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***Radiation Protection and Radiation Measurement
Issues with Non-Traditional Radiopharmaceuticals***

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RADIATION PROTECTION AND RADIATION MEASUREMENT ISSUES WITH NON-TRADITIONAL RADIOPHARMACEUTICALS

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to provide an update of alpha-emitting and beta-emitting therapeutic radiopharmaceuticals including radiation protection and radiation measurement issues. This lesson describes specific alpha and beta radionuclides used for labeling radiopharmaceuticals, their advantages and the radiation protection issues associated with each. Specific alpha- and beta-emitting radiopharmaceuticals are described with an emphasis on rationale for use, radiolabeling methodology, pharmacokinetics, clinical protocols and radiation protection issues.

Radiation dose measurement issues specifically related to therapeutic beta-emitting radiopharmaceuticals, and their gamma imaging analogs, are discussed. Effects of geometry and attenuation on dose measurements of radiopharmaceuticals are addressed. Specific step-by-step instructions are provided in calibrating dose calibrators for specific beta-emitting radiopharmaceuticals. Alternate calibration methods are discussed.

Upon completion of this lesson, the reader should be able to:

1. List specific alpha-emitting radionuclides used in targeted therapies.
2. Identify specific alpha-emitting therapeutic radiopharmaceuticals, their properties and clinical use.
3. Describe advantages and disadvantages of alpha-emitting radiopharmaceuticals.
4. Elaborate on radiation protection issues related to alpha-emitting radiopharmaceuticals.
5. List specific beta-emitting radionuclides, their properties and applications in targeted therapy.
6. Summarize specific beta radionuclides conjugated to beta-emitting therapeutic radiopharmaceuticals, including advantages and disadvantages of each.
7. Identify specific beta-emitting therapeutic radiopharmaceuticals used in clinical practice including properties and pharmacokinetics.
8. Describe radiation protection issues related to beta-emitting radiopharmaceuticals including radiation protection related to radiopharmaceutical formulation, dispensing and patient administration.
9. Describe radiation protection issues related to patients receiving therapeutic beta-emitting radiopharmaceuticals.

10. Understand the issues and specific procedures related to radiation dose measurements of therapeutic radiopharmaceuticals.

COURSE OUTLINE

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- C. Bismuth-212 Radiopharmaceuticals
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- E. Actinium-225 Radiopharmaceuticals
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III. BETA-EMITTING RADIONUCLIDES

- A. Classification of Beta Radionuclides and Tumor Therapy Rationale
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RADIATION PROTECTION AND RADIATION MEASUREMENT ISSUES WITH NON-TRADITIONAL RADIOPHARMACEUTICALS

By

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I. INTRODUCTION

Within the last decade, radionuclide therapy has become increasingly more important in nuclear medicine. Specific radiopharmaceuticals used for therapies include radioiodine, P-32 sodium phosphate and chromic phosphate, radiolabeled peptides, radiolabeled particles or microspheres, radiopharmaceuticals for palliation of painful bone metastases and radiopharmaceuticals for radioimmunotherapy. Newer targeted therapies use radiopharmaceutical labeled with alpha-emitting and beta-emitting radionuclides. Some of these specific newer targeted radionuclide therapies and therapeutic radiopharmaceuticals will be discussed. In addition, whenever appropriate, specific issues related to dose measurement of therapeutic radiopharmaceuticals will be discussed. Also, radiation safety issues of alpha and beta-emitting radionuclides, including shielding requirements and radiation exposures to radiation workers and to members of the general public, will also be discussed.

For radionuclide therapy, the likelihood of treatment success depends on a number of parameters. These include the following: the concentration of the radiopharmaceutical in tumor; the radiation absorbed dose in tumor; the delivery of the radiation dose (dose rate and fractionation); the sensitivity and response of tumor cells to the specific radiation; and tumor size compared to the type of radionuclide emission and the energy of emission.^{1,2} For beta-emitting radionuclides, there appears to be a relationship between the mean energy emitted from beta radionuclides and the optimal tumor size which results in

radiocurability (1). Optimal tumor cure diameters range from less than 1 mm for short-range beta emitters such as Lu-177 and Au-199 to several centimeters for long-range beta-emitters such as Y-90 and P-32. As a result, future radionuclide therapies may include tailoring specific beta-emitting radionuclides to specific tumor sizes, including the use of a radionuclide therapy “cocktail” consisting of several different beta-emitting radionuclides for more effective tumor treatment.¹

When selecting a specific radionuclide for radionuclide therapy, a number of factors should be considered. One factor is tumor size, as mentioned previously, and another is tumor heterogeneity. The availability and cost of the radionuclide is an important factor. In addition, an acceptable nuclear decay of the specific radionuclide, a physical half-life conducive to radiopharmaceutical preparation and tumor pharmacokinetics, fairly rapid and stable attachment of the radionuclide to the desired chemical species and appropriate gamma ray emissions for imaging to aid in biodistribution and imaging are also important.

II. ALPHA-EMITTING RADIO- PHARMACEUTICALS

A. Rationale for Use

Alpha-emitting radionuclides have physical properties that are useful for cancer treatment. Alpha-emitting radionuclides produce high densities of ionization. Energetic alpha emitters have a tissue range of 40–80 microns (μm) as opposed to tissue ranges of

3000–6000 μm for energetic beta-emitting radionuclides.³ As a result, the effective treatment radius is several cell diameters, thus making alpha-emitters ideal for therapeutic treatment at a cellular or micrometastases level.⁴ The short tissue path length also reduces non-specific irradiation of distant tissue. Alpha-emitting radionuclides also have a high linear energy transfer (LET). High LET of alpha radiation results in effective cell killing by limiting the ability of cells to repair damage to DNA. The effectiveness of alpha particles in cell killing can be demonstrated by the fact that the number of beta particles required to elicit the same effect is more than 1000 times higher as compared to alpha particles. Additional advantages of alpha emitters in targeted therapy include their independence of cell cycle position and also the cell hypoxic state.^{4,5}

There are limitations associated with alpha-emitting radionuclides for therapy and, as such, may hamper their widespread clinical use. Once conjugated to the specific chemical moiety, release of unbound alpha-emitting radionuclides may result in severe toxicities. The complexity of conjugation, using either bifunctional chelating agents or attachment to non-activated aromatic rings, is another limitation. As alpha radionuclides decay, bifunctional chelating agent may not appropriately bind daughter radionuclides ultimately leading to the release of the unbound daughter radionuclide. Because alpha radionuclide decay results in a deposition of high radiation within a very small volume,

radiolysis may also be significant. Radiolysis can result in protein degradation, including protein fragmentation, and, in the case of monoclonal antibodies, may result in loss of antibody radioimmunoactivity.⁶ Other limitations of alpha-emitters include the lack of commercial availability and unfamiliarity in regards to radiation safety issues.

Alpha-emitting radionuclides are produced by cyclotron or reactor irradiation. Some alpha radionuclides may be incorporated into a generator system, which is subsequently eluted prior to use. Some common alpha-emitting radionuclides used for radionuclide therapy are listed in Table 1. As shown in the table, many alpha-emitting radionuclides also emit beta and gamma rays. Some gamma ray emission energies from alpha-emitting radionuclides are appropriate for biodistribution and imaging studies, which may be performed prior to initiation of therapy.

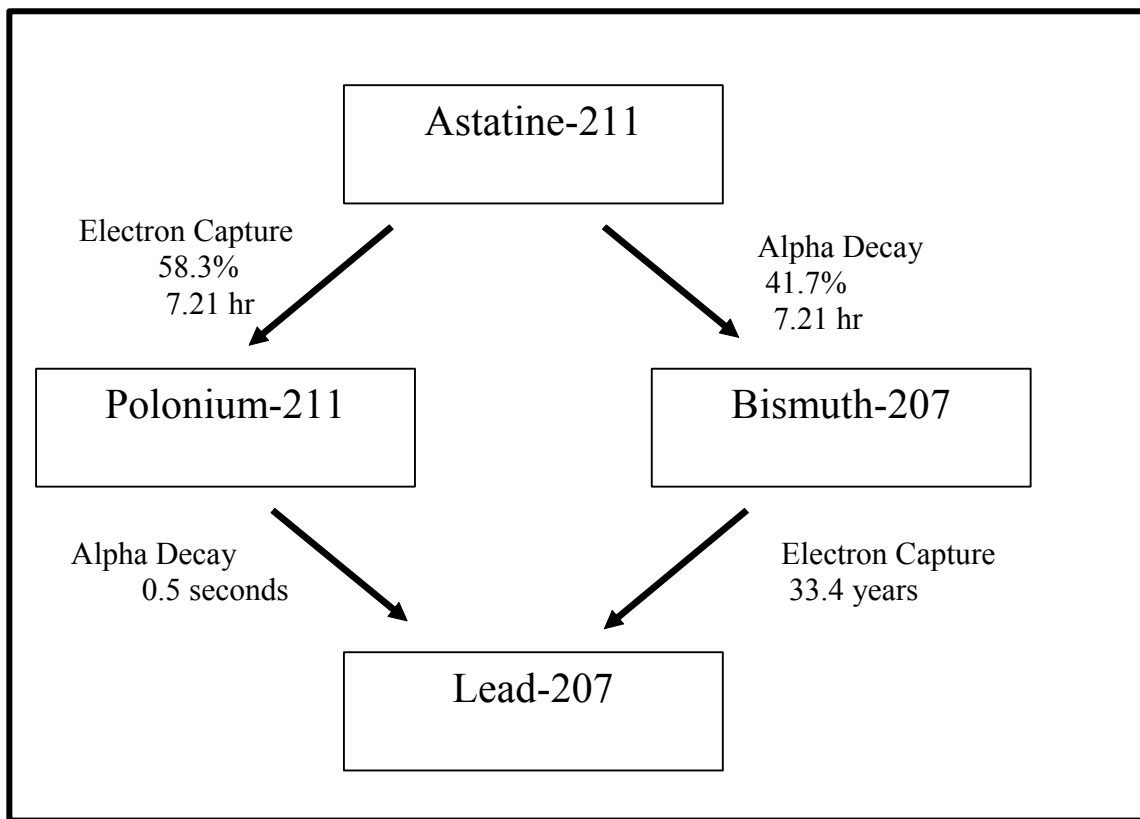
B. Astatine-211 Radiopharmaceuticals

Astatine-211 is the heaviest halogen with a 7.2-hour half-life. The Astatine-211 decay scheme is shown in Figure 1. It decays by a double-branch pathway with alpha energies of 5.9 and 7.5 MeV. The short range in tissue, 55–70 μm , and high LET of the alpha particles make the radionuclide attractive for radionuclide therapy. During Astatine-211 decay, x-rays of 77 keV and 97 keV are produced, allowing for external gamma imaging and biodistribution studies. Radiolabeling of proteins with Astatine-211, including

Table 1. Physical Properties of Some Common Alpha-Emitting Radionuclides for Radionuclide Therapy

Nuclide	Half-life (hours)	Energy _{α} (MeV)	Energy _{β} (MeV)	Energy _{γ} (MeV)
At-211	7.21	5.9, 7.5	-----	0.070, 0.080, 0.570, 1.0
Bi-212	1.01	6.04, 6.08, 9.0	0.492, 0.56	0.51, 0.58, 2.60
Bi-213	0.76	5.9	0.444	0.440
Ac-225	240	6.0	-----	0.218
Ra-223	273.6	7.02	-----	0.08, 0.270

Figure 1. Astatine-211 Decay Scheme



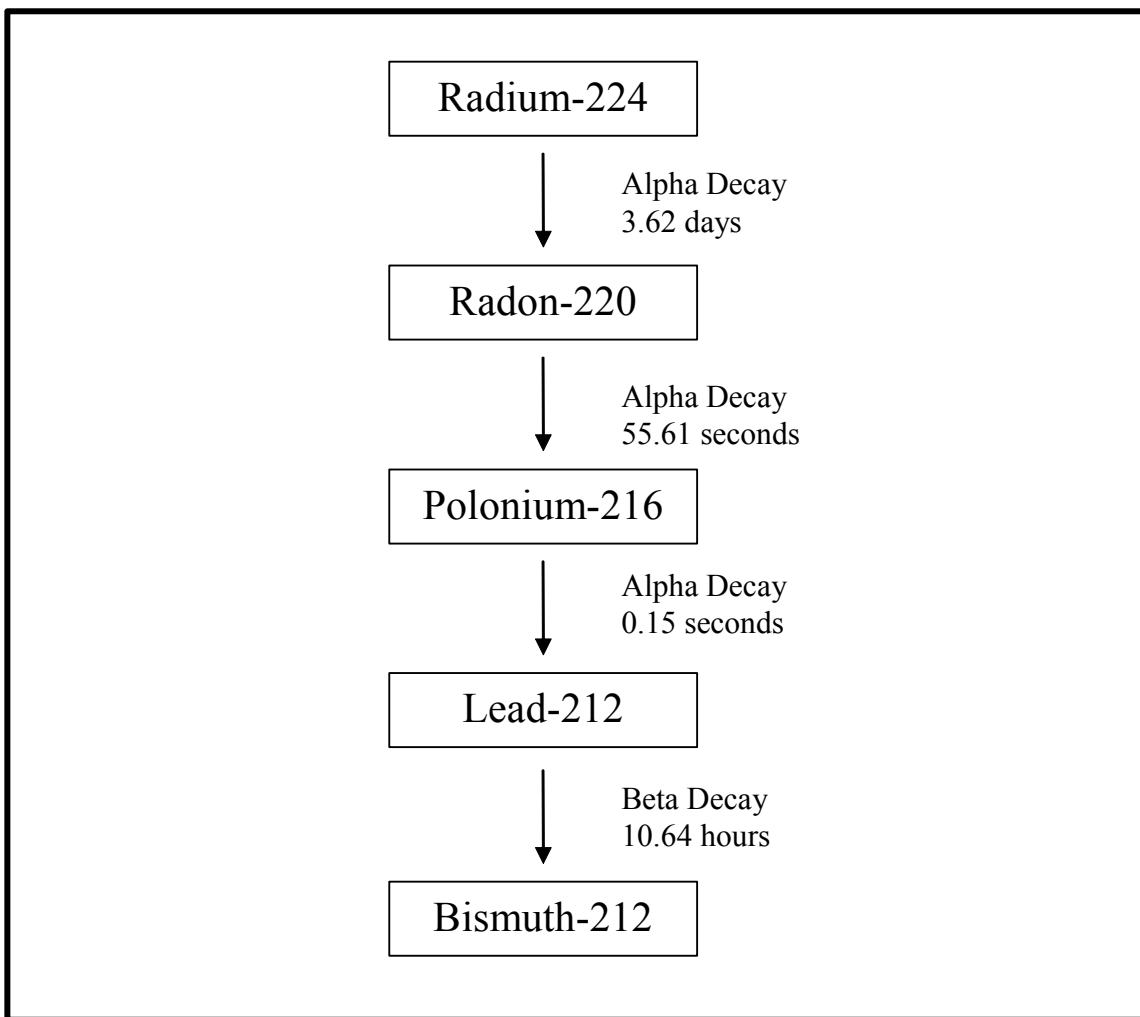
monoclonal antibodies and antibody fragments, has been successfully accomplished using a two-step procedure.^{7,8} Initially, N-succinimidyl 3-(At-211)astatobenzoate was synthesized from the corresponding tri-n-butyl tin precursor. The radiolabeled precursor was then reacted with the specific antibody at slightly basic pH. Zalutsky et al.⁶ radiolabeled a chimeric antitenascin monoclonal antibody, 81C6, with At-211 using the two-step method described. The chimeric monoclonal antibody binds to tenascin, a molecule that is over expressed in human glioma lines but not in normal brain tissue. Following radiolabeling with At-211, the immunoreactivity of the radiolabeled monoclonal antibody was maintained. Phase I clinical trials of At-211 labeled chimeric antitenascin antibody have been initiated in patients with recurrent malignant glioma.^{6,9} The trial included the direct administration of the radiolabeled monoclonal antibody into

surgically created brain tumor resection cavities. Clinical trials are progressing and results appear to be encouraging.

C. Bismuth-212 Radiopharmaceuticals

Bi-212, with a short half-life of 1.01 hours, can be produced from a Ra-224 generator. The decay scheme for a Ra-224/Bi-212 generator system is shown in Figure 2. Ra-224, the parent, has a half-life 3.6 days. After separation from the parent, thorium-228, radium-224 is evaporated to dryness and the residue dissolved in 0.1 M HCl. The acidic solution is then absorbed onto AGMP-50 cation exchange resin contained within a Teflon tube. By varying the generator elution conditions, the percent Bi-212 yield or its parent Pb-212 can be controlled. Due to high and intermediate gamma emissions in the Ra-224 decay scheme, the generator system must be heavily shielded to minimize radiation exposure. The generator must also be placed in

Figure 2. Ra-224/Bi-212 Generator Decay Scheme

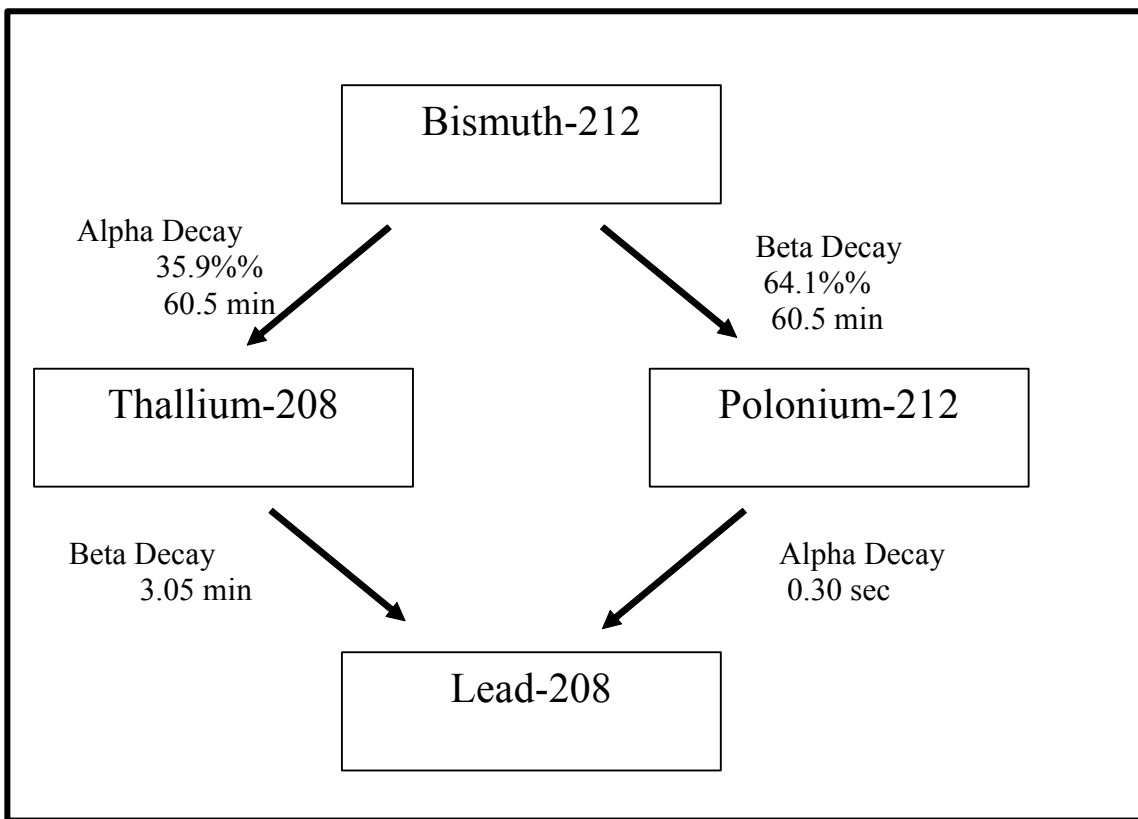


a trapped or gas-tight enclosure because of the production of a radioactive gas Rn-220, a daughter in the decay scheme.¹⁰

Bi-212 decays with a branched pathway to Tl-208 and Po-212.⁴ The decay scheme for Bi-212 is shown in Figure 3. As a result of decay, multiple alpha emissions with energies of 6.04 MeV, 6.08 MeV and 9.0 MeV are produced. Some alpha production is due to the decay of the daughter, polonium Po-212. Decay of Bi-212 produces densely ionizing radiation over a 40 μm –100 μm range, limiting cellular toxicity to a very small radius. In addition, beta-emissions from

Bi-212 and daughters may increase cellular toxicity over a wider range, resulting in more effective cell kill, especially where tumor cell antigen heterogeneity exists.⁴ Conventional DTPA-based bifunctional chelating agents used in radiolabeling Bi-212 have resulted in poor in vivo stability, limiting their use to intraperitoneal and intralymphatic infusion.¹¹ Newer macromolecular chelating agents, including a DOTA (1,4,5,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) derivative, have resulted in improved stability of Bi-212 labeled radioimmunoconjugates.¹²

Figure 3. Bismuth-212 Decay Scheme



D. Bismuth-213 Radiopharmaceuticals

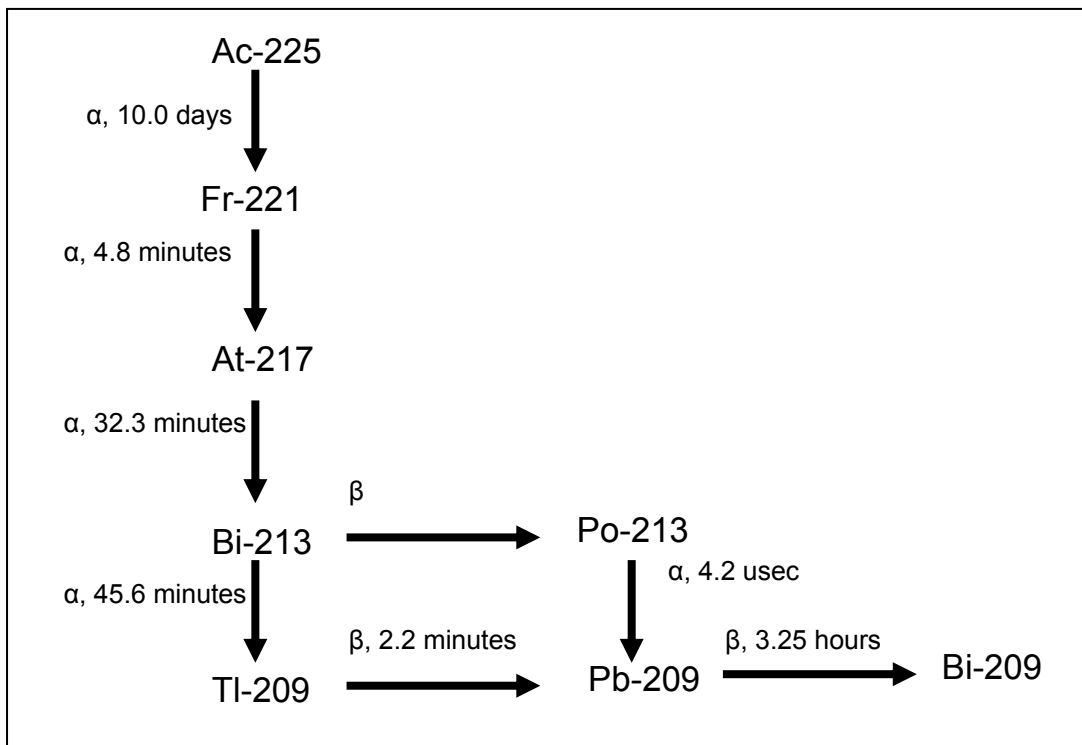
Bi-213 decays with multiple mixed emissions including an alpha emission of 5.9 MeV. Due to the short 0.76-hour half-life of Bi-213, a generator system, consisting of the parent Ac-225, has been developed.¹³⁻¹⁵ The decay scheme for Ac-225 is shown in Figure 4. The parent is adsorbed onto an inorganic silica based actinide resin.¹⁵ The generator system is eluted with 0.1 M hydroiodic acid providing about 25–65 mCi of pure Bi-213. Shielding and other radiation safety measures associated with the generator system are minimal. Following elution, protein conjugation of bismuth can be completed within 20–30 minutes using a bifunctional chelating agent.¹⁶ Imaging studies can be performed using the 440 keV gamma emissions. Clinical trials using targeted radioimmunotherapy for myeloid leukemia were performed with Bi-213 conjugated to a humanized anti-CD33 monoclonal antibody HuM195.¹⁷ Radiolabel-

ing was accomplished using a bifunctional chelating agent CHX-DTPA resulting in a radiolabeling efficiency of 81% with radioimmunoreactivity of 89%. Eighteen patients with relapsed and refractory acute myelogenous leukemia or chronic myelomonocytic leukemia were treated with 0.28–1.0 mCi/kg of Bi-213 HuM195. Nearly all of the radiolabeled antibody localized and was retained in areas of leukemic involvement. No significant extramedullary toxicity was noted. All seventeen evaluable patients developed myelosuppression, which was resolved.

E. Actinium-225 Radiopharmaceuticals

As shown in Figure 4, Actinium-225, with a 10-day half-life, emits several daughter radionuclides resulting in four alpha particle emissions. Due to this fact, Ac-225 has been proposed as an in vivo generator of alpha particles.¹⁸ Although the cytotoxicity of Ac-225 is approximately 1000 times more

Figure 4. Actinium Ac-225 Decay Scheme



potent on a mCi basis than Bi-213, the varied chemical periodicity of the daughters of Ac-225 decay make conjugation to monoclonal antibodies extremely difficult. This is because no single chelating agent will effectively bind all the daughters of Ac-225. It has been proposed that an appropriate chelating agent could stably bind Ac-225 to the antibody, so as to deliver the radioimmunoconjugate to the cellular site, where other mechanism would cause internalization of the radio-labeled monoclonal antibody. Once internalized, the daughters of Ac-225 would remain within the cell.¹⁸

Preclinical trials to assess dosimetry and toxicity of a specific Ac-225 labeled monoclonal antibody in primates have been published. Actinium-225 was conjugated to HuM195, an anti-CD33 monoclonal antibody using a bifunctional chelating agent (DOTA derivative). In one experiment, monkeys received a 28 kBq/kg (0.75 μ Ci/kg) single injection of Ac-225 HuM195. In another study,

monkeys received a dose escalation schedule (3 doses) with a cumulative activity of 377 kBq/kg (10.2 μ Ci/kg). Prolonged blood retention ($t_{1/2} = 12$ days) was observed. The prolonged blood retention was attributed to the fact that monkeys do not express CD33 antigens. No toxicity at the single dose of 28 kBq/kg was observed at 6 months after dosing whereas, with the cumulative dosing schedule, severe toxicity was observed including renal toxicity and anemia. Human studies using Ac-225 HuM195 are planned beginning at lower dose levels of 28 kBq/kg (0.75 μ Ci/kg).¹⁹

F. Radiation Protection Issues

Due to the unfamiliarity in dealing with alpha-emitting radionuclides, radiation safety aspects are of concern. Because alpha emitters are limited in their ability to penetrate matter, the dead outer layers of the skin will absorb all alpha radiation from external radioactive sources. As a result, alpha radiation

does not pose an external radiation hazard.²⁰ However, if internalized, the shielding effect of the dead layer of skin is absent, and the alpha energy is deposited in living tissue. Epidemiological studies have indicated an association between internal exposure of alpha emitters and cancer, specifically between exposure to radon gas and the incidence of lung cancer.²¹ Due to the internalization risk, allowable removable contamination levels for alpha-emitting radionuclides are significantly less than for beta/gamma emitting radionuclides. In addition, special monitoring equipment and facilities may be needed to limit or prevent contamination or airborne release of alpha emitting radionuclides during handling and/or storage.⁵

III. BETA-EMITTING RADIONUCLIDES

A. Classification of Beta Radionuclides and Tumor Therapy Rationale

Beta-emitting radionuclides have been widely used in targeted radionuclide therapy. A list of some common beta-emitting radionuclides used for therapy is found in Table 2. The listed beta emitting radionuclides are divided into three distinct groups depending on the tissue range of each beta particle. Specific groups include beta emitting radionuclides with mean tissue penetration ranges of less than 200 microns, beta emitting radionuclides with mean tissue penetration ranges of 200–1000 microns and beta emitters with greater than 1000 micron penetration range. As stated previously, for treatment effectiveness, there appears to be a correlation between tumor size and beta energy emitted.¹ Beta-emitting radionuclides with relatively low energies are more effective in treating micrometastases whereas beta-emitting radionuclides with higher beta energies are more effective in treating larger tumors.

Table 2. Physical Properties of Some Beta-Emitting Radionuclides used in Targeted Therapy

Nuclide	Half-Life	Mean Beta Energy
Beta-Emitting Radionuclides with Mean Tissue Penetration Range Less than 200 microns		
Lu-177	6.71 days	147 keV
Au-199	3.13 days	142 keV
Beta-Emitting Radionuclides with Mean Tissue Penetration Range between 200 microns and 1 mm		
Cu-67	2.58 days	154.1 keV
I-131	8.02 days	192.3 keV
Re-186	3.78 days	340.8 keV
Sm-153	1.95 days	269 keV
Beta-Emitting Radionuclides with Mean Tissue Penetration Range Greater than 1 mm		
P-32	14.28 days	695 keV
Y-90	2.67 days	939 keV
Re-188	0.71 days	778 keV
Ho-166	1.12 days	694 keV
Sr-89	50.5 days	580 keV

B. Clinical Radionuclide Therapies

Common therapeutic beta-emitting radiopharmaceuticals include I-131 sodium iodide for the treatment of thyroid disease and carcinoma; P-32 sodium phosphate for treating polycythemia vera; P-32 chromic phosphate for intracavitary therapies; and P-32 orthophosphate, Sr-89 chloride and Sm 153 leixidronam for palliation of painful bone metastases. Newer beta emitting radiopharmaceuticals for targeted radionuclide therapy include beta-emitting radionuclides bound to microspheres, radiolabeled peptides for therapy and radiimmunotherapeutic agents.

C. Radioimmunotherapy-Non-Hodgkin's Lymphoma

Recently, two radioimmunotherapy agents, I-131 tositumomab and Y-90 ibritumomab tiuxetan, have been introduced for the treatment of non-Hodgkin's lymphoma. Advantages of using radiolabeled mono-

clonal antibodies in the treatment of non-Hodgkin's lymphoma include:

1. Radiolabeled monoclonal antibodies target radiation to tumor sites limiting effects to non-antigen bearing normal cells.
2. Tumor cells distant from the bound antibody can be killed by ionizing radiation from beta-emitting radionuclides, which is especially important in bulky or poorly vascularized tumors. This is called the crossfire effect.
3. Lymphoma cells are inherently sensitive to radiotherapy.
4. Specific monoclonal antibodies recognize and react specifically with antigens present on tumor are commercially available.

D. Y-90 Ibritumomab Tiuxetan

Y-90 Zevalin (ibritumomab tiuxetan) is a pure beta-emitting radioimmunotherapy agent used for the treatment of relapsed or refractory non-Hodgkin's lymphoma. Zevalin consists of ibritumomab, an anti CD20 murine monoclonal antibody, and the chelator tiuxetan (MX-DTPA), which stably binds radiometals including In-111 and Y-90. A kit for radiolabeling the monoclonal antibody is provided by the manufacturer. Radiolabeling of ibritumomab is accomplished by adding the radiometal, either In-111 or Y-90, to sodium acetate. After mixing, ibritumomab tiuxetan is added and the solution is incubated at room temperature for either 5 or 30 minutes, depending on the specific radiometal. Formulation buffer is then added to terminate the reaction and also to stabilize the radiolabeled monoclonal antibody preparation. Using the method outlined above, our nuclear medicine department has radiolabeled over 200 In-111- and Y-90-Zevalin preparations with radiolabeling efficiencies consistently greater than 95%.²²

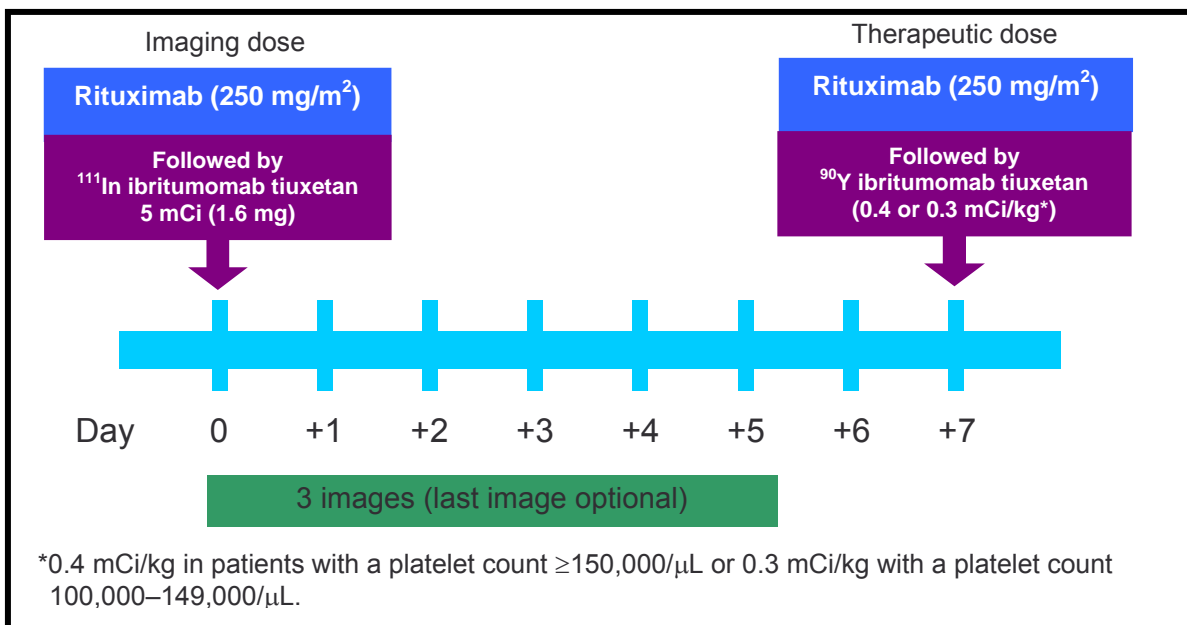
The dosing schedule for radiolabeled ibritumomab is illustrated in Figure 5. Patients

receive an infusion of rituximab (Rituxan®), a chimeric construct of ibritumomab, at 250 mg/m², to optimize biodistribution of the radiolabeled antibody, followed immediately by an imaging dose of In-111 Zevalin (5 mCi on 1.6 mg of ibritumomab) by slow IV injection over 10 minutes. Imaging is then performed, to assess altered biodistribution, at two or three different days after injection. One week after In-111 injection, patients without an altered biodistribution receive a second infusion of rituximab (250 mg/m²) immediately followed by a slow IV injection of Y-90 Zevalin over a 10-minute time period at a dose of either 0.3 mCi/kg or 0.4 mCi/kg, depending on platelet count, with a maximum injection dose of 32 mCi.²³

An accurate measurement of pure beta-emitting radionuclides with a well-type gas-ionization chamber or a dose calibrator is difficult due to source geometry. The special shape of a source can result in differences in self-absorption and also different containers can result in different degrees of attenuation. In addition, altering the volume of source material can significantly alter the response of the dose calibrator. Because the primary radiation measured for Y-90 is bremsstrahlung, effects of various containers may be opposite to that expected. Increases in the atomic number of the material in the container may increase the response of the dose calibrator due to the increased bremsstrahlung production.²⁴ For example, use of lead containers as opposed to aluminum or plastic containers will increase bremsstrahlung production from less than one percent to approximately 6%,²⁵ resulting in a higher response from a dose calibrator. Proposed methods for the accurate measurement of Y-90 Zevalin in dose calibrators include the following:

1. Dose calibrator settings, or a range of settings, can be obtained from the manufacturer or from a qualified expert who has performed and documented calibrations for the dose calibrator in question.

Figure 5. Dosing Schedule for Ibritumomab Tiuxetan



2. Dose calibrators can be calibrated with an appropriate NIST-traceable standard, contained in a 10-ml syringe, to yield a single best dial setting.
3. Dose calibrators can be calibrated using a solution of Y-90 reference material, for which the activity has been measured using a NIST-traceable standard. The procedure involves the transfer of known activity into a 10-ml syringe and includes either determining the single best setting or determining a dial setting as a function of syringe volume.

The dose calibrator utilized in our nuclear medicine department was calibrated using method 3 outlined above and included determining a specific dial setting as a function of syringe volume. A known activity of Y-90 was added to a glass vial to total volume of 10 ml. With a 10-ml syringe, serial 1.0 ml aliquots were withdrawn up to a total of 9.0 ml, placed in the dose calibrator in the same geometry, and the dial setting altered to reflect the calculated total activity. Results are shown in Table 3 and graphically expressed in Figure 6. With this method, dose meas-

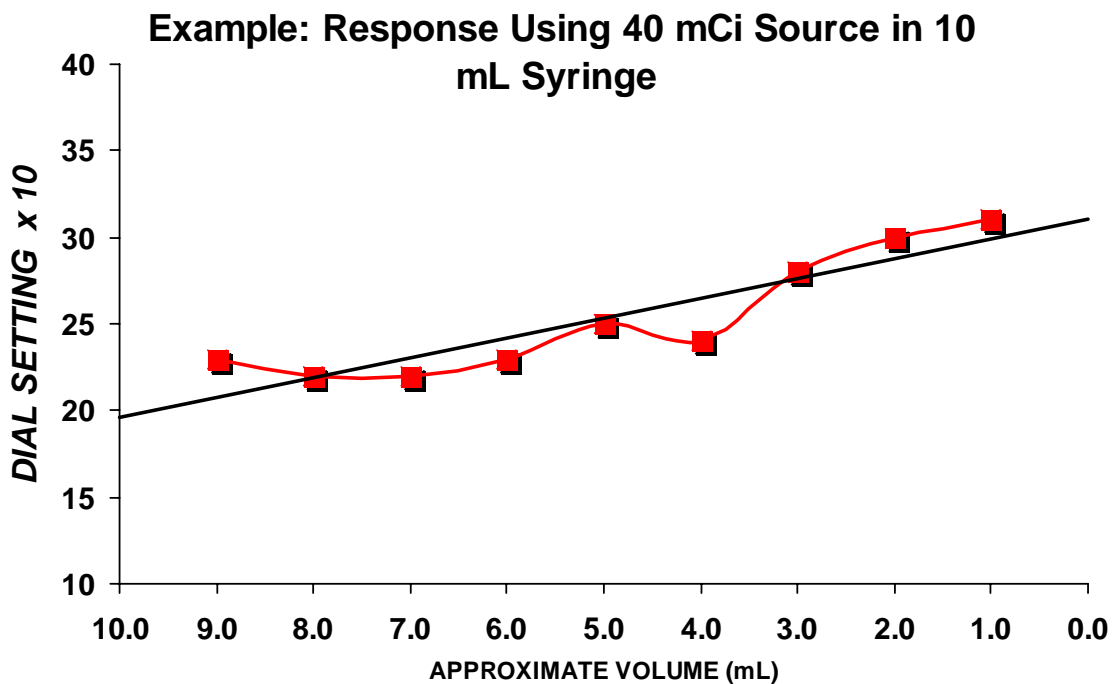
urements of Y-90 Zevalin are accurate as long the same dose calibrator and the same geometry are utilized. In the event that the activity of a unit dose measurement at a clinical site differs from the stated activity of the dispensing nuclear pharmacy, NRC has stated that the discrepancy should be resolved prior to the administration of the therapeutic radiopharmaceutical.²⁴

For many therapeutic pure beta-emitting radiopharmaceuticals, biodistribution and imaging studies are conducted using an appropriate gamma-emitting radionuclide analogue including indium-111. Accurate dosage measurements of In-111 labeled radiopharmaceuticals are also difficult due to variations in source geometry. In-111 emits low energy characteristic x-rays, in the range of 23 to 26 keV, which can result in variations in dose measurements when different container materials are used. Errors in In-111 dosage measurements ranging from 6.8% in glass vials to 31.4% in 1-ml syringes have been documented.²⁶ The use of a 0.6 mm thick copper absorber lining positioned in the gas-ionization chamber can significantly

Table 3. Calibration Setting for Y-90 Using a 10-ml Syringe

Volume (mL)	Calculated Activity Concentration (mCi/mL)	Calculated Total Activity (mCi)	Dial Setting
1.0	3.91	3.91	56
2.0	3.91	7.82	55
3.0	3.91	11.73	55
4.0	3.91	15.64	53
5.0	3.91	19.55	48
6.0	3.91	23.46	48
7.0	3.91	27.37	47
8.0	3.91	31.28	47
9.0	3.91	35.19	48

Figure 6. Dose Calibrator Response Using 40 mCi Y-90 Zevalin in a 10-ml Syringe



reduce the low energy x-ray emissions from In-111 resulting in accurate dose calibrator measurements regardless of container geometry.²⁷ When using the copper filter, dose calibrator setting for In-111 must be recalibrated. A copper filter for dose calibrators is currently commercially available.

Radiation precaution issues related to Y-90 Zevalin include radionuclide handling,

radiopharmaceutical preparation and patient injection. In addition, patient radiation precautions and radiation precautions related to potential exposures to members of the family and members of the public are of concern. Due to bremsstrahlung production, shielding requirements for beta-emitting radionuclides require materials with a low atomic number. As shown by the formula in Figure 7, the

fraction of incident beta energy converted to bremsstrahlung is a function of the atomic number of the absorbing or shielding material and the energy of the beta-emitting radionuclide. For beta-emitting radionuclides, shielding with a low atomic number, such as acrylic or plastic, or composite shielding, such as aluminum/lead, is essential in minimizing bremsstrahlung production. For Y-90 Zevalin, with an energetic 2.3 MeV beta-emission, effective shielding requirements are necessary for vial shields, syringe shields and transport shields. Our department has evaluated the effectiveness of a number of shielding devices using thermoluminescent dosimeters.²⁸ High surface dose rates were recorded from an unshielded glass vial and plastic syringe containing clinical activities of Y-90 Zevalin (366 rads/hr and 1287 rads/hr, respectively). Use of an acrylic vial shield or a composite (aluminum/lead) vial shield reduced the radiation levels by a factor of 1800–3600. Using an acrylic or composite (acrylic/lead) syringe shield also reduced radiation levels by a factor of 4000–6000.

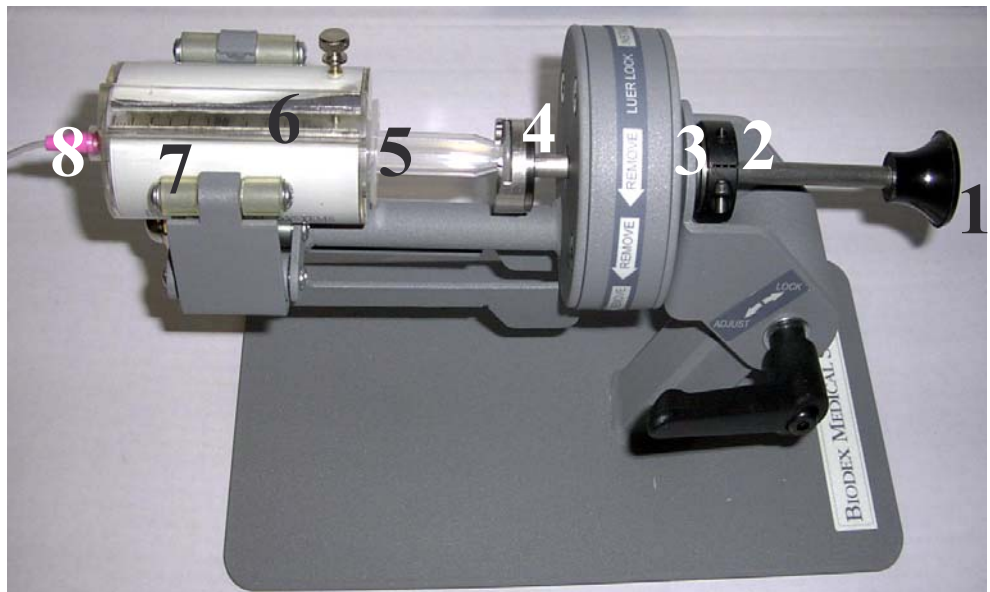
Figure 7. Bremsstrahlung Production as a Function of Atomic Number of Absorber and Beta-Emitting Radionuclide Energy

$$f = 3.5 \times 10^{-4} ZE$$

f = the fraction of the incident beta energy converted into photons
 Z = atomic number of the absorber
 E = maximum energy of the beta particle in MeV

Patient dose administration of Y-90 Zevalin includes a slow 10-minute intravenous injection through a 0.2 micron filter. Appropriate shielding and the use of a manual or remote injector system are necessary to minimize radiation exposure. Our department evaluated the radiation levels from a typical Y-90 Zevalin injection using a manual injector system with a composite acrylic/lead syringe shield. Dose rates were evaluated using thermoluminescent dosimeters and results are shown in Figure 8. Radiation exposures were significantly reduced using the injection device. This included radiation levels in the area of the injection plunger of the manual injector system, which were minimal.

Figure 8. Dose Rates from Shielded Y-90 Zevalin Injection using a Manual Injector System



- 1- Bkground
- 2- 1 mrad/hr
- 3- Bkground
- 4- 32 mrad/hr
- 5- 304 mrad/hr
- 6- 106 mrad/hr
- 7- 64 mrad/hr
- 8- 285280 mrad/hr

Radioimmunotherapy treatments with Y-90 Zevalin can be performed on an outpatient basis. Immediately following injection, dose rates at 1 meter from patients receiving Y-90 Zevalin are less than 0.5 mR/hr. As a result, patient instructions following Y-90 Zevalin administration are minimal and are found in Table 4. Instructions deal primarily with possible radiation contamination problems related to urine and body fluids and generally extend for a period of three days. In addition, the use of condoms for sexual relations is encouraged for a period of 7 days.²⁹

Table 4. Patient Release Instructions Following Y-90 Zevalin Administration

3 days	Clean Spilled Urine and Dispose of Any Fluid Contaminated Material
7 days	Use Condoms for Sexual Relations

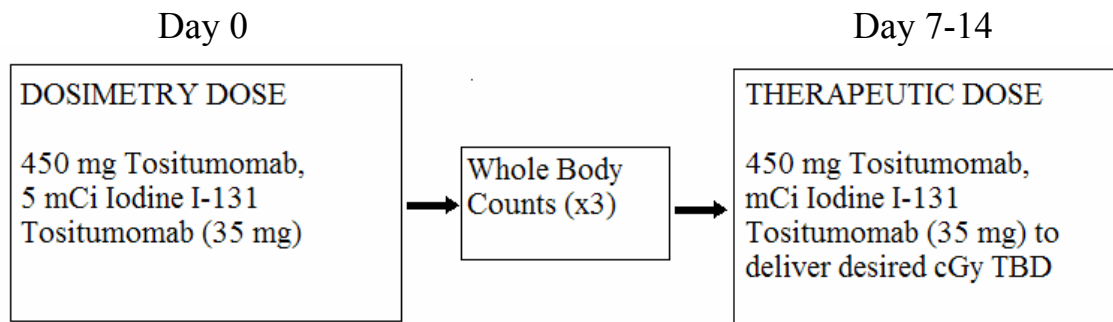
Following release of patients receiving Y-90 Zevalin therapy, radiation exposures to members of the public and especially members of the immediate family are of concern. In a study conducted by Wiseman et al.,³⁰ family members of patients receiving Y-90 Zevalin, with unrestricted access to the patient, were issued radiation monitoring devices for a period of 7 days following therapy. Results showed that radiation exposures to family members were minimal, ranging

from 1.4–7.9 mrem, for a seven-day period. As a result, no radiation precautions to family members of patients receiving Y-90 Zevalin are warranted.

E. I-131 Tositumomab

Another radioimmunotherapy agent for the treatment of non-Hodgkin’s lymphoma is I-131 tositumomab (Bexxar), a murine IgG2 monoclonal antibody that binds to CD20 antigen on lymphoma cells. For this radioimmunotherapy agent, therapeutic doses are customized to the individual patient based on whole body clearances. Prior to treatment, patients receive supersaturated potassium iodide (SSKI) to block thyroid uptake. The treatment regimen, as outlined in Figure 9, consists of an initial dosimetric dose of I-131 tositumomab (5 mCi) preceded by a 1-hour administration of unlabeled tositumomab (450 mg). Total body counts, usually performed with a gamma scintillation camera, are obtained three times over a 6–7 day period to determine residence time of the radio-labeled monoclonal antibody. A therapeutic dose is then calculated from the residence time so that the patient receives a whole body absorbed dose of 75 cGy. The therapeutic activity of I-131 tositumomab is usually in the range of 33–161 mCi.^{31,32}

Figure 9. Treatment Schema for I-131 Tositumomab



Radioimmunotherapy using I-131 tositumomab may require hospitalization, depending on the regulatory requirements of the respective states. NRC regulated states have amended regulations related to the criteria for the release of patients administered radioactive materials. The new criteria for patient release may be based on limiting the total effective dose equivalent (TEDE) to less than 500 mrem for the maximally exposed individual. Siegel et al.³³ developed a methodology for the release of patients administered I-131 tositumomab. As a result, radioimmunotherapy with I-131 tositumomab could be performed on an outpatient basis in NRC regulated states.

Shielding during I-131 tositumomab formulation, dispensing and patient injections is important in reducing radiation exposure to occupational radiation workers. I-131 is a mixed emitter, with the major beta-emission of 606 keV (86%) and the major gamma-emission of 364 keV (81%). As a result, shielding requirements must be appropriate for both types of emissions. The range of beta-emission of I-131 in lead is 0.17 mm and the fraction of beta-emissions converted to bremsstrahlung in lead is low (1.7%). In addition, only about 1% of the x-rays generated from bremsstrahlung have energies greater than 360 keV.²⁰ From the data, it would appear that lead shielding for the gamma component of I-131 is also effective in shielding the beta component.

Radiation safety issues related to I-131 tositumomab administration deal with radiation doses to the patient as well as radiation exposure to family members and members of the general public. Immediately following therapeutic administration of I-131 tositumomab, the mean measured dose rate at 1 meter from patients was 10.9 mrem/hr with a range of 4–24 mrem/hr.³³ Radiation levels decreased with increasing patient body size. In order to assure compliance to dose limiting criteria, radiation exposures to family mem-

bers of patients receiving I-131 tositumomab were measured directly with appropriate radiation dosimeters.³⁴ The mean radiation exposure to family members was 144 mrem, with a range of 10–354 mrem, which was well below the dose limit allowed to members of the general public (500 mrem).

In order to minimize radiation exposures to others, patient radiation safety instructions must be issued following radioimmunotherapy treatment with I-131 tositumomab. Instructions are based on total body residence times and measured patient dose rates. Typical instructions for a patient receiving I-131 tositumomab with a total effective dose equivalent (TEDE) of 365 mrem would include the following:³³

1. Sleep in separate bed (at least 2 meter separation) for 8 days.
2. Do not take long trips (more than 4 hrs) sitting near others for 1 day.
3. Stay at least two meters from children and pregnant women for 7 days.
4. Minimize time spent in close contact with others and delay return to work for 4 days.

F. Radiolabeled Peptides for Therapy

The use of radiolabeled peptides for therapeutic applications is a new and exciting area of clinical nuclear medicine research. Because peptides generally consist of less than 50 amino acids, they have a low molecular weight. As such, they tend to have fast clearances and rapid tissue and tumor accumulation. A wide range of peptides, having an affinity for specific receptors over expressed on a large number of tumor cell types, have been identified. Some interesting peptides under clinical investigation include somatostatin and analogues of somatostatin, bombesin, gastrin, and epidermal growth factor.³³

Although radiolabeled peptides have generated great interest in imaging and therapy, there are concerns regarding their clinical

use. As the size of peptides increase, they tend to more slowly diffuse into tumors and are also highly susceptible to proteolysis. Some endogenous peptides may also have unwanted physiological side effects. Radiolabeling of peptides usually involves the incorporation of a bifunctional chelating agent onto the peptide. With its relatively high molecular weight of the chelator, the molecular weight of the peptide complex may distort peptide conformation resulting in altered target binding.³⁵

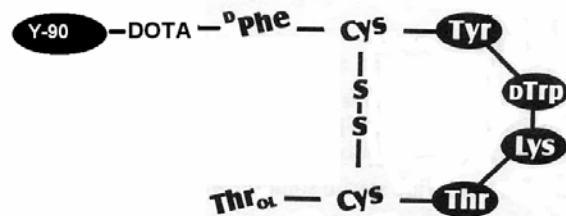
A number of beta-emitting radionuclides have been utilized for peptide receptor radionuclide therapy, including Y-90, Lu-177 and Cu-64³⁶⁻³⁸. Coupling to peptides is usually accomplished via a peptide bond using bifunctional chelating agents such as DOTA (1,4,5,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) and TETA (1,4,8,11-tetraazacyclotetradecane-N',N'',N'''-tetraacetic acid).

G. Y-90-DOTA-Octreotide

Clinical trials in peptide receptor radionuclide therapy have been initiated using a somatostatin analogue, DOTA-D₁Phe¹-Tyr³-Octreotide (DOTATOC) (36). With this conjugated peptide, stable Y-90 incorporation was achieved. The schematic presentation of Y-90 DOTATOC is found in Figure 10. DOTATOC is an 8 amino acid structure in which DOTA is bound to phenylalanine. Clinical studies in patients with histologically confirmed subtype 2 somatostatin tumor receptors (sst₂) have been initiated using Y-90 DOTATOC. Besides neuroendocrine tumors, somatostatin receptors have been identified in cancers of the central nervous system, breast, lung, and lymphatic tissue. Patients received either a number of cycles of Y-90 DOTATOC, with an 8-week interval between treatments. Y-90 DOTATOC was, in some cases, administered in a dose-escalating manner, ranging between 24–150 mCi per treatment, with a cumulated dose of 260–576 mCi. Administration of Y-90 DOTATOC involved a

slow intravenous infusion of 50-100 ml over 20 minutes. Some patients received an amino acid infusion, consisting of lysine and arginine, prior to radionuclide therapy in order to reduce radiation dose to kidneys. The maximum tolerated dose per cycle was defined as 150 mCi Y-90 DOTATOC. Objective therapeutic responses, either partial or complete, were documented in more than 20% of the treated patients. No major acute reactions were noted after peptide therapy administration. Moderate gastrointestinal toxicity, including nausea and/or vomiting, and some transient hematologic toxicity were observed in some patients.

Figure 10. Schematic Presentation of Y-90 Labeled DOTA-D₁Phe¹-Tyr³-Octreotide (DOTATOC)



Dose measurement issues related to Y-90 are similar to those stated previously. Due to differences in source geometry, especially volume differences, dose calibrators must be recalibrated as previously described.

Shielding requirements for Y-90 DOTATOC are similar to those described for other Y-90 labeled radiopharmaceuticals. Initially, bremsstrahlung production is minimized by use of shielding materials with a low atomic number, such as glass, acrylic or aluminum. Bremsstrahlung, or energetic x-ray emissions, can then be effectively attenuated using lead or other materials with a high atomic number. Radiation safety issues related to radiation exposure to ancillary personnel, including family members, must be considered in light of regulatory constraints. In order to assess radiation exposures from beta-emitting radionuclides, a “specific bremsstrahlung

constant”, with units of $R\text{-cm}^2/\text{mCi-h}$, has been proposed.²⁵ This constant is somewhat analogous to a specific gamma-ray constant. Using the specific bremsstrahlung constant, it would appear that patients could be treated on an outpatient basis with activities of several thousand mCi Y-90 radiopharmaceuticals, based on regulatory constraints of 0.5 rem total dose equivalent.²⁵

H. Y-90 Microspheres

Y-90 microspheres are classified as devices intended for regional radionuclide brachytherapy. As a radionuclide brachytherapy source, two specifications must be met: 1) The device must minimize the leakage of possibly hazardous radiation, and 2) the encapsulated material must be biocompatible and not cause significant adverse tissue reaction.³⁹

The intrahepatic arterial administration of Y-90 microspheres includes the use of catheters and an administration apparatus. An appropriate catheter is accurately positioned within the right or left hepatic arteries corresponding to the desired treatment target area. Y-90 microspheres are then administered through an administration apparatus consisting of a variety of sterile apyrogenic components including water for injection, saline, sealed tubing, acrylic shields, inlet and outlet lines and three-way connection system.⁴⁰

One of the limitations associated with the clinical use of Y-90 microspheres is arteriovenous shunting which can result in increased radiation doses to ancillary organs or tissues. In order to limit radiation doses to ancillary organs, especially the lungs, the degree of shunting must be determined prior to radionuclide therapy using Tc-99m macroaggregated albumin. Following administration of Tc-99m MAA (2–6 mCi), perfusion imaging is performed to evaluate the degree of pulmonary and gastric tract shunting. Patients may only be treated with Y-90 microspheres if the total cumulative lung dose does not exceed 3000 rads.⁴⁰

At the present time, there are two Y-90 microsphere preparations in clinical use, SIR-Spheres (Sirtex Medical) and TheraSphere (MSD Nordion). SIR-Spheres consists of biocompatible microspheres with a mean diameter of 32 μm and a range of 20–40 μm . SIR-Spheres is commercially available in glass vials containing 3 GBy (81 mCi) \pm 10% per 5 ml of Y-90 microspheres (40–80 million particles) suspended in water for injection. Each sterile, pyrogen-free vial is crimp sealed to allow individual patient doses to be withdrawn. SIR-Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy of Floxuridine.⁴¹

Y-90 microspheres (TheraSphere) consist of insoluble glass microspheres in which Y-90 is imbedded. The microspheres have a mean diameter of 25 μm \pm 10 μm (standard deviation), with less than 5% smaller than 15 μm and less than 10% larger than 35 μm . Each milligram contains between 22,000 and 73,000 microspheres. Y-90 microspheres are supplied in 0.05 ml of sterile, pyrogen-free, water that is contained in a dose vial shielded with polystyrene. Y-90 microspheres are commercially available in six dose sizes of 81 mCi, 135 mCi, 189 mCi, 270 mCi, 405 mCi and 540 mCi. Y-90 microspheres (TheraSphere) are currently approved by the U.S. Food and Drug Administration under the provisions of a “Humanitarian Device Exemption) (HDE No. H9800006) which includes unique restrictions on the medical use of the device. TheraSpheres is indicated for use in radiation treatment of patients with unresectable hepatocellular carcinoma (HCC).³⁹

Patients with unresectable hepatocellular carcinoma have been successfully treated with intrahepatic arterial administrations of Y-90 microspheres.^{40,42} Total activity of Y-90 microspheres administered is based on liver volume and the desired radiation dose

delivered to the liver, usually between 100–150 Gy (10,000–15000 rad). After catheter placement in left or right hepatic arteries corresponding to the desired treatment area, Y-90 microspheres are injected via a specific administration system, as described previously.

Results of Phase I and Phase II studies with Y-90 microspheres have been encouraging; both in stabilizing the disease process and also in increased survival benefit.³⁹ Radionuclide therapy with Y-90 microspheres has been well tolerated with low toxicities, including mild fatigue and fever. Some gastrointestinal toxicities have been observed in a limited amount of patients.³⁹

Radiation safety issues related to the clinical use of Y-90 microspheres are important and are an integral part of the therapy procedure. Administration of Y-90 microspheres is generally performed in interventional radiology suites. Control measures to limit radiation contamination are essential. Dose measurements of the administration device, prior-to and following Y-90 microsphere injection, are important determining the total administered activity. Patient monitoring is important in assessing radiation doses to members of the public and also in meeting release criteria.

IV. CONCLUSION

This review has attempted to provide an update of therapeutic radiopharmaceuticals that are in current clinical use or are under investigation. It is important to note that several therapeutic radiopharmaceuticals for radioimmunotherapy, including Y-90 Ibtritu-momab Tiuxan and I-131 Tositumomab, have been approved for general use. In addition, research endeavors related to alpha-emitting radiopharmaceuticals are increasing due to the attractive therapeutic properties of specific alpha radionuclides. Although some radionuclide therapeutic agents have been classified as brachytherapy devices, including Y-90 microspheres, radiopharmaceutical dis-

persing is still required. In addition, radiation safety issues related to unsealed sources must be considered.

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VI. QUESTIONS

1. Which of the following parameters is not important for radionuclide therapy success?
 - a. Absorbed radiation dose to tumor
 - b. Concentration of radiopharmaceutical in tumor
 - c. The degree of disease progression
 - d. The sensitivity of tumor to radiation
2. Which alpha-emitting radionuclide uses a generator system in which the parent is Ac-225?
 - a. At-211
 - b. Bi-212
 - c. Bi-213
 - d. Ra-226
3. Which of the following statements is not true for Ac-225?
 - a. Ac-225 can stably bind to monoclonal antibodies
 - b. Ac-225 emits four alpha particles
 - c. Ac-225 has a 10-day half-life
 - d. Ac-225 has been proposed as an in vivo alpha generator
4. Which of the following statements is not true in radiation protection of alpha-emitting radionuclides?
 - a. Alpha-emitters are stopped by the dead outer layers of the skin
 - b. Alpha-emitters pose a danger if ingested
 - c. Alpha-emitters pose a significant external radiation hazard
 - d. Alpha-emitters pose a danger if inhaled
5. Which of the following beta-emitting radionuclides is ideal for treating tumors with diameters less than 1 mm?
 - a. P-32
 - b. I-132
 - c. Lu-177
 - d. Y-90
6. Which monoclonal antibody is used for the treatment of Non-Hodgkin's lymphoma?
 - a. anti-tenascin antibody
 - b. ibritumomab
 - c. HuM195
 - d. T101
7. Which therapeutic radionuclide is conjugated to ibritumomab?
 - a. Y-90
 - b. I-131
 - c. Re-186
 - d. In-111
8. For dose measurement issues related to In-111, inaccurate measurements are due to which of the following?
 - a. Attenuation of energetic gamma emissions
 - b. Attenuation of low energy x-rays
 - c. Attenuation by the plastic insert
 - d. Attenuation of radionuclidic impurities
9. I-131 tositumomab is a radioimmunotherapy agent used to treat what disease?
 - a. Ovarian cancer
 - b. Non-Hodgkin's lymphoma
 - c. T-cell lymphoma
 - d. Prostate cancer

10. Following I-131 tositumomab administration, which of the following statements is not true?
 - a. Patients can be treated with I-131 tositumomab on an outpatient basis in NRC regulated states.
 - b. Patients must be issued radiation safety precautions after therapy.
 - c. Patient release criteria are based on limiting the total effective dose equivalent to less than 500 mrem for the maximally exposed individual
 - d. Patients must be hospitalized following therapy.
11. Radiolabeled peptides for therapy include which of the following?
 - a. Y-90 microspheres
 - b. Y-90 Octreotide
 - c. In-111 Octreotide
 - d. Y-90 Ibritumomab
12. Beta-emitting radionuclides used for peptide imaging include all of the following except?
 - a. Y-90
 - b. Lu-177
 - c. P-32
 - d. Cu-64
13. Y-90 TheraSpheres consist of which of the following?
 - a. Y-90 labeled to macroaggregated albumin
 - b. Y-90 labeled to human albumin microspheres
 - c. Y-90 imbedded insoluble glass microspheres
 - d. Y-90 biocompatible microspheres
14. For Y-90 microsphere therapy, what is the desired radiation dose delivered to the liver?
 - a. 25-50 Gy
 - b. 50-100 Gy
 - c. 100-150 Gy
 - d. 150-200 Gy
15. For Y-90 Ibritumomab radioimmunotherapy, what is the maximum dose administered to patients?
 - a. 32 mCi
 - b. 40 mCi
 - c. 0.4 mCi/kg body weight
 - d. 0.3 mCi/kg body weight
16. Beta-emitting radionuclides with mean tissue penetration range greater than 1 mm include all of the following except one?
 - a. Sr-89
 - b. I-131
 - c. Y-90
 - d. P-32
17. Following an imaging dose of In-111 ibritumomab, how many images must be taken to assess biodistribution?
 - a. 1 image
 - b. 2 images
 - c. 3 images
 - d. 4 images
18. Bremsstrahlung production from beta-emitting radionuclides depends on all the following parameters except one?
 - a. range of beta-emitting radionuclide
 - b. energy of beta-emitting radionuclide
 - c. atomic number of the shielding material
 - d. the atomic number of the container
19. A remote injection device is needed for Y-90 patient administration due to the following?
 - a. inject large volume of radiopharmaceutical
 - b. reduce radiation exposure to personnel
 - c. allow the slow infusion of radiopharmaceutical
 - d. needed due to 0.2 micron filter

20. The formulation buffer is added when radiolabeling Y-90 ibritumomab for all of the following except one?
- to terminate the reaction sequence
 - to stabilize the radiolabeled monoclonal antibody preparation
 - to increase the radiolabeling efficiency
21. Y-90 SIR-Spheres consist of the following?
- Y-90 labeled to macroaggregated albumin
 - Y-90 labeled to human albumin microspheres
 - Y-90 imbedded insoluble glass microspheres
 - Y-90 biocompatible microspheres
22. Y-90 TheraSpheres microsphere particles have a mean diameter of?
- 10 μm
 - 25 μm
 - 35 μm
 - 50 μm
23. Accurate dosage measurements of In-111 labeled radiopharmaceuticals in a dose calibrator are difficult due to?
- attenuation of gamma emissions
 - attenuation of low energy x-ray emissions
 - attenuation of beta emissions
 - all of the above
24. Which of the following describe the specific bremsstrahlung constant?
- has units of R-cm²/mCi-h
 - is analogous to a specific gamma-ray constant
 - describes the radiation exposures from beta-emitting radionuclides
 - all of the above
25. Rituximab is a monoclonal antibody with the following characteristics?
- is a chimeric construct of ibritumomab
 - is a chimeric construct of tositumomab
 - is a humanized construct of ibritumomab
 - is a murine construct of tositumomab