Tositumomab and ^{131}I Therapy in Non-Hodgkin's Lymphoma

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Tositumomab and ^{131}I-tositumomab constitute a relatively new radioimmunotherapeutic regimen for patients with CD20+ follicular non-Hodgkin's lymphoma (NHL). Currently, it is approved for use in patients whose disease has relapsed after chemotherapy and is refactory to rituximab, including patients whose tumors have transformed to a higher histologic grade. This review outlines the current and evolving status of this therapeutic regimen at nonmyeloablative doses. **Methods:** Clinical data from multiple published studies and preliminary communications encompassing more than 1,000 patients were reviewed to describe the current status of tositumomab and ^{131}I-tositumomab therapy. The therapy is delivered in 2 parts, a dosimetric dose and a therapeutic dose. The therapeutic radioactivity millicurie dose is calculated on a patient-individualized ("tailored") basis. A series of 3 total-body γ-camera scans are used to determine the patient-specific pharmacokinetics (total-body residence time) of the radiolabeled antibody conjugate required to deliver the desired total-body radiation dose, typically 75 cGy. **Results:** In clinical trials, objective response rates in patients who had been extensively pretreated with chemotherapy ranged from 47% to 68%. Tositumomab and ^{131}I-tositumomab therapy also was effective in patients who had failed to respond to or who had relapsed after rituximab therapy, with a 68% overall response rate. Thirty percent of such patients achieved complete responses that were generally of several years duration. Single-center trials using tositumomab and ^{131}I-tositumomab therapy alone or after chemotherapy in previously untreated patients have shown response rates in excess of 90%, with most responses complete. Retreatment with tositumomab and ^{131}I-tositumomab and use of lower total-body radiation doses of tositumomab and ^{131}I-tositumomab to treat patients who have relapsed after stem cell transplantation have been shown feasible in limited clinical studies. Toxicity is predominately hematologic; however, human antimouse antibodies, hypothyroidism, and myelodysplastic syndrome have been reported in a small fraction of patients. **Conclusion:** Tositumomab and ^{131}I-tositumomab therapy at patient-specific, nonmyeloablative doses is safe and effective in treatment of relapsed and refractory follicular NHL. Toxicity is mainly hematologic and reversible. Tositumomab and ^{131}I-tositumomab therapy is assuming a growing role in this common malignancy.

Key Words: tositumomab and ^{131}I-tositumomab therapy; radioimmunotherapy; non-Hodgkin's lymphoma

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Non-Hodgkin's lymphoma (NHL) is expected to be newly diagnosed in 54,370 patients in the United States in 2004. It currently represents the sixth most common cause of cancer deaths and is increasing in frequency (*1*). From 85% to 90% of NHLs are of B-cell origin and express B-cell surface antigenic markers. A substantial fraction of these tumors will be of follicular histology, and these patients have a median survival of about 8–10 y. Although generally treatable, these tumors are typically incurable (*2*). These follicular tumors often respond to initial therapy but, after failing treatment, typically are less likely to respond again. If they do, the response is often shorter with each treatment (*3*). This type of lymphoma can transform to a higher histologic grade and is then extremely aggressive and even more difficult to treat. The pathologic classification of lymphomas continues to evolve, but the majority of tumors previously classified as low-grade NHL by the International Working Formulation are of follicular histology (World Health Organization/Real Classification) (*2*). Some of the early papers on tositumomab and ^{131}I-tositumomab therapy referred to low-grade rather than follicular histology.

Radioimmunotherapy (RIT) using radiolabeled anti-CD20 antibodies has been explored most extensively in follicular lymphomas and follicular lymphomas that have transformed to a higher grade. At present, two radiolabeled anti-CD20 antibodies are approved by the U.S. Food and Drug Administration for clinical use in the United States: tositumomab and ^{131}I-tositumomab (Bexxar®; Corixa/GlaxoSmithKline), and ^{90}Y-ibritumomab tiuxetan (Zevalin®; Biogen Idec, Inc.). The use of the Zevalin RIT regimen is discussed in detail elsewhere in this supplement. This review focuses on the clinical experience with the Bexxar therapeutic regimen at radiation doses designed not to require stem cell support (nonmyeloablative doses). However, a growing literature also exists on the use of tositumomab and ^{131}I-tositumomab at myeloablative doses, where considerable therapeutic activity has been demonstrated (*4*).

The rationale for ^{131}I-CD20 antibody therapy and methods for patient-specific whole-body dosimetry were previously described in detail in 1998 in a supplement to *The Journal of Nuclear Medicine* dedicated to this form of therapy (*5,6*). The tositumomab and ^{131}I-tositumomab therapeutic regimen includes 2 steps. In the dosimetric step,

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unlabeled tositumomab is infused first, followed by a dosimetric dose of ^{131}I-tositumomab. In the therapeutic step, unlabeled tositumomab is followed by a patient-specific therapeutic dose of ^{131}I-tositumomab. Tositumomab is a murine IgG2a λ-murine monoclonal antibody directed against the CD20 antigen. The choice of CD20 as an antigenic target for RIT was a reasoned one; however, a broad spectrum of possible antigenic targets are expressed on B-cells and are potential targets for RIT. Although completely tumor-specific antibodies can be generated in NHL and directed against the specific idiotypic determinants of the B-cell surface immunoglobulin, these antibodies are not easily transformed into therapeutic radiopharmaceuticals because of their inherent variability from tumor to tumor, making it nearly logistically impossible in the current regulatory environment to develop a new antibody unique for each patient. Most efforts with RIT for NHL have focused instead on targeting tumor-associated B-cell antigens that are preferentially expressed on tumors but that are not necessarily tumor specific. CD37, CD19, CD22, CD52, idiotypic antibodies, and HLA-DR have all been used as antigenic targets for RIT (*7–13*).

CD20 is an approximately 35-kd transmembrane glycoprotein. The CD20 antigen is densely expressed on the surface of nearly all B-cell lymphomas but is a pan B-cell marker and is thus expressed on normal B-cells. However, CD20 is not expressed on hematopoietic stem cells, is not rapidly internalized, and is not shed when radioantibody binds, and thus CD20 represents a potentially attractive target for RIT (Fig. 1) (*14*). In addition, binding of antibody to the CD20 antigen can result in apoptosis, which appears to be caspase independent in some experiments (*15*).

Because the CD20 antigen is expressed on normal circulating B-cells in the blood and normal spleen, these nontumor sites expressing CD20 potentially represent barriers preventing delivery of the radiolabeled antibody to tumor sites. In designing the tositumomab and ^{131}I-tositumomab therapeutic regimen, there was a concern that administration of a relatively low protein mass (typically about 15–30 mg) of radioantibody might result in the radiolabeled antibody being diverted from reaching the tumor because of binding to CD20-positive B-cells in the circulation or spleen. This challenge was dealt with by "predosing" with unlabeled

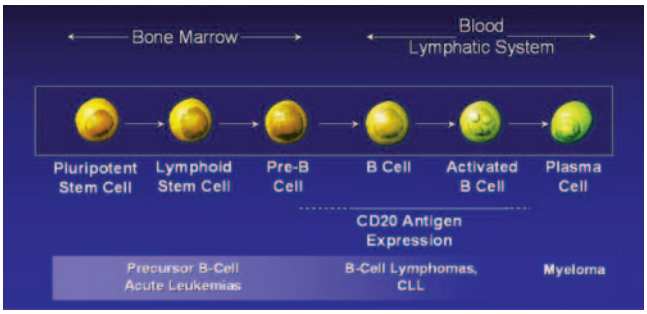

FIGURE 1. CD20 expression profile.

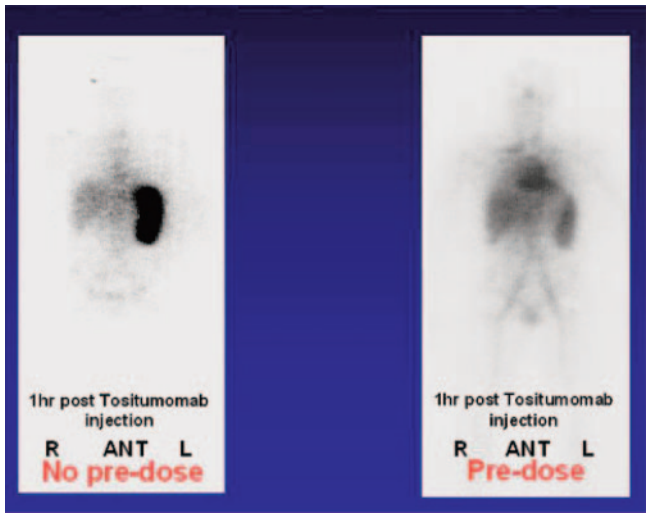

FIGURE 2. Rationale for antibody predosing. Image of hot spleen (left) (without predosing) or with cold antibody predosing (right).

CD20 antibody before administering the radiolabeled antibody for dosimetric or therapeutic purposes. The rationale for predosing was to allow the initially administered unlabeled antibody to first bind to the accessible B-cells in the blood and spleen, thus allowing the subsequently administered radioantibody to substantially bypass binding to these sites and remain bioavailable when it reached the more distant and possibly less accessible malignant B-cells in the lymphomas. We have shown that this predosing approach increases the serum radioantibody half-life and can improve tumor dosimetry when compared with the rest of the body, especially in patients with bulky tumors or large spleens (*6,16–17*). There is also evidence for antitumor activity of unlabeled murine anti-CD20 antibody (as well as for chimeric mouse–human anti-CD20 antibodies) suggesting higher doses of unlabeled antibody may contribute to more antitumor activity (*18,19*). Potential disadvantages of unlabeled antibody predosing include the possibility of diminishing tumor targeting by blocking antigen binding sites on tumors with unlabeled antibody; however, we have not observed this in our studies to date. An example of a change in biodistribution with unlabeled antibody predosing as visualized on γ-camera imaging is shown in Figure 2.

Lymphomas are radiosensitive tumors and have been shown to have a significant radiation dose–response relationship for external beam therapy (*20*). Delivering the maximum possible dose of radiation to tumors (while sparing the normal tissues of toxicity) was viewed as highly desirable in the design of the tositumomab and ^{131}I-tositumomab therapeutic regimen (*6,17*). Another expectation with the anti-CD20 antibody, which reacts with normal B-cells, was that there could be substantial variability from patient to patient in the pharmacokinetics and clearance of the radioantibody. Because it is possible to directly, noninvasively measure the γ-emitter-labeled radioantibodies, ei-

ther sequential blood measurements of radioactivity or sequential whole-body measurements of radioactivity by a probe system or γ-camera could allow for the adjustment of the therapeutic dose in millicuries for variability in the clearance of the radioantibody, so as to deliver a specified absorbed radiation dose to the marrow or blood, which are often closely related. Patients who cleared radioactivity more rapidly than average rates would be given more millicuries than the average patient, whereas those patients who cleared the radioantibody more slowly would be given fewer millicuries than the average amount, so as to deliver the same total-body radiation-absorbed dose in centigrays (Fig. 3) (*7*).

^{131}I was selected as the radiolabel for this therapeutic regimen for several reasons: (a) the γ-emission of ^{131}I allows the use of noninvasive imaging to follow the exact whole-body clearance rate, biodistribution, and dosimetry of the tracer used for therapy; (b) the chemistry and biodistribution of free ^{131}I were quite well understood as well as potential toxicities; (c) free iodine is substantially excreted through the kidneys in patients on thyroid blockade; (d) the β-particle pathlength of ^{131}I is relatively short (typically about 1 mm), suggesting that small foci of tumor could be treated more effectively and possibly more safely than with more "energetic" β-particles (with which much of the energy is deposited ineffectively beyond the tumor), yet ^{131}I was expected to be energetic enough to allow crossfire irradiation to deal with heterogenous antibody deposition in tumor; (d) no free ^{131}I would bind to bone cortex, as might be seen with any free radiometal that dissociated from the antibodies; and (e) the 8-d half-life of ^{131}I was well matched to the relatively slow biologic localization but prolonged tumor retention of the radioantibody at tumor sites and the relatively slow clearance of background normal tissue radioactivity (*6*). Other radioisotopes have been used in anti-CD20 RIT, including ^{90}Y and ^{186}Re (*21,22*).

By administering a tracer amount of ^{131}I-labeled CD20 antibody and determining the total-body clearance rate, it is possible to determine a patient-specific injected dose of RIT that should deliver a specified total-body radiation-absorbed dose in millicuries. Originally, our dosimetry approach required performance of total-body counts at up to 8 time points after the tracer dose was administered. It was relatively quickly observed that total-body clearance of radioactivity administered as ^{131}I-labeled CD20 antibody was essentially monoexponential, as has been seen with other radioantibodies (*6*). This monoexponential clearance allowed the development and implementation of a simplified

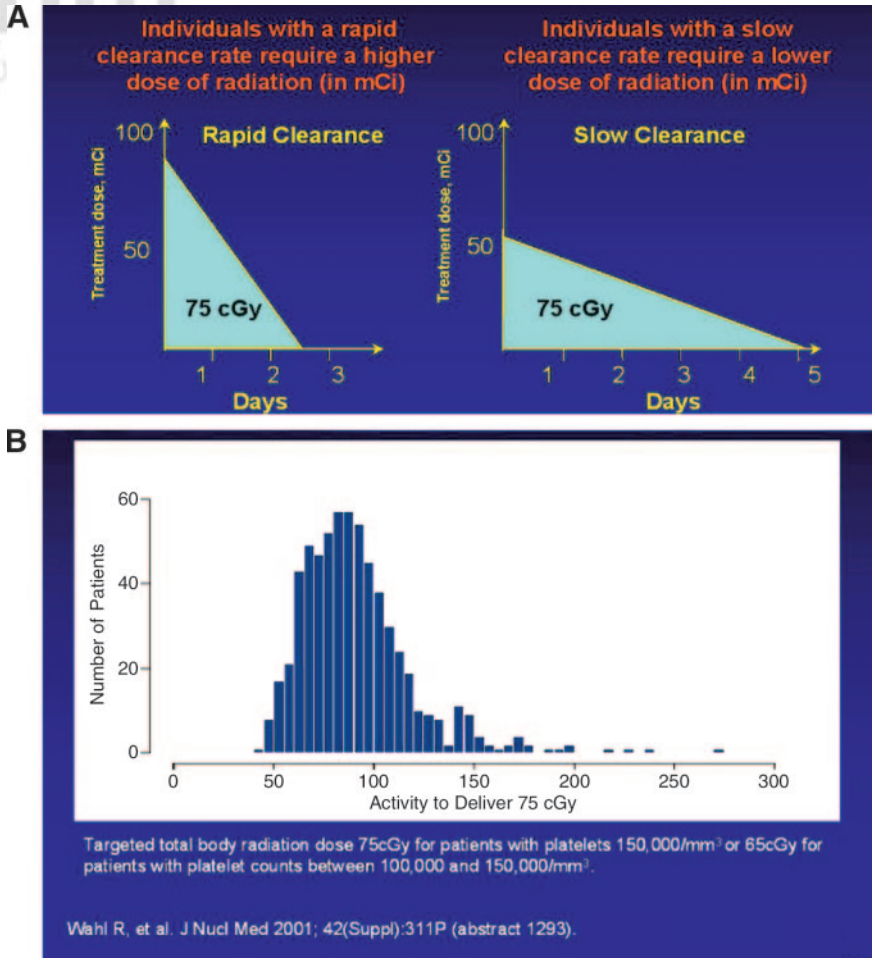

FIGURE 3. (A) Rationale for patient-specific dosimetry (fast vs. slow clearance). Comparable area under curve. (B) Actual therapeutic millicuries required to deliver specified total body radiation dose of 65 or 75 cGy (n = 634).

TABLE 1
Estimated Radiation-Absorbed Organ Doses with Tositumomab and ^{131}I-Tositumomab Therapy

Organ regions of interest	Absorbed Doses	
	Median (mGy/MBq)	Range (mGy/MBq)
Thyroid	2.71	1.4–6.2
Kidneys	1.96	1.5–2.5
Upper large intestinal wall	1.34	0.8–1.7
Lower large intestinal wall	1.30	0.8–1.6
Heart wall	1.25	0.5–1.8
Spleen	1.14	0.7–5.4
Testes	0.83	0.3–1.3
Liver	0.82	0.6–1.3
Lungs	0.79	0.5–1.1
Red marrow	0.65	0.5–1.1
Stomach wall	0.40	0.2–0.8

3-point dose estimation algorithm. This has been described in detail previously (*6*). This 3-point dosimetric approach allows for adjustment of the injected dose to yield the proper dose for each patient. The method assumes, correctly, that the total-body absorbed radiation dose is related to the marrow radiation dose (*23*). Substantial patient-to-patient variability in required doses is shown in Figure 3B (*23*). Estimated radiation-absorbed organ doses are shown in Table 1.

Unlabeled anti-CD20 antibody has been approved by the U.S. Food and Drug Administration (FDA) for several years as a treatment for NHL in the form of the chimeric mouse–human CD20 monoclonal antibody known as rituximab. In its pivotal trial in 166 patients with NHL, rituximab showed a 48% overall response rate with a 6% complete response rate (*24*). Based on this study, multiple other studies have been performed with rituximab. More recently, rituximab combined with chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), has been used extensively in the treatment of NHL (*25*). The use of rituximab has substantially altered the treatment of lymphoma, with most patients receiving rituximab quite early in the course of their disease, not uncommonly as the initial treatment combined with the CHOP regimen (R-CHOP) (*26*).

A possible limitation of unlabeled antibody therapy is that not all antibody molecules reach all areas and depths of the tumors (*27*). In general, for antibody-dependent cell killing or complement-mediated cytolysis to be effective, the antibody should reach most or all tumor cells. RIT with β-emitters offers the ability for antibody-delivered β-particle crossfire, which can deliver radiation to tumor cells that may have no or only limited amounts of radioantibody bound to them. The β-pathlength of iodine is sufficient to deal with moderate heterogeneity in intratumoral radioantibody distribution. Highly energetic β-particles can deliver more uniform doses to areas with more heterogeneous antibody biodistribution, but the very energetic β-emitters have the potential to deliver much of their energy beyond the tumor in small tumors and to deliver additional radiation dose to nearby normal tissues. These are possible limitations to treating small tumors with high-energy β-particles and could lead to increased toxicity (*28*).

The current design of the tositumomab and ^{131}I-tositumomab therapeutic regimen is shown in Figure 4 and includes both unlabeled antibody predosing and the 3 whole-body γ-camera counting procedures to calculate total-body dosimetry. Examples of whole-body images at 2 and 6 d after 5 mCi of tositumomab and ^{131}I-tositumomab are shown in Figure 5. Dosimetry for the tositumomab and ^{131}I-tositumomab regimen has shown that tumor targeting is specific and significantly higher than that for the total body, often in the range of a 10:1 ratio or higher (*6,29*). Dosimetry with SPECT has shown some relationship between radiation dose and tumor response, but it is a weak and variable relationship, suggesting radiation-absorbed dose to tumor to be but one of several factors involved in determining whether RIT of NHL will be successful in a given patient (*29,30*).

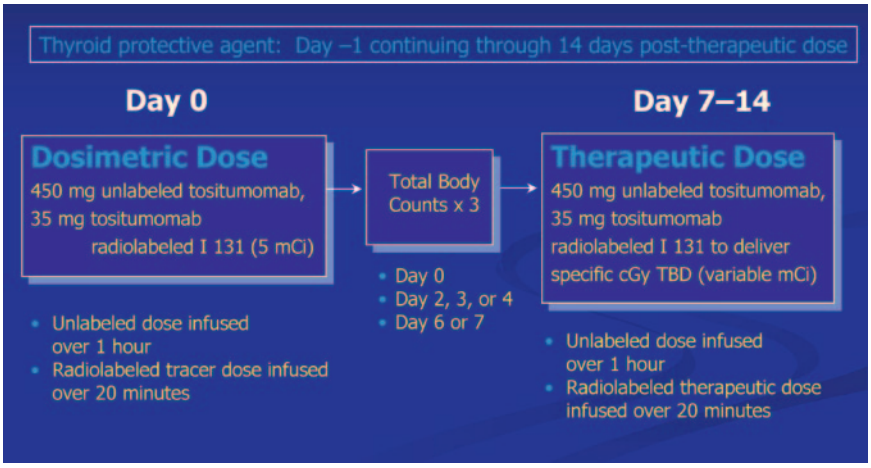

FIGURE 4. Tositumomab and ^{131}I-tositumomab therapeutic regimen.

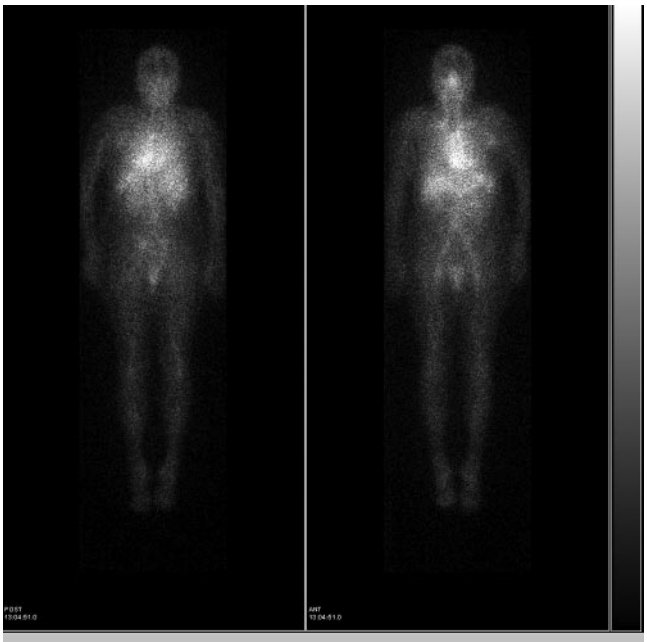

FIGURE 5. Sample whole-body dosimetric count images after tracer dose, showing localization to left axillary tumor focus. Note otherwise normal biodistribution of radiotracer after 5-mCi dose.

CLINICAL RESULTS WITH TOSITUMOMAB AND ^{131}I-TOSITUMOMAB THERAPY

Phase I Dose Escalation Trial

Initial studies of nonmyeloablative RIT were performed at the University of Michigan using patient-specific dosimetry. In the phase I trial, a radiation-absorbed dose escalation and protein-mass dose escalation were undertaken. Patients eligible for this trial had histologic diagnoses of NHL, CD20 positive tumors, had relapsed from or failed to respond to at least 1 chemotherapy regimen, had ≤25% bone marrow involvement with tumor, were not pregnant, were ≥18 y of age, had no obvious infections, had grossly normal hepatic and renal function, had platelet counts of ≥100,000, and had not undergone prior bone marrow or stem cell transplants. Subsequently, the trial was expanded to include patients who had undergone stem cell transplants. A dose escalation was performed in groups of 3 patients, with doses ranging from 25 to 85 cGy predicted total-body dose in 10-cGy increments. In these studies, the maximum tolerated total-body dose was found to be 75 cGy in patients who had not had prior marrow transplantations. Patients who had undergone prior bone marrow transplantations had a lower maximum tolerated dose, approximately 45 cGy. In both the transplanted and nontransplanted groups, moderate-to-severe reversible thrombocytopenia and granocytopenia 4–6 wk after treatment were seen at the 75- and 45-cGy levels, respectively, and were dose limiting. In this study, the protein mass predose was also escalated. Higher protein mass predoses enhanced the biodistribution of the radiolabeled antibody over lower doses, particularly in patients with bulky disease or enlarged spleens (Fig. 2). Thus an unlabeled protein predose of 450 mg was selected as the appropriate dose for subsequent phase II and III trials (*17,31*)

In this phase I trial, clinical efficacy was clearly demonstrated. Fifty-nine patients were entered on the expanded phase I study, and 53 were treated. Of the 59 entered, 42 (71%) responded, as assessed by the investigators. Twenty (34%) had complete responses. Response rates were significantly higher (83%) (35 of 42 patients) in low-grade or transformed low-grade histologies than in de novo intermediate-grade NHL (41%) (7 of 17 patients). For the responding patients, the mean progression-free survival for all patients was 12 mo and at least 20.3 mo for those in complete response. Toxicity was reversible and hematopoietic. Human antimouse antibodies (HAMA) were observed in 17% of patients, with hypothyroidism and myelodysplastic syndrome seen in 5 patients each. Of note are some very long-term survivors in this study, despite the presence of lymphomas that had been poor or nonresponders to chemotherapy.

A second clinical trial was the phase II multicenter trial of tositumomab and ^{131}I-tositumomab in chemotherapy-relapsed or -refractory low-grade lymphomas (*32*). This study was designed to evaluate the feasibility of performing patient-specific dosimetry in a multicenter fashion, as well as to establish the efficacy and safety of the therapy in a larger group of patients who had failed therapy for low-grade or transformed low-grade lymphomas. In this study, 45 of the 47 enrolled patients were treated, all using the patient-specific therapeutic dosing method. Twenty-seven (57%) patients responded. Thirty-two percent of patients achieved a complete response, including 5 patients with transformed low-grade NHL. Median duration of complete response was 19.9 mo, similar to that in the phase I study. In this study, the response rate was similar in low-grade (57%) and transformed low-grade (60%) lymphomas. Median duration of overall response was approximately 10 mo. Toxicity was mainly hematologic, with declines in platelet and neutrophil counts. Fatigue, nausea, and fever, although generally mild, were not uncommon. Only one patient in this study developed HAMA, possibly because there was only 1 dosimetric and 1 therapeutic antibody infusion in contrast to the multiple dosimetric infusions in many of the patients in the phase I study (*32*).

A subsequent multicenter "pivotal study" of tositumomab and ^{131}I-tositumomab therapy was performed in a group of 60 patients with NHL (*33*). These patients had failed as least 2 qualifying chemotherapies and had not responded or progressed within 6 mo after their last qualifying chemotherapy. Responses of these patients' tumors to tositumomab and ^{131}I-tositumomab therapy at the 75-cGy dose was compared with the response seen to the conventional therapy preceding tositumomab and ^{131}I-tositumomab. In this study, response was observed in 65% of patients, 28% of these

patients after no response to their preceding qualifying chemotherapy. The median duration of response was 6.5 mo after tositumomab and ^{131}I-tositumomab versus 3.4 mo after the last qualifying chemotherapy ($P < 0.01$). A complete response was observed in 20% of patients after tositumomab and ^{131}I-tositumomab and in only 3% after their last qualifying chemotherapy. Clearly, tositumomab and ^{131}I-tositumomab therapy was more efficacious than the last qualifying chemotherapy. Toxicity was again noted to be predominantly hematologic. Eight percent of patients developed HAMA, and only 1 patient developed an elevated thyroid-stimulating hormone (TSH) level. Myelodysplastic syndrome was observed in 4 patients on follow-up. This study supported the observation that tositumomab and ^{131}I-tositumomab therapy has substantial antitumor activity in patients who previously failed standard chemotherapy (*33*).

As discussed previously, rituximab therapy has substantially changed the practice of lymphoma treatment. Although rituximab on its own has a relatively low complete response rate (6%) and overall response rate (48%), it is an effective therapy. Thus it was important to determine whether tositumomab and ^{131}I-tositumomab therapy was effective in patients who had failed rituximab treatment. A single-arm, multicenter study was conducted at 3 sites enrolling 40 patients with low-grade, transformed low-grade, or follicular large-cell NHL whose disease had failed to respond to or progressed after rituximab therapy (*34,35*). Overall response, complete response, and time to progression were assessed by a panel unaware of previous histories. This study included patients who had on average 4 prior therapies. Approximately half of the patients had bulky disease. Eighty-eight percent of patients had not responded or had responded for less than 6 mo to the last rituximab therapy. In this group of patients, the overall response to tositumomab and ^{131}I-tositumomab therapy was 68%, with a median duration of response of 16 mo. Complete responses were seen in 33% of patients, and the median duration of complete response was longer than 25 mo (*34*). Thus the tositumomab and ^{131}I-tositumomab regimen was efficacious in patients who had failed rituximab therapy.

Because unlabeled anti-CD20 antibodies (murine and chimeric) can have antitumor activities of several types, it was also important to compare the efficacy of tositumomab and ^{131}I-tositumomab therapy with unlabeled tositumomab therapy in a cross-over study (*36,37*). The study comparing labeled (tositumomab and ^{131}I-tositumomab) versus unlabeled tositumomab included 78 patients. Patients enrolled had low-grade or transformed low-grade lymphomas and had undergone 1–5 prior chemotherapies. Similar to the previously described patients, they had ≤25% bone marrow involvement, measurable disease, and had received no prior myeloablative therapy. Patients were randomized either into the tositumomab and ^{131}I-tositumomab group or tositumomab alone at comparable protein doses. An opportunity to cross over to tositumomab and ^{131}I-tositumomab therapy was provided if tositumomab therapy failed. Forty-two patients with NHL received tositumomab and ^{131}I-tositumomab initially, and 36 received unlabeled tositumomab. The confirmed overall response rate was 55% in the tositumomab plus ^{131}I-tositumomab group, whereas this rate was only 17% in the tositumomab-only group. The confirmed complete response rate was significantly higher (33%) in the ^{131}I-tositumomab than in the tositumomab-only group (8%), supporting the added value of the radioactivity conjugated to the CD20 antibody. Progression-free survival was significantly longer in the tositumomab and ^{131}I-tositumomab group (6.3 mo) than in the tositumomab-only group (5.5 mo). Patients who failed tositumomab but were crossed over and treated with tositumoamb and ^{131}I-tositumomab had a 42% complete response rate and a 68% overall response rate. In these patients, disease-free survival was on average 12.4 mo. Thus, the ^{131}I component in ^{131}I-tositumomab is very important for therapeutic efficacy (*36,37*).

Additional supporting data regarding efficacy have been provided from a multicenter expanded access study performed in 65 institutions including both university and community sites and including 475 patients, of whom 394 were evaluable. Preliminary data suggest an overall response rate of 59%, with a median duration response of 15 mo and a 26% complete response rate. Thus, with expanded access to a much broader group of patients, efficacy remained reasonably strong (*34,38*). All of these studies used the tositumomab and ^{131}I-tositumomab therapy regimen as is shown in Figure 4. Typical whole-body images using predosing after a 5-mCi (185 MBq) dosimetric dose are shown in Figure 5.

Transformed Low-Grade Lymphoma

In the report of the expanded phase I study, 14 patients with transformed low-grade lymphoma were identified. The overall response rate in this group of patients was 79% with a 50% complete response rate (*31*). This was significantly higher than the complete response rate for newly diagnosed intermediate-grade tumors, which had a 41% overall response rate but no complete responses. Larger numbers of patients have been studied across multiple studies with transformed lymphoma. In 71 evaluable patients with transformed low-grade lymphoma who were treated with the tositumomab and ^{131}I-tositumomab therapeutic regimen in 5 trials, the overall response rate was 39% with a median duration of 20 mo. In addition, 25% of patients had complete responses with a median duration of 36.5 mo. Thus a significant fraction of patients with transformed low-grade lymphoma will respond to tositumomab and ^{131}I-tositumomab therapy, some with durable complete responses (*38*).

Newly Diagnosed Lymphoma

The use of tositumomab and ^{131}I-tositumomab in newly diagnosed lymphoma patients has been preliminarily communicated in a study of 76 patients with newly diagnosed advanced follicular lymphomas (*39,40*). In this phase II study conducted at the University of Michigan, 72 of 76

patients (95%) achieved responses and 75% achieved complete responses. The complete responses appear to be quite durable (*38–40*). HAMA appeared to be much more common in this initial therapy study than in studies in which tositumomab and ^{131}I-tositumomab therapy was used after other chemotherapies.

Other approaches to using RIT early in NHL therapy have been reported. The S9911 Southwest Oncology Group phase II trial consisted of 6 cycles of CHOP chemotherapy followed 4–8 wk later by tositumomab and ^{131}I-tositumomab therapy in 90 eligible untreated NHL patients (*41*). In this study, the overall response rate for the entire treatment regimen was 90%, including a 67% complete response rate. Of the patients who were fully evaluable, 57% achieved a complete response with the tositumomab and ^{131}I-tositumomab therapy, despite not having achieved such a response after chemotherapy alone. Two-year survival was reported at 97%. Reversible myelosuppression was seen and was more severe after the chemotherapy than after the RIT (*40*). Current FDA approval for the Bexxar tositumomab and ^{131}I-tositumomab regimen does not include use as the initial treatment of NHL.

Preliminary results have also been communicated regarding a regimen using fludarabine followed by tositumomab and ^{131}I-tositumomab therapy in the treatment of patients with newly diagnosed NHL. This treatment also achieved a high complete response rate in patients with NHL who had not previously been treated. In this study, 77% of patients achieved complete responses, and all patients achieved some response, as assessed by the investigator (*38,41*).

Retreatment

The ability to administer more than 1 dose of tositumomab and ^{131}I-tositumomab therapy has been investigated in a limited number of patients. In the initial phase I study, 16 patients who had initially responded to tositumomab and ^{131}I-tositumomab and then experienced progression were retreated with tositumomab and ^{131}I-tositumomab. Nine of 16 retreated patients responded, and 5 had complete responses (*31*). Results from a single-arm open-labeled multicenter phase II trial were recently reported, in which patients who had responded to initial tositumomab and ^{131}I-tositumomab therapy for >3 mo (either a partial or complete response) and who had adequate baseline physiologic function could be treated effectively with tositumomab and ^{131}I-tositumomab (*42*). Thirty-two patients were entered into the study, and 28 of the 32 patients received the complete therapeutic dose. Fifty-six percent of patients entered responded to the therapy, with 25% of responses complete. Complete responses were reasonably durable (average 35 mo). Several patients who had initially achieved partial responses achieved complete responses on retreatment. The frequency of grade 3 or 4 toxicity in absolute neutrophil count (ANC) was 44% and in platelets 38%. The median time to count nadir was 43 d for ANC and 34 d for platelets, similar to times observed after primary therapy. Seven percent of patients developed an elevated TSH level, and a myeloproliferative disorder was observed in 4 patients. Thus, although evaluated only to a limited extent and not part of the current FDA-approved product labeling, retreatment with the Bexxar tositumomab and ^{131}I-tositumomab regimen appears to be feasible and reasonably effective in HAMA-negative patients who have had previous tositumomab and ^{131}I-tositumomab therapy and responded.

Across the wide range of studies from the initial phase I through the single-dose, single-center initial treatment studies, the durability of responses to the tositumomab and ^{131}I-tositumomab therapy have been quite long for those patients whose tumors completely responded to the treatment. In a pooled analysis of 269 evaluable patients with low-grade or transformed low-grade lymphomas across multiple clinical studies, the median complete response duration was 3.25 y, and the median confirmed complete response duration was 5 y, with some responses much more durable (*38*).

Myeloablative Doses of ^{131}I-Tositumomab

A substantial effort has been undertaken in a research setting to use ^{131}I-tositumomab in very high doses as a part of a myeloablative conditioning regimen as either a single agent or as part of the combined chemotherapy regimen (*4,43,44*). Results in these studies have shown high response rates and fairly high durability of response. Toxicities with myeloablative tositumomab and ^{131}I-tositumomab therapy are more substantial than those with nonmyeloablative therapies but may be less than those of total body irradiation. Cardiopulmonary toxicity has been reported as dose limiting with high doses of ^{131}I-tositumomab. This area is beyond the scope of the current review, but the author is referred to several publications by Press and colleagues who have pioneered this effort (*43,44*). Of particular interest is the recent report that high-dose RIT and stem cell transplantation appears to improve survival versus conventional high-dose chemotherapy and stem cell transplantation in patients with NHL (*44*).

Toxicity

Tositumomab and ^{131}I-tositumomab therapy in nonmyeloablative doses had been used in at least 995 evaluable patients before FDA approval. Thus substantial data are available regarding the safety profile of this agent. Toxicity data in the acute setting are from a dataset of 230 patients, whereas more chronic toxicity is assessable from the group of 995 patients (which includes the 230 patients and the patients from the expanded access trial). The FDA has judged the drug to be safe and effective in the target population, and it is clear that there is a generally predictable spectrum of hematologic toxicity after tositumomab and ^{131}I-tositumomab therapy. Predictable declines in platelet counts and ANC and occasionally hematocrit are seen with this therapy. A detailed description of the hematologic tox-

TABLE 2
Hematologic Toxicity Associated with Tositumomab and ^{131}I-Tositumomab Therapy (230 Patients)

Endpoint	Values
Platelets	
Median nadir (cells/mm^3)	43,000
Per-patient incidence* platelets <50,000/mm^3	53% (n = 123)
Median† duration of platelets <50,000/mm^3	32 d
Grade 3/4 without recovery to grade 2	16 patients (7%)
Per-patient incidence‡ platelets <25,000/mm^3	21% (n = 17)
ANC	
Median nadir (cells/mm^3)	690
Per-patient incidence* ANC <1,000 cells/mm^3	63% (n = 145)
Median† duration of ANC <1,000 cells/mm^3	31 d
Grade 3/4 without recovery to grade 2	15 patients (7%)
Per-patient incidence‡ ANC <500 cells/mm^3	25% (n = 57)
Hemoglobin	
Median nadir (g/dL)	10
Per-patient incidence* <8 g/dL	29% (n = 66)
Median† duration of hemoglobin <8.0 g/dL	23 d
Grade 3/4 without recovery to grade 2	12 patients (5%)
Per-patient incidence‡ hemoglobin <6.5 g/dL	5% (n = 11)

*Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between week 5 and week 3.

†Duration of grade 3/4 of 1,000+ days (censored) was assumed for those patients with undocumented grade 3/4 and no hematologic data on or after week 3.

‡Grade 4 toxicity was assumed if patient had documented grade 3 toxicity and was missing 2 or more weeks of hematology data between week 5 and week 9.

icity of tositumomab and ^{131}I-tositumomab therapy is shown in Table 2 (*34*).

The product insert for Bexxar states that the mean nadir in platelet counts is 43,000 cells/mm^3 and that 21% of patients have platelet counts lower than 25,000 transiently. The product insert also states mean ANC nadir is 690 mm^3, with 25% of patients having platelet count nadirs <500 cells/mm^3. Hemoglobin count nadirs averaged 10 g/dL, with levels <8 g/dL in 25% of patients. Durations of count nadirs were typically 20–32 d, and nadirs occurred at 4–5 wk after treatment (*34*). These values are somewhat conservative (i.e., may be overestimates of the toxicity rates that will be observed in typical use of the drug), because they assumed that absent counts in a clinical profile (missing data) were grade 4 toxicities (see table footnote). When assessed by differing methods, grade 4 neutropenia was relatively infrequent, at about 16%, with grade 4 thrombocytopenia seen in only about 3% of the 677 patients assessed (*38*). Regardless of the method of assessment, severe drops in platelet and white counts are reasonably common with tositumomab and ^{131}I-tositumomab therapy, and although quite manageable in general, it is critically important to recognize that the time to count nadirs (3–6 wk) is substantially longer for RIT with tositumomab and ^{131}I-tositumomab therapy than with typical chemotherapy. Plots of mean platelet, ANCs, and hematocrit are shown in Figure 6 for patients after tositumomab and ^{131}I-tositumomab therapy (count nadir profiles). In view of the hematologic toxicity of tositumomab and ^{131}I-tositumomab therapy in the target population, a "boxed warning label" describing hematologic toxicity appears in the product insert, and it is important that blood counts are closely monitored during follow-up after treatment.

In general, hematopoietic toxicity is more severe the more extensive the prior therapy. In the 76 patients who had never been treated, hematopoietic toxicity was less, and it would be extremely rare for tositumomab and

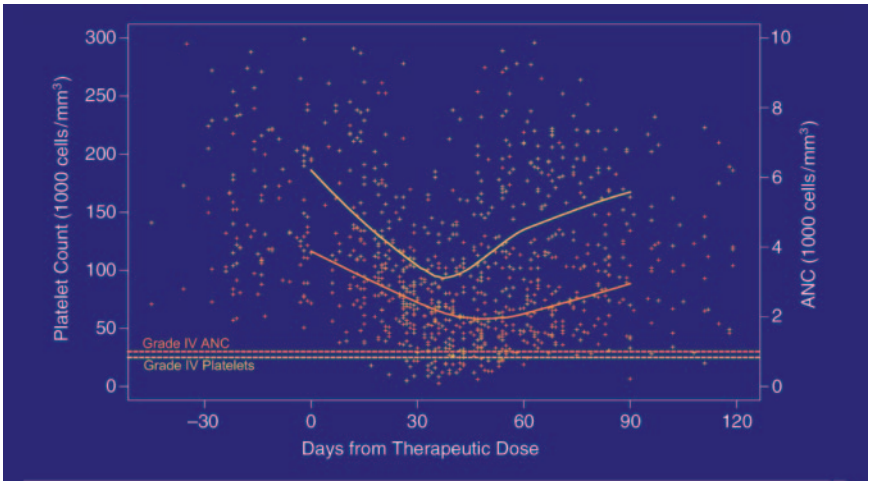

FIGURE 6. Mean and raw platelet count and upper and lower quartile bounds of platelet count, absolute neutrophil count, and hematocrit after tositumomab and ^{131}I-tositumomab therapy.

^{131}I-tositumomab therapy as a single therapy used in untreated patients at the 75-cGy total-body dose

Tositumomab and ^{131}I-tositumomab therapy has been shown to be reasonably safe in patients with fairly extensive bone marrow involvement of 20%–25%, 50% of whom had grade 4 neutropenia (*38*). This may be an advantage over other forms of RIT but warrants additional study. Tositumomab and ^{131}I-tositumomab therapy have not been extensively evaluated in patients with >25% marrow involvement. In the elderly, tositumomab and ^{131}I-tositumomab therapy appears to be well tolerated (*38*).

Giving radionuclide therapy to patients who have had prior extensive chemotherapy raises a concern for possible secondary malignancies. Myelodysplastic syndromes and acute myeloid leukemia have been observed in about 3.2% of 995 patients who received tositumomab and ^{131}I-tositumomab therapy (*34*). This is similar to the incidence reported in lymphoma patients 5–6 y after initial cytoxic therapy. Patients may sometimes have myelodysplastic syndrome at entry into the study. Nonetheless, myelodysplastic syndrome clearly does occur in a limited fraction of patients after tositumomab and ^{131}I-tositumomab therapy. It is not clear that RIT increases the risk over the baseline risk, which is clearly increased over the general population in patients with NHL after chemotherapy. Of note in studies performed by Gopal et al. (*44*) with high-dose RIT and stem cell support, rates of myelodysplastic syndrome were not increased for the patients treated with ^{131}I-anti-CD20 versus patients treated with high-dose chemotherapy with or without total-body irradiation. Clearly, however, myelodysplastic syndrome is a serious concern after tositumomab and ^{131}I-tositumomab therapy, but it is not clear that it is linked specifically to this therapy.

Other toxicities include that of free radioiodine. Patients are given thyroid blockade with a saturated solution of potassium iodide to prevent the development of hypothyroidism. However, elevated TSH levels have been observed in a fraction of patients. Some patients had preexisting elevated TSH before treatment was started. Of the 995 patients evaluated for the safety data in the Bexxar product approval process, 9.5% developed elevated TSH levels at 2 y after treatment, whereas the incidence was 17.4% at 4 y after treatment (*34*). Clearly, it is critical to be certain that patients take their thyroid-blocking agents to minimize the risk of hypothyroidism, but the risk of hypothyroidism must be considered as one of the most common longer-term risks of tositumomab and ^{131}I-tositumomab therapy.

Development of HAMAs was uncommon in patients who had been treated previously with chemotherapy and was observed in 10% of the 995 patients evaluated for safety for FDA approval (*34*). The HAMA frequency in the phase I study may have been higher, because its design included multiple repeated infusions of radioantibody. In the single-center "up front" study with no additional chemotherapy, the frequency of HAMA was substantially greater than 50% in preliminary communications (*39*). The frequency of a positive HAMA test is highly dependent on the assay technique used. HAMA is probably of greatest relevance because it potentially can interfere with laboratory-based assays using antibody reagents (such as enzyme-linked immunosorbent assays) and potentially could interfere with or increase the risks associated with subsequent doses of therapeutic or diagnostic antibodies.

Acute severe reactions during tositumomab and ^{131}I-tositumomab therapy infusion are infrequent, but hypersensitivity reactions of a severe nature are possible. These infusions must be done in a setting where it is possible to effectively manage potentially severe allergic reactions. Slowing the rate of unlabeled antibody infusion or stopping the infusion can abrogate infusion-related symptoms such as chills or fever. Nonhematologic acute and subacute toxic events can occur as well, with fevers not uncommon, as well as asthenia. As can be seen in Table 3, grade 3–4 nonhematologic adverse reactions are uncommon.

Radiation Safety Considerations with Tositumomab and ^{131}I-Tositumomab Therapy

We have previously reported the feasibility of treating patients with ^{131}I-tositumomab and unlabeled tositumomab as outpatients in the United States (*45,46*). This is now feasible in all Nuclear Regulatory Commission (NRC) states and nearly all "agreement states" in the United States. Since these rules were put in place about 6 y ago for NRC states, virtually all of the many tositumomab and ^{131}I-tositumomab therapies the author has administered have been given as outpatient treatments. It is only extremely rarely that a patient is unable to accommodate therapy on an outpatient basis. In such instances, hospitalization or ^{90}Y-anti-CD20 therapy are reasonable alternatives. The specific NRC requirements for outpatient therapy with radionuclides have been described previously, and specifics of this approach as regards tositumomab and ^{131}I-tositumomab therapy have been reviewed (*45,46*). The goal of such regulations is to ensure that <500 mR are delivered from the treatment to the general public (in general, the spouse or caregiver of the NHL patient). By knowing the precise total-body residence time of the patient (which is determined in each tositumomab and ^{131}I-tositumomab therapy study from the dosimetric scans) and by measuring the exposure rate from the patient at the end of therapeutic infusion, it is possible to predict and describe behavior patterns designed to limit the caregiver's and general public's exposure to <500 mR after a tositumomab and ^{131}I-tositumomab therapeutic administration.

Examination of actual residence times and measurable dose exposure rates have shown that virtually all patients treated with tositumomab and ^{131}I-tositumomab therapy who are competent to follow instructions can be instructed so as to minimize exposure to the general public to <500 mR and can be treated as outpatients. Certain behaviors must be avoided to comply with these rules, such as treated patients avoiding sleeping closely with other individuals for

TABLE 3
Incidence of Clinical Nonhematologic Adverse Experiences Regardless of Relationship to Study Drug Occurring in ≥5% of Patients Treated with Bexxar Therapeutic Regimen* (n = 230)

Body system	All grades (96%)	Grade 3/4 (48%)
Body as a whole	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection†	21%	<1%
Pain	19%	1%
Chills	18%	1%
Headache	16%	0%
Abdominal pain	15%	3%
Back pain	8%	1%
Chest pain	7%	0%
Neck pain	6%	1%
Cardiovascular system	26%	3%
Hypotension	7%	1%
Vasodilatation	5%	0%
Digestive system	56%	9%
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
Endocrine system	7%	0%
Hypothyroidism	7%	0%
Metabolic and nutritional disorders	21%	3%
Peripheral edema	9%	0%
Weight loss	6%	<1%
Musculoskeletal system	23%	3%
Myalgia	13%	<1%
Arthralgia	10%	1%
Nervous system	28%	3%
Dizziness	5%	0%
Somnolence	5%	0%
Respiratory system	44%	8%
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	0%
Skin and appendages	44%	5%
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%

*Excludes laboratory-derived hematologic adverse events.
†The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other terms are mapped to preferred terms (e.g., pneumonia and sepsis).

a week or more, not taking long trips on an airplane for several days, and avoiding children and pregnant women for a week or longer. Occasionally, incontinent or uncooperative patients or patients with very confined living quarters that include small children may not be suitable for tositumomab and ^{131}I-tositumomab therapy because of radiation safety considerations. Thus, tositumomab and ^{131}I-tositumomab therapy can generally be considered an outpatient therapy in the United States.

Specific written instructions are typically provided to patients undergoing tositumomab and ^{131}I-tositumomab therapy, and these have been shown to be quite effective in minimizing exposure to the general public. The efficacy of this approach was evaluated in a study at the University of Nebraska, where investigators showed that average exposure to caregivers was 144 mR when following instructions designed to limit exposure to <500 mR to those individuals caring for the patient (*47*). Most treatment centers in the United States administer ^{131}I therapy for thyroid disease in the outpatient setting, and the requirements for tositumomab and ^{131}I-tositumomab therapy are quite similar. Nonetheless, patients must be appropriately educated to minimize the possibility of irradiating the general public.

Tositumomab and ^{131}I-Tositumomab Therapy Delivery

The ability to apply patient-specific dosimetry is particularly attractive for patients who may have accelerated or markedly slowed clearance of radioantibody from the blood and whole body. Examples could include patients with bulky disease, patients with limited disease, and patients without a spleen or with a large spleen. These patients may well differ markedly from average in their pharmacokinetics. In addition to these identifiable parameters, there is substantial variability in total-body clearance rates from patient to patient (*6*). It is not particularly difficult to implement whole-body dosimetry using the simplified 3-point methodology. γ-cameras must be appropriately calibrated, but many are suitable and are available at most institutions. We have previously demonstrated that medium- and high-energy collimators provide comparable results in terms of the calculated dosimetry (*48*). Although the whole-body images used to derive the count data are presented as images and should be examined for biodistribution altered from that expected for an intact murine monoclonal antibody, it is very rare for this to occur when cold antibody predosing is used, as in the current tositumomab and ^{131}I-tositumomab therapeutic regimen. In the United States, it is necessary for verification and certification of a site by the drug manufacturer in 3 cases before they are considered adequately trained in delivering this therapy and before they can begin to deliver these treatments independently.

Operating Model for Tositumomab and ^{131}I-Tositumomab Therapy

Tositumomab and ^{131}I-tositumomab therapy, although well tolerated in general, can result in severe hematologic and sometimes other types of toxicities. Appropriate selection of patients, careful education of patients, and a suitable strategy for patient follow-up, including management of toxicities, must be in place to optimally deliver this therapy. In general, a close working relationship among medical oncology, pathology, nuclear medicine, radiation oncology, medical physics, and the referring physicians is necessary to properly manage a

patient undergoing tositumomab and ^{131}I-tositumomab therapy. Because the unlabeled tositumomab infusion is reasonably well tolerated, one of several potential models for tositumomab and ^{131}I-tositumomab therapy is to evaluate the potential patient on a consultative basis in nuclear medicine after a referral from a capable medical oncologist who views RIT as a suitable option. Appropriate review of the patient history, review of the pathology to demonstrate that it is CD20+ and of the proper histology, appropriate marrow sampling to demonstrate adequate cellularity and lack of tumor involvement of an extensive nature, and a complete history and physical are required. Moreover, it is necessary to counsel the patient in issues related to RIT and radiation safety as well as the risks and benefits of the treatment to be certain they are suitable for tositumomab and ^{131}I-tositumomab therapy. It is, however, quite possible, given the relative safety of the unlabeled anti-CD20 antibody, to infuse under careful supervision the unlabeled antibody on an outpatient basis in nuclear medicine, with the tracer dose also being given in nuclear medicine, if appropriate training of physicians and nurses has been achieved and if suitable resuscitative equipment is present. It is then possible to perform sequential assessments of the patient in nuclear medicine to determine the total-body counts at baseline, days 2–4, and days 5–7, as well as generate the images for review for biodistribution. From these data, the dosimetric dose can then be used to calculate the required therapeutic becquerels to give a 75- or 65-cGy total-body dose, depending on the platelet count (75 cGy if $>$150,000/mm^3 and 65 cGy if platelet count is 100,000–150,000/mm^3). The therapeutic dose can then be given in nuclear medicine on an outpatient basis. Thus the patient can be fully evaluated and treated in nuclear medicine and then can be followed on a weekly basis for blood counts through the next 12-wk period. This follow-up can be done in nuclear medicine or by the referring medical oncologist. If patients are referred from some distance, the counts can be checked by a medical oncologist weekly near the patient's home, and the patient will be seen in follow-up in nuclear medicine at 6 and 12 wk. Close follow-up is necessary to determine whether colony-stimulating factors, antibiotics, or platelet transfusions are required, and appropriate arrangements must be present to deal with emergent events, such as the need to hospitalize for neutropenic fevers, which would generally be coordinated with the referring oncologist. Excellent cooperation with radiation safety is also necessary. For such a model to work, nurses must be fully trained in the administration of therapeutic antibodies. Either this can be done in oncology nursing or radiology nurses can be trained by oncology nursing to infuse the antibodies. Although a model with patient consultation and treatment in nuclear medicine is feasible, it is important that the patient have all therapeutic options presented. Seeing a medical oncologist at the radiopharmaceutical treatment center and having the case reviewed by a lymphoma tumor board can help ensure that patients do not miss out on alternative therapies that might be more appropriate in some instances. Nonetheless, informed oncologists who have selected RIT may be inclined to refer directly to nuclear medicine for the treatment.

We administer the full tositumomab and ^{131}I-tositumomab therapeutic regimen in nuclear medicine at Johns Hopkins, but there are close interactions with oncology and pathology and the members of the lymphoma tumor board in implementing this treatment. A suitable method to follow the patient and to deal with complications of therapy must be in place for such a model to work. However, for patients referred from some distance, this approach can be quite workable.

There are multiple alternative models for tositumomab and ^{131}I-tositumomab therapy delivery, including delivering the unlabeled tositumomab by medical oncology in their infusion center and delivery of only the radiolabeled materials by nuclear medicine or radiation oncology, depending on local expertise. This model can also work well and is likely the most common model. Because rituximab infusions are typically given in medical oncology and can have a side effect profile that is more severe than that for tositumomab, dealing with infusion-related toxicities and complications of chemotherapy are common clinical issues for medical oncologists. The key is that the patient is carefully and rigorously evaluated for suitability for RIT before the decision to treat is entered into and that proper education, follow-up, and management of possible complications are arranged for. Also necessary for any model is clear and frequent communication with the referring physician, the patient, and the entire oncology team, which also includes radiation safety.

We strongly recommend that marrow cellularity, tumor histology, fraction of marrow involved, and CD20 status be reviewed by pathologists very familiar with making these assessments to avoid the potential of treating patients who are not suitable candidates. We have occasionally observed significant discrepancies among readers in these assessments, most often in the fraction of marrow involvement. At our own center, it is very common to secure a PET scan with ^{18}F-FDG (or PET/CT) before treatment is initiated, with a follow-up study performed at 12 wk and 24 wk after treatment. This delay is in place because it is important that sufficient time be allowed so the therapy can be efficacious, because tumors do not necessarily shrink immediately in response to the therapy. The optimal logistical and organizational methods for delivering tositumomab and ^{131}I-tositumomab therapy will differ based on site and will evolve based on local clinical strengths and interests.

Choices of RIT for NHL

Bexxar is one of two anti-CD20 RITs approved for the treatment of patients with follicular NHL who have not responded well or have failed to respond to previous chemotherapies or immunotherapies. At present, it is clear that both Zevalin and Bexxar therapies offer substantial antitumor activity in such patients and are safe and effective in the treatment of NHL when used as directed. Although the drugs are similar in mechanism of action, they differ in several ways: the Bexxar therapeutic regimen uses mouse

monoclonal antibodies only, whereas the Zevalin regimen includes both a mouse monoclonal anti-CD20 and a mouse–human chimeric antibody (rituximab) as part of the regimen. The Zevalin regimen does not require dosimetry (it is weight based), and ^{90}Y is a pure β-emitter with an energetic β and a 2.7-d half-life. With Zevalin, the tracer dose of ^{111}In is similar but not identical to the therapeutic radiopharmaceutical in its biodistribution, but imaging is required at several time points to exclude an "altered" biodistribution. With Bexxar, ^{131}I is used as both the tracer and the therapy, so that biodistributions should be identical for both tracer and treatment doses, the half-life is 8 d for ^{131}I, ^{131}I emits a γ-ray that can be imaged, the β-particle energy for ^{131}I is lower than ^{90}Y, and free ^{131}I can cause hypothyroidism. ^{131}I images are also examined for "altered biodistributions," but the images provide only limited scintigraphic information.

One might predict that the behaviors of Bexxar and Zevalin might differ, therefore, despite major similarities in the treatments. Zevalin clearly would be better in a patient who could not comply with radiation safety precautions required for Bexxar, and Zevalin would seem unlikely to cause hypothyroidism. Bexxar would probably be better tolerated in patients who have had adverse reactions to rituximab infusions (an obligate part of Zevalin therapy) and may be expected to be advantageous in patients in whom biokinetics are expected to be "nonaverage," such as those with large spleens or very low tumor burdens. However, it remains to be objectively demonstrated in direct comparative clinical trials whether the greater efficacy and safety that might be predicted to accrue to Bexxar as a result of its patient-individualized dosimetry are in fact demonstrated in practice. Similarly, the lower-energy β-particle of ^{131}I and its longer half-life might be expected to result in a higher probability of durable complete responses for patients with small tumor burdens than would be seen for more energetic and shorter-lived β-particles such as those of ^{90}Y—and possibly a higher rate of durable complete responses of larger heterogeneous tumors for a ^{90}Y agent versus an ^{131}I agent. Until direct randomized studies compare Bexxar and Zevalin in the same population with similar intensity and methods of follow-up, it will not be possible to determine if this speculation based on physics and immunology translates into one agent being superior to the other in terms of safety or efficacy profiles. It is clear, however, that both Bexxar and Zevalin are active treatments for NHL and must currently be considered when standard treatments are ineffective.

CONCLUSION

Tositumomab and ^{131}I-tositumomab therapy is safe and efficacious in patients with relapsed and refractory follicular lymphomas. At present it is being used most commonly in patients whose tumors have failed to respond to chemotherapy and have become refractory or nonresponsive to rituximab therapy. Clinical data suggest response rates are higher the earlier tositumomab and ^{131}I-tositumomab therapy is used in the therapeutic course. Currently, Bexxar is approved only for single-dose administration, but preliminary data from limited clinical trials suggest that at least 1 repeated dose is well tolerated and active in patients who are HAMA negative and who have previously responded to treatment. Data on the use of Bexxar in first-line therapy of NHL show a very high response rate, although as a single agent without chemotherapy HAMA rates are frequent, which may be problematic in terms of altering immunologically based blood tests and in possibly changing the delivery of a second antibody therapy. Bexxar is not FDA approved as first-line treatment at this time. At present, clinical trials comparing CHOP plus rituximab versus CHOP plus tositumomab and ^{131}I-tositumomab as initial treatments of NHL are ongoing and will be of substantial interest. With 2 choices available in anti-CD20 RIT, direct comparative trials of ^{131}I and ^{90}Y agents will also be of great interest to determine if the predicted improved safety of ^{131}I using patient-individualized treatment will be demonstrated in practice. Moreover, it should be determined whether the relatively high rate of durable complete remissions observed with tositumomab and ^{131}I-tositumomab therapy will be significantly more frequent with the ^{131}I or ^{90}Y agent, given the differences in isotope physical characteristics. RIT of lymphoma has been established as an effective technique in the last 14 y, and its applications are expected to grow in the coming years. This author's expectation is that the therapy will ultimately be used earlier in the course of the illness than in current clinical practice and will assume a growing role in the treatment of this common disease.

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