

Multicenter Phase II Clinical Study of Iodine-131–Rituximab Radioimmunotherapy in Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma

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A B S T R A C T

Purpose

To evaluate efficacy and safety of iodine-131 (¹³¹I) –rituximab chimeric anti-CD20 antibody radioimmunotherapy in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (NHL).

Patients and Methods

After a standard loading dose of rituximab 375 mg/m², individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of ¹³¹I-rituximab followed by administration of a therapeutic activity of ¹³¹I-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy.

Results

Ninety-one patients were entered onto the trial: 78 patients (86%) had follicular lymphoma, six patients (7%) had mucosa-associated lymphoid tissue/marginal zone lymphoma, and seven patients (8%) had small lymphocytic lymphoma. The objective overall response rate (ORR) was 76%, with 53% attaining a complete response (CR) or CR unconfirmed (CRu). Median duration of response for patients achieving CR/CRu was 20 v 7 months for those with a partial response ($P = .0121$). Median progression-free survival for the entire cohort was 13 months, with 14% remaining relapse free beyond 4 years. Median follow-up was 23 months, with a 4-year actuarial survival rate of 59% ± 10%. Toxicity was principally hematologic; grade 4 thrombocytopenia occurred in 4% and neutropenia occurred in 16% of patients, with nadirs at 6 to 7 weeks after treatment.

Conclusion

¹³¹I-rituximab radioimmunotherapy of relapsed or refractory indolent NHL achieves high ORR and CR rates with minimal toxicity.

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is becoming more prevalent and is now the fifth most common malignancy in the United States.¹ The advent of immunotherapy with rituximab anti-CD20 monoclonal antibody (Mab) in combination with chemotherapy results in prolonged remission and improved survival in patients with indolent B-cell NHL,^{2,3} as exemplified by an estimated 4-year overall survival (OS) rate of 91% after initial treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab.⁴ For patients with relapsed NHL, immunotherapy with rituximab alone has an overall response rate (ORR) of 50% and median response duration of 11 months.⁵

Radioimmunotherapy with an anti-CD20 Mab conjugated to a beta-emitting radioisotope will deliver radiation not only to tumor cells that bind the antibody but also, due to a cross-fire

effect, to neighboring tumor cells inaccessible to the antibody or with insufficient antigen expression. Indolent NHL cells are inherently radiosensitive and rituximab synergistically enhances radiation-induced apoptosis.⁶

Anti-CD20 antibodies radiolabeled with yttrium-90 (⁹⁰Y) –ibritumomab tiuxetan (Zevalin; Biogen Idec Inc, San Diego, CA, and Schering AG, Berlin, Germany) or iodine-131 (¹³¹I) –tositumomab (Bexxar; Corixa Corp, Seattle, WA) are available commercially for radioimmunotherapy of relapsed NHL and achieve ORRs of 75% to 80%, including complete response (CR) in 20% to 50% of patients, with a response duration of 10 to 14 months.^{7,8}

Treatment with murine antibody radiolabeled conjugates may induce human antimouse antibodies (HAMA). Neither of the commercially available agents is approved for repeat administration, although there are preliminary data on safety of re-treatment.⁹

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Freedom from HAMA is especially important if first-line radioimmunotherapy is contemplated. Although initial treatment with ¹³¹I-tositumomab achieved excellent response rates of 95% and a CR rate of 75%, the 62% incidence of HAMA¹⁰ in such relatively immunocompetent patients may compromise therapeutic options at relapse. Given that relapse of indolent NHL is probable despite the increasing efficacy of current therapies, we chose to radioiodinate the human/murine chimeric anti-CD20 Mab rituximab to obviate induction of HAMA and to allow repeat administration.

A pilot study of 10 patients with relapsed or refractory indolent B-cell lymphoma demonstrated the efficacy and safety of rituximab 375 mg/m² administered with ¹³¹I-rituximab tracer and a therapeutic prescribed dose of 0.75 Gy to the whole body. The methodology has been described previously, and preliminary data from 31 of the patients in this study were included in that report.¹¹

This was a physician-sponsored trial with individualized prospective dosimetry with nonmyeloablative intent.

PATIENTS AND METHODS

Institutional Ethics Committee approval in accordance with Australian National Health and Medical Research Council guidelines and the Declaration of Helsinki, and written informed consent from each patient was obtained. The trial was registered with the Therapeutic Goods Administration of the Commonwealth Government of Australia.

Ninety-one patients with relapsed (n = 76) or refractory (n = 15) follicular, mucosa-associated lymphoid tissue (MALT) /marginal zone, or small lymphocytic NHL were entered onto the study (Table 1) between May 2000 and December 2004 at Fremantle Hospital (Fremantle, Western Australia) and the Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia). Eligible patients were required to have histologically confirmed disease, be ≥ 18 years old, have a WHO performance status of less than 3, and a life expectancy of more than 3 months. Patients who had received previous rituximab (MabThera; Roche Products Pty Ltd, Dee Why, Australia) were eligible if more than 6 months had elapsed from treatment. Exclusion criteria included blood neutrophils less than 1.5 × 10⁹/L or platelets less than 100 × 10⁹/L; significant impairment of cardiac, renal, or hepatic function; or the administration of chemotherapy or radiotherapy within 6 weeks. The percentage of bone marrow involvement was not a study exclusion criterion.

Patients with follicular lymphoma were evaluated further according to the Follicular Lymphoma International Prognostic Index (FLIPI)¹² and were stratified into low-, intermediate-, and high-risk groups. In six patients, baseline data were insufficient to assess the FLIPI score.

Dosimetry and Radioimmunotherapy

Rituximab was radioiodinated at each institution with ¹³¹I-sodium iodide (Australian Radioisotopes and Industrials, Lucas Heights, New South Wales, Australia) using a chloramine-T method as described previously.¹¹ Radiolabeling yield was more than 98% and immunoreactive fraction of labeled antibody was more than 80%.¹¹ A tracer activity of 200 MBq ¹³¹I-rituximab was administered intravenously after a dose of 375 mg/m² rituximab unlabeled antibody. Within an hour, whole-body imaging and background scans were performed, and were repeated at 4 and 7 days under the same imaging conditions. The residence time of ¹³¹I-rituximab was calculated from whole-body gamma camera counts at these time points.¹¹ Imaging was performed 8 days after therapy. The radioimmunotherapeutic dose was administered 7 to 14 days after an additional 375 mg/m² loading dose of unlabeled rituximab. The administered activity was estimated to deliver a whole-body radiation absorbed dose of 0.75 Gy. This prescribed radiation dose was based on the dose-escalation studies of Kaminski et al¹³ with ¹³¹I-tositumomab.

To minimize risk of hypothyroidism from free radio-iodine, administration of Lugol's iodine was commenced 24 hours before the tracer dosimetry study and continued for 7 days after ¹³¹I-radioimmunotherapy in the first 35

Table 1. Patient Characteristics (n = 91)

Characteristic	No. of Patients	%
Age, years		
Median	62	
Range	30-84	
> 60	52	57
Sex		
Male	55	60
Female	36	40
Performance status (WHO)		
Median	1	
Serum LDH		
Normal	60	66
Elevated	26	29
Unknown	5	5
Serum beta ₂ -microglobulin		
Normal	50	55
Elevated	25	27
Unknown	16	18
Histology		
Follicular, grade		
1	43	47
2	20	22
3	15	16
MALT/marginal zone	6	7
Small lymphocytic	7	8
Maximum tumor diameter, mm		
≥ 50	23	25
< 50	68	75
FLIPI (follicular, n = 78)		
0-1	30	38
2	24	31
≥ 3	18	23
Unknown	6	8
Bone marrow involvement		
Yes	28	31
≥ 25%	9	32
No	63	69
Previous chemotherapy regimens		
1	28	31
2	29	32
≥ 3	34	37
Prior rituximab		
Yes	59	65
No	32	35
Response to prior therapy		
Refractory	15	16
Relapsed	76	84
Stage at study entry		
I/II	31	34
III/IV	60	66

Abbreviations: LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoma tissue; FLIPI, Follicular Lymphoma International Prognostic Index.

patients and for 21 days in all subsequent patients, based on evidence of thyroid uptake on post-treatment imaging in the initial cohort.

The treatment protocol for the phase II clinical trial was the same at the two institutions. However, referring physicians had discretion to prescribe the standard four-dose regimen of 375 mg/m² rituximab in conjunction with the radioimmunotherapy. Thus 59 patients were administered two additional 375 mg/m² doses of rituximab administered during the 2 weeks after the tracer and therapeutic administrations. The remaining 32 patients received only the

two unlabeled doses of 375 mg/m² rituximab administered on the days of the tracer and therapeutic doses of ¹³¹I-rituximab.

Three patients who received initial treatment with ¹³¹I-rituximab before entry to this study and three who experienced relapse on study and were re-treated received only two doses of 375 mg/m² rituximab.

Response and Toxicity Evaluation

Disease status was evaluated by physical examination; serial computed tomography (CT) scans of chest, abdomen, and pelvis; and bone marrow biopsies (if bone marrow was involved at baseline) at 3, 6, and 12 months after radioimmunotherapy, and then as clinically indicated. Response evaluation was in accord with the International Workshop of Standardized Response Criteria for NHL.¹⁴

The National Cancer Institute Common Toxicity Criteria Version 2 were used.¹⁵ Hematologic assessment with full blood counts was carried out weekly from treatment until count recovery, then every 3 months for 2 years. Hepatic and renal function was assessed weekly for 6 weeks, then every 3 months. Thyroid function was monitored at 3-month intervals. Human antichimeric antibodies were not assayed in this study but tracer whole-body dosimetry imaging before radioimmunotherapy in each patient was used to monitor biodistribution of ¹³¹I-rituximab.

Statistical Methods

The primary measurement of efficacy was the response rate 3 months after treatment. The Kaplan-Meier product limit method was used to estimate OS, progression-free survival (PFS), and response duration.

RESULTS

Response to Treatment

All 91 enrolled patients (Table 1) received the whole-body prescribed radiation absorbed dose of 0.75 Gy by administered activities of 1.36 to 5.34 GBq ¹³¹I-rituximab (median, 2.4 GBq). Objective response was observed in 69 patients (76%). Forty-eight patients (53%) achieved a CR/CRu (CRu, complete response unconfirmed) at the 12-week assessment. The median duration of response for responding patients was 10 months (range, 1 to 48 months); for patients in CR/CRu, median duration of response was 20 months (range, 1 to 48 months), and for partial response (PR), median duration of response was 7 months (range, 1 to 20 months; Fig 1). The median PFS for all responding patients was 13 months with 14% ± 6% of patients estimated to be free of progression beyond 4 years (Fig 2).

With a median follow-up of 23 months (range, 4 to 58 months) the estimated median survival was 50 months, with a 4-year actuarial

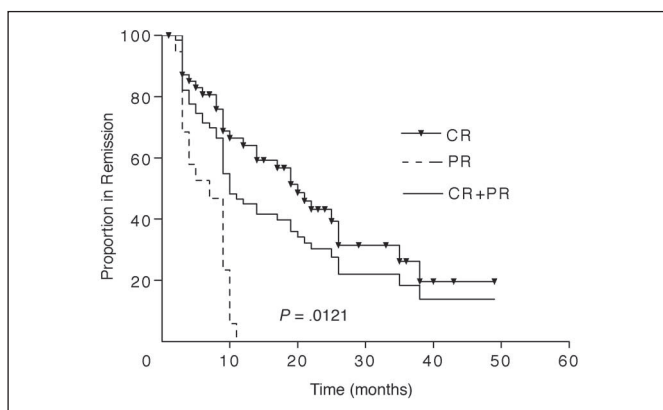


Fig 1. Duration of response by remission status. CR, complete response; PR, partial response.

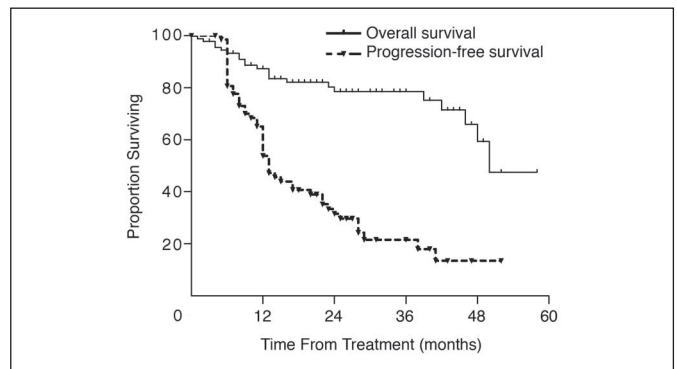


Fig 2. Overall and progression-free survival.

survival rate of 59% ± 10% (Fig 2). Survival of complete responders was significantly longer than that of nonresponders ($P < .0001$; Fig 3).

In a univariate analysis (Table 2), stage I/II disease and fewer than two prior chemotherapy regimens were associated with a higher ORR ($P \leq .02$), whereas age ≤ 60 , stage I/II disease, and low FLIPI score were associated with a significantly higher CR/CRu rate ($P \leq 0.012$). Histology was not associated strongly with response, although all six patients with MALT/marginal zone NHL responded. The presence of marrow involvement, prior rituximab treatment, elevated serum levels of β_2 -microglobulin and lactate dehydrogenase, and tumor bulk were not associated with a significant reduction in ORR or CR rate. Bulky tumors accumulated high levels of ¹³¹I-rituximab activity (Fig 4).

The median duration of response for the FLIPI low-, intermediate-, and high-risk groups was 14, 12, and 9 months, respectively ($P = .377$) but neither this trend nor OS were significantly different between these groups.

Of the six patients who were re-treated, four had achieved CR and two had achieved PR with initial therapy. The median response duration was 12 months (range, 5 to 49 months). Four of these patients achieved a second response (three CRs and one PR), with a median response duration of 11 months (range, 8 to 14 months). The median time interval between radioimmunotherapy treatments was 23 months (range, 9 to 54 months). Hematologic toxicity was not increased with re-treatment (Table 3).

Toxicity

Toxicity was principally hematologic, with grade 4 thrombocytopenia occurring in 4% and grade 4 neutropenia in 16% of patients

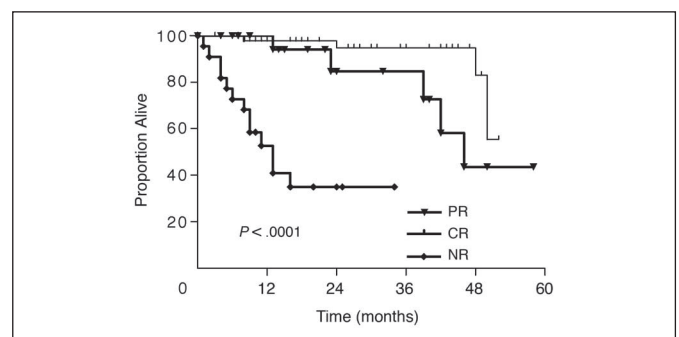


Fig 3. Survival by remission status. PR, partial response; CR, complete response; NR, no response.

Table 2. Subgroup Analysis for Response

Characteristic	No. of Patients	ORR (n = 69)		P*	CR/CRu (n = 48)		P*
		No.	%		No.	%	
Age at therapy, years							
≤ 60	39	33	85	.090	28	72	.002
> 60	52	36	69		20	38	
Stage at entry							
I or II	31	28	90	.020	22	71	.012
III or IV	60	41	68		26	43	
FLIPI							
0-1	30	25	83	.11	22	73	.003
2	24	18	75		12	50	
≥ 3	18	10	56		4	22	
Histology							
Follicular, grade				.10			.17
1	43	35	81		24	56	
2	20	15	75		13	65	
3	15	8	53		5	33	
MALT/marginal zone	6	6	100		5	83	
Small lymphocytic	7	5	71		1	14	
Bone marrow involvement				.90			.73
Yes	28	21	75		14	50	
No	63	48	76		34	54	
Prior rituximab				.89			.35
Yes	59	45	76		29	49	
No	32	24	75		19	59	
Prior chemotherapy regimens				.011			.14
1	28	26	93		18	64	
≥ 2	63	43	68		30	48	
Serum beta ₂ -microglobulin				.25			.102
Normal	50	40	80		30	60	
Elevated	25	17	68		10	40	
Unknown	16	12	75		8	50	
Serum LDH				.366			.367
Normal	60	47	78		34	57	
Elevated	26	18	69		12	46	
Unknown	5	4	80		2	40	
Maximum tumor diameter, cm				.80			.30
≥ 5	23	17	74		10	43	
< 5	68	52	76		38	56	

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; MALT, mucosa-associated lymphoma tissue; ORR, overall response rate; CR, complete response; CRu, unconfirmed complete response; LDH, lactate dehydrogenase.
*χ² analysis for comparison of response rates among subgroups.

(Table 4). Three patients required platelet transfusion, one patient required packed RBCs, and one patient received granulocyte colony-stimulating factor. Oral antibiotics were administered to one patient for febrile neutropenia, but no patient was hospitalized with infection. The median time to platelet nadir was 6 weeks ($80 \times 10^9/L$; range, 4 to $223 \times 10^9/L$), 7 weeks for neutrophils ($1.6 \times 10^9/L$; range, 0.03 to $9.1 \times 10^9/L$), and 8 weeks for hemoglobin (118 g/L; range, 75 to 151).

Platelet nadirs were lower in patients with bone marrow involvement $\geq 25\%$, but the incidence of grade 4 toxicity did not differ from that observed in patients with less than 25% bone marrow involvement (Table 5).

Five patients (5.5%), median age 66 years (range, 48 to 70 years), developed a myelodysplastic syndrome (MDS) after a median follow-up of 23 months. One patient experienced disease progression to acute myeloid leukemia (AML). All of the MDS patients had received prior chemotherapy (median, two prior therapies; range, one to four prior

therapies), two had received external-beam radiotherapy, and one had received two prior treatments with ¹³¹I-rituximab.

At the time of study entry, an elevated thyroid-stimulating hormone or pre-existing clinical hypothyroidism requiring thyroxine replacement was present in 10 patients. At follow-up, an additional seven patients had an elevated thyroid-stimulating hormone, representing a 9% incidence of treatment-related subclinical or clinical hypothyroidism.

DISCUSSION

A single therapeutic dose of ¹³¹I-rituximab resulted in a high ORR (76%) and CR/CRu (53%). Median duration of response was 10 months for all responders and 20 months for CR/CRu. These results are comparable to ¹³¹I-tositumomab therapy median response duration in

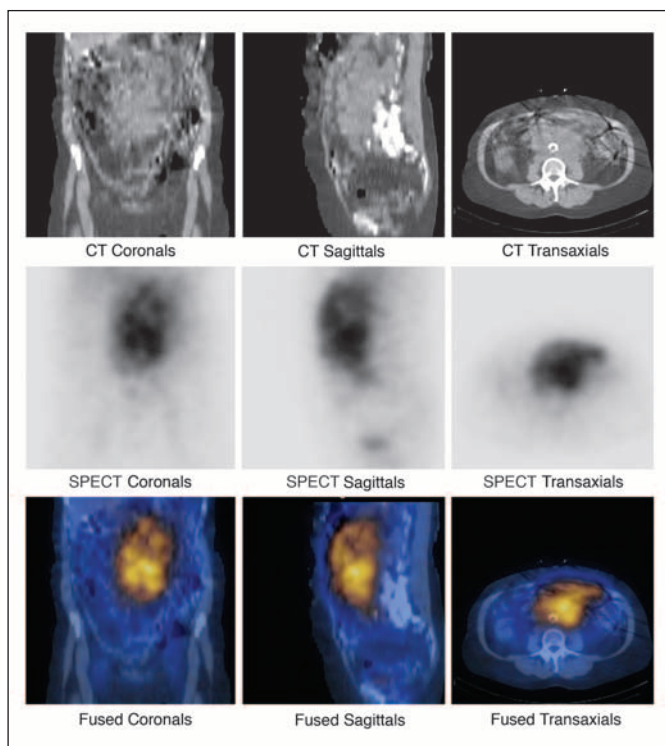


Fig 4. Single-photon emission computed tomography (SPECT)/computed tomography (CT) coregistered images 8 days after intravenous administration of 2.7 GBq iodine-131-rituximab radioimmunotherapy showing intense activity throughout the 6 × 12 cm retroperitoneal para-aortic lymphoma mass. Whole-body imaging at the same time shows no significant radioactivity outside the tumor, which subsequently regressed, measuring 4 × 6 cm on magnetic resonance imaging follow-up at 9 months.

relapsed/refractory follicular NHL of 13.6 months, of whom 18 of 32 had a CR of median duration 14.5 months.⁹ They are also in accord with results of radioimmunotherapy of NHL using ⁹⁰Y-ibritumomab tiuxetan.^{7,8}

In a comparison of ⁹⁰Y-ibritumomab tiuxetan with single-agent rituximab in patients with low-grade refractory or relapsed or transformed CD20⁺ NHL, radioimmunotherapy resulted in an ORR of 80% (34% CR/CRu and 45% PR) compared with an ORR of 56% (20% CR/CRu and 36% PR) for rituximab therapy alone.⁷ Our study shows similarly high response and CR rates with ¹³¹I-

rituximab radioimmunotherapy. The additional expense of radio-labeling rituximab in-house above the acquisition cost of the drug is modest, at around US \$1,000.

The main toxicity of ⁹⁰Y-ibritumomab tiuxetan radioimmunotherapy is reversible myelosuppression with grade 4 neutropenia seen in 32%, thrombocytopenia seen in 5%, and anemia seen in 3% of patients.⁷ Grade 3-4 myelosuppression occurred in 30% to 40% of patients with relapsed NHL receiving ¹³¹I-tositumomab, with nadirs typically at week 4 to 6.⁸ Grade 4 neutropenia occurred in 16%, grade 4 thrombocytopenia occurred in 3%, and grade 4 anemia occurred in 2% of 677 previously treated patients.⁸ These figures are similar to our study, in which grade 4 neutropenia occurred in 16% and grade 4 thrombocytopenia occurred in 4% of patients.

All patients in the current study had had significant prior therapy, rendering evaluation of MDS risk (MDS occurred in five patients) difficult. The incidence of MDS/AML in 995 patients with relapsed/refractory low-grade NHL treated with ¹³¹I-tositumomab was 3.5%, with an annualized incidence of 1.6%,¹⁶ compared with our study of 91 patients in which the incidence of MDS was 5.5%. The rate of development of MDS/AML in NHL after radioimmunotherapy is comparable to that of conventionally treated NHL patients of 1% to 1.5% per year of therapy.¹⁷

The relatively modest hematologic toxicity of radioimmunotherapy using ¹³¹I-tositumomab or ¹³¹I-rituximab is likely to be related to calculation of prospective individualized dosimetry, allowing a standard prescribed whole-body radiation dose of 0.75 Gy.^{11,18} Prospective quantitative dosimetry cannot be performed with ⁹⁰Y-ibritumomab tiuxetan due to the absence of gamma emission from ⁹⁰Y, but surrogate imaging of ¹¹¹In-ibritumomab tiuxetan showed no correlation of hematologic toxicity with estimates of total body absorbed radiation dose or dose to red marrow.¹⁹

Monte Carlo-based dosimetric analysis of quantitative single-photon emission CT-CT images in 27 of our patients after ¹³¹I-rituximab radioimmunotherapy validated the whole-body dosimetry method and demonstrated that the standard prescribed radiation absorbed dose of 0.75 Gy corresponded with a median dose to red marrow of 1.9 Gy.²⁰ This radiation exposure of hematopoietic marrow was less than the 2-Gy threshold for myelotoxicity and is reflected in the minor, self-limited myelosuppression encountered in this study.

Table 3. Hematologic Toxicity of Six Patients Receiving a Second ¹³¹I-Rituximab Treatment

Parameter	Median Nadir	Range	Time to Nadir (week No.)	Grade 4 Toxicity (%)	P*
Platelets					
First treatment	74 × 10 ⁹ /L	34-105 × 10 ⁹ /L	7	0	.51
Second treatment	62 × 10 ⁹ /L	48-83 × 10 ⁹ /L	7	0	
Neutrophils					
First treatment	1.6 × 10 ⁹ /L	0.7-3.4 × 10 ⁹ /L	7	0	.29
Second treatment	1.1 × 10 ⁹ /L	0.7-1.6 × 10 ⁹ /L	8	0	
Hemoglobin					
First treatment	124 g/L	120-134 g/L	8	0	.66
Second treatment	120 g/L	108-132 g/L	9	0	

NOTE. According to National Cancer Institute Common Toxicity Criteria Version 2.
*Paired *t* test.

Table 4. Hematologic Toxicity (n = 91)

Parameter	Median Nadir	Range	Time to Nadir (week No.)	Grade 4 Toxicity (%)	Median Duration Toxicity (days)	Range (days)
Platelets	80 × 10 ⁹ /L	4-223 × 10 ⁹ /L	6	4	14	7-21
Neutrophils	1.6 × 10 ⁹ /L	0.03-9.1 × 10 ⁹ /L	7	16	14	7-28
Hemoglobin	118 g/L	75-151 g/L	8	0		

NOTE. According to National Cancer Institute Common Toxicity Criteria Version 2.

Hematologic toxicities associated with ¹³¹I-tositumomab treatment of NHL have not been shown to correlate with the extent of bone marrow involvement.²¹ In our patients the incidence of CR/CRu to ¹³¹I-rituximab was the same for those with (50%) as without (54%) baseline bone marrow involvement (Table 2), and toxicities were comparable.

Humanized Mab is cleared from the circulation at a slower rate than murine antibodies, thus prolonging radiation exposure and potentially increasing dose to normal tissue and increasing toxicity.²² Our study using ¹³¹I-rituximab has shown similar efficacy to those reported using ¹³¹I-tositumomab or ⁹⁰Y-ibritumomab tiuxetan^{7,8,23} without increased incidence of myelosuppression. The biodistribution and tissue kinetics of ¹³¹I-rituximab have been shown to be specific for each patient and remain constant during unlabeled antibody therapy.²⁴ Radioimmunotherapy radiation doses can therefore be extrapolated reliably from a preceding dosimetry study using the whole-body effective half-life normalized to ideal body weight to calculate an administered activity of ¹³¹I-rituximab radioimmunotherapy sufficient to deliver a prescribed whole-body radiation dose of 0.75 Gy.²⁰

The advent of combined immunochemotherapy regimens for treatment of follicular NHL has resulted in major clinical benefits, both in untreated patients^{2,3} and those with relapsed/refractory disease.^{25,26} Rituximab immunotherapy as a single-agent treatment of newly diagnosed advanced follicular NHL has also been advocated as an alternative to previous watch-and-wait policies, with reported ORR of 72% with 36% CR and median time to progression of 2.2 years.²⁷

Thus, it may be anticipated that the majority of patients with relapsed or refractory indolent NHL referred for consideration of radioimmunotherapy will have been exposed to rituximab previously. In our patient population, two thirds had received prior

rituximab, but the subsequent response to radioimmunotherapy with ¹³¹I-rituximab was not impaired (Table 2). Radioimmunotherapy with ¹³¹I-tositumomab has also been shown to be effective in follicular grade 1 and 2 NHL with progression after prior rituximab, with ORR of 86%, including CR in 57% and 3-year PFS 48% in nonbulky disease.²⁸

In our study the CR/CRu rate of 43% was reduced modestly in patients with tumors ≥ 5 cm diameter compared with that seen in nonbulky disease (Table 2), consistent with previous reports suggesting poorer response in patients with larger tumor burden.^{28,29} Post-therapy imaging in our patients, however, demonstrated that the tumor uptake of radiolabeled antibody is substantial throughout even large lymphoma masses (Fig 4), suggesting that tissue delivery may not be limiting.

Although post-therapy single-photon emission CT-CT imaging provides validation of marrow dosimetry,²⁰ quantitation of radiation absorbed dose to tumor remains challenging. External-beam radiotherapy is pulsed intermittently at approximately 60 Gy/h, but effective dose rates as low as 0.05 Gy/h can stop the growth of radiosensitive NHL cells.³⁰ However, measurement of such a parameter in radioimmunotherapy patients is difficult.

In the few patients in whom tumor dose has been reported, the mean 2.86 Gy/GBq for ¹³¹I-anti CD 20 murine Mab (n = 5) is similar to the mean of 3.86 Gy/GBq for ¹³¹I-rituximab.³¹ Tumor dose estimates in three patients on our study ranged from 6.9 to 20.8 Gy (data not shown), which is comparable to the mean of 15 Gy to tumor reported for ¹³¹I murine anti-CD 20 Mab.³¹

It is likely that there is a threshold for effective radiation dose to tumor, which apparently is attained when a surrogate whole-body dose of 0.75 Gy is used. A prescribed whole-body ¹³¹I-rituximab dose of 0.45 Gy appeared to be less clinically

Table 5. Hematologic Toxicity in Patients With Bone Marrow Involvement (< 25%, n = 19; ≥ 25%, n = 9)

Parameter	Median Nadir	Range	Time to Nadir (week No.)	Grade 4 Toxicity (%)	P*
Neutrophils					
< 25%	1.38 × 10 ⁹ /L	0.46-3.54 × 10 ⁹ /L	9	26	.29
≥ 25%	1.23 × 10 ⁹ /L	0.41-3.2 × 10 ⁹ /L	8	22	
Platelets					
< 25%	77 × 10 ⁹ /L	15-210 × 10 ⁹ /L	5	10	.0071
≥ 25%	44 × 10 ⁹ /L	12-109 × 10 ⁹ /L	5	11	
Hemoglobin					
< 25%	118 g/L	81-142 × 10 ⁹ /L	8	0	.0034
≥ 25%	106 g/L	89-111 × 10 ⁹ /L	8	0	

NOTE. According to National Cancer Institute Common Toxicity Criteria Version 2.

*Paired t test.

effective in patients with aggressive lymphoma who were more heavily pretreated than in our study.³² However, this study also used a reduced loading dose of cold antibody, 2.5 mg/kg rituximab, in contrast to the 375 mg/m² used in our study. Whether the total dose of unlabeled antibody influences the efficacy of radioimmunotherapy is conjectural, and no significant difference in outcome was evident in our study between patients

receiving two or four doses of cold rituximab in association with ¹³¹I-rituximab radioimmunotherapy.

Our study demonstrates that ¹³¹I-rituximab radioimmunotherapy of patients with relapsed or refractory indolent NHL is safe and effective. This nonmyeloablative approach may be performed on an outpatient basis and preserves radioimmunotherapeutic re-treatment options for relapse.

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