
Essential Role of Nuclear Medicine Technology in Tositumomab and ^{131}I -Tositumomab Therapeutic Regimen for Non-Hodgkin's Lymphoma*

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Nuclear medicine technology has traditionally focused on diagnostic imaging, with therapeutics left mostly to other medical disciplines. However, after many years in development, radioimmunotherapy (RIT) has finally become a clinical reality in many nuclear medicine departments. The nuclear medicine technologist is a key player in the successful implementation of RIT. Delivery of a therapeutic regimen of tositumomab and ^{131}I -tositumomab provides a model for the technologist's roles and responsibilities in the developing field of RIT. This article examines the clinical rationale, logistic requirements, and imaging and dosimetry procedures required by this treatment regimen. Upon completion of this article, the reader should be able to describe the target patient population and identify the roles and responsibilities of various members of the treatment team. The reader will also gain an understanding of the treatment process, including drug administration, imaging, and therapeutic dose calculations.

Key Words: non-Hodgkin's lymphoma; radioimmunotherapy
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Nuclear medicine technology has long been focused on diagnostic imaging. With few exceptions (e.g., thyroid ablation with ^{131}I -NaI), therapeutics have been left to other medical disciplines. A new era for nuclear medicine is at hand: radioimmunotherapy (RIT). In RIT, the anticancer properties of specific immunoglobulins, commonly referred to as antibodies, are combined with the cell-killing potential of radionuclides. Antibodies are believed to act against cancer cells through the processes of antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, and apoptosis induction. With the addition of a radionuclide to the antibody, there is an additional cell-killing effect resulting from ionizing radiation. To maximize the therapeutic

effect, the radionuclide selected is generally a β -emitter, such as ^{131}I or ^{90}Y , based on the higher absorbed fraction of energy deposited in tissue by β -emitters versus pure γ -emitters. The nuclear medicine technologist is a key player in the successful implementation of RIT. The delivery of tositumomab and ^{131}I -tositumomab (the BEXXAR therapeutic regimen; GlaxoSmithKline; approved by the U.S. Food and Drug Administration in June 2003) provides a model for the technologist's roles and responsibilities in the developing field of RIT.

BEXXAR is an RIT regimen containing an unlabeled anti-CD20 IgG2a murine monoclonal antibody, tositumomab, and a radiolabeled antibody, ^{131}I -tositumomab. This therapeutic regimen is indicated for the treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed non-Hodgkin's lymphoma (NHL), including patients with rituximab-refractory NHL.

That being said, why is a new treatment for NHL needed? NHL is the fifth leading and second-fastest-growing cause of cancer-related deaths in the United States. The American Cancer Society reported that in 2005, the total number of patients with newly diagnosed NHL was expected to reach 56,390, and 19,200 patients would be expected to succumb to this disease (1). Patients with low-grade NHL often have multiple relapses and eventually become refractory to therapy. With each subsequent treatment, patients are less likely to respond, and the duration of the response is shortened (Fig. 1) (2). As in many other cancers, radiation and chemotherapy are mainstays of the initial treatment for NHL. RIT is part of a relatively new category of therapy called biologic therapy and has yielded some impressive clinical results that were summarized in a recent review (3).

Kaminski et al. (4) recently reported a complete response for 75% of 76 patients who received the tositumomab and ^{131}I -tositumomab therapeutic regimen as the initial treatment for follicular lymphoma. Forty (70%) of these patients remained in remission for 4.3-7.7 y.

Here we describe the logistics of the tositumomab and ^{131}I -tositumomab therapeutic regimen and the vital role that nuclear medicine can play in its effective implementation.

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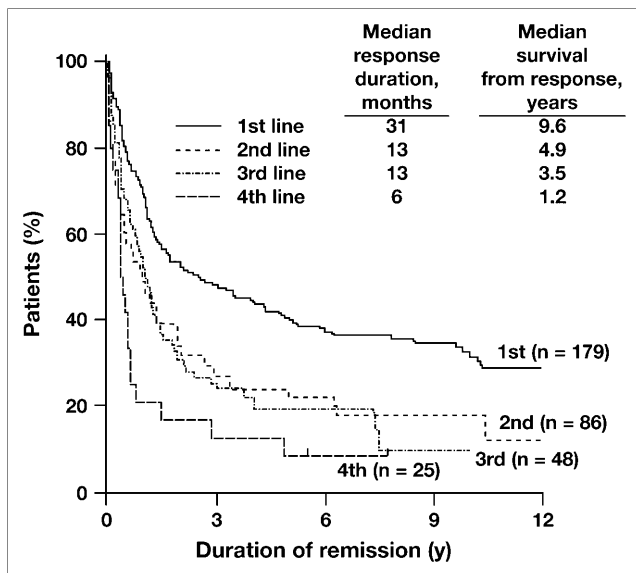


FIGURE 1. Duration of response. (Reprinted with permission of (2).)

METHODOLOGIES

Medical Professionals

A number of medical professionals may become involved with the tositumomab and ^{131}I -tositumomab therapeutic regimen, and each is important for successful treatment. Among these individuals may be a hematologist or oncologist, oncology nurse, nuclear medicine physician, radiation oncologist, nuclear medicine technologist, nuclear pharmacist, hospital pharmacist, radiation safety officer, and medical physicist. The U.S. Food and Drug Administration mandates that these medical professionals receive training by GlaxoSmithKline on-site trainers. Table 1 lists some of the main functions required in the successful implementation of the tositumomab and ^{131}I -tositumomab therapeutic regimen.

Throughout the process, a site coordinator is responsible for communication among all team members in an effort to provide a cohesive treatment regimen for the patient. Specifically, the site coordinator plans the treatment schedule, submits order documents to the nuclear pharmacist, and coordinates patient scheduling with all participating team members. The site coordinator may be any one of the health professionals listed above or another staff member capable of effectively managing simultaneous tasks. Given the nature of the tositumomab and ^{131}I -tositumomab therapeutic regimen, the nuclear medicine technologist is often the logical choice for site coordinator. Figure 2 summarizes the main steps in the tositumomab and ^{131}I -tositumomab regimen.

Training

Training of site personnel is a critical component of successful implementation of the tositumomab and ^{131}I -tositumomab therapeutic regimen. As part of the training

process, each treatment site must demonstrate competency in patient dose administration and calculations. Competency is documented by the completion of the imaging and dose determination steps after 3 successful attempts in 6 possible attempts. Information is collected on manufacturer-provided dosimetry worksheets, which are faxed to the Bexxar Service Center (BSC), a single point of contact for all aspects of the tositumomab and ^{131}I -tositumomab therapeutic regimen. A template (Excel; Microsoft Corp.) has been developed to aid in performing the dosimetry calculations. Once a site has successfully completed this certification process, it is no longer necessary to submit the dosimetry worksheets to the BSC. However, the BSC is always willing to provide assistance even after the certification process is complete.

Premedications

Thyroid-blocking agents are commonly used in nuclear medicine. For the tositumomab and ^{131}I -tositumomab therapeutic regimen, one of the following regimens must be started at least 24 h before the dosimetric dose and continued for 2 wk after the therapeutic dose: a saturated solution of potassium iodide (4 drops orally 3 times per day), Lugol's solution (20 drops orally 3 times per day), or potassium iodide tablets (130 mg orally once per day).

In addition to thyroid protection, patients should receive premedication with 650 mg of acetaminophen and 50 mg of diphenhydramine 30–60 min before the administration of each of the unlabeled (“cold”) tositumomab doses to reduce the incidence of possible infusion-related events (e.g., fever, rigor or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea). If any of these events do occur, reduction of the infusion to 50% of the initial rate (450 mg of unlabeled tositumomab over 60 min) is recommended. It may be necessary to interrupt the infusion if the symptoms are severe. Many times, the infusion of unlabeled tositumomab is conducted in the oncology infusion area, so a nuclear medicine technologist may actually administer only the ^{131}I -tositumomab—a brief 20-min infusion followed by a flush.

Dosage and Dose Administration

The tositumomab and ^{131}I -tositumomab therapeutic regimen is administered intravenously in 2 steps: the dosimetric step and the therapeutic step. Each step consists of 2 separate components: the unlabeled, or cold, infusion and the radiolabeled, or hot, infusion. The prescribed dosage for each step is shown in Table 2. The therapeutic dose of ^{131}I -tositumomab is given in centigrays, the unit of absorbed dose. Dosimetry, the process of relating the prescribed absorbed dose to a specific megabecquerel value, is described in detail in the next section.

Both the dosimetric and the therapeutic infusions involve 2 nearly identical components: cold-antibody (tositumomab) infusion and hot-antibody (^{131}I -tositumomab) infusion. The only difference between the two is the activity of the hot antibody infused (diagnostic versus therapeutic activity levels).

TABLE 1

Roles of Health Care Team Members During Administration of Tositumomab and ¹³¹I-Tositumomab Therapeutic Regimen

Role	Responsible Party								
	Hematologist or oncologist	Radiation oncologist	Nuclear medicine physician	Nuclear medicine technologist	Radiation safety officer	Oncology nurse	Nuclear pharmacist	Hospital pharmacist	Medical physicist
Review radioactive material license					X		X		X
Identify and refer patients	X								
Prescribe therapy		X	X						
Educate patients	X	X	X	X	X	X	X	X	X
Place order with BSC							X		
Report platelet counts for dose calculation	X								
Prescribe thyroid block	X	X	X						
Prescribe premedications	X								
Receive packaging and prepare doses							X		
Administer cold infusion	X	X		X		X			
Monitor patient	X	X	X	X		X			
Administer hot infusion		X	X	X					
Report adverse events	X	X	X	X	X	X	X	X	X
Perform quality control procedures and acquire images				X					
Calculate estimated dose (after second scan)		X	X	X					X
Calculate therapeutic dose		X	X	X					X
Send completed dosimetry worksheets to nuclear pharmacy				X					X
Report final dose calculation to BSC							X		X
Determine when patient can be released				X	X				X
Instruct patient regarding radiation safety precautions		X	X	X	X				X
Perform patient follow-up	X								

Dose shielding, prevention of spills and contamination, and minimization of exposure to personnel are important considerations for each step.

After the administration of premedications, 450 mg of unlabeled tositumomab antibody are first delivered to the patient over 1 h. The antibody is prepared in a volume of

50 mL and delivered to the patient via an infusion pump. This step often takes place in the oncology infusion area.

Immediately after the cold infusion, the patient is administered the radiolabeled, or hot, ¹³¹I-tositumomab antibody. This step is often performed in the nuclear medicine department. The hot antibody is prepared and delivered to

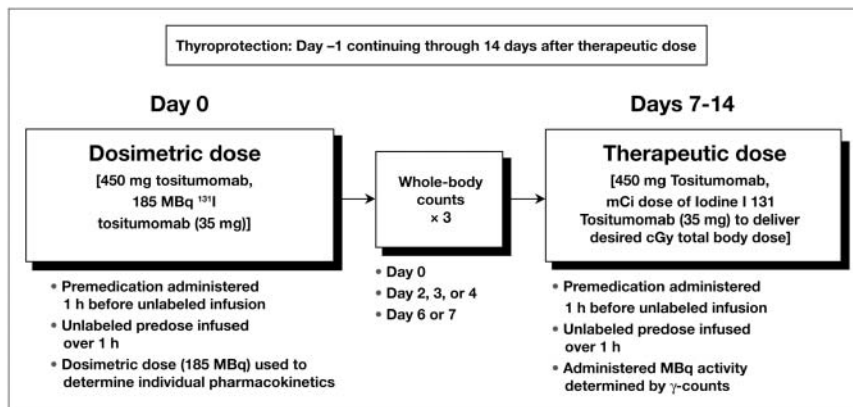


FIGURE 2. Steps in tositumomab and ¹³¹I-tositumomab therapeutic regimen.

TABLE 2
 Prescribed Dosage for Each Step of Tositumomab and ¹³¹I-Tositumomab Therapeutic Regimen

Dose	Tositumomab	¹³¹ I Tositumomab
Dosimetric	450 mg	185 MBq (5 mCi)
Therapeutic	450 mg	75 cGy (platelet count > 150,000/mm ³) 65 cGy (platelet count > 100,000/mm ³ and < 150,000/mm ³) Regimen is not indicated for patients with platelet count < 100,000/mm ³

the site of the infusion in a 30-mL total volume in a 60-mL syringe. The syringe is loaded into a syringe pump, and the total volume is delivered over 20 min; this step is followed by a thorough flush of the tubing with 0.9% saline. It is strongly recommended that personnel responsible for setting up and administering the hot infusion thoroughly familiarize themselves with the procedure by making several practice runs with nonradioactive syringes, tubing, syringe pump, and shielding before patient arrival to minimize unanticipated problems that may arise. To minimize the risk of contamination, exposed work surfaces, such as countertops, infusion chairs, and floors, should be draped with absorbent pads. Throughout the infusion process, every effort should be made to adhere to the concept of “as low as reasonably achievable” by minimizing the amount of time spent near the source, maximizing the distance from the source, and using shielding whenever possible to reduce the dose to infusion personnel. Finally, after the infusion is complete, the area should be surveyed for contamination with a survey meter.

Imaging and Dosimetry

Nuclear medicine technologists are focused primarily on patient imaging. However, what role does imaging have in therapy? The ultimate goal in drug therapy is to provide the most effective dose to optimize benefit and minimize toxicity. The tositumomab and ¹³¹I-tositumomab therapeutic regimen seeks to approach this goal by evaluating individual patient drug distribution and elimination over time. These aspects of drug behavior are termed pharmacokinetics. With conventional pharmaceutical agents, the best that clinicians can do in this regard is to measure the time course for the drug (or metabolites) in the blood. With radiolabeled agents, however, a much more accurate estimate of patient-specific pharmacokinetics is possible. Because ¹³¹I is both a γ -emitter and a β -emitter, it is possible to obtain whole-body γ -counts from imaging of the patient after a relatively small (dosimetric) dose (184 MBq [5 mCi]) of ¹³¹I-tositumomab to estimate the total-body residence time (TBRT). This determination allows consideration of the factors shown to be influential in the pharmacokinetics of the tositumomab and ¹³¹I-tositumomab therapeutic reg-

imen, such as extent of disease, bone marrow involvement, spleen size, and renal function (5). In addition to enabling an estimation of TBRT, imaging also provides an opportunity for the nuclear medicine physician to evaluate biodistribution with the same isotope, unlike other regimens that use a γ -emitting surrogate to predict biodistribution. However, unlike most nuclear medicine imaging procedures, this process is intended to evaluate gross biodistribution only, not provide detailed diagnostic information. The expected biodistribution after a dosimetric dose of ¹³¹I-tositumomab is illustrated by whole-body scans of a patient with the typical pattern for NHL (Fig. 3), whereas biodistribution may be different in patients with solid tumors or other cancer types, such as a retroperitoneal tumor with thyroid uptake (Fig. 4) or cutaneous lymphoma (Fig. 5), respectively. In addition to visual inspection of the images, biodistribution also may be assessed by evaluating the TBRT (day 6 or 7). For the tositumomab and ¹³¹I-tositumomab therapeutic regimen, the expected biodistribution is defined as a TBRT of between 50 and 150 h.

As imaging takes place at 3 different times (day 0 within 1 h of dosing; day 2, 3, or 4; and day 6 or 7) after the dosimetric administration of ¹³¹I-tositumomab, it is important to maintain constant imaging parameters. For example, it is important that images are acquired by use of the same camera with the same head-to-table distance, scan length (in cm), scan speed, collimator, field of view, region of interest, and energy window. Simply put, the imaging parameters must be exactly the same for each imaging session. This requirement also applies to obtaining background and standard counts.

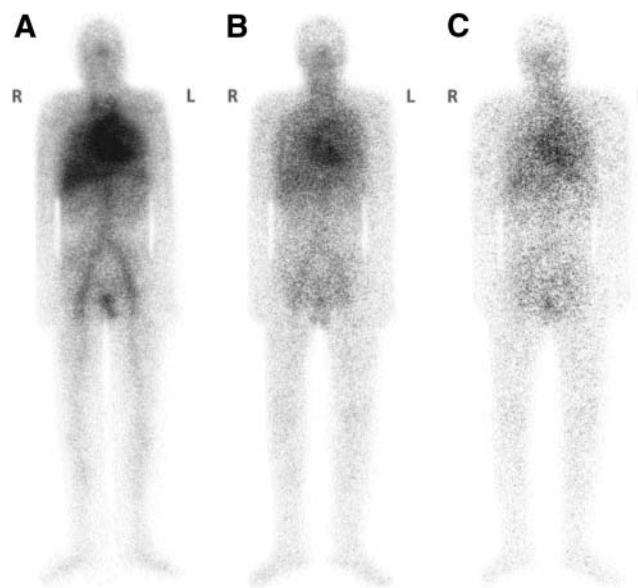


FIGURE 3. Expected biodistribution showing blood-pool activity in heart and major vessels on first scan (A) decreasing in intensity on second scan (B) and third scan (C) for patient with NHL. Moderate uptake in liver and spleen on first scan progressively diminishes in intensity on second and third scans. Views are anterior.

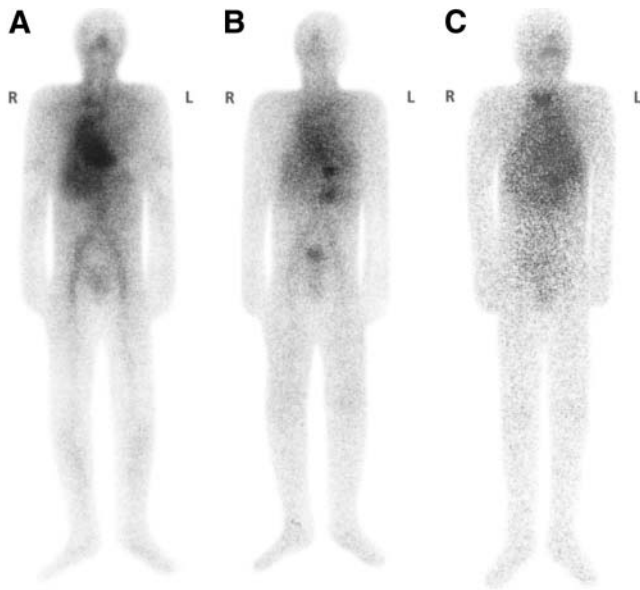


FIGURE 4. Expected biodistribution showing blood-pool activity in heart and major vessels on first scan (A) decreasing in intensity on second scan (B) and third scan (C) for patient with retroperitoneal adenopathy. Moderate uptake in liver and spleen on first scan progressively diminishes in intensity on second and third scans. Tumor uptake is seen as 2 focal areas of moderate uptake in upper to middle abdomen, best seen on second scan, corresponding to retroperitoneal adenopathy seen on CT scan. “Butterfly”-shaped uptake seen in neck on third scan represents thyroid uptake. Views are anterior.

Determining the TBRT is done by simply drawing a “best-fit” straight line between the whole-body counts obtained on day 0 and those obtained on subsequent days on a semilogarithmic graph of percentage injected activity on the y-axis and time from the dosimetric dose on the x-axis. In the first estimate of TBRT after the second imaging time, one simply connects the dots. This first estimation is done only to determine whether the radiopharmacy may require 2 vials of ^{131}I -tositumomab instead of 1 to prepare the patient-specific dose. The need for 2 vials becomes important if the estimated therapeutic dose to the patient may exceed 3,700 MBq (100 mCi). The final estimation of TBRT at 3 imaging times requires the best-fit straight line between the second and third time points (Fig. 6). The TBRT can be used in the calculation of the required megabecquerel amount of ^{131}I -tositumomab: ^{131}I activity (MBq) = [activity hours (mCi·h)/residence time (h)] × [desired total body dose/75 cGy].

The value for activity hours (describing the amount of activity in the body and the time that it is there, on the basis of patient sex and effective mass or weight) is obtained from a table provided in the training. The last element of the equation describes the fact that the recommended total body dose (cGy) for the tositumomab and ^{131}I -tositumomab therapeutic regimen is 75 cGy for patients with a platelet count of more than 150,000/mm³. For cases of mild thrombocytopenia (platelet count of 100,000/mm³–150,000/mm³), the recommended total body dose is

attenuated to 65 cGy. The tositumomab and ^{131}I -tositumomab therapeutic regimen is not indicated for patients with a platelet count of less than 100,000/mm³. Although it is important to understand the basic concepts for calculating the patient-specific dose, the template mentioned previously will automatically perform all calculations and curve fitting.

Residual Activity

The determination of residual activity is another critical element required to obtain an accurate measure of the injected activity, thereby ensuring that the patient received the full prescribed dose of ^{131}I -tositumomab. The process is simply to gather all infusion-related equipment, including the syringe used for the radioactive dose, and analyze the equipment with a dose calibrator as soon as practicable after the infusion is completed. The residual activity is subtracted from the measured activity in the syringe before administration and results in the net administered activity. Measuring and recording residual activity is required in both the dosimetric and the therapeutic steps and is critically important.

Patient Release Methodology

Although it will be the responsibility of the radiation safety officer to determine when a patient can be released after a therapeutic dose of tositumomab and ^{131}I -tositumomab, the nuclear medicine technologist may be called upon to assist, and it is useful to review the principles governing that determination. Patient release is not dependent on the

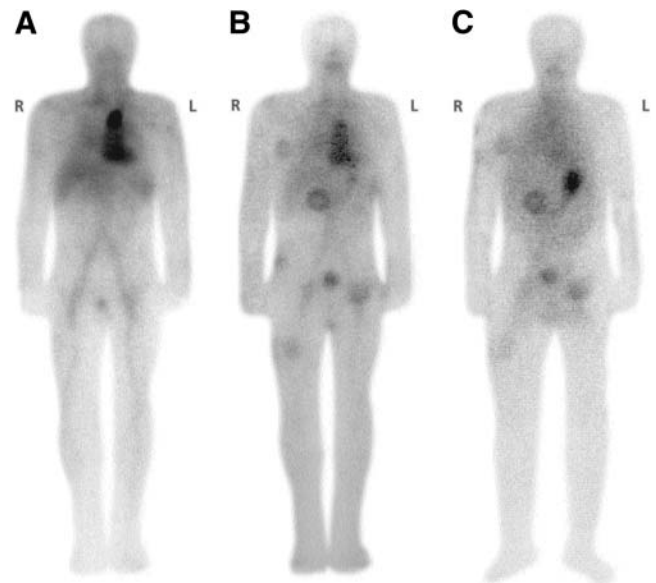


FIGURE 5. Expected biodistribution for patient with lymphomatous nodules. Multiple areas of various sizes, configurations, and intensities are seen in right upper chest wall laterally, epigastric region just to right of midline, lower right abdomen laterally, bilateral inguinal regions, and proximal right thigh on second scan (B). Some of these areas persist on third scan (C). These areas represent cutaneous lymphomatous nodules. Focal intense uptake is first seen in left upper abdomen on third scan, most likely representing activity in fundus of stomach. Views are anterior.

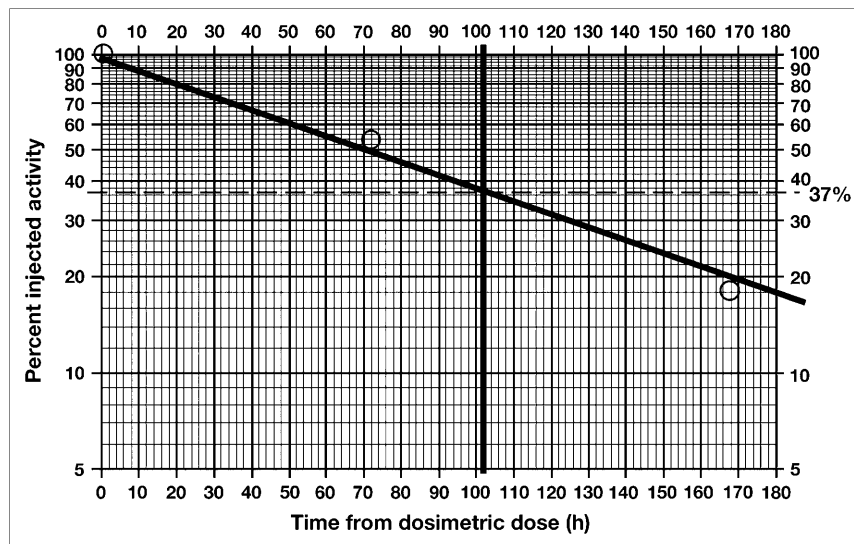


FIGURE 6. Example of TBRT after dosimetric administration of tositumomab and ^{131}I -tositumomab. Best-fit line for 2 assessment time points and 100% initial time point are shown.

dosimetric dose of ^{131}I -tositumomab, as the 185-MBq (5-mCi) dosimetric dose is below the 1,221-MBq (33-mCi) limit specified by 10CFR35.75 for immediate outpatient release. The therapeutic dose of ^{131}I -tositumomab, however, usually will exceed the 1,221-MBq (33-mCi) limit. Nuclear Regulatory Commission agreements in most states do allow the release of patients receiving this dose according to 10CFR35.75, which notes that a licensee may release a patient administered greater than 1,221 MBq (33 mCi) of a radiopharmaceutical or a permanent radioactive implant, provided that the total effective dose equivalent (TEDE) to any other individual from exposure to the released patient is not likely to exceed 5 mSv (500 mrem). (It should be noted that some states have specific requirements for compliance, while still allowing tositumomab and ^{131}I -tositumomab therapy to be performed in an outpatient setting. The BSC can assist with state-specific information.) In order to comply with this “5-mSv rule,” 2 parameters are used: the TBRT and the dose rate at 1 m from the patient immediately after the therapeutic dose (6,7). The TBRT is determined in the dosimetric step. Therefore, the next step in determining when a patient can be released is measuring the dose rate at 1 m with a calibrated ionization chamber, or QT π . An ionization chamber is necessary because these instruments are energy independent and yield accurate dose rates regardless of the radionuclide being measured. The official equation used to determine the TEDE (mSv) to any exposed individual is $0.25 \times \text{dose rate at 1 m} \times (8.95 + 0.99\text{TBRT})$.

The value 0.25 refers to the occupancy factor, which is an estimate of the fraction of a 24-h day that a patient will spend at a distance of 1 m from another individual. Other values—for example, 0.5 or 0.125—are used if it is assumed that a greater or a lesser fraction of the day will be spent within this proximity to others. The dose rate is measured at 1 m with the calibrated ionization chamber. Training provided for the tositumomab and ^{131}I -tositumomab therapeutic regimen includes a table to assist in this calculation. In addition to determining the TEDE, an appropriate patient

release procedure requires the following additional steps: An evaluation of the patient’s living and working conditions is needed to limit radiation exposure to others. Factors that should be considered include the patient’s willingness and ability to follow patient safety guidelines, to perform self-care, and to delay returning to work; the patient’s living arrangements; the potential for exposure to others during the trip home after treatment; the procedures for notification of health care workers in the event that the patient is hospitalized or in need of medical care; and the presence of urinary incontinence. A record of the interview used to make these evaluations must be kept for 3 y.

Instructions need to be provided to the patient ready for release. Some of the instructions, which should be adhered to on a temporary basis, typically 1–2 wk, include sleeping in a separate bed (at least 1.8 m [6 ft] from anyone else), avoiding long trips (4 h or more) sitting near others, staying at least 1.8 m (6 ft) from children and pregnant women, minimizing the time spent in close contact with others, and delaying returning to work. The length of time needed to comply with any of the instructions is dependent on the TEDE as determined above. A table is provided to simplify this determination.

The template designed for determining the TBRT and the therapeutic dose calculation also contains spreadsheets to assist in determining when a patient can be released and providing instructions to the patient ready for release.

CONCLUSION

Nuclear medicine plays a major role in the successful implementation of RIT, as exemplified by the tositumomab and ^{131}I -tositumomab therapeutic regimen. This signifies a new era of involvement for nuclear medicine in patient care with respect to cancer treatment and completes the circle for nuclear medicine as a resource for both diagnostic and therapeutic interventions. Nuclear medicine professionals are

now afforded the opportunity to expand the impact of their direct patient contact to benefit patients at 2 very important stages of their interaction in the larger disease management environment. Nuclear medicine professionals should welcome these new challenges and responsibilities as further demonstration of their professionalism and commitment to the best patient care possible.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures, 2005*. Atlanta, GA: American Cancer Society; 2006.
2. Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol*. 1995;13:140–147.
3. Wahl RL. Tositumomab and ¹³¹I therapy in non-Hodgkin's lymphoma. *J Nucl Med*. 2005;46(suppl 1):128S–140S.
4. Kaminski MS, Tuck M, Estes J, et al. ¹³¹I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med*. 2005;352:441–449.
5. Kostakoglu L, Leonard JP, Coleman M, et al. Patient-specific characteristics correlate with the effective half-life of ¹³¹I-tositumomab in non-Hodgkin's lymphoma [abstract]. *J Nucl Med*. 2000;41(suppl):79P.
6. Siegel JA, Kroll S, Regan D, Kaminski MS, Wahl RL. A practical methodology for patient release after tositumomab and ¹³¹I-tositumomab therapy. *J Nucl Med*. 2002;43:354–363.
7. GlaxoSmithKline. *BEXXAR Site Training Manual*. Research Triangle Park, NC: GlaxoSmithKline; 2005.