Logistics of Radioimmunotherapy With Yttrium 90 Ibritumomab Tiuxetan (Zevalin)

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Radioimmunotherapy is a promising new therapeutic option for the treatment of B-cell non-Hodgkin's lymphoma. Several monoclonal antibody and radionuclide conjugates, including I-131 tositumomab and Y-90 ibritumomab, have been investigated in clinical trials. Yttrium 90 ibritumomab tiuxetan (Zevalin; Biogen Idec Inc, Cambridge, MA) is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular non-Hodgkin's lymphoma. The ibritumomab tiuxetan regimen requires coordination of a multidisciplinary team on which the nuclear medicine physician (or radiation oncologist) plays a major role. The nuclear medicine physician (or radiation oncologist) is responsible for overseeing the administration of the radioimmunoconjugates and for interpreting the imaging scans to determine the expected or altered biodistribution of the radioimmunoconjugate.

THE ibritumomab tiuxetan regimen requires the close coordination of a multidisciplinary team—including a nuclear medicine physician, an oncologist or hematologist, a nuclear medicine technologist, an oncology nurse, a radiopharmacist, and possibly a radiation oncologist—on which the nuclear medicine physician plays a major role.[1] The nuclear medicine physician is responsible for overseeing the administration of the radioimmunoconjugates and for interpreting the imaging scans after the administration of the ^{111}In ibritumomab tiuxetan to determine the biodistribution of the radioimmunoconjugate. The nuclear medicine physician also explains the treatment to the patient to ensure that the patient understands the regimen and its safety requirements. Because of the number of persons involved, and the coordination of the regimen, communication among the team members is crucial to ensure that every member is prepared and that the timing of each step is optimal.

DOSING SCHEDULE OF ^{90}Y IBRITUMOMAB TIUXETAN

Ibritumomab Tiuxetan Regimen

The dosing schedule of ibritumomab tiuxetan (Fig 1) consists of the administration of rituximab (Rituxan; Genentech, Inc, South San Francisco, CA, and Biogen Idec Inc, Cambridge, MA) 250 mg/m^2 to improve the biodistribution of the radiolabeled monoclonal antibody, followed within 4 hours by ^{111}In-labeled ibritumomab tiuxetan for imaging, or ^{90}Y-labeled ibritumomab tiuxetan for therapy.[2] It has been shown that predosing with an unlabeled monoclonal antibody to CD20 improves the biodistribution of the radiolabeled antibody, from binding 18% of the known disease sites without a predose of unlabeled antibody to binding up to 92% of the known disease sites after the administration of ibritumomab 1 or 2.5 mg/kg.[2,3] The therapeutic dose of ^{90}Y ibritumomab tiuxetan 0.4 mCi/kg (0.3 mCi/kg in patients with a platelet count of 100×10^9/L to 149×10^9/L) is administered 7 to 9 days after the imaging dose of ^{111}In ibritumomab tiuxetan. The maximum total dose of ^{90}Y ibritumomab tiuxetan is 32 mCi. Both ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan are administered as 10-minute intravenous infusions through a 0.22-μm low-protein-binding filter. Neither should be administered as a rapid intravenous bolus.

The infusions of rituximab are generally administered in a clinic by the oncology staff, and the radioimmunoconjugates are administered in a nuclear medicine department by workers who have been trained and certified in the use and administration of radiolabeled therapeutics.[1] Communication and coordination between the workers at both sites are essential to ensure the safe and effective delivery of the ibritumomab tiuxetan regimen. After the first infusion of rituximab (in the medical oncology office) the patient is given the imaging dose of ^{111}In ibritumomab tiuxetan 5 mCi (in the nuclear medicine department) and undergoes two gamma scans. (A third scan is optional and may be performed to rule out any ambiguities.) From these scans the nuclear medicine physician confirms that

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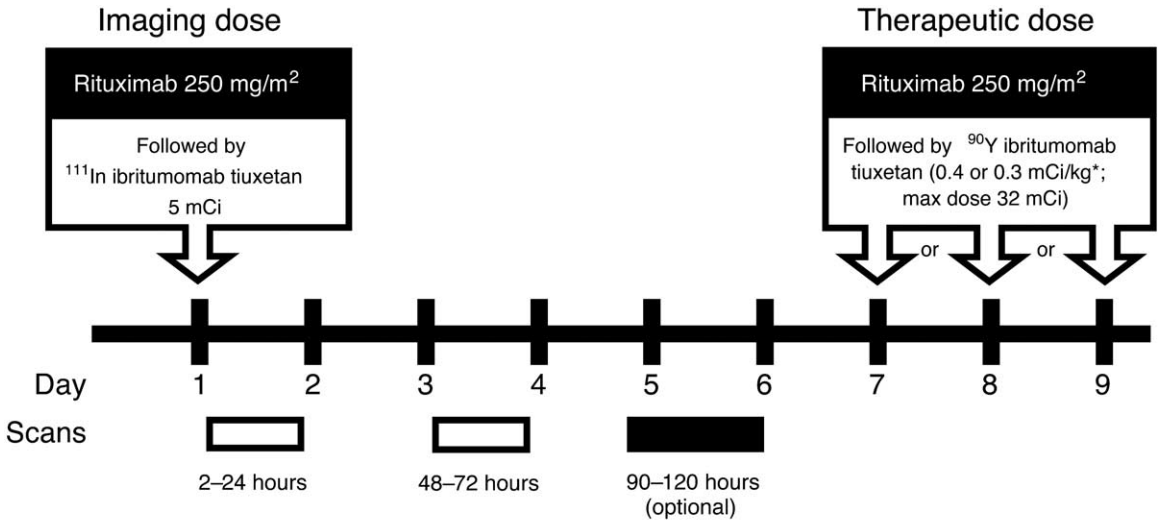

*0.4 mCi/kg in patients with a platelet count ≥150,000/μL or 0.3 mCi/kg with a platelet count 100,000–149,000/μL. Maximum dose is 32 mCi.

Fig 1. The ibritumomab tiuxetan regimen.[2]

the biodistribution of the radioimmunoconjugate is as expected and continues with the therapeutic regimen. (If the nuclear medicine physician determines that the biodistribution is altered, the patient should not be treated with ^{90}Y ibritumomab tiuxetan.) Although no cases of altered biodistribution were observed during the registrational trials, altered biodistributions have been observed in less than 1% of patients treated with the ibritumomab tiuxetan regimen following product commercialization (data on file, Biogen Idec Inc). The therapeutic phase occurs 7 to 9 days later, when the patient is given the second infusion of rituximab and within 4 hours the therapeutic dose of ^{90}Y ibritumomab tiuxetan.

Pharmacokinetics of ^{90}Y Ibritumomab Tiuxetan

The pharmacokinetics of ^{90}Y ibritumomab tiuxetan have been estimated from measurements of the activity of ^{90}Y in the blood or plasma in phase I-II and phase III studies.[4,5] In a phase I-II study in 57 patients with relapsed or refractory low-grade, intermediate-grade, or mantle cell non-Hodgkin's lymphoma, the median effective half-life of ^{90}Y in the blood and plasma was estimated to be 28 hours (range, 14 to 36 hours). The median biologic half-life of the antibody was 48 hours (range, 18 to 77 hours).[4] The ^{90}Y area under the time-concentration curve was estimated to be 24 and 22 μg · h/mL in the blood and the plasma, respectively (range, 4 to 48 μg · h/mL). In a phase III study in 143 patients with non-Hodgkin's lymphoma (73 patients treated with ^{90}Y ibritumomab tiuxetan), the median effective half-life of ^{90}Y in the blood was 27 hours (range, 17 to 44 hours) and the median biologic half-life of the antibody was 47 hours (range, 22 to 140 hours).[5]

Imaging With Ibritumomab Tiuxetan

Imaging with a fixed dose of ^{111}In ibritumomab tiuxetan 5 mCi is performed to confirm the expected biodistribution of the antibody before the therapeutic dose of ^{90}Y ibritumomab tiuxetan is given.[13] Whole body anterior and posterior gamma scan images are obtained at 2 to 24 hours and at 48 to 72 hours after the administration of ^{111}In ibritumomab tiuxetan (with an optional third scan at 90 to 120 hours).[12]

Expected biodistribution of ^{111}In ibritumomab tiuxetan is defined as easily detected uptake in the blood pool areas on the first images, with less activity on the second and third images; moderately high or high uptake in the normal liver and spleen on the first, second, and third images; and moderately low or very low uptake in the kidneys, urinary bladder, and bowel on all images (Fig 2).[2,6] Altered biodistribution of ^{111}In ibritumomab tiux-

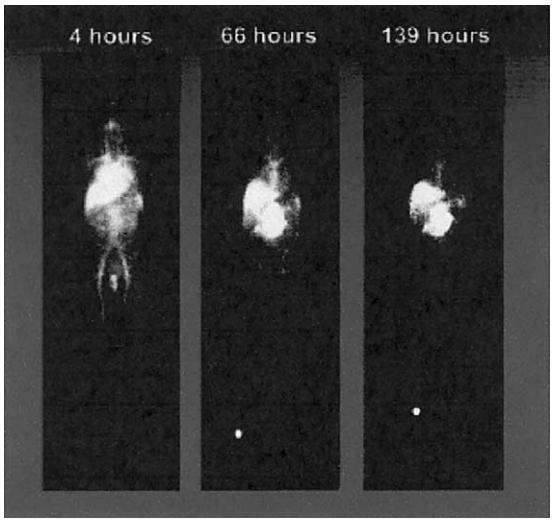

Fig 2. Expected biodistribution of ^{111}In ibritumomab tiuxetan, shown in serial whole body anterior gamma scan images. (Reprinted with permission.[6])

etan is characterized by diffuse uptake in the normal lung, which is more intense than that in the cardiac blood pool on the first images or more intense than the uptake in the liver on the second or third images; uptake in the kidneys more intense than that in the liver on the posterior view of the second or third images; or more intense areas of uptake throughout the normal bowel compared with the uptake in the liver on the second or third images. Although extremely rare, altered biodistribution is sufficient to halt treatment. Imaging, however, has not been shown to effectively indicate, and should therefore not be interpreted to assess, tumor uptake.

PREPARATION OF IBRITUMOMAB TIUXETAN

Ibritumomab tiuxetan is supplied in two separate kits that contain all the nonradioactive components necessary to prepare a single dose of ^{111}In ibritumomab tiuxetan or ^{90}Y ibritumomab tiuxetan. Rituximab and ^{111}In chloride are ordered separately from the ibritumomab tiuxetan kits, and ^{90}Y chloride sterile solution is supplied by a commercial provider when the ^{90}Y ibritumomab tiuxetan kit is ordered.

The ^{111}In and ^{90}Y ibritumomab tiuxetan kits each contain 4 vials:

Vial 1–Ibritumomab tiuxetan 3.2 mg in 2 mL of 0.9% sodium chloride solution.

Vial 2–Sodium acetate trihydrate 13.6 mg in 2 mL of water for injection (50 mmol/L).

Vial 3–Formulation buffer containing human albumin 750 mg, sodium chloride 76 mg, sodium phosphate dibasic heptahydrate 21 mg, pentetic acid 4 mg, potassium phosphate monobasic 2 mg, and potassium chloride 2 mg in 10 mL of water for injection (pH 7.1).

Vial 4–Empty sterile reaction vial.

Several materials that are not provided in the kits are also required for preparing the doses of ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan. These include ^{111}In chloride sterile solution (for ^{111}In ibritumomab tiuxetan), ^{90}Y chloride sterile solution (for ^{90}Y ibritumomab tiuxetan), and three sterile 1-mL syringes, one sterile 3-mL syringe, two sterile 10-mL syringes with 18- to 20-gauge needles, instant thin-layer chromatography silica gel strips, 0.9% sodium chloride solution for the chromatography solvent, developing chamber for chromatography, suitable radioactivity-counting apparatus, low-protein-binding 0.22-μm filters, and vial and syringe shields (for both ^{111}In and ^{90}Y ibritumomab tiuxetan).

Detailed directions for labeling ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan are provided in the ibritumomab tiuxetan prescribing information, and are briefly described below. The radiolabeling of ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan is performed at local commercial radiopharmacies, and the ^{111}In- or ^{90}Y-labeled ibritumomab tiuxetan is delivered to the clinic for on-site dose preparation and administration.[13]

Labeling of ^{111}In Ibritumomab Tiuxetan

Before the labeling reaction is initiated, the components of the kit are allowed to reach room temperature and the quantity of each component necessary for the labeling reaction is determined. The ^{111}In ibritumomab tiuxetan labeling reaction must contain 5.5 mCi of ^{111}In chloride (available commercially), sodium acetate 50 mmol/L (1.2 times the volume of the 5.5 mCi of ^{111}In chloride), and 1.0 mL of ibritumomab tiuxetan (1.6 mg/mL). After the addition of each component to the reaction vial (in the order of sodium acetate, ^{111}In, and ibritumomab tiuxetan) the reaction mixture is mixed by gentle inversion or rolling. The labeling reaction is allowed to proceed at room temperature

for exactly 30 minutes, followed immediately by the addition of formulation buffer to bring the final volume of the preparation to 10 mL.[2] The volume required for a dose of ^{111}In ibritumomab tiuxetan 5 mCi is then withdrawn from the reaction vial with a 10-mL syringe fitted with an 18- to 20-gauge needle, and the syringe and its contents are assayed in a dose calibrator. The syringe should contain the exact dose to be administered to the patient and should be clearly marked with the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration. ^{111}In ibritumomab tiuxetan is stored at 2 to 8°C until use, and should be administered within 12 hours after radiolabeling.[2]

Labeling of ^{90}Y Ibritumomab Tiuxetan

The labeling procedure for ^{90}Y ibritumomab tiuxetan is similar to that for ^{111}In ibritumomab tiuxetan, but significant differences do exist. The ^{90}Y ibritumomab tiuxetan labeling reaction must contain 40 mCi of ^{90}Y chloride (shipped direct from a commercial supplier when the ^{90}Y ibritumomab tiuxetan kit is ordered), sodium acetate 50 mmol/L (1.2 times the volume of the 40 mCi of ^{90}Y chloride), and 1.3 mL of ibritumomab tiuxetan (1.2 mg/mL). After the addition of each component to the reaction vial (in the order of sodium acetate, ^{90}Y, and ibritumomab tiuxetan) the reaction mixture is mixed by gentle inversion or rolling. The labeling reaction is allowed to proceed at room temperature for exactly 5 minutes, and formulation buffer is immediately added to the reaction vial to bring the final volume of the preparation to 10 mL.[2] The volume required for a dose of ^{90}Y ibritumomab tiuxetan 0.4 mCi/kg (in patients with a platelet count $\geq 150 \times 10^9$/L) or 0.3 mCi/kg (in patients with a platelet count of 100×10^9/L to 149×10^9/L) is then withdrawn from the reaction vial with a 10-mL syringe fitted with an 18- to 20-gauge needle, and the syringe and its contents are assayed in a dose calibrator. The syringe should contain the prescribed dose (within 10% of the actual prescribed dose; maximum of 32 mCi) and should be clearly marked with the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration. ^{90}Y ibritumomab tiuxetan is stored at 2 to 8°C until use, and should be administered within 8 hours after radiolabeling.[2]

Quality Control of ^{111}In Ibritumomab Tiuxetan and ^{90}Y Ibritumomab Tiuxetan

The quality control and safety measures for radiolabeled antibodies for clinical use are stringent. It is necessary to determine the radioactivity in millicuries per milliliter, the identity of the antibody and radioisotope, the retention of antibody activity, physical integrity, absence of pyrogens, sterility, and radiochemical purity (percentage of free radionuclide) of the radioimmunoconjugate.[7]

The radiochemical purity of ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan is determined by instant thin-layer chromatography with silica gel strips. Indium 111 ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan can be released if the radiochemical purity test is at least 95%.[1,2]

CALIBRATION OF DOSE CALIBRATOR

The patient's doses of ^{111}In ibritumomab tiuxetan and ^{90}Y ibritumomab tiuxetan should be measured immediately before their administration by using a suitable calibration system. The dose calibrator must be operated according to the manufacturer's instructions for measuring ^{111}In or ^{90}Y. Because dose calibrators are designed to assay gamma emissions and ^{90}Y is a pure beta emitter, accurately assaying ^{90}Y requires correcting the calibration setting for ^{90}Y for different geometries. Instructions for ^{90}Y calibration are provided in Fig 3. Additionally, Geiger-Müller survey counters can be calibrated to accurately detect ^{90}Y low-energy bremsstrahlung.[13] If the dose of ^{90}Y ibritumomab tiuxetan is supplied by the radiopharmacy as a unit dosage, only a single dose calibrator dial setting is required for accurate dose calibrator measurement for all ^{90}Y ibritumomab tiuxetan activity prescriptions, with no correction required for different volumes.[8]

RADIATION SAFETY ISSUES

Shielding Requirements

Because the ibritumomab tiuxetan regimen uses ^{111}In and ^{90}Y, the radiolabeled compounds must be safe for patients and personnel involved in labeling, handling, and transporting these agents. Radiation exposure to healthcare workers and the patient's family members from ^{90}Y is low.[1,9] The use of vial, syringe, and transport shields is mandatory to reduce radiation exposure. The use of acrylic

A

1. Set "background activity" to zero.
2. Set "other button" dial to manufacturer's suggested setting for ^{90}Y (048) with "manual setting" dial.
3. Draw 40 mCi ^{90}Y with 1-mL TB syringe.
4. Change needle on TB syringe.
5. Assay 1-mL syringe starting at 048 setting (starting dial setting for Capintec).
6. Change manual dial setting until 4.0 mCi is displayed, multiply by 10.
7. Transfer 40 mCi to glass reaction vial and qS to 10.0 mL total volume.
8. To determine actual activity added to reaction vial, assay residual activity left in 1-mL syringe and subtract from 40 mCi.
9. Using 10-mL syringe, remove and assay consecutive 1-mL aliquots from reaction vial and assay until entire volume of ^{90}Y is in 10-mL syringe.
10. Change manual dial setting at each aliquot to equal calculated activity contained in table shown in 3B.
11. Record dial setting at each volume- aliquot in 3B.

Use dial settings from table to plot graph for slope as shown in 3C.

B

Volume (mL)	Calculated activity concentration (mCi/mL)	Calculated total activity (mCi)	Calculated total activity (mCi)
1	3.91	3.91	56
2	3.91	7.82	55
3	3.91	11.73	55
4	3.91	15.64	53
5	3.91	19.55	48
6	3.91	23.46	48
7	3.91	27.37	47
8	3.91	31.28	47
9	3.91	35.19	48

C

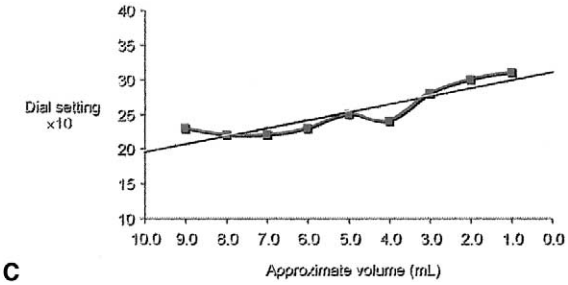

Fig 3. Calibrating the dose of ^{90}Y ibritumomab tiuxetan. (A) Instructions for ^{90}Y calibration, (B) typical calibration of 10-mL syringe containing 40 mCi of ^{90}Y, (C) typical calibration plot for a syringe containing a 40-mCi source of ^{90}Y.

shields or composite (either acrylic/lead or aluminum/lead) shields is essential to reduce bremsstrahlung production. Use of acrylic or composite vial shields and syringe shields reduced the radiation levels from 3.66 Gy/hour to 1 to 2 mGy/hour (from a 41.9-mCi ^{90}Y ibritumomab tiuxetan preparation), and from 12.87 Gy/hour to 2 to 3 mGy/hour (from a 10-mL syringe containing 31.0 mCi ^{90}Y ibritumomab tiuxetan).[10] Lead shielding alone should not be used to shield ^{90}Y ibritumomab tiuxetan, because of increased production of bremsstrahlung, which are x-rays emitted when beta particles suffer rapid acceleration. Bremsstrahlung production, using lead shielding alone, is approximately 6%, while using either acrylic or aluminum shielding reduces bremsstrahlung production to less than 1%. Once bremsstrahlung is produced, lead shielding is very effective.

Patient Radiation Safety

Yttrium 90 ibritumomab tiuxetan is routinely and safety administered as an outpatient procedure. The specific bremsstrahlung constant (a newly devised constant analogous to the specific gamma constant) for ^{90}Y in soft tissue in a 70-kg patient is 1.41×10^{-4} C/kg-cm^2/MBq-hour (5.64×10^{-3} R-cm^2/mCi-h).[11] This means that the administered dose of ^{90}Y ibritumomab tiuxetan would have to exceed several thousand millicuries to exceed Nuclear Regulatory Commission outpatient exposure limits, which is based on a total effective dose equivalent at 1 m of 0.5 cSv. Because the administered dose of ^{90}Y ibritumomab tiuxetan is usually between 21 and 30 mCi, and is never more than 32 mCi, Nuclear Regulatory Commission requirements for outpatient therapy are uniformly met without additional safety measures.[1]

Moreover, the radiation exposure in the first week after treatment to persons who have contact with a patient who has been treated with ^{90}Y ibritumomab tiuxetan has been found to be similar to background radiation.[9] Patients treated with ^{90}Y ibritumomab tiuxetan are released immediately after treatment, and only the standard universal precautions to avoid contact with body fluids are required.[1] The release instructions include cleaning up any spilled urine and disposing of any body

fluid–contaminated material (flushing it down the toilet or placing it in a plastic bag in the household trash) for the first 3 days after the treatment. Patients should also wash their hands thoroughly after using the toilet (for 3 days) and use condoms during intercourse for the first week after treatment.[1]

The use of the ibritumomab tiuxetan regimen is regulated by strict safety and quality guidelines. Ibritumomab tiuxetan is generally radiolabeled at local commercial radiopharmacies and is delivered to the clinic for on-site dose preparation and administration. Ibritumomab tiuxetan is provided as a single-dose kit, and the radiolabeled product is released for patient administration if its radiochemical purity is at least 95%.

Treatment with ^{90}Y ibritumomab tiuxetan requires an understanding of the materials and procedures that are used with radionuclides. These include using appropriate shielding during labeling, transport, handling, and administration, and following the standard universal precautions to avoid contact with body fluids after treatment with the agent. Nuclear medicine physicians play a key role in the administration of the ibritumomab tiuxetan regimen, especially in interpreting the gamma camera images to assess the biodistribution of the radiolabeled antibody.

REFERENCES

1. Wagner HN Jr, Wiseman GA, Marcus CS, et al: Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-labeled anti-CD20 monoclonal antibody. J Nucl Med 43:267-272, 2002

2. Zevalin (ibritumomab tiuxetan) prescribing information. San Diego, CA, IDEC Pharmaceuticals Corporation, 2002

3. Knox SJ, Goris ML, Trisler K, et al: Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. Clin Cancer Res 2:457-470, 1996

4. Wiseman GA, White CA, Stabin M, et al: Phase I/II ^{90}Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. Eur J Nucl Med 27:766-777, 2000

5. Wiseman GA, White CA, Sparks RB, et al: Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit Rev Oncol Hematol 39:181-194, 2001

6. Wiseman GA, Leigh B, Erwin WD, et al: Radiation dosimetry results for Zevalin radioimmunotherapy of rituximab-refractory non-Hodgkin lymphoma. Cancer 94(suppl 4): 1349-1357, 2002

7. Colcher D: Centralized radiolabeling of antibodies for radioimmunotherapy. J Nucl Med 39:11S-13S, 1998 (suppl 8)

8. Siegel JA, Zimmerman BE, Kodimer K, et al: A single dose calibrator dial setting accurately measures ^{90}Y ibritumomab tiuxetan activity. J Nucl Med 44:317P, 2003 (suppl 1137)

9. Wiseman G, Leigh B, Witzig T, et al: Radiation exposure is very low to the family members of patients treated with yttrium-90 Zevalin anti-CD20 monoclonal antibody therapy for lymphoma. Eur J Nucl Med 28:1198, 2001 (abstr)

10. Zimmer AM, Carey AM, Spies SM: Effectiveness of specific vial and syringe shields in reducing radiation exposure from Y-90 Zevalin. J Nucl Med 43:45P, 2002

11. Zanzonico PB, Binkert BL, Goldsmith SJ: Bremsstrahlung radiation exposure from pure beta-ray emitters. J Nucl Med 40:1024-1028, 1999