Comparison of ^{90}Y-Ibritumomab Tiuxetan and ^{131}I-Tositumomab in Clinical Practice

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We retrospectively evaluated our single-center clinical experience with ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab for therapy of refractory non-Hodgkin's lymphoma (NHL). We evaluated the hypothesis that the patient-specific dosing regimen used with ^{131}I-tositumomab results in less bone marrow toxicity than does the weight-based dosing regimen used with ^{90}Y-ibritumomab tiuxetan. **Methods:** Thirty-eight patients (25 male and 13 female; median age, 64 y) received radioimmunotherapy for NHL (20 received ^{90}Y-ibritumomab tiuxetan; 18 received ^{131}I-tositumomab). Patient and disease characteristics were evaluated to determine whether any were prognostic indicators of short- or long-term clinical response. The 12-wk response rate and clinical and hematologic toxicities attributable to each therapy were assessed. The response rate at 12 wk was correlated with long-term overall survival. **Results:** Twenty-six patients received full-radiation-dose radioimmunotherapy and 12 received attenuated doses because of hematologic concerns. The 12-wk overall response rate for all patients was 47%, and the complete response rate was 13%. The 12-wk overall response rate did not significantly differ between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups. Responses at 12 wk were more frequent in patients with normal levels of serum lactate dehydrogenase, no bone marrow involvement, and International Prognostic Index scores of no more than 2 ($P \leq 0.04$). Grade 3 or 4 thrombocytopenia occurred in 57% and 56% of patients treated with ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, respectively. Grade 3 or 4 neutropenia was observed in 57% and 50%, respectively. The time to the absolute neutrophil count nadir was shorter for the ^{90}Y-ibritumomab tiuxetan group than for the ^{131}I-tositumomab group (36 ± 9 vs. 46 ± 14 d, $P = 0.01$). The mean percentage decline in platelet count after radioimmunotherapy was greater in the ^{90}Y-ibritumomab tiuxetan group than in the ^{131}I-tositumomab group (79% ± 17% vs. 63% ± 28%, $P = 0.04$). Overall survival was longer in responders than in nonresponders 12 wk after therapy ($P \leq 0.05$). **Conclusion:** Both ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab were well tolerated. We observed response rates at the lower range of those reported in the literature, possibly because of referral bias, dose attenuation, and reasonably liberal acceptance criteria for a patient to receive therapy. Initial response assessments 12 wk after radioimmunotherapy predict longer-term response. ^{131}I-tositumomab caused significantly less severe declines in platelet counts than did ^{90}Y-ibritumomab tiuxetan and may be a more appropriate choice for patients with limited bone marrow reserve, but large, randomized, prospective trials are needed to better compare the performance of these 2 treatments.

Key Words: radioimmunotherapy; ^{90}Y-ibritumomab tiuxetan; ^{131}I-tositumomab; Zevalin; Bexxar; dosimetry

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The radiolabeled monoclonal antibodies ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab are part of the Zevalin (Biogen IDEC (*1*)) and Bexxar (GlaxoSmithKline (*2*)) therapeutic regimens, respectively. Both have been approved by the Food and Drug Administration (FDA) for the treatment of refractory or relapsed low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL). The agents have similar mechanisms of action. Both target the CD20 antigen, which is found on the surface of pre–B lymphocytes, mature B lymphocytes and more than 90% of B-cell NHL (*3,4*). The antibodies recognize epitopes in the extracellular domain of the CD20 antigen, and formation of the antibody–antigen complex induces apoptosis, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity (*5,6*). The radioisotopes also contribute to the mechanism of action of the drugs by emitting β-particles, which deposit enough energy in the tumor to result in cell death (*7*).

The efficacies reported thus far for therapeutic regimens containing ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab are similar in patients with previously treated and chemotherapy-refractory low-grade relapsed NHL, with overall response rates in the 60%–83% range and complete response (CR) rates ranging from 15% to 52% (*8–15*). ^{131}I-tositumomab has a higher overall response rate (95%) and CR rate (75%) when applied as initial therapy for follicular NHL (*16*). In general, both agents are well tolerated and appear to have similar safety profiles.

The most common adverse events for these radioimmunotherapies in patients previously treated with chemotherapy are serious cytopenias, which are experienced by most patients receiving either ^{90}Y-ibritumomab tiuxetan or

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^{131}I-tositumomab. The similarities in treatment efficacy and site of toxicity are expected since both agents deliver significant radiation to the bone marrow because of less than perfect tumor targeting of the anti-CD20 antibodies and the less than completely tumor-specific location of the CD20 antigen; however, the data are based on single-agent studies that used different entry criteria for patient selection. To our knowledge, no prospective or retrospective studies directly comparing ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab have been performed.

A major difference between ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab is the method for determining the dosage of therapeutic radioactivity to administer to each patient. In the United States, a tracer dose scan with ^{111}In-ibritumomab tiuxetan is used to predict the biodistribution of the subsequently administered amount of radioactivity of ^{90}Y-ibritumomab tiuxetan, because ^{90}Y is a pure β-emitter and cannot be easily imaged. Although some patient-to-patient variability exists in normal-tissue pharmacokinetics and dosimetry, only modest correlations between pharmacokinetic and dosimetric parameters using ^{111}In-ibritumomab tiuxetan and hematologic toxicity have been demonstrated across a relatively narrow dosing range (*17,18*); therefore, the amount of radioactivity to administer for the therapeutic dosage is calculated on the basis of platelet count and patient weight. On the other hand, ^{131}I-tositumomab likely has more variable pharmacokinetics in patients. The γ-photons emitted by ^{131}I (in addition to the β-particles) and the longer half-life of ^{131}I allow for imaging and patient-specific calculation of dosimetry and the amount of radioactivity to administer to achieve the desired therapeutic dose (*19–21*). Additionally, when compared with ^{90}Y, ^{131}I has been shown to have a tighter distribution of tumor-absorbed doses of radiation from a given tumor site and is predicted to be more efficacious in the treatment of lung nodules, particularly those with radii less than 2 cm, presumably because of the shorter pathlength of ^{131}I. This finding may be of particular relevance in small tumor foci near normal structures, if these findings can be extrapolated beyond the lungs (*22*).

Both ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab are used at our institution in the clinical setting. Because ^{90}Y-ibritumomab tiuxetan was the first radioimmunotherapeutic agent approved by the FDA, initially, it was the only agent available for radioimmunotherapy studies. Once ^{131}I-tositumomab was FDA-approved, a choice between agents could be made. Currently at our center, when a patient is believed to be a candidate for radioimmunotherapy, one of the agents is chosen on the basis of patient and disease characteristics and of referring physician preference and familiarity. Radiation safety issues are also considered. After using radioimmunotherapy for 4 y in our clinical setting, we retrospectively examined patient and disease characteristics at the time of radioimmunotherapy that could be used as prognostic indicators of short-term and long-term clinical response, response rates to each therapy, and clinical and hematologic toxicity attributable to each therapy. We hypothesized that the patient-specific dosing method of ^{131}I-tositumomab would result in less bone marrow toxicity than would the weight-based method of ^{90}Y-ibritumomab tiuxetan without compromising efficacy.

MATERIALS AND METHODS

This study was a single-institution, retrospective, observational study of 38 patients treated in a clinical setting with radioimmunotherapy for NHL between 2002 and 2006. Patients had refractory or relapsed B-cell NHL. Twenty patients were treated with ^{90}Y-ibritumomab tiuxetan, and 18 received ^{131}I-tositumomab. Permission to conduct this retrospective study was obtained from our Institutional Review Board.

Monitoring Patients During Radioimmunotherapy

All patients were initially seen in the nuclear medicine radioimmunotherapy clinic for a full consultation and subsequently were treated with radioimmunotherapy using the ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab therapeutic regimen. After radioimmunotherapy, patients were monitored at least weekly for hematologic toxicity with complete blood counts with differential for 12 wk or until count recovery. In addition to their usual oncology follow-up visits, 25 patients were seen in the radioimmunotherapy clinic 6 wk after radioimmunotherapy and 25 were seen 12 wk after therapy.

At the time of radioimmunotherapy, the following patient and disease characteristics were recorded: age, sex, NHL histology, disease stage, International Prognostic Index (IPI), number of prior chemotherapy regimens (including rituximab), prior treatment (specifically with rituximab and fludarabine), response to prior chemotherapy (including rituximab), bone marrow tumor involvement, history of prior stem cell transplantation, history of prior radiation therapy, and serum lactate dehydrogenase (LDH) level. The therapeutic dose of radioimmunotherapy was recorded. Twenty-six patients received full-dose radioimmunotherapy, either 14.8 MBq of ^{90}Y-ibritumomab tiuxetan per kilogram of body weight ($n = 14$) or a 75-cGy total-body radiation dose of ^{131}I-tositumomab ($n = 12$). Twelve patients received attenuated radiation doses for radioimmunotherapy (^{90}Y-ibritumomab tiuxetan, 11.1 MBq/kg [$n = 6$]; ^{131}I-tositumomab, a 65-cGy total-body radiation dose [$n = 3$]; ^{131}I-tositumomab, a 45-, 55-, or 60-cGy total-body radiation dose [$n = 1$ each]).

Assessment of Response to Treatment

Short-term response to radioimmunotherapy was assessed in 30 patients (18 of the 18 who received ^{131}I-tositumomab and 12 of the 20 who received ^{90}Y-ibritumomab tiuxetan) 12 wk after radioimmunotherapy on the basis of available radiographic and clinical follow-up data. Most of these 30 patients had an ^{18}F-FDG PET/CT scan 12 wk after radioimmunotherapy (18 of the 18 who received ^{131}I-tositumomab and 8 of the 12 who received ^{90}Y-ibritumomab tiuxetan). Four additional ^{90}Y-ibritumomab tiuxetan patients underwent standard contrast-enhanced CT at 12 wk. Changes in tumor size were determined using the unenhanced-CT portion of the ^{18}F-FDG PET/CT scan or standard contrast-enhanced CT examinations if available. Short-term responses 12 wk after radioimmunotherapy were classified as CR, partial response (PR), stable disease, or progression on the basis of the International Workshop Criteria (*23*). For this report, imaging criteria for response at 12 wk after radioimmunotherapy did not include evaluation of changes in tumor metabolism. ^{18}F-FDG PET/CT results were subsequently evaluated and will be reported separately.

Long-term response to radioimmunotherapy was determined on the basis of all available clinical and radiographic follow-up, which included clinical notes, anatomic studies, and any additional ^{18}F-FDG PET/CT scans. Determination of long-term response was based on the referring physicians' overall impression from clinical notes.

The duration of survival from the date of radioimmunotherapy until December 2006 was determined. Patient and disease characteristics at the time of radioimmunotherapy were correlated with short- and long-term clinical responses to determine whether any were predictors of response. This correlation was done for the 30 patients who had 12-wk radiographic follow-up and then for the subgroups of ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab patients. Twelve-week short-term response was then correlated with long-term overall survival.

Hematologic Toxicity

Hematologic data before and after radioimmunotherapy were available for 14 of the 20 patients who received ^{90}Y-ibritumomab tiuxetan and all 18 patients who received ^{131}I-tositumomab. The 6 patients who received ^{90}Y-ibritumomab tiuxetan but did not have hematologic toxicity data available were outside referrals who were followed by their referring oncologists after radioimmunotherapy. Platelet counts and absolute neutrophil counts (ANCs) were recorded at baseline and then weekly for 12 wk after radioimmunotherapy or until count recovery. The absolute nadir value, the maximum percentage decline from baseline, and the time from baseline to nadir were calculated. The number of patients in whom grade III and IV thrombocytopenia or neutropenia developed (by the National Cancer Institute Common Toxicity Criteria, version 3.0) was determined.

Statistical Analyses

Comparisons of frequencies between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups and univariate analyses to determine prognostic factors of response rate were performed using the Fisher exact test. Means were compared using 1-tailed t tests. Overall survival was defined as the time from the therapeutic dose of radioimmunotherapy until death from any cause. Overall survival was analyzed using Kaplan–Meier curves and log-rank (Mantel–Cox) tests. P values of less than 0.05 were considered statistically significant.

RESULTS

Patient and disease characteristics before radioimmunotherapy are listed in Table 1. Twenty-eight patients had follicular lymphoma (15 received ^{90}Y-ibritumomab tiuxetan; 13 received ^{131}I-tositumomab), 2 had small lymphocytic lymphoma (both received ^{131}I-tositumomab), 4 had diffuse large B-cell lymphoma (3 received ^{90}Y-ibritumomab tiuxetan; 1 received ^{131}I-tositumomab), and 1 each had mantle cell lymphoma (treated with ^{131}I-tositumomab), mucosa-associated lymphoid tissue lymphoma (treated with ^{131}I-tositumomab), marginal zone lymphoma (treated with ^{90}Y-ibritumomab tiuxetan), and posttransplant lymphoproliferative disorder (treated with ^{90}Y-ibritumomab tiuxetan). Three patients were treated with radioimmunotherapy for an indication outside those labeled by the FDA (1 with posttransplant lymphoproliferative disorder, 1 with de novo diffuse large B-cell lymphoma, and 1 with mantle cell lymphoma). Four patients had CD20$^+$ low-grade nonfollicular lymphomas (2 with small lymphocytic lymphoma, 1 with mucosa-associated lymphoid tissue lymphoma, and 1 with marginal zone lymphoma), in which radioimmunotherapy has not been as well studied. Overall, patient and disease characteristics did not significantly differ between the patients who received ^{90}Y-ibritumomab tiuxetan and those who received ^{131}I-tositumomab. The baseline platelet counts tended to be lower in the ^{131}I-tositumomab group than in the ^{90}Y-ibritumomab tiuxetan group ($P = 0.09$, supplemental Table 1 [supplemental materials are available online only at http://jnm.snmjournals.org]).

The data to perform an initial response assessment 12 wk after radioimmunotherapy were available for 30 patients. The overall response rate for these patients was 47% (14/30). Four patients achieved a CR (1 who received ^{90}Y-ibritumomab tiuxetan; 3 who received ^{131}I-tositumomab), 10 had a PR (5 who received ^{90}Y-ibritumomab tiuxetan; 5 who received ^{131}I-tositumomab), 3 had stable disease (1 who received ^{90}Y-ibritumomab tiuxetan; 2 who received ^{131}I-tositumomab), and 13 had progressive disease (5 who received ^{90}Y-ibritumomab tiuxetan; 8 who received ^{131}I-tositumomab). The 12-wk overall response rates were not significantly different between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups (Table 2).

As shown in Table 3, no patient characteristic at the time of radioimmunotherapy predicted response to ^{90}Y-ibritumomab tiuxetan, although those with normal LDH levels tended to be more likely to respond to radioimmunotherapy at 12 wk. In the ^{131}I-tositumomab group, patients were more likely to respond at 12 wk if they had a normal LDH level or an IPI score of 2 or less at the time of therapy. Response to ^{131}I-tositumomab was more frequent in patients without than with bone marrow involvement at the time of therapy, although the difference was not statistically significant ($P = 0.09$). When data from both radioimmunotherapy agents were combined, patients with normal LDH levels, no bone marrow involvement, and IPI scores of 2 or less were significantly more likely to respond at 12 wk ($P \leq 0.04$). None of the patients who had an elevated serum LDH level at the time of radioimmunotherapy and none of the patients who had bone marrow involvement at the time of radioimmunotherapy responded to either agent at 12 wk. Responses to radioimmunotherapy at 12 wk tended to be more frequent in patients with indolent histologies than in patients with aggressive histologies (60% vs. 20%, $P = 0.06$).

As expected, the most serious toxicities were hematologic (supplemental Table 1). Grade 3 or 4 thrombocytopenia was experienced in 57% (8/14) of those who received ^{90}Y-ibritumomab tiuxetan and 56% (10/18) of those who received ^{131}I-tositumomab, whereas grade 3 or 4 neutropenia was experienced in 57% (8/14) and 50% (9/18), respectively. The duration of grade 4 thrombocytopenia lasted longer than 1 wk in 3 patients in the ^{90}Y-ibritumomab tiuxetan group and in 3 patients in the ^{131}I-tositumomab group. The duration of grade

TABLE 1
Patient and Disease Characteristics Before Radioimmunotherapy

Characteristic	All patients (n = 38)	^{131}I-Tositumomab (n = 18)	^{90}Y-Ibritumomab tiuxetan (n = 20)	P*
Age at radioimmunotherapy (y)				0.07
Median	64	60	67	
Range	40–80	41–78	40–80	
Age > 60 y (n)	24 (63%)	9 (50%)	15 (75%)	0.18
Male sex (n)	25 (66%)	13 (72%)	12 (60%)	0.51
Histology at radioimmunotherapy (n)				1.00
Indolent	27 (71%)	13 (72%)	14 (70%)	
Aggressive	11 (29%)	5 (28%)	6 (30%)	
Transformed from original histology (n)				1.00
Yes	6 (16%)	3 (17%)	3 (15%)	
No	32 (84%)	15 (83%)	17 (85%)	
Stage at radioimmunotherapy (n)				1.00
I–II	8 (21%)	4 (22%)	4 (20%)	
III–IV	30 (79%)	14 (78%)	16 (80%)	
IPI score† (n)				0.28
0–2	14 (47%)	10 (56%)	4 (33%)	
3–5	16 (53%)	8 (44%)	8 (67%)	
Prior treatment regimens (n)				
Median	3	3	2	
Range	1–8	1–8	1–7	
Prior treatment with rituximab (n)	37 (97%)	17 (94%)	20 (100%)	0.47
Prior treatment with fludarabine (n)	10 (26%)	5 (28%)	5 (25%)	1.00
Normal LDH (118–273 mg/dL) at radioimmunotherapy‡ (n)	18 (58%)	9 (60%)	9 (56%)	1.00
Bone marrow involvement at radioimmunotherapy§ (n)	8 (22%)	4 (22%)	4 (21%)	1.00
Prior bone marrow transplantation (n)	4 (11%)	3 (17%)	1 (5%)	0.33
Prior radiation therapy (n)	8 (21%)	6 (33%)	2 (10%)	0.12
Full-dose treatment‖ (n)	26 (68%)	12 (67%)	14 (70%)	1.00

*Fisher exact test, 2-tailed.
†Eight unknown: ^{90}Y-ibritumomab tiuxetan.
‡Seven unknown: 3 ^{131}I-tositumomab and 4 ^{90}Y-ibritumomab tiuxetan.
§One unknown: ^{90}Y-ibritumomab tiuxetan.
‖^{131}I-tositumomab (75 cGy) and ^{90}Y-ibritumomab tiuxetan (14.8 MBq/kg).

4 neutropenia lasted longer than 1 wk in 1 patient in the ^{90}Y-ibritumomab tiuxetan group and in at least 2 patients in the ^{131}I-tositumomab group. Complete data were not available for 1 patient with grade 4 neutropenia in the ^{131}I-tositumomab group. Trends in platelet counts and ANC over time after radioimmunotherapy for individual patients are shown in Figure 1. The mean maximum percentage decline in platelet count was significantly greater in the ^{90}Y-ibritumomab tiuxetan group than in the ^{131}I-tositumomab group (79% ± 17% vs. 63% ± 28%, P = 0.04; supplemental Table 1). The mean maximum percentage decline in ANC from baseline to nadir was also higher in the ^{90}Y-ibritumomab tiuxetan group than in the ^{131}I-tositumomab group, but this difference only tended toward significance (75% ± 16% vs. 63% ± 29%, P = 0.09; supplemental Table 1). The time from treatment to ANC nadir was shorter for the ^{90}Y-ibritumomab tiuxetan group than for the ^{131}I-tositumomab group (36 ± 9 d vs. 46 ± 14 d, P = 0.01). We did not have sufficiently dense data to fully evaluate the time from count nadir to count recovery.

In the 12-wk initial follow-up period after radioimmunotherapy, 2 of 20 patients in the ^{90}Y-ibritumomab tiuxetan group required both blood and platelet transfusions, 3

TABLE 2
Twelve-Week Overall Response and CR Rates

Response rate	All patients	^{131}I-Tositumomab (n = 18)	^{90}Y-Ibritumomab tiuxetan (n = 12)	P*
Overall (n)	14 (47%)	8 (44%)	6 (50%)	1.00
Complete (n)	4 (13%)	3 (17%)	1 (8%)	0.63

*Fisher exact test P value: ^{131}I-tositumomab vs. ^{90}Y-ibritumomab tiuxetan.

TABLE 3
Frequency of Response Rate at 12 Weeks vs. Patient and Disease Characteristics

Characteristic	Response rate		
	All patients (n = 30)	^{131}I-Tositumomab (n = 18)	^{90}Y-Ibritumomab tiuxetan (n = 12)
Age at radioimmunotherapy (y)			
≤60	6/12 (50%)	4/9 (44%)	2/3 (67%)
>60	8/18 (44%)	4/9 (44%)	4/9 (44%)
P	1.00	1.00	1.00
Sex (*n*)			
Male	11/20 (55%)	6/13 (46%)	5/7 (71%)
Female	3/10 (30%)	2/5 (40%)	1/5 (20%)
P	0.26	1.00	0.24
Histology at radioimmunotherapy (*n*)			
Indolent	12/20 (60%)	7/13 (54%)	5/7 (71%)
Aggressive	2/10 (20%)	1/5 (20%)	1/5 (20%)
P	0.06	0.31	0.24
Transformed from original histology (*n*)			
Yes	2/4 (50%)	1/3 (33%)	1/1 (100%)
No	12/26 (46%)	7/15 (47%)	5/11 (45%)
P	1.00	1.00	1.00
Stage at radioimmunotherapy (*n*)			
I–II	3/5 (60%)	2/4 (50%)	1/1 (100%)
III–IV	11/25 (44%)	6/14 (43%)	5/11 (45%)
P	0.64	1.00	1.00
Chemotherapy regimens before radioimmunotherapy (*n*)			
1–2	6/14 (43%)	3/6 (50%)	3/8 (38%)
3+	8/16 (50%)	5/12 (42%)	3/4 (75%)
P	0.73	1.00	0.55
Refractory to rituximab* (*n*)			
Yes	8/14 (57%)	4/6 (67%)	4/8 (50%)
No	5/15 (33%)	3/11 (27%)	2/4 (50%)
P	0.27	0.16	1.00
LDH at radioimmunotherapy† (*n*)			
Normal (118–273 mg/dL)	10/15 (67%)	6/9 (67%)	4/6 (67%)
Elevated	0/10 (0%)	0/6 (0%)	0/4 (0%)
P	<0.01	0.03	0.08
Bone marrow involvement at radioimmunotherapy (*n*)			
Yes	0/5 (0%)	0/4 (0%)	0/1 (0%)
No	14/25 (56%)	8/14 (57%)	6/11 (55%)
P	0.04	0.09	1.00
Prior bone marrow transplantation (*n*)			
Yes	1/3 (33%)	1/3 (33%)	0/0 (0%)
No	13/27 (48%)	7/15 (47%)	6/12 (50%)
P	1.00	1.00	1.00
Prior radiation therapy (*n*)			
Yes	3/7 (43%)	2/6 (33%)	1/1 (100%)
No	11/23 (48%)	6/12 (50%)	5/11 (45%)
P	1.00	0.64	1.00
IPI score (*n*)			
0–2	10/14 (71%)	7/10 (70%)	3/4 (75%)
3–5	4/16 (25%)	1/8 (13%)	3/8 (38%)
P	0.03	0.02	0.55
Full-dose treatment‡ (*n*)			
Yes	9/20 (45%)	5/12 (42%)	4/8 (50%)
No	5/10 (50%)	3/6 (50%)	2/4 (50%)
P	1.00	1.00	1.00

*One unknown: ^{131}I-tositumomab.
†Five unknown: 3 ^{131}I-tositumomab and 2 ^{90}Y-ibritumomab tiuxetan.
‡^{131}I-tositumomab (75 cGy) and ^{90}Y-ibritumomab tiuxetan (14.8 MBq/kg).
Fisher exact test *P* values compare subsets within a characteristic.

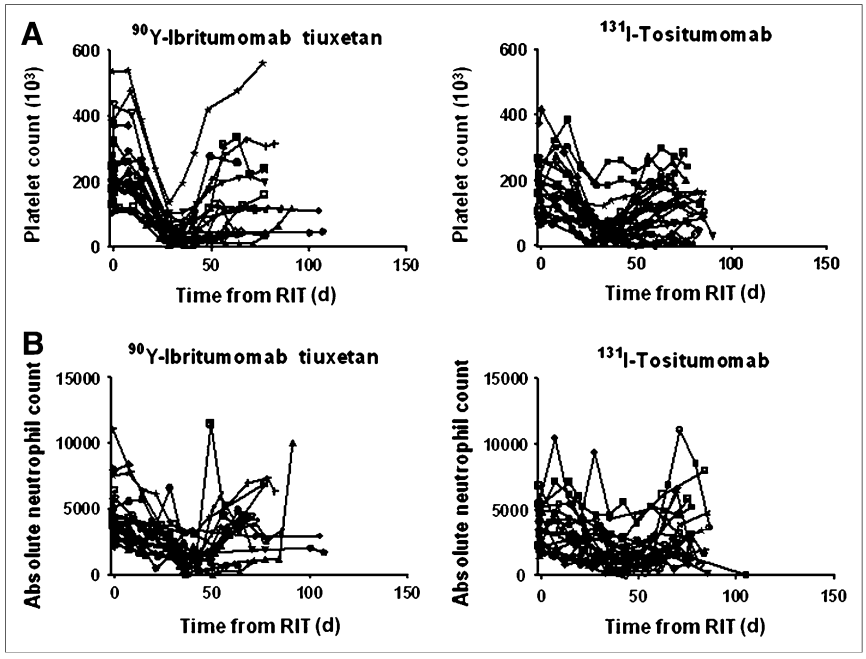

FIGURE 1. Platelet counts (A) and ANCs (B) vs. days from radioimmunotherapy are shown for each patient. Mean maximum percentage decline in platelet count was greater in ^{90}Y-ibritumomab tiuxetan group than in ^{131}I-tositumomab group (79% ± 17% vs. 63% ± 28%, $P = 0.04$). Mean maximum percentage decline in ANC from baseline to nadir was also higher in ^{90}Y-ibritumomab tiuxetan group than in ^{131}I-tositumomab group, but this difference was not statistically significant (75% ± 16% vs. 63% ± 29%, $P = 0.09$). Time from treatment to ANC nadir was shorter for ^{90}Y-ibritumomab tiuxetan group than for ^{131}I-tositumomab group (36 ± 9 vs. 46 ± 14 d, $P = 0.01$). Frequency of hematologic support after radioimmunotherapy was similar between ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups ($P = 1.00$, Fisher exact test). Seven patients in ^{90}Y-ibritumomab tiuxetan group and 8 patients in ^{131}I-tositumomab group required blood, platelets, or granulocyte-colony stimulating factor therapy, contributing to sharp upslopes in some curves.

required platelet transfusions, and 3 received granulocyte-colony stimulating factor therapy. In the ^{131}I-tositumomab group, 3 of 18 patients received both blood and platelet transfusions, 2 received platelet transfusions, and 4 received therapy with granulocyte-colony stimulating factor. Overall, the frequency of hematologic support after radioimmunotherapy was similar between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups ($P = 1.00$, Fisher exact test).

Nine patients had baseline platelet counts of less than 150,000 and were considered likely to have limited bone marrow reserve (decreased ability of the stem cell pool to repopulate the peripheral blood after radioimmunotherapy). Three patients received ^{90}Y-ibritumomab tiuxetan, and 6 received ^{131}I-tositumomab. Seven of the 9 patients in this subgroup received reduced-dose radioimmunotherapy, and there was an equal frequency of prior history of fludarabine use ($P = 1.00$, Fisher exact test). No significant differences in baseline platelet counts or ANC were found between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups (supplemental Table 2). Platelet and ANC nadirs were lower, maximum percentage declines in counts were higher, and time to ANC nadir was shorter for the ^{90}Y-ibritumomab tiuxetan group, but the differences were not statistically significant.

Limited data have suggested that hematologic toxicity after radioimmunotherapy is greater in patients who have previously received fludarabine chemotherapy (*24*). Four of the 20 patients in the ^{90}Y-ibritumomab tiuxetan group and 5 of the 18 in the ^{131}I-tositumomab group received fludarabine chemotherapy before radioimmunotherapy and had both baseline and nadir blood counts available for review. The frequency of patients who received attenuated doses of radioimmunotherapy was the same between the patients with (22%) and without (36%) a previous history of fludarabine chemotherapy ($P = 0.68$). Baseline platelet counts and ANC were not significantly different between those patients who previously received fludarabine and those who did not (supplemental Table 3). Nadir platelet counts were significantly lower in those patients with a history of fludarabine chemotherapy (38,122 ± 23,176 vs. 64,086 ± 53,680, $P = 0.04$). The ANC nadir tended to be lower in the fludarabine group (880 ± 623 vs. 1,370 ± 1,222, $P = 0.08$), but this difference was not statistically significant. The percentage change from baseline platelet count and ANC to nadir was the same for the fludarabine-treated group and the no-fludarabine group (supplemental Table 3). The proportion of patients who experienced grade 3 or 4 thrombocytopenia or neutropenia was the same between the fludarabine and no-fludarabine groups (data not shown). Further subgroup analysis between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups was not performed because of the limited number of patients in each group.

The other clinical toxicities reported were minor and similar between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups. The most commonly reported nonhematologic side effects were fatigue, cough, low-grade fever, and diarrhea. Patients treated with ^{131}I-tositumomab received potassium iodide tablets to block thyroid uptake of ^{131}I, and in none of these patients did clinically apparent hypothyroidism develop during the follow-up time of this study.

The median time from radioimmunotherapy to the last clinical follow-up examination in the ^{90}Y-ibritumomab

tiuxetan group was 9 mo (range, 2–41 mo). At the last clinical follow-up examination, 3 patients were alive and free of clinically apparent NHL, 9 were alive with NHL, and 8 were deceased. The duration of response was 10 mo for the 1 patient who had a CR at 12 wk.

For the ^{131}I-tositumomab group, the median time from radioimmunotherapy to the last clinical follow-up examination was 12 mo (range, 4–31 mo). Three patients were still alive and free of clinically apparent NHL, 9 were alive with NHL, and 6 were deceased. Of the 3 patients who achieved a CR at 12 wk after radioimmunotherapy, 2 were still in a CR at the last clinical follow-up examination (26 mo and 10 mo after therapy). The other patient died 11 mo after treatment of an unrelated illness.

Cumulative overall survival for patients with and without a response at 12 wk after radioimmunotherapy is presented in Figure 2. Overall survival was longer for patients who had a response to radioimmunotherapy at 12 wk after therapy ($P \leq 0.05$). Overall survival was not significantly different between the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups (Fig. 3).

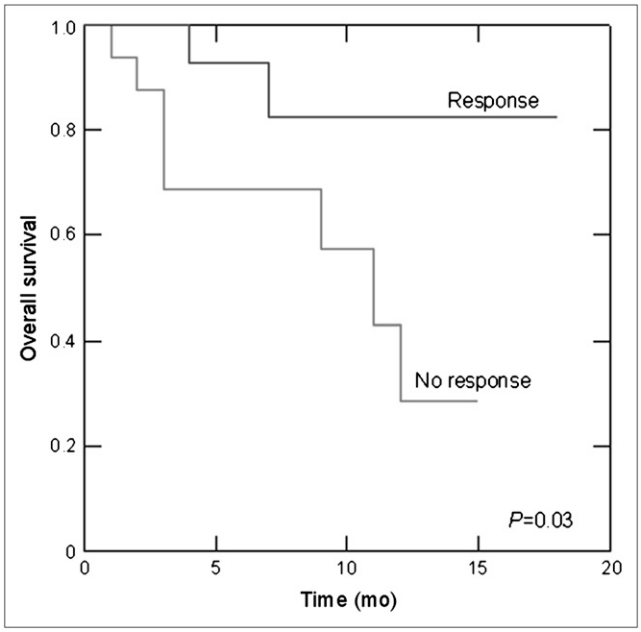

FIGURE 2. Fourteen of 30 patients (47%) had response at 12 wk after radioimmunotherapy. Four had CR (13%) and 10 had PR (33%). Cumulative overall survival was significantly longer for patients who responded to radioimmunotherapy at 12 wk than for those who did not ($P \leq 0.05$).

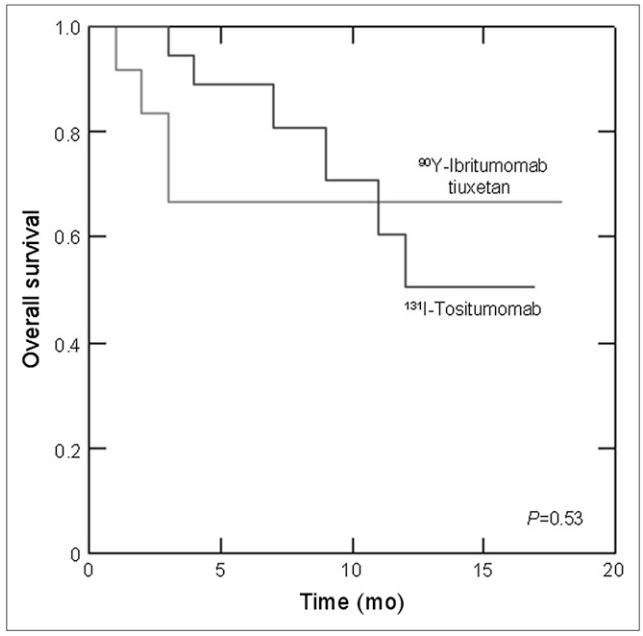

FIGURE 3. Overall survival did not significantly differ between patients who received ^{90}Y-ibritumomab tiuxetan and those who received ^{131}I-tositumomab.

DISCUSSION

Since the FDA approved ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab for the treatment of NHL, we have treated 38 patients with these agents clinically in a nontrial setting. In this population, the combined overall response rate of NHL to radioimmunotherapy at 12 wk after therapy was 47% and the CR rate was 13%. Comparing ^{90}Y-ibritumomab tiuxetan with ^{131}I-tositumomab, overall response rates and CR rates were similar (50% vs. 44% and 8% vs. 16%). The most common and severe toxicities were hematologic, but in general both therapies were very well tolerated.

The 47% overall response rate and 13% CR rate observed in our patient population are lower than the reported response rates of NHL to radioimmunotherapy. In clinical trials investigating ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab in patients with recurrent NHL after treatment, overall response rates have ranged from 60% to 83% and CR rates, from 15% to 52% (*8–15*). Several factors may have contributed to the lower response rates we observed. First, unlike the clinical setting, the research setting requires that patients meet rigid inclusion and exclusion criteria to receive treatment. The presence of a single exclusion criterion or the absence of a single inclusion criterion would make the patient ineligible for the trial even if clinically the study treatment was believed to be the best therapeutic option. In the clinical setting, eligibility criteria are not as strictly applied and clinician judgment plays a larger role. Additionally, inclusion and exclusion criteria often eliminate the sicker patients from participating in clinical trials, and this factor could make a therapy appear more efficacious in a clinical trial than in practice.

Our lower observed response rates may also have resulted from the referral of a sicker patient population for radioimmunotherapy at Johns Hopkins Hospital, which is a tertiary care center. Many of our patients had received multiple chemotherapy regimens before being referred for radioimmunotherapy, although their response did not appear to depend on the number of prior chemotherapy

regimens. It is possible that more patients in a tertiary care clinical setting may have disease that has transformed to a more aggressive histology or is further along in its course, possibly making them less likely to respond to radioimmunotherapy. Lower response rates in aggressive histologies have been previously reported, and our data further support this finding (*8,12,15*).

In our clinical experience, patients who received ^{131}I-tositumomab had lower baseline platelet counts but also had a lower percentage decline in platelets during treatment than did those who received ^{90}Y-ibritumomab tiuxetan (63% ± 28% vs. 79% ± 17%, $P = 0.04$). Baseline ANC was also similar between the 2 groups, but the percentage decline in ANC may have been lower in the ^{131}I-tositumomab group (63% ± 29% vs. 75% ± 16%, $P = 0.09$). The lack of statistical significance could be due to the small number of patients in each group in this study. Despite small patient numbers, the ANC nadir clearly occurred significantly earlier in the ^{90}Y-ibritumomab tiuxetan group than in the ^{131}I-tositumomab group (36 ± 9 d vs. 46 ± 14 d, $P = 0.01$). These data suggest that ^{131}I-tositumomab may be the preferable agent for patients with lower baseline blood counts or for those with less bone marrow reserve; that is, a decreased ability of the stem cell pool to repopulate the peripheral blood with platelets and neutrophils after radioimmunotherapy, because of extensive prior therapy.

A patient's bone marrow reserve is not routinely determined before chemotherapy, external-beam therapy, or radioimmunotherapy, but peripheral blood cell counts are used as a surrogate marker of an adequate stem cell pool. Other surrogate markers of decreased bone marrow reserve include a shortened time to nadir and a prolonged recovery time for a given therapy (*25*). We had 9 patients with baseline thrombocytopenia (platelet counts < 150,000). All these patients had normal baseline ANCs. In this subgroup, platelet and ANC nadirs were lower, maximum percentage declines in counts were higher, and time to ANC nadir was shorter for the ^{90}Y-ibritumomab tiuxetan group, but the differences were not statistically significant. These data are limited by the small numbers of patients, and drawing any definitive conclusions is difficult. However, the possibility is further raised that ^{131}I-tositumomab might be the preferable agent in patients with a limited bone marrow reserve, suggesting that further randomized, prospective studies are needed to answer this question.

^{131}I has a longer half-life than ^{90}Y and emits both γ- and β-radiations, whereas ^{90}Y is a pure β-emitter. The ability to image the ^{131}I-labeled antibody makes it possible for the megabecquerel amount of radiation administered to be adjusted so that the specific maximally tolerated whole-body radiation dose can be given to all patients despite variability in the rate of antibody clearance from individual patients (*21*). In theory, patient-specific dosing might optimize tumor dosimetry and minimize undesirable bone marrow toxicity even if patients have heterogeneous pharmacokinetics.

^{131}I-Tositumomab patient-specific dosing is compared with the weight-based dosing of ^{90}Y-ibritumomab tiuxetan in which patients of equal body weight might receive slightly different radiation doses because of some variability in clearance rates despite the administration of equal megabecquerel amounts. However, only modest correlations between pharmacokinetic parameters using ^{111}In-ibritumomab tiuxetan and hematologic toxicity have been demonstrated over a narrow dose range (*17,18*). Our finding that ^{131}I-tositumomab resulted in somewhat less severe declines in platelet counts and ANC than did ^{90}Y-ibritumomab tiuxetan, without major differences in efficacy, supports this theory. In addition, the earlier ANC nadir and the more severe myelotoxicity with ^{90}Y-ibritumomab tiuxetan may in part be explained by higher dose-rate effects with ^{90}Y because of its shorter half-life than that of ^{131}I. In animal models, greater myelotoxicity at lower red marrow doses is seen with higher initial dose rates (*26,27*). It is also possible that the lower β-energy of ^{131}I than of ^{90}Y and the lack of mechanisms for free iodine to target to the bone marrow, in contrast to the bone-targeting potential of free radiometals such as ^{90}Y, may contribute to the lower fractional declines in platelet counts seen with ^{131}I-tositumomab.

We found that patients with IPI scores of less than 2 and normal serum LDH levels were more likely to have responded to radioimmunotherapy at 12 wk than were those with elevated IPI scores or elevated LDH levels. Patients whose disease had an indolent histology and no bone marrow involvement at radioimmunotherapy also tended to be more likely to have responded at 12 wk. These findings were expected and are some of the patient and disease characteristics that previous investigators have found to be prognostic indicators (*8,12,15*). For ^{90}Y-ibritumomab tiuxetan, Witzig et al. in one study found that patients with indolent histologies, lower tumor grade, fewer than 2 sites of disease, and less bulky (<7 cm) disease were more likely to respond (*12*) but in another study found that no factors were clear prognostic indicators (*10*).

Considering the results of five ^{131}I-tositumomab clinical trials, Fisher et al. found that in a univariate analysis, older age, prior radiotherapy, less than a 75-cGy dose of total-body radiation, bulky disease, prior anthracycline-containing chemotherapy regimens, and no response to the last chemotherapeutic regimen were predictive of a lower overall response rate (*28*). Age, prior radiotherapy, and less than a 75-cGy dose of total-body radiation were not predictive in our relatively small patient population, and we did not assess the other parameters. Our patients were slightly older than those in previous ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab clinical trials.

An interesting finding in our study was that for both ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab no patient who presented with an elevated serum LDH level or bone marrow involvement at the time of radioimmunotherapy responded to therapy. Elevated baseline LDH levels at radioimmunotherapy and bone marrow involvement have been associated with

lower overall response and CR rates in some studies (*8,16*) but not in others (*9,10,12–14,16*). Thus, the clinical relevance of this finding is unclear. The association between baseline LDH level and response to radioimmunotherapy may be on a continuum, and it is possible that our patients had higher baseline LDH levels than did those in the previous studies. In patients with elevated baseline LDH levels and bone marrow involvement, the risks and benefits of therapy need to be carefully weighed, particularly in the face of other poor prognostic indicators such as bulky disease or nonindolent histologies.

Fludarabine is a chemotherapeutic agent used for indolent lymphoproliferative disorders. It is a purine analog that disrupts normal DNA transcription and ultimately results in the initiation of apoptosis and cell death. The dose-limiting toxicity of fludarabine is myelosuppression, and cumulative myelotoxicity can occur (*29*). In a summary of the safety of ^{90}Y-ibritumomab tiuxetan, the subset of 95 patients previously treated with fludarabine had lower baseline platelet counts and hemoglobin levels, were more likely to experience grade 3 or 4 cytopenias, and had a longer median duration of grade 3 or 4 thrombocytopenia than did the 254 patients without a history of fludarabine treatment (*24*).

In our small, single-center study, baseline and nadir platelet counts and ANCs were lower in the fludarabine group, but the differences were not statistically significant. Our patient numbers were limited, but our data suggest that patients with a history of fludarabine chemotherapy might be more susceptible to the hematologic toxicities of radioimmunotherapy. ^{131}I-Tositumomab might be the preferable agent in the subset of patients with a history of fludarabine chemotherapy, because of these findings and because of the observation of possibly less hematologic toxicity with ^{131}I-tositumomab.

The biologic effects of radiation therapy are not as rapid as those seen with chemotherapy, and the optimal time to initially assess the response after radioimmunotherapy is not clear. We found that a response at 12 wk after radioimmunotherapy correlated with long-term overall survival. We propose that performing the initial evaluation at this time point (12 wk after radioimmunotherapy) is reasonable. A watch-and-wait approach could be taken for those with a PR, near-CR, or CR, because a further response could occur beyond 12 wk after therapy. For those who have not responded at 12 wk, alternative therapies could be initiated after radioimmunotherapy. The overall impact of such an algorithm on patient outcomes needs further prospective study. Data on the use of ^{18}F-FDG PET/CT for monitoring the response of NHL to radioimmunotherapy will be reported elsewhere.

A limitation of this study was its retrospective nature and the small number of patients in subgroup analyses. We were unable to obtain complete hematologic toxicity data for 6 (30%) of the 20 patients treated with ^{90}Y-ibritumomab. In addition, we did not have clinical or imaging follow-up at 12 wk after radioimmunotherapy for 8 (40%) of the 20 patients treated with ^{90}Y-ibritumomab tiuxetan. These patients were treated earlier in our experience with radioimmunotherapy and were referred from some distance. It is unknown whether the additional data from these patients would have altered our results comparing the 2 agents. At present, after radioimmunotherapy, hematologic studies are performed at our institution, or we receive copies of the results, and most patients undergo baseline and 12-wk ^{18}F-FDG PET/CT to assess their response to therapy. Finally, the evaluation of response (changes in tumor size) was sometimes based on an unenhanced CT scan, which may be less accurate than a contrast-enhanced CT scan. Emerging data support the use of integrated ^{18}F-FDG PET, anatomic imaging, and clinical evaluation for assessing the response of lymphoma to therapy (*30,31*). The 12-wk response of 3 of the patients in the current population changed (2 CR to PR; 1 PR to CR) when the revised International Workshop Criteria, which include PET, were applied (data not shown). These changes did not change the results of this study because all 3 patients were within the "response" group.

CONCLUSION

Both ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab are generally well tolerated, and hematologic toxicities were as expected on the basis of the published literature. Lower overall response and CR rates in our study were most likely due to referral bias and the application of less stringent acceptance criteria for a patient to receive therapy. ^{131}I-tositumomab therapy, which is based on patient-specific dosimetry, appears to result in less severe declines in platelet counts than does ^{90}Y-ibritumomab tiuxetan therapy, for which dosimetry measures are not performed. ANC nadirs occurred significantly earlier with ^{90}Y-ibritumomab tiuxetan than with ^{131}I-tositumomab. ^{131}I-tositumomab may be a more appropriate choice for patients with a limited bone marrow reserve and prior fludarabine therapy, but a direct prospective, randomized comparison of the agents is necessary for such a conclusion to be drawn definitively. Finally, a short-term response to radioimmunotherapy agents at 12 wk appears to be associated with longer overall survival, and assessing the initial response at that time should be helpful for making further management decisions.

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Comparison of ^{90}Y-Ibritumomab Tiuxetan and ^{131}I-Tositumomab in Clinical Practice

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