Administration Guidelines for Radioimmunotherapy of Non-Hodgkin's Lymphoma with ^{90}Y-Labeled Anti-CD20 Monoclonal Antibody

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^{90}Y-ibritumomab tiuxetan is a novel radioimmunotherapeutic agent recently approved for the treatment of relapsed or refractory low-grade, follicular, or CD20+ transformed non-Hodgkin's lymphoma (NHL). ^{90}Y-ibritumomab tiuxetan consists of a murine monoclonal antibody covalently attached to a metal chelator, which stably chelates ^{111}In for imaging and ^{90}Y for therapy. Both health care workers and patients receiving this therapy need to become familiar with how it differs from conventional chemotherapy and what, if any, safety precautions are necessary. Because ^{90}Y is a pure β-emitter, the requisite safety precautions are not overly burdensome for health care workers or for patients and their families. ^{90}Y-ibritumomab tiuxetan is dosed on the basis of the patient's body weight and baseline platelet count; dosimetry is not required for determining the therapeutic dose in patients meeting eligibility criteria similar to those used in clinical trials, such as <25% lymphomatous involvement of the bone marrow. ^{111}In- and ^{90}Y-ibritumomab tiuxetan are labeled at commercial radiopharmacies and delivered for on-site dose preparation and administration. Plastic and acrylic materials are appropriate for shielding during dose preparation and administration; primary lead shielding should be avoided because of the potential exposure risk from bremsstrahlung. Because there are no penetrating γ-emissions associated with the therapy, ^{90}Y-ibritumomab tiuxetan is routinely administered on an outpatient basis. Furthermore, the risk of radiation exposure to patients' family members has been shown to be in the range of background radiation, even without restrictions on contact. There is therefore no need to determine activity limits or dose rate limits before patients who have been treated with ^{90}Y radioimmunotherapy are released, as is necessary with patients who have been treated with radiopharmaceuticals that contain ^{131}I. Standard universal precautions for handling body fluids are recommended for health care workers and patients and their family members after ^{90}Y-ibritumomab tiuxetan administration. In summary, ^{90}Y-ibritumomab tiuxetan introduces ^{90}Y into clinical practice and expands the role nuclear medicine plays in the care of patients with cancer. Understanding the unique properties of this novel radioimmunoconjugate will facilitate its safe and effective use.

Key Words: radioimmunotherapy; non-Hodgkin's lymphoma; ^{90}Y-ibritumomab tiuxetan; anti-CD20 monoclonal antibodies; guidelines

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Anti-CD20 monoclonal antibodies labeled with ^{90}Y are novel radioimmunotherapeutic agents that are being investigated for the treatment of non-Hodgkin's lymphoma (NHL) and other hematologic malignancies. One such agent, ^{90}Y-ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals Corp., San Diego, CA), has been extensively investigated in relapsed or refractory low-grade, follicular, or CD20+ transformed NHL and has recently received U.S. Food and Drug Administration approval for commercialization. This agent consists of ibritumomab, the parent murine monoclonal antibody from which the widely used rituximab (Rituxan; IDEC Pharmaceuticals) was developed, and tiuxetan, which stably chelates ^{111}In for imaging and ^{90}Y for therapy. The safety and efficacy of ^{90}Y-ibritumomab tiuxetan in the treatment of NHL have been described in detail elsewhere. Briefly, using International Workshop response criteria for NHL, ^{90}Y-ibritumomab tiuxetan has produced response rates of 74%–83% in patients with relapsed or refractory low-grade, follicular, or CD20+ transformed NHL, including an impressive 83% response rate in a clinical trial conducted on patients for whom prior rituximab therapy had failed (1–4). Nuclear medicine professionals will be important members of the multidisciplinary teams

that are necessary to administer this agent. In this review, we recommend administration guidelines for ^{90}Y radioimmunotherapy.

Radionuclide therapy involves administering radioactive materials, often β-emitters, to deliver therapeutic doses of radiation to specific targets within the patient. An underlying premise in this review is that all physicians, nurses, technologists, and other health care workers who are involved before, during, and after the use of ^{90}Y radioimmunotherapy must be familiar with the safety measures it entails. Patients should also understand how this treatment differs from conventional chemotherapy and what safety measures are necessary to prevent radiation exposure to others. It is incumbent on nuclear medicine physicians and other health care workers to explain these new treatments and their safety precautions to their patients so that they can be treated in the safest manner possible. The radiation safety requirements with ^{90}Y, a pure β-emitter, are not overly cumbersome for either health care providers or patients.

RADIOIMMUNOTHERAPY WITH ^{90}Y

Physical Characteristics of ^{90}Y

^{90}Y is a pure β-emitter with a half-life of 64 h (2.7 d) that decays to ^{90}Zr. It has high β-energy and an effective pathlength of 5.3 mm, meaning that 90% of its energy is absorbed within a sphere with a 5.3-mm radius (5). This pathlength corresponds to 100–200 cell diameters, giving ^{90}Y a broad crossfire effect when it is conjugated to a monoclonal antibody such as ibritumomab (Table 1) (6,7).

TABLE 1
Features of ^{90}Y-Ibritumomab Tiuxetan Regimen for Non-Hodgkin's Lymphoma

Category	Feature
Antibody	IgG1 κ murine monoclonal antibody
Stability of immunoconjugate	Stable urea-type bond
Antibody used before therapeutic dose to enhance biodistribution	Rituximab (chimeric)
Effective blood half-life	Mean, 27 h (range, 14–44 h)
Urinary excretion	7.3% ± 3.2% over 7 d
Dosimetry	Not necessary for approved indication: ^{111}In-ibritumomab tiuxetan used as surrogate in imaging performed to confirm expected biodistribution as additional safety measure
Administration	Outpatient
Treatment duration	8 d
Development of human antimouse or human antichimeric antibodies	1%–2% of patients

Features are from Wiseman et al. (6) and Zelenetz (7).

This crossfire effect is postulated to increase tumor killing beyond that of nonradiolabeled antibodies, by irradiating tumor cells that are not bound to the antibody. This effect may be particularly beneficial in patients with bulky tumors or tumors that are poorly vascularized.

Dosimetry and Dosing

The therapeutic index of a radionuclide is the ratio of the radiation absorbed dose delivered to cancerous cells and the dose delivered to normal tissues. Dosimetry was performed in the clinical trials of ^{90}Y-ibritumomab tiuxetan to determine its therapeutic index and ensure that the radiation exposure to healthy organs and the red marrow was well within acceptable limits (8).

Dosimetry was initially an important component of therapy with ^{90}Y-ibritumomab tiuxetan in patients with low-grade NHL. The researchers sought to determine whether it was necessary or helpful to measure the organ-specific accumulation of a radiotherapeutic surrogate in each patient before treatment with ^{90}Y-ibritumomab tiuxetan. A tracer dose of ibritumomab labeled with ^{111}In, which emits γ-radiation, was used as an imaging agent to predict the distribution within the body of the subsequent therapeutic dose of ^{90}Y-ibritumomab tiuxetan. Preclinical studies had shown that the biodistribution of ^{90}Y-ibritumomab tiuxetan, assessed by direct determination of the presence of ^{90}Y, is in fact predicted by the biodistribution of the ^{111}In-labeled antibody (9).

Wiseman et al. (10) have evaluated the estimated dose to solid organs and the marrow after the administration of a tracer dose of ^{111}In-ibritumomab tiuxetan in a phase 1–2 clinical trial. Patients with histologically confirmed relapsed or refractory low-grade, intermediate-grade, or mantle cell NHL in whom chemotherapy had failed and in whom there was no more than 25% involvement of the bone marrow space (as determined by bone biopsy) were eligible for the trial. Quantitative gamma camera imaging, serial blood sampling, and MIRDOSE3 software (Radiation Internal Dose Information Center, Oak Ridge, TN) were used to estimate the radiation absorbed doses before treatment with ^{90}Y-ibritumomab tiuxetan. The radiation absorbed doses to normal organ and the marrow were within the specified upper limits of 20 Gy for solid organs and 3 Gy for red marrow in all 56 patients in the study. The median estimated radiation absorbed dose to tumor was 17 Gy (range, 5.8–67 Gy). The tumor–to–normal organ (i.e., the normal organ with the highest radiation absorbed dose) ratio was 7:1. Because of the acceptable radiation absorbed doses to normal solid organs and the marrow, it was possible to give the therapeutic ^{90}Y-ibritumomab tiuxetan dose in all patients. Furthermore, the estimated radiation absorbed dose to the red marrow did not correlate with hematotoxicity manifested as transient thrombocytopenia, neutropenia, or anemia. These findings indicate that, although the primary toxicity of therapy with ^{90}Y-ibritumomab tiuxetan is hematologic, such toxicity in this population of heavily pretreated
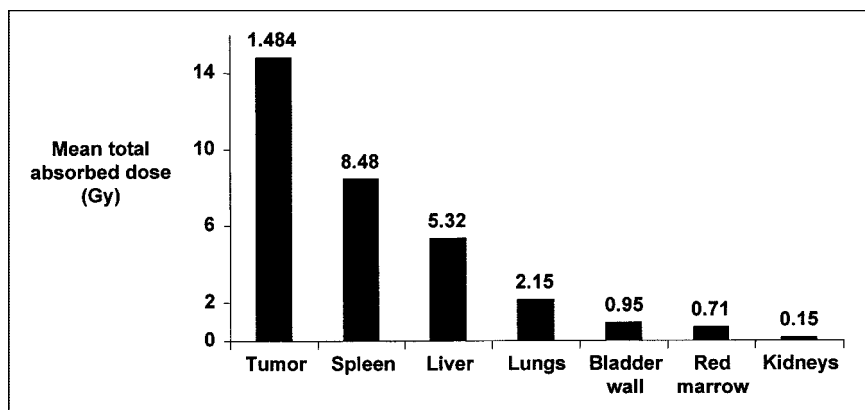
FIGURE 1. Mean radiation absorbed doses to tumor and organs for patients treated with ^{90}Y-ibritumomab tiuxetan ($n = 72$) in a multicenter phase 3 randomized trial (11).

patients with NHL could be predicted not by dosimetry but by the patients' bone marrow reserves.

Additional dosimetry results in 72 patients who were treated with ^{90}Y-ibritumomab tiuxetan in a phase 3 clinical trial confirmed the initial results in the phase 1–2 study (Fig. 1) (11). Further analyses of these data found no significant correlations between the grade of hematologic toxicity and pharmacokinetic or dosimetric parameters, including whole-blood half-life, whole-blood residence time, red marrow radiation dose (blood- and image-derived), and total body dose (Table 2) (11).

On the basis of the dosimetry results and the results in dosing based on patient body weight and platelet count, investigators have concluded that ^{90}Y-ibritumomab tiuxetan can be safely used in doses based on patient body weight

TABLE 2

Lack of Correlation Between Hematologic Toxicity Grade and Pharmacokinetic and Dosimetric Measures in Phase 3 Trial of ^{90}Y-Ibritumomab Tiuxetan ($n = 72$)

Measure	Grade of hematologic toxicity (nadir)			
	0–2	3	4	P
Blood half-life (h)				
Neutropenia	27	30	27	0.08
Thrombocytopenia	27	28	29	0.38
Blood residence time (h)				
Neutropenia	25	30	27	0.43
Thrombocytopenia	26	27	23	0.95
Blood-derived RM dose (Gy)				
Neutropenia	0.66	0.82	0.70	0.22
Thrombocytopenia	0.69	0.71	0.59	0.80
Image-derived RM dose (Gy)				
Neutropenia	1.02	1.15	1.16	0.64
Thrombocytopenia	1.01	1.10	1.32	0.26
Total body dose (cGy)				
Neutropenia	0.59	0.61	0.22	0.34
Thrombocytopenia	0.58	0.61	0.57	0.13

RM = red marrow.
Data are from Wiseman et al. (11).

and pretreatment platelet counts (14.8 MBq/kg [0.4 mCi/kg] in patients with platelet counts of 150×10^9/L or higher, and 11.1 MBq/kg [0.3 mCi/kg] in patients with counts of 100×10^9/L to 149×10^9/L). Dosimetry was not necessary in the cohort of patients in the clinical trials who met the criteria for pretreatment platelet count and percentage of marrow involvement with lymphoma ($<25\%$ as determined by bone marrow biopsy), and clinical trials without dosimetry in such patients are ongoing. Dosimetry should be performed, however, when ^{90}Y-ibritumomab tiuxetan is used as an investigational treatment in indications (e.g., in the myeloablative setting) different from the one defined in the registration trials in patients with low-grade NHL. Imaging with ^{111}In-ibritumomab tiuxetan is performed to confirm the expected biodistribution as an additional safety measure before administering the therapeutic dose of ^{90}Y-ibritumomab tiuxetan.

It should also be noted that pharmacokinetic studies have shown that almost the entire radioactivity in the therapeutic dose of ^{90}Y-ibritumomab tiuxetan is retained within the body. Urinary excretion is the primary clearance mechanism, and it accounts for the elimination of only $7.3\% \pm 3.2\%$ of the administered dose over 7 d (12).

Radioimmunoconjugate Preparation and Administration

Radiolabeling to produce ^{90}Y-ibritumomab tiuxetan begins with 1,480 MBq (40 mCi) ^{90}Y. A typical patient dose range is 777–1,110 MBq (21–30 mCi), with a maximum administered activity of 1,184 MBq (32 mCi). Ibritumomab tiuxetan is provided as a solution containing 3.2 mg of the immunoconjugate (the linker-chelator tiuxetan covalently attached to the murine antibody ibritumomab) in 2 mL of saline solution. Only 1.3 mL of this solution is required to incorporate the 1,480-MBq (40 mCi) dose of ^{90}Y, resulting in a relatively small final murine antibody dose for the patient.

Because of the relatively short physical half-life of ^{90}Y, centralized radiolabeling before drug shipment is neither practical nor cost-effective (13). The radiolabeling is performed by regional commercial radiopharmacies and the

In- and ^{90}Y-labeled ibritumomab tiuxetan is delivered for on-site dose preparation and administration.

Materials with a low atomic number, such as plastic or acrylics, make ideal shields for preparing the drug. The β-particles are completely absorbed in approximately 1 cm of these materials. In addition, bremsstrahlung production is proportional to the atomic number (or the effective atomic number for compounds), which is low for these materials (14,15). For comparison, the effective Z of polyethylene is 5.9; of acrylic, 7.5; and of water, 7.9. In the case of ^{90}Y, the percentage of the total β-energy that is converted to bremsstrahlung when it passes through a material with a Z of 7.9 is only 0.6%. Geiger–Müller survey counters are extremely efficient for detecting these low-energy photons but could give erroneously high readings unless they have been calibrated for ^{90}Y bremsstrahlung. Syringe shields made of materials such as acrylic are preferred over conventional shields made with lead or leaded glass for use during radiolabeling and preparation. If lead is used, the higher-energy bremsstrahlung produced will necessitate thicker shielding than is commonly used.

Before ^{90}Y-ibritumomab tiuxetan is released from the nuclear pharmacy, it must be tested for radiochemical purity, to assess the percentage of ^{90}Y that has been chelated by the antibody–tiuxetan complex. A commercial kit for instant thin-layer chromatography can be used. The test is performed in triplicate and the results are averaged. The radioimmunoconjugate can be released for patient administration if its radiochemical purity is ≥95%.

When the drug is administered, it should also be shielded as described above. In addition to the 1 cm of plastic surrounding the syringe, lead (or more plastic) can be used for shielding the low-energy bremsstrahlung.

^{90}Y-ibritumomab tiuxetan is administered as a slow intravenous push over approximately 10 min. The drug should not be given as a rapid intravenous bolus. As shown in Table 1, therapy with ^{90}Y-ibritumomab tiuxetan is preceded by a dose of rituximab, which is administered to enhance the biodistribution of the subsequent radiolabeled antibody by blocking readily accessible CD20 sites in the peripheral blood and preventing indiscriminate uptake of the radiolabeled antibody in the reticuloendothelial system (7). As such, rituximab is given at a dose of 250 mg/m² by slow intravenous infusion. Ideally, ^{90}Y-ibritumomab tiuxetan should be administered within 4 h of completion of the rituximab dose (16).

The most common nonhematologic adverse events reported during clinical trials of ^{90}Y-ibritumomab tiuxetan included, but were not limited to, asthenia, nausea, infection, chills, fever, and abdominal pain. Because of the potential for anaphylactic and other hypersensitivity reactions related to the administration of proteins to patients, medications for the treatment of such reactions, such as epinephrine, antihistamines, and corticosteroids, should be readily available during the administration of both rituximab and ^{90}Y-ibritumomab tiuxetan.

Precautions After ^{90}Y Administration

^{90}Y-ibritumomab tiuxetan can be routinely administered on an outpatient basis. Treatment with ^{90}Y-labeled antibodies results in the emission of β-radiation and low-level bremsstrahlung radiation, but there is no emission of penetrating γ-radiation, as there is with radiopharmaceuticals that contain ^{131}I, for example. Because no penetrating γ-waves are produced during treatment with ^{90}Y, there is minimal risk of radiation exposure to health care workers or to patients' family members and others with whom they have contact. Patients can be released immediately after treatment, in accordance with the guidelines in Nuclear Regulatory Commission (NRC) Regulatory Guide 8.39, corresponding to Title 10 Code of Federal Regulations, parts 20 and 35 (17,18). Because of the minimal risk of exposure to other persons, there is no need to determine activity limits or dose rate limits before patients who have been treated with ^{90}Y radioimmunotherapy are released, as is necessary with patients who have been treated with radiopharmaceuticals that contain ^{131}I.

The radiation exposure to persons with whom a patient treated with ^{90}Y radioimmunotherapy has contact can be calculated. The specific bremsstrahlung constant for ^{90}Y in soft tissue in a 70-kg patient is 1.52 μGy · cm²/MBq · h (19). The NRC guidelines require inpatient stays for patients from whom radiation exposure to others is likely to exceed 5 mSv (500 mrem). Assuming some absorption of the bremsstrahlung by the patient, an inpatient stay for a patient treated with ^{90}Y-ibritumomab tiuxetan would be required only if activities > 4,180 GBq (113,000 mCi) were administered. Even with radiation absorption by the patient's body disregarded, the administered dose would have to be at least 1,425 GBq (38,500 mCi) for the outpatient exposure limit of 5 mSv (500 mrem) to be exceeded. Because the typical patient dose of ^{90}Y-ibritumomab tiuxetan is at least a thousandfold less than this (777–1,110 MBq [21–30 mCi]), the NRC requirements for outpatient treatment will always be met.

Furthermore, in a study to quantify the radiation risks to family members with unrestricted contact with patients who had been treated with ^{90}Y-ibritumomab tiuxetan, it was determined that radiation exposure in the first week after treatment is very low, in the range of background radiation (20). The patients in this study were not isolated from their family members, nor was any type of patient shielding used. The only recommendations to the family were to avoid contamination from body fluids (saliva, blood, urine, stool). The family member with closest contact to the patient wore a DoseGUARD Plus personal electronic dosimeter (AEA Technology QSA, Inc., Burlington, MA) for the first 7 d after treatment with ^{90}Y-ibritumomab tiuxetan. The median deep dose equivalent radiation exposure was a total accumulation of 0.035 mSv over the 7-d period (range, 0.014–0.079 mSv), which is within the range of what might be expected from normal background radiation. The standard

triad of precautions against radiation exposure—minimizing the duration of exposure, maximizing distance from the source, and using shielding—are therefore not necessary with patients who have been treated with ^{90}Y radioimmunotherapy. Standard universal precautions to avoid contact with body fluids are all that are required.

Another consideration in radiation safety precautions for patients treated with ^{90}Y-ibritumomab tiuxetan is the pharmacokinetic profile. The median effective half-life of ^{90}Y-ibritumomab tiuxetan in the blood in clinical trials was 27 h (range, 14–44 h) (9). As was noted above, urinary excretion is the main route of elimination, as determined by the correlation of urinary-excretion and whole-body-retention data (12). Urinary excretion has been reported as 7.3% ± 3.2% over 7 d (12). Assuming a urinary excretion of 7.3% over a week and a maximum dose of 1,184 MBq (32 mCi), the total urinary excretion in that period would be 85 MBq (2.3 mCi). The activity per urination would be in kilobecquerels (microcuries), making this an unlikely source of exposure. Even if the radioactive compound were swallowed (e.g., in food that had been contaminated by contaminated hands), it would be transported through the gastrointestinal tract and not be absorbed (21). Ordinary amounts of blood, such as through menstruation, a severe laceration, or hemorrhoids, will not contain appreciable radioactivity. The recommended release instructions for patients who have been treated with ^{90}Y-ibritumomab tiuxetan are given in Table 3.

Some patients may be treated with ^{90}Y-ibritumomab tiuxetan as inpatients, not because of any radiation risk to others, but because it is medically required. Medical personnel handling blood or urine routinely wear gloves that would absorb the small amount of radiation that might be present and take other measures to avoid contact with these body fluids. In addition, the bags, vials, and tubes that are normally used to contain these fluids in the hospital would also absorb any radiation that might be present, making contamination of personnel highly unlikely. No additional special precautions beyond the standard universal precautions already in place are therefore necessary for hospital caregivers of inpatients treated with ^{90}Y-ibritumomab tiuxetan.

TABLE 3
Recommended Patient Release Instructions After Treatment with ^{90}Y-Ibritumomab Tiuxetan

Interval after treatment	Recommended instruction
3 d	Clean up spilled urine and dispose of any body fluid–contaminated material to prevent its being handled (e.g., flush it down toilet or place it in plastic bag in household trash) Wash hands thoroughly after using toilet
1 wk	Use condoms for sexual relations

CONCLUSION

^{90}Y radioimmunotherapy combines the targeting benefits of a monoclonal antibody with the efficacy of radiation in the treatment of NHL, an exquisitely radiosensitive hematologic malignancy. Advances in radioimmunotherapy are increasing the role that nuclear medicine professionals play in the treatment of patients with cancer. ^{90}Y-ibritumomab tiuxetan introduces ^{90}Y into clinical medicine, and understanding this radionuclide and how it can safely be handled and used is necessary. Because ^{90}Y is a pure β-emitter, radiation safety precautions for caregivers and patients after treatment are minimal.

Because of the low risk of radiation exposure to other persons from patients who have been treated with ^{90}Y radioimmunotherapy, this treatment can be safely administered on an outpatient basis, with minimal or no disruption to patients' daily routines. Dosimetry calculations have been found to be unnecessary for determining the dose of ^{90}Y-ibritumomab tiuxetan in patients with low-grade NHL; body weight and platelet count are all that is required in patients who meet the criteria of <25% bone marrow involvement (as measured by bone biopsy). Patients with low-grade NHL who meet the criteria established in the registration trials of ^{90}Y-ibritumomab tiuxetan can safely receive a standard weight-based dose. Dosimetry should, however, be performed for investigational use of this agent in other indications. Because only patients with NHL involvement of <25% of intratrabecular bone marrow space have been treated in clinical trials, the role of dosimetry in patients with greater bone marrow involvement is not known. This new approach to the treatment of relapsed or refractory low-grade, follicular, or CD20+ transformed NHL presents an opportunity for a greater multidisciplinary approach to patient care, and it gives patients a new option that compares favorably with the currently available chemotherapeutic options.

REFERENCES

1. Knox SJ, Goris ML, Trisler K, et al. Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. *Clin Cancer Res.* 1996;2:457–470.
2. Witzig TE, White CA, Flinn IW, et al. Zevalin™ radioimmunotherapy of rituximab-refractory follicular non-Hodgkin's lymphoma [abstract]. *Blood.* 2000;96:507a.
3. Witzig TE, Gordon LI, Wiseman GA, et al. Reduced dose Zevalin is safe and effective in patients with relapsed or refractory, low grade, follicular or CD20+ transformed B cell non-Hodgkin's lymphoma (L/F/T NHL) and mild thrombocytopenia [abstract]. *Blood.* 2000;96:728a.
4. Witzig TE, White CA, Gordon LI, et al. Final results of a randomized controlled study of the Zevalin™ radioimmunotherapy regimen versus a standard course of rituximab immunotherapy for B-cell NHL [abstract]. *Blood.* 2000;96:831a.
5. Kuzel TM, Rosen ST. Radioimmunotherapy of lymphomas and leukemias. In: Henkin RE, Boles MA, Dillehay GL, et al, eds. *Nuclear Medicine.* Vol 1. St. Louis, MO: Mosby-Year Book Inc.; 1996:594–600.
6. Wiseman GA, White CA, Witzig TE, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with Zevalin, a ^{90}Y-labeled anti-CD20 monoclonal antibody. *Clin Cancer Res.* 1999;5(suppl):3281s–3286s.
7. Zelenetz AD. Radioimmunotherapy for lymphoma. *Curr Opin Oncol.* 1999;11:375–380.
8. Wiseman GA, Leigh BR, Gordon LI, et al. Zevalin radioimmunotherapy (RIT)

for B-cell non-Hodgkin's lymphoma (NHL): biodistribution and dosimetry results [abstract]. *Proc Am Soc Clin Oncol.* 2000;19:10a.

9. Chinn PC, Leonard JE, Rosenberg J, Hanna N, Anderson DR. Preclinical evaluation of ^{90}Y-labeled anti-CD20 monoclonal antibody for treatment of non-Hodgkin's lymphoma. *Int J Oncol.* 1999;15:1017–1025.

10. 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.* 2000;27:766–777.

11. 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.* 2001;39:181–194.

12. Wiseman GA, Leigh BR, Erwin WD, et al. Urinary clearance of ^{90}Y activity following Zevalin™ radioimmunotherapy of B-cell non-Hodgkin's lymphoma [abstract]. *J Nucl Med.* 2001;42(suppl):268P.

13. Colcher D. Centralized radiolabeling of antibodies for radioimmunotherapy. *J Nucl Med.* 1998;39(suppl):11S–13S.

14. Sorenson JA, Phelps ME. *Physics in Nuclear Medicine.* New York, NY: Grune and Stratton; 1980:138–139.

15. Shleien B, Slaback LA Jr, Brikky BK, eds. *Handbook of Health Physics and Radiological Health.* 3rd ed. Baltimore, MD: Williams and Wilkins; 1998.

16. Wiseman G, Gordon L, Leigh B, et al. Safety and efficacy of the Zevalin radioimmunotherapy regimen are not diminished by extending the time interval between rituximab infusion and Zevalin injection [abstract]. *Blood.* 2000;96:251b.

17. Nuclear Regulatory Commission. *Criteria for the Release of Individuals Administered Radioactive Material.* Washington, DC: U.S. Nuclear Regulatory Commission; 1997. Title 10 CFR parts 20 and 35:62 FR 4120.

18. Nuclear Regulatory Commission. *Release of Patients Administered Radioactive Materials.* Washington, DC: U.S. Nuclear Regulatory Commission; 1997. Regulatory Guide 8.39.

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

20. Wiseman GA, Leigh B, Witzig T, Gansen D, White C. Radiation exposure is very low to the family members of patients treated with yttrium-90 Zevalin™ anti-CD20 monoclonal antibody therapy for lymphoma [abstract]. *Eur J Nucl Med.* 2001;28:1198.

21. Marcus CS, Lengemann FW. Use of radioyttrium to study food movement in the small intestine of the rat. *J Nutr.* 1962;76:179–182.