the *^{166}Ho-microspheres* (average diameter about 37 μm) consisting of a poly(L-lactic acid) matrix containing ^{166}Ho. In addition to its emission of β^- particles (with maximum energies of 1.74 and 1.85 MeV), this radionuclide (that decays with a physical half-life of 26.8 h) also emits low-energy γ-rays (81 keV) that are suitable for imaging with a conventional gamma camera. Therefore, pretreatment evaluation of tumor perfusion is possible by injecting intra-arterially a scout activity of ^{166}Ho-microspheres rather than ^{99m}Tc-MAA for preliminary SPECT/CT imaging. Furthermore, holmium has strong paramagnetic properties, which make it possible to acquire MR imaging of the intrahepatic distribution of the ^{166}Ho-microspheres injected intra-arterially. Although the clinical experience acquired with this new preparation is limited, good disease control has been demonstrated in about 70–75% of the patients submitted to therapy with ^{166}Ho-microspheres. Different levels of activities administered to patients have been investigated, ranging from 1260 to 5040 MBq per kg of body weight. In addition to their use for treatment of liver tumors, ^{166}Ho-microspheres are also being investigated for other locoregional intra-arterial treatment, e.g., in patients with inoperable squamous cell head and neck cancers.

Key Learning Points

- Selective/superselective intra-arterial administration of particles that remain trapped at tumor sites because of local microembolization is the basis for therapy of either primary or metastatic liver cancer lesions.
- Lipiodol, a particulate suspension of a mixture of iodized esters of poppy seed oil fatty acid, which can be loaded with either ^{131}I or ^{188}Re is used for intra-arterial therapy of hepatocellular carcinoma.
- The most commonly employed form of intra-arterial radio-embolization for treatment of either primary or metastatic liver cancers is based on particles (microspheres) containing either ^{90}Y or ^{166}Ho.
- Microspheres containing ^{90}Y can be made either of glass or of a resin.

4.5.6 ^{90}Y- or ^{177}Lu-Labeled Somatostatin Analogs

Somatostatin (SST) is an oligopeptide comprising either 14 or 28 amino acids produced endogenously mainly in the central nervous system; its recognized physiologic functions include regulation of the secretion of various hormones, e.g., insulin and glucagon. Receptors for SST are overexpressed

in most neuroendocrine tumors; five different types of SST receptors (transmembrane molecule weighing approximately 80 kDa) have been identified, named SSTR1-5 (type 2 being divided into subtypes 2a and 2b). Native SST has a very short biological half-life in blood (3 min), limiting its use as a pharmacologic agent. Several stabilized SST analogs with longer half-lives have been developed, to treat patients with neuroendocrine tumors expressing SST receptors (mostly to palliate symptoms). Some of these analogs have been modified by introducing a chelating agent to radiolabel the SST analog (e.g., ^{111}In-DTPA-octreotide, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE) (see Chaps. 2 and 3 of this book). The DOTA chelator, which allows more stable binding of metallic radionuclides emitting β^- particles with energy suitable for therapy, has been selected for the production of SST analogs to be used as radiopharmaceuticals for therapy.

The radiolabeled SST analogs that are currently used in clinical practice with the most promising results for therapy include ^{90}Y-DOTA-TOC and ^{177}Lu-DOTA-TATE. Receptor-mediated internalization and intracellular retention of the radio-peptide allow the so-called peptide receptor radionuclide therapy (PRRT) [13].

DOTA-TOC is a derivatized SST analog, abbreviated form of [DOTA^0,Tyr^3]-octreotide (a modified octreotide), where DOTA stands for the bifunctional chelating agent 1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetic acid, a macrocyclic chelator that allows radiolabeling and formation of stable complexes with both metallic isotopes, ^{90}Y and ^{177}Lu. This peptide shows a high affinity for SSTR2 but lower affinities for SSTR5 and SSTR3.

DOTA-TATE is also a derivatized SST analog, abbreviated form of [DOTA^0,Tyr^3,Thr^8]-octreotide or [DOTA^0,Tyr^3]-octreotate. This peptide has a six- to ninefold greater affinity for SSTR2 than DOTA-TOC, but has no affinity for either SSTR5 or SSTR3.

Advantages of ^{177}Lu-DOTA-TATE over ^{90}Y-DOTA-TATE include the emission of an associated γ-radiation, which makes it possible to acquire conventional gamma camera scintigraphic imaging for radiation dosimetry estimates; furthermore, the shorter tissue range of the β^- particles emitted by ^{177}Lu allows a higher radiation dose be delivered to smaller tumors. The use of ^{177}Lu also results in lower nephrotoxicity of the PRRT regimens versus ^{90}Y-labeled SST analogs (see further below). On the other hand, the use of ^{90}Y-labeled SST analogs (which emits β^- particles with higher energies and longer tissue ranges) would be more suitable for the treatment of larger tumors, in case of bulky and/or heterogeneous masses. Recently, a combination radionuclide therapy using ^{177}Lu- and ^{90}Y-labeled peptides has been proposed in order to improve efficacy in patients with tumors of various sizes and inhomogeneous receptor distribution.

Therapy with the radiolabeled SST analogs is administered by slow i.v. infusion over approximately 30 min. Standard clinical protocols of PRRT consist of the systemic administration of a radiolabeled somatostatin analog, fractionated in sequential cycles (usually 4–5), 6–9 weeks apart, until the intended total amount of radioactivity has been administered. The total activity of ^{90}Y-DOTA-SST analog generally does not exceed 3.7 GBq/m^2 body surface area, while a flat activity of 7.4 GBq is considered for therapy with the ^{177}Lu-DOTA-SST analogs.

The radiolabeled peptides are cleared through the kidneys, where they are reabsorbed and partially retained in the proximal tubules. Nephrotoxicity is the dose-limiting factor. Co-administration of negatively charged amino acids (L-lysine and/or L-arginine) competitively inhibits the proximal tubular reabsorption of the radiopeptides leading to a significant reduction of the radiation burden to the kidney. Therefore, the standard protocol for therapy with either ^{177}Lu- or ^{90}Y-labeled DOTA-SST analogs includes prior i.v. infusion of L-lysine and L-arginine (50–75 g each). Besides long-term renal toxicity, the other critical target is the bone marrow; reduced bone marrow reserve may occur, and, very infrequently (1–2%), myelodysplastic syndrome and occasionally leukemia have been sporadically reported.

After injection, ^{177}Lu-DOTA-TATE is rapidly cleared from the blood. In fact, at 4 h after administration, ^{177}Lu-DOTA-TATE is concentrated in the kidneys, tumor lesions, liver and spleen, and in some patients in the pituitary gland and in the thyroid.

General contraindications are pregnancy and kidney failure with creatinine clearance <30 mL/min. Candidates for PRRT are basically all the SST receptor-expressing tumors or metastatic/inoperable NETs. SSTR2-expressing tumors include GEP and bronchial neuroendocrine tumors but may also include patients with pheochromocytoma, paraganglioma, neuroblastoma, or medullary thyroid carcinoma.

Pre-therapy scintigraphy with ^{111}In-pentetreotide is currently the most validated method to assess for the presence of SSTR overexpression. Nevertheless, PET imaging with ^{68}Ga-DOTA-TOC or ^{68}Ga-DOTA-TATE is now becoming the new pre-therapy standard evaluation, since these radiopharmaceuticals mimic in vivo patterns of biodistribution of their ^{90}Y- or ^{177}Lu-labeled counterparts used for PRRT.

Key Learning Points

- Somatostatin analogs used for therapy of neuroendocrine tumors expressing somatostatin receptors can be labeled with either ^{90}Y or ^{177}Lu.
- The metallic nature of these radionuclides requires the use of a suitable bifunctional chelating agent

(1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetic acid, or DOTA) for radiolabeling of the somatostatin analogs used for therapy.
- Different somatostatins with varying binding affinity for the somatostatin receptors have been developed, including octreotide and octreotate.
- Nephrotoxicity, the main side effect of therapy with radiolabeled somatostatin analogs, is minimized by pre-administration of the negatively charged amino acids L-lysine and/or L-arginine that competitively inhibit the proximal tubular reabsorption of the radiopeptides and thus significantly reduce the radiation burden to the kidney.
- Neuroendocrine tumors candidates for the so-called peptide receptor radionuclide therapy (PRRT) are basically all the somatostatin receptor-expressing tumors, including gastro-entero-pancreatic and bronchial neuroendocrine tumors; occasionally, also some pheochromocytomas, paragangliomas, neuroblastomas, or medullary thyroid carcinomas express somatostatin receptors with high density.

4.5.7 ^{32}P-Orthophosphate

This radiopharmaceutical was the first radiolabeled agent used for the treatment of metastatic bone pain [14] and was the most widely used agent until the 1980s.

Bone metastases are a frequent complication of advanced stages of neoplastic disease. Bone metastases occur in about 70% of patients with prostate cancer or breast cancer and in 30–50% of those with cancers of the lung, bladder, and thyroid. The major complications associated with skeletal metastases are pain (initially mild to medium intensity and then increasing and becoming severe—requiring the use of opioid medication for palliation), hypercalcemia, radicular compression, and/or spinal cord and pathological fractures.

In patients with metastatic involvement of multiple skeletal segments (therefore not amenable to external radiotherapy and/or surgery), therapy with therapeutic bone-seeking radiopharmaceuticals constitutes an important strategy for palliation of bone pain. Therapeutic agents include ^{32}P-orthophosphate (rarely used today), ^{89}Sr-chloride (infrequently used today), ^{153}Sm-EDTMP, and ^{186}Re-HEDP, recently the α-particle emitter ^{223}Ra-dichloride (see further below).

Accumulation of ^{32}P in the bone mineral matrix mirrors the degree of active osteogenesis, thus being enhanced primarily in areas of metastatic involvement (predominantly osteoblastic or mixed metastasis) with significantly greater concentrations than in the surrounding normal bone. Treatment with this radionuclide is therefore indicated in patients with multiple painful osteoblastic skeletal metastases exhibiting high uptake of ^{99m}Tc-labeled bisphosphonates confirmed on a conventional bone scan prior to therapy.

Following i.v. administration of ^{32}P-orthophosphate, 85% of the injected activity accumulates in the hydroxyapatite crystals as inorganic phosphate, while the remainder localizes in soft tissues, including active red bone marrow. In soft tissues, ^{32}P is predominantly distributed intracellularly, especially in the cytoplasm and cell nucleus, thus inducing non-negligible DNA damage. For this reason and also taking into account the rather long beta β^- particle path range in soft tissue, administration of this radiopharmaceutical causes a significant radiation burden to the bone marrow, with possible hematopoietic side effects (leukopenia and thrombocytopenia) reaching a nadir about 4–5 weeks after injection and recovering at 6–7 weeks. Hematologic toxicity limits the use of ^{32}P-orthophosphate to those circumstances where other less toxic bone-seeking radiopharmaceuticals are not available.

The therapeutic administered activity is usually 185–370 MBq intravenously (often in divided doses) or 370–444 MBq orally. Clearance occurs predominantly by renal excretion.

Bone pain palliation is usually noticed within 14 days after administration, with a range of 2 days to 4 weeks. The response rate to therapy with ^{32}P-orthophosphate is about 80%, and the mean duration of response is 5 ± 2.5 months.

It should be mentioned that therapy with ^{32}P-orthophosphate has also been successfully employed for treatment of polycythemia vera, based on the relatively high radiation burden delivered to the active red bone marrow.

The main radiation dosimetry estimates to patients following administration of ^{32}P-orthophosphate are reported here below, normalized to unit of administered activity:

- Tissues/organs with the highest values of absorbed dose:
  - Bone surface 10 mGy/MBq
  - Red bone marrow 7.6 mGy/MBq
  - Lower bowel wall 0.01 mGy/MBq

4.5.8 ^{89}Sr-Chloride ($^{89}SrCl_2$)

The use of the bone-seeking radiopharmaceutical ^{89}Sr-chloride is indicated for palliation of bone pain in patients with painful skeletal metastases.

Upon administration, $^{89}SrCl_2$ quickly clears from the blood; the $^{89}Sr^{2+}$ ions follow the same in vivo metabolic fate as calcium, with rapid incorporation into the inorganic mineral matrix of the bone. Thus, the radiopharmaceutical selectively localizes in bone mineral, with at least 50% of the

injected activity localized in the skeleton within 2–3 h post-administration. About 30–35% of the administered activity remains in normal bone for 10–14 days postinjection, whereas, retention in osteoblastic areas is as high as 85–90% at 3 months after administration.

About two-thirds of the fraction of ^{89}Sr not bound to the bone is excreted in the urine, while about one-third is excreted through the fecal route. Urinary excretion is greatest in the first 2 days following administration. ^{89}Sr-Chloride is administered by slow i.v. injection, over about 1–2 min.

The recommended activity of $^{89}SrCl_2$ is 150 MBq or alternatively 1.5–2.2 MBq/kg body weight. The major side effect is myelosuppression that may occur particularly with higher administered activity, reducing the platelet and leukocyte counts by almost 25–30%. For this reason, patients should have a minimum platelet count of 60,000/mm^3 and a leukocyte count of 2400/mm^3 at the time of administration.

Initial relief of pain is usually noticed within 3 days after administration, but it may be as late as 25 days. Mean duration of pain relief is about 3–6 months; therefore, re-treatments with ^{89}Sr may be considered every 3–6 months. Complete remission of pain is experienced by 5–20% of the patients after ^{89}Sr treatment, while almost 80% of the patients experience some relief of pain from osteoblastic metastasis. In 10% of the patients, there is an initial transient worsening of bone pain within 3 days of therapy that subsides in about a week (flare phenomenon).

The main radiation dosimetry estimates to patients following administration of $^{89}SrCl_2$ are reported here below, normalized to unit of administered activity [15]:

- Tissues/organs with the highest values of absorbed dose:
  - Bone surface 17 mGy/MBq
  - Red bone marrow 11 mGy/MBq
  - Lower bowel wall 4.7 mGy/MBq

4.5.9 ^{153}Sm-Lexidronam (^{153}Sm-EDTMP)

This bone-seeking radiopharmaceutical is indicated for relief of bone pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on the radionuclide bone scan.

^{153}Sm-EDTMP (Fig. 4.5) has biodistribution properties similar to those of other radiolabeled bisphosphonates, as it accumulates avidly on the surface of newly formed hydroxyapatite crystals through a chemisorption mechanism.

Following i.v. administration, ^{153}Sm-EDTMP clears rapidly from the blood with a half-life of 5.5 min; less than 1% of the administered activity remains in the circulation 5 h postinjection. Up to 55–60% of injected activity remains stably bound to the skeleton and accumulates in osteoblastic metastatic lesions in a 5:1 ratio compared with normal bone uptake. The main excretory route is through the kidneys; almost 35% of the injected tracer is excreted in the urine by 6 h postinjection. The recommended administered activity is 37 MBq/kg. Concomitant γ-emission of ^{153}Sm allows gamma camera imaging to confirm satisfactory targeting of the lesions.

The onset of pain relief is generally noticed within 2 weeks after radiopharmaceutical administration, with a mean duration of pain relief of 3–4 months, but it may last up to 11 months.

Further relief of pain is achieved with repeat treatments. Since the critical organ regarding radiation dosimetry is the bone marrow, a minimum interval of 8 weeks should be allowed between subsequent administrations in order to allow for adequate recovery of bone marrow function. However, hematological side effects are generally mild.

Transient exacerbation of the preexisting pain (flare phenomenon) after ^{153}Sm-EDTMP is reported by 12–20% of patients.

The main radiation dosimetry estimates to patients following i.v. administration of ^{153}Sm-EDTMP are reported here below, normalized to unit of administered activity [15]:

- Tissues/organs with the highest values of absorbed dose:
  - Bone surface 6.8 mGy/MBq
  - Red bone marrow 1.5 mGy/MBq
  - Urinary bladder wall 1 mGy/MBq

4.5.10 $^{186/188}$Re-Etidronate ($^{186/188}$Re-HEDP)

The bone-seeking agent hydro-ethylidene-di-phosphonate (etidronate, or HEDP) binds to hydroxyapatite crystals by forming hydroxide bridges, through the mechanism of chemisorption (Fig. 4.5). HEDP can be radiolabeled with either ^{188}Re or ^{186}Re, both radionuclides being suitable for therapeutic applications.

Due to binding with plasma proteins, ^{186}Re-HEDP is cleared from the circulation with a longer plasma half-life than most of the other bone pain agents (41 ± 6 h). The mean effective half-life of labeled HEDP in the bone is about 16 h. Approximately 70% of the administered ^{186}Re-HEDP activity is excreted in the urine within 24 h in patients without bone metastases. The standard activity administered for therapy is 1295 MBq, given by i.v. injection. Pain relief occurs early after administration.

Although the typical tumor/bone marrow absorbed dose ratio is 14:1, there may be some transient myelosuppression, which is important in patients with reduced bone marrow reserve. Typical marrow recovery times range from 4 to 6 weeks.

^{188}Re-HEDP has similar biodistribution as ^{186}Re-HEDP, with rapid excretion in urine (60% ± 12% of administered

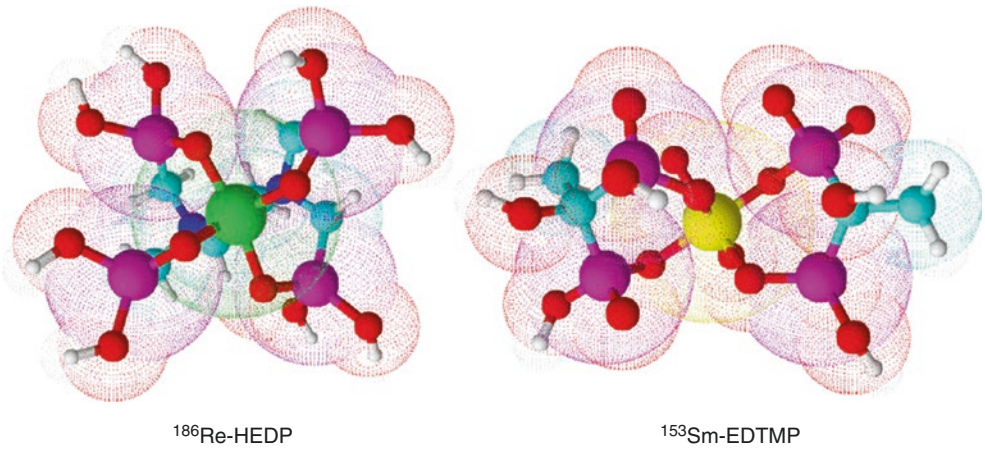

Fig. 4.5 3D structure of radiolabeled bone-seeking bisphosphonates employed for palliation therapy of bone pain from skeletal metastasis: ^{186}Re-HEDP (left) and ^{153}Sm-EDTMP (right). Color codes: *green*, ^{186}Re; *yellow*, ^{153}Sm; *red*, O; *white*, H; *fuchsia*, P; *light blue*, C; *dark blue*, N

activity in 48 h. The fraction of the dose excreted in the urine varies with renal function and extent of osteoblastic metastases).

The main radiation dosimetry estimates to patients following i.v. administration of ^{188}Re-HEDP are reported here below, normalized to unit of administered activity [15]:

- Tissues/organs with the highest values of absorbed dose
  - Bone surface 1.4 mGy/MBq
  - Red bone marrow 1.3 mGy/MBq
  - Lower bowel wall 0.57 mGy/MBq

Key Learning Points

- Radiopharmaceuticals labeled with β^- emitters used for therapy of skeletal metastases (mainly with the purpose of bone pain palliation) include ^{32}P-ortophosphate, ^{89}Sr-chloride, ^{153}Sm-EDTMP, ^{188}Re-HEDP, and ^{186}Re-HEDP.
- All such bone-seeking radiopharmaceuticals localize at metastatic sites characterized by significant osteoblastic reaction, similarly as the diagnostic bone-seeking tracers used for imaging.
- The mechanism of accumulation at the metastatic site is based on chemisorption at the surface of the newly formed mineral component of the bone.

4.6 Alpha-Emitting Radiopharmaceuticals

4.6.1 ^{223}Ra-Dichloride

This α^{++} emitting agent (trade name Xofigo) is indicated for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease.

$^{223}RaCl_2$ is a calcium analog, with a biodistribution similar to $^{89}SrCl_2$. It selectively accumulates in the bone, with increased uptake in areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high LET of its α-emission (80 keV/μm) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a localized antitumor effect on bone metastases. The α^{++} particle range from ^{223}Ra is less than ten cell diameters (about 100 μm), which minimizes damage to the surrounding normal tissue.

^{223}Ra-Dichloride is administered over 1 min by i.v. injection; it then clears rapidly from the blood and distributes primarily into the bone and bone metastases. Fifteen minutes after injection, about 20% of the administered activity remains in the blood, while only <1% is still in the circulation at 24 h. No specific accumulation is seen in other normal organs such as the heart, liver, kidney, gallbladder, stomach, and spleen.

A major difference between ^{223}Ra-dichloride and other bone-seeking radiopharmaceuticals is excretion occurs through the gastrointestinal tract, which causes some gastrointestinal toxicity. At 48 h postinjection, the cumulative fecal excretion is about 13%, with a range of 0–34%. Only 5% is excreted in the urine. However the rate of elimination of ^{223}Ra-dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates among patients. There is little myelotoxicity and no long-term toxicity. In general, most adverse events are mild to moderate in severity and include nausea, bone pain, diarrhea, and fatigue. No dose-limiting hematologic toxicity has been observed in any patients.

The dose of ^{223}Ra-dichloride is 55 kBq/kg of body weight. A treatment cycle includes six administrations at 4-week intervals, and it has been recognized that therapy with $^{223}RaCl_2$ induces not only palliation of bone pain but also a significant benefit in survival.

The main radiation dosimetry estimates to patients following i.v. administration of ^{223}Ra-dichloride are reported here below, normalized to unit of administered activity:

- Tissues/organs with the highest values of absorbed dose:
  - Osteogenic cells 1.152 mGy/MBq
  - Red bone marrow 0.139 mGy/MBq
  - Lower large bowel wall 0.047 mGy/MBq

Key Learning Points

- ^{223}Ra-Dichloride is the only approved α-emitting radiopharmaceutical.
- ^{223}Ra accumulates at metastatic sites because of its chemical analogy with calcium.
- At variance with the most commonly used agents for treatment of bone metastases emitting β^- particles (that are excreted mainly through the kidneys), ^{223}Ra has a significant fecal excretion, which results in some gastrointestinal toxicity.

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