Radioimmunotherapy with iodine ^{131}I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience

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CD20-targeted radioimmunotherapy is a promising new treatment for B-cell non-Hodgkin lymphoma (NHL). We now provide updated and long-term data on 59 chemotherapy-relapsed/refractory patients treated with iodine ^{131}I tositumomab in a phase I/II single-center study. Fifty-three patients received individualized therapeutic doses, delivering a specified total-body radiation dose (TBD) based on the clearance rate of a preceding dosimetric dose. Six patients received dosimetric doses only. Dose-escalations of TBD were conducted separately in patients who had or had not undergone a prior autologous stem cell transplant (ASCT) until a nonmyeloablative maximally tolerated TBD was established (non-ASCT = 75 cGy, post-ASCT = 45 cGy). Fourteen additional non-ASCT patients were treated with 75 cGy. Unlabeled antibody was given prior to labeled dosimetric and therapeutic doses to improve biodistribution. Forty-two (71%) of 59 patients responded; 20 (34%) had complete responses (CR). Thirty-five (83%) of 42 with low-grade or transformed NHL responded versus 7 (41%) of 17 with de novo intermediate-grade NHL (*P* = .005). For all 42 responders, the median progression-free survival was 12 months, 20.3 for those with CR. Seven patients remain in CR 3 to 5.7 years. Sixteen patients were re-treated after progression; 9 responded and 5 had a CR. Reversible hematologic toxicity was dose limiting. Only 10 patients (17%) had human anti-mouse antibodies detected. Long-term, 5 patients developed elevated thyroid-stimulating hormone levels, 5 were diagnosed with myelodysplasia and 3 with solid tumors. A single, well-tolerated treatment with iodine ^{131}I tositumomab can, therefore, produce frequent and durable responses in NHL, especially low-grade or transformed NHL. (Blood. 2000;96:1259-1266)

Introduction

Although the majority of patients with non-Hodgkin lymphoma (NHL) achieve remissions after initial treatment with chemotherapy with or without radiation therapy, only about 25% of patients are cured.[1] In general, only patients diagnosed with intermediate- or high-grade NHL are cured, whereas patients with low-grade NHL are rarely cured.[1,2] Indeed, the natural history of low-grade NHL has not been altered since the 1960s.[2] Although the median survival of patients with low-grade NHL is 7 to 8 years, patients typically experience multiple relapses of the disease. Response rates and duration of response diminish with re-treatment, and many patients experience transformation to a higher-grade histology, termed transformed NHL.[2,3] Likewise, for patients with relapsed intermediate- or high-grade NHL, the prognosis is poor. High-dose chemotherapy with or without external-beam total-body irradiation with bone marrow or peripheral blood autologous stem cell transplantation (ASCT) has been reported to cure 20% to 50% of such patients.[4] Many patients, however, are inappropriate candidates for this treatment because of advanced age, comorbid conditions, or primary resistance to chemotherapy.[5,6] Thus, new treatments based on novel therapeutic principles are needed for NHL.

Among new treatments being developed for NHL, radioimmunotherapy (RIT) has shown promise. RIT involves the administration of radionuclide-labeled monoclonal antibodies reactive with a tumor cell-surface antigen. Provided the tumor-associated antigen is expressed by the tumor cells and minimally or not expressed by other tissues, selective targeting of radiation to tumor sites can be theoretically accomplished with relative sparing of radiation exposure of normal tissues. Moreover, the antibody moiety carrying the radionuclide can potentially recruit host cytolytic immune mechanisms or produce direct antiproliferative effects against targeted tumor cells.

NHL is a particularly appropriate choice for this treatment approach for several reasons. First, lymphomas are highly radiosensitive. Second, a variety of lymphoid lineage-specific antigens have been identified as potential targets for antibody-based therapies. Third, unlabeled monoclonal antibodies directed against some of these antigens have demonstrated antitumor activity in patients with NHL.[7-12]

The CD20 antigen fulfills many of the desired features of a target antigen for RIT of B-cell NHL, the most common type of NHL. This 35-kd transmembrane glycoprotein is abundantly

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expressed by more than 95% of B-cell NHL.[13,14] Although some normal B cells express CD20, it is not expressed on the cell surface by early progenitor B cells or by mature plasma cells.[13] The antigen is not shed into the circulation nor is it internalized on antibody binding,[15,16] providing a prolonged antibody residence on the cell surface and, consequently, an extended exposure of the tumor to radiation. In addition, CD20 is involved in the differentiation and proliferation of B cells.[17,18]

Tositumomab (previously referred to as anti-B1 antibody) is a mouse immunoglobulin G2a (IgG2a) monoclonal antibody specific for CD20.[13] Our group has demonstrated that tositumomab can mediate cytolysis of human B-cell tumor cells in vitro in conjunction with human peripheral blood mononuclear cells, as well as inhibit the growth of human lymphoma xenografts in nude mice.[19] More recently, tositumomab and other anti-CD20 antibodies have been found to be able to induce apoptosis of human B-cell tumor cell lines.[20-22]

Given the favorable features of CD20 as a target for RIT and the preclinical data on tositumomab, we initiated a phase I/II study of tositumomab labeled with iodine-131 (iodine ^{131}I tositumomab) in 1990 for patients with relapsed or refractory B-cell NHL. Iodine-131 (^{131}I) was selected for radiolabeling because of its short path-length beta particle emission, its gamma emission, its well-established labeling chemistry, its appropriately long half-life, and its common use in clinical practice. The beta emission allows the irradiation of small and large foci of targeted tumor tissue with relatively little exposure of surrounding normal tissues. The gamma emission permits noninvasive tumor imaging, quantitative tumor and organ dosimetry, as well as patient-specific dosing based on calculation of an individual patient's clearance of total-body radioactivity. Early reports of results obtained in the initial patients entered in this study suggested high response rates and excellent tolerability.[23-25] We now report results on the entire cohort of this unique set of patients, including long-term safety and survival data up to 8 years after treatment.

Patients, materials, and methods

Patient selection

The study enrolled 59 patients from April 24, 1990, to January 17, 1996. Eligible patients were required to have a histologically confirmed diagnosis of CD20-positive B-cell NHL, to be at least 18 years old, to have measurable disease, to have relapsed or failed to respond to at least one prior chemotherapy regimen, and to have not received treatment for at least 4 weeks before study entry. In addition, patients were required to have less than 25% of their marrow space affected by lymphoma (as assessed by bilateral iliac crest bone marrow biopsy), an absolute neutrophil count greater than 1500/μL, a platelet count greater than 100 000/μL, normal hepatic and renal function, a Karnofsky performance score of at least 60, a life expectancy of at least 3 months, no serum human antimouse antibodies (HAMA), and no serious coexisting illness. The study was approved by the Institutional Review Board of the University of Michigan; written informed consent was required of all patients.

Preparation of iodine ^{131}I tositumomab

Tositumomab was provided by Coulter Pharmaceutical, Inc (South San Francisco, CA). The antibody was radiolabeled on-site with ^{131}I, and the product was purified and tested for immunoreactivity and pyrogen contamination as previously described.[23,26,27] Antibody concentration was originally estimated on the basis of an optical density extinction coefficient of 1.0. Subsequently, the correct extinction coefficient was found to be 1.45 at 280 nm. All doses in this report are based on the corrected extinction coefficient, which has the net effect of apparently "lowering" the injected mass of tositumomab from previously published reports.[23,24] For example, doses of 95 mg and 475 mg in this report were previously presented as 135 mg and 685 mg, respectively.

Dosimetric doses

Because of individual patient variability in clearance of iodine ^{131}I tositumomab, a dosimetric dose consisting of 10 mg of the antibody labeled with approximately 5 mCi ^{131}I was first given intravenously over 30 minutes. Total-body clearance kinetics were then measured by serial quantitative total-body radioactivity counts obtained 1 hour after injection and daily for at least 5 days with the use of an NaI scintillation probe and a gamma camera. This information was then used to calculate the number of millicuries needed in the labeling of a therapeutic dose so that a specified total-body-radiation dose (TBD) could be delivered by a therapeutic dose. The methods for these calculations have been previously described.[23,25,28,29] Serial quantitative gamma camera images were also obtained to determine tumor and normal organ doses.

All patients were admitted to the hospital and were premedicated before antibody infusion with oral doses of 50 mg of diphenhydramine and 650 mg of acetaminophen. Saturated solution of potassium iodide (SSKI) was administered as 2 drops orally, 3 times daily, beginning 1 day before the initial antibody infusion and continuing for at least 14 days following the last infusion, to inhibit potential thyroid uptake of free ^{131}I.

The first 25 patients underwent an evaluation to determine whether an infusion of unlabeled tositumomab prior to the infusion of radiolabeled antibody could optimize biodistribution and tumor targeting by preblocking normal CD20 antigenic sinks, such as B cells in the peripheral blood, bone marrow, and spleen. Dosimetric doses of iodine ^{131}I tositumomab were immediately preceded by no predose or a 60-minute infusion of 95 mg or 475 mg of unlabeled tositumomab on successive weeks in the first 25 patients. The last 34 patients received a single 475-mg infusion prior to the dosimetric dose when it was determined that this dose of unlabeled antibody decreased splenic targeting, increased the terminal half-life of the radiolabeled antibody, and appeared to cause tumor regression in some patients.[23,24]

Therapeutic doses

A therapeutic dose of iodine ^{131}I tositumomab was administered at least 1 week after a dosimetric dose. There were no specific requirements with regard to biodistribution of the dosimetric dose that precluded patients from receiving a therapeutic dose. Each therapeutic dose consisted of a patient-specific millicurie amount of iodine ^{131}I tositumomab adjusted to deliver a specified TBD. As previously described, a phase I dose escalation was initially performed until a maximally tolerated dose (MTD) was established.[23,24] Subsequently, additional patients were treated at the MTD (75 cGy) in the phase II part of the study. A separate determination of MTD was conducted for patients who had undergone prior ASCT. This determination was initiated at a 65-cGy TBD and escalated or deescalated in 10-cGy increments.

In the initial 25-patient cohort, the radiolabeled therapeutic dose was preceded by an infusion of unlabeled tositumomab (0, 95, or 475 mg) that resulted in the highest tumor-to-TBD ratio. All subsequent therapeutic doses were preceded by a 475-mg infusion of unlabeled tositumomab. Patients were again premedicated with diphenhydramine and acetaminophen, and SSKI was continued for 14 days. In addition, oral potassium perchlorate (200 mg, 3 times daily) was given for 7 days, beginning the day of infusion.

Patients who had tumor regression were considered for re-dosing in an attempt to upgrade the response after it was determined that there was no further regression of disease after the preceding dose. Patients were not allowed to be re-dosed any sooner than 6 weeks following a therapeutic dose. For patients who had achieved a partial or complete response and had not developed HAMA, re-treatment was considered following progression of disease. Re-dosing or re-treatment was given at the original TBD unless grade 2 or greater toxicity had been encountered, in which case an attenuated dose was administered (generally 10 cGy less than the original dose).

Response criteria and evaluation

Complete response (CR) was defined as the complete disappearance of all detectable disease (including bone marrow involvement) for at least 1 month or a lack of change in a minimal residual radiographic abnormality for at least 6 months. A partial response (PR) was defined as a reduction by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 1 month. Responses not meeting the above criteria were categorized as stable disease. Progressive disease was defined as the appearance of new lesions or a more than 25% increase in the sum of the products of the longest perpendicular diameters of all measurable lesions. Patients withdrawing from the study prior to a response assessment were classified as having progressive disease.

Disease status was evaluated by physical examination; computed tomography (CT) scans of the chest, abdomen, and pelvis; and bone marrow biopsies if the bone marrow was positive for lymphoma at baseline. Evaluations were performed 6 weeks and 12 weeks after therapy and every 3 months until 2 years after treatment at which time evaluations were scheduled every 6 months.

Evaluation of toxicity

The National Cancer Institute common toxicity criteria were used. Complete blood cell and platelet counts were obtained weekly for at least 6 weeks and twice weekly whenever any hematologic toxicity was encountered until recovery or stabilization of counts. Hepatic, renal, and electrolyte studies were performed at 2, 6, and 12 weeks and every 3 to 6 months after RIT. Serum thyroid-stimulating hormone (TSH) was measured every 3 to 6 months.

All adverse events were monitored for 12 weeks after treatment, and all possibly related adverse events were recorded after 12 weeks. Hematologic toxicity was recorded as an adverse event only if a therapeutic intervention was administered.

Peripheral blood B and T cells were quantitated by flow cytometry as previously described[23] at study entry, 6 and 12 weeks after RIT, and every 3 months thereafter until the number of B cells returned to normal. Serum immunoglobulin concentrations were measured each time peripheral blood B and T cells were quantitated.

HAMA

Serum was tested for HAMA before each dosimetric and therapeutic dose and at 2, 6, and 12 weeks after a therapeutic dose, and prior to consideration of a re-treatment dose. A previously described enzyme-linked immunosorbent assay was used,[24] as well as a commercial test kit (ImmunoSTRIP, Immunomedics, Morris Plains, NJ).

Statistical methods

The response rates were summarized for all patients who received any study drug (ie, intent-to-treat) and for all patients who received the therapeutic dose (ie, evaluable patients). Kaplan-Meier censored data techniques were used to estimate duration of response, progression-free survival (PFS), and survival.[30] Log-rank tests were used to perform subgroup comparisons of the duration of response.[31] The Cox proportional hazards model was used to perform multivariate analyses of PFS, and the logistic regression model was used to perform multivariate analyses of response.[32] The McNemar test for proportions using exact binomial probabilities was used to compare the response to iodine ^{131}I tositumomab to the response to the last chemotherapy.[33] A matched pairs test generalized to censored duration data was used to compare the PFS after iodine ^{131}I tositumomab to the PFS after the last chemotherapy.[34] In the latter test, paired durations of response within 1 month of each other were considered equivalent.

Results

Patient characteristics

The characteristics of the 59 enrolled patients are detailed in Table 1. The median age was 50 years (range 23-75). Eighty-eight percent had Ann Arbor stage III or IV disease at study entry. Seventy-one percent had either low-grade or transformed NHL at entry, and the rest had de novo intermediate- or high-grade NHL at time of diagnosis. The median time from diagnosis to study entry was 45 months. In general, patients had been heavily pretreated with a median of 3 (mean, 3.9) prior chemotherapy regimens and a median of 4 prior therapeutic interventions (range, 1-13) that included chemotherapy, radiation, and biologics. Forty-eight percent had not responded to their most recent chemotherapy. Fourteen patients had undergone ASCT. The percentages of patients with a tumor burden more than 500 grams (as determined by volumetric measurements from CT scans[23,24]) or an elevated serum lactate dehydrogenase (LDH) level were 36% and 51%, respectively.

Table 1. Clinical and demographic characteristics of 59 patients with B-cell lymphoma

Characteristics	Number	Percent
Age (yr)		
≤60	49	83
>60	10	17
Gender		
Male	37	63
Female	22	37
Stage of disease		
I/II	7	12
III/IV	52	88
Histology*		
Low-grade	28	47
Transformed low-grade	14	24
De novo intermediate/high-grade	17	29
Tumor burden >500 grams		
Yes	21	36
No	38	64
Bone marrow involvement		
None	38	68
1%-25%	17	29
>25%	1	2
Lactate dehydrogenase (LDH)		
Elevated	30	51
Normal/low	29	49
Prior bone marrow transplant		
Yes	14	24
No	45	76
Number of prior therapies		
1-3	20	34
≥4	39	66
Response to last therapy		
No response	28	48
Response (PR + CR)	30	52

*According to the International Working Formulation,[35] of the 28 patients with low-grade non-Hodgkin lymphoma (NHL), 16 had follicular small-cleaved, 11 had follicular mixed small-cleaved and large cell, and 1 had small lymphocytic lymphoma. Of the 14 patients with transformed low-grade NHL, 8 had diffuse large cell, 2 had immunoblastic large cell, and 4 had follicular large cell. Of the 17 patients with intermediate- or high-grade lymphoma at diagnosis, 9 had diffuse large cell, 4 had mantle cell, 2 had diffuse mixed large and small cell, and 2 had immunoblastic large cell lymphoma. PR indicates partial response; CR, complete response.

Dosimetric studies

The mean effective half-life of iodine ^{131}I tositumomab was 59.3 hours (range, 24.6-88.6). Because patients had markedly different rates of clearance of the radiolabeled antibody, there was considerable variation in the millicurie dose needed to achieve the desired TBD. The 20 patients treated at the 75-cGy dose level were administered a mean (± SD) of 97.3 ± 26.0 mCi, but the range extended from 56.8 to 153 mCi. Tumor-specific targeting was observed with gamma camera scanning; tumor absorbed radiation dose with a 475-mg predose was 1010 cGy ± 696 per 75 cGy whole-body dose. This dose was higher than that to any normal tissue, including the spleen, which received 399 cGy ± 215. A detailed account of dosimetric and pharmacokinetic data will be published separately.

Tumor responses and survival

On an intent-to-treat basis, a CR or PR was achieved in 42 (71%; 95% confidence interval [CI]: 58%-82%) of the total 59 patients, and 20 of 59 (34%; 95% CI: 22%-47%) patients achieved a CR. Six patients underwent dosimetric studies but did not receive a therapeutic dose because of early disease progression in 2 patients, development of HAMA after multiple dosimetric studies in 3 patients, or an adverse event in 1 patient. Forty (75%) of the 53 patients who received a therapeutic dose responded. With a median follow-up of 3.1 years, the 5-year Kaplan-Meier estimates for all 59 patients are 42% for overall survival and 14% for PFS (Figure 1). Twenty-five patients are alive and 7 remain disease- and progression-free after their initial treatment for 3 to 5.7 years. The median PFS was 12 months for all responders and 20.3 months for patients who achieved a CR (Figure 2).

The 42 patients with low-grade or transformed low-grade NHL had a higher response rate (83%) than the 17 patients with de novo intermediate or high-grade disease (41%) (*P* = .005) (Table 2). Response rates and PFS were similar for low-grade and transformed low-grade NHL. Response rates of 86% and 79%, CR rates of 46% and 50%, and median PFS for responders of 12.3 and 13.9 months were observed for low-grade and transformed low-grade NHL, respectively (Table 2, Figure 3). The median PFS and response rate with iodine ^{131}I tositumomab for the 31 patients with response durations of less than 6 months after their last chemotherapy was 7 months and 77%. The median PFS and response rate for the 11 patients with response durations of more than 6 months after their last chemotherapy was 17.2 months and 100%.

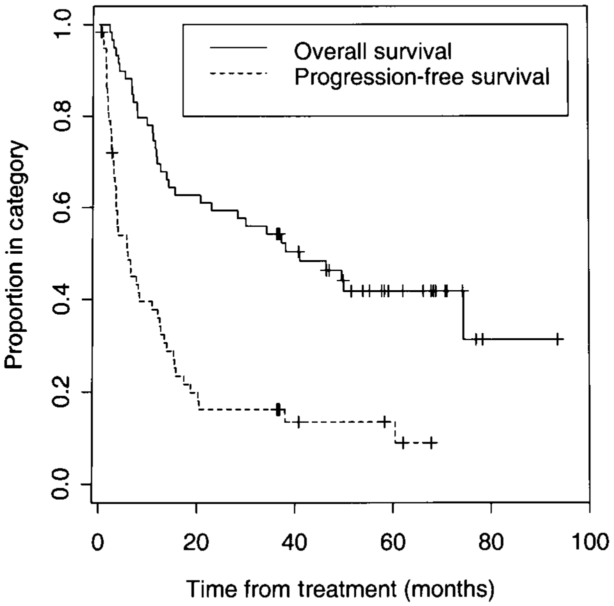

Figure 1. Overall and PFS of 59 patients with relapsed or refractory B-cell lymphoma who received dosimetric and/or therapeutic doses of iodine ^{131}I tositumomab.

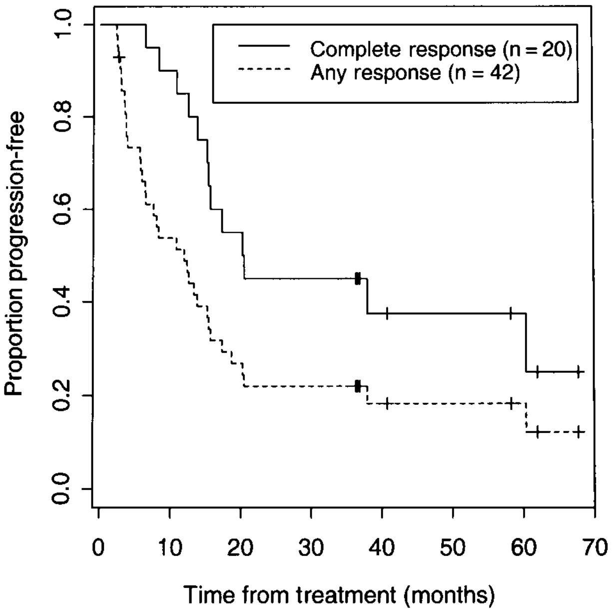

Figure 2. PFS of 59 patients according to response after receiving iodine ^{131}I tositumomab.

Seven (41%) of 17 patients with de novo intermediate or high-grade NHL had a response, but none of these patients achieved a CR and responses were short-lived (Figure 3).

Age, stage at entry, the number of prior treatment regimens, and the last response to chemotherapy did not appear to significantly affect response rates and PFS (Table 2). A normal serum LDH level was predictive for a response; patients with normal levels responded more frequently (86%) than those with elevated levels (57%) (*P* = .012). Most patients with high tumor burdens responded (52%) but not as frequently as those with low tumor

Table 2. Response rates by patient subgroup

	No. of patients	Response		Complete response	
		% (N)	*P* value	% (N)	*P* value
Age					
>60	10	60 (6)		20 (2)	
≤60	49	73 (36)	.391	37 (18)	.308
Histology					
Low grade	28	86 (24)		46 (13)	
Low transformed	14	79 (11)		50 (7)	
De novo intermediate/high	17	41 (7)	.005	0 (0)	.002
Lactate dehydrogenase (LDH)					
Elevated	30	57 (17)		17 (5)	
Normal/low	29	86 (25)	.012	52 (15)	0.005
Bulky disease					
No	38	82 (31)		37 (14)	
Yes	21	52 (11)	.018	29 (6)	.521
Prior bone marrow transplant					
No	45	78 (35)		33 (15)	
Yes	14	50 (7)	.045	36 (5)	.869
Stage of disease					
I/II	7	57 (4)		29 (2)	
III/IV	52	73 (38)	.382	35 (18)	.751
Prior chemotherapies (No.)					
1-2	16	69 (11)		31 (5)	
≥3	43	72 (31)	.801	35 (15)	.793
Last chemotherapy					
No response	28	75 (21)		29 (8)	
Response	30	70 (21)	.670	40 (12)	.360

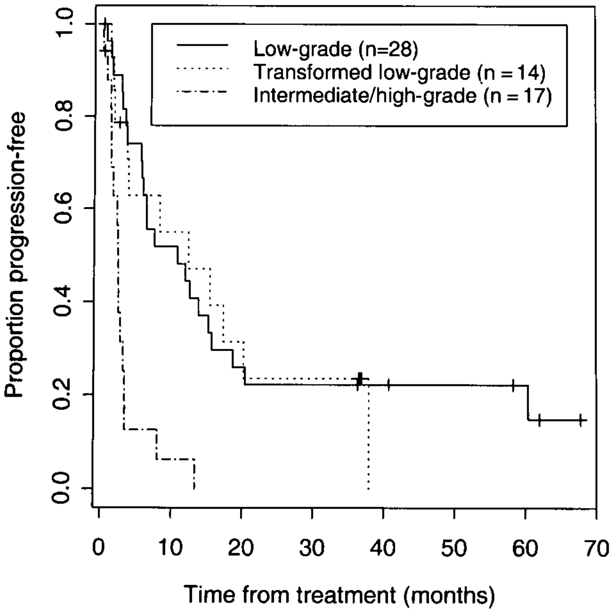

Figure 3. PFS of 59 patients according to the histologic grade of B-cell lymphoma.

burdens (82%) (P = .018). Higher response rates and more durable CRs were seen with increasing TBD. The response rate to a TBD under 65 cGy was 57% compared with 86% to doses of 65 cGy or higher (P = .012). PFS among patients who received at least 55 cGy was significantly longer than that of patients who received lower doses. All patients with a response longer than 1.5 years received at least 55 cGy. Patients who had relapsed after ASCT also responded, although at a lower rate than patients who had not undergone ASCT (50% versus 78%, P = .045). Among the post-ASCT patients, the median PFS of responders was not reached after 4.7 years, and 4 patients remain disease-free more than 3 years after therapy.

In a multivariate analysis, only de novo intermediate grade histology (odds ratio [OR] = 7.9; P = .009), the presence of high tumor burden (OR = 9.3; P = .008), and TBD below 55 cGy (OR = 6.2; P = .02) were associated with reduced response rates. Only de novo intermediate-grade histology was associated with a reduced PFS (relative risk [RR] = 4.8; $P < .0001$).

Seven patients were re-dosed in an attempt to upgrade or to prolong their response before disease progression after achieving stable disease (1 patient), a PR (5 patients), or a CR (1 patient) after the first dose. The patient who had stable disease converted to a PR, but no upgrade occurred in the response of the other 6 patients. Sixteen patients who responded to the initial therapeutic dose were re-treated following disease progression. Nine (56%) of 16 patients achieved a second response with a median PFS of 11.4 months. Five (31%) patients achieved a CR of which 3 continue to be progression-free up to 37 months after re-treatment.

Each patient's response to his or her most recent chemotherapy regimen was used as a paired control for the response to iodine ^{131}I tositumomab therapy. The 71% response rate to iodine ^{131}I tositumomab was significantly higher than the 52% response rate to the last prior chemotherapy (P = .021). The results for patients with low-grade or transformed low-grade NHL were more striking. In these 42 patients, 83% responded to iodine ^{131}I tositumomab compared with a 50% response rate to the last prior chemotherapy (P = .0013). Furthermore, the duration of response was 11.7 months after iodine ^{131}I tositumomab compared with 8.0 months after the last chemotherapy regimen (P = .032, McNemar test). Indeed, 28 patients had a longer remission by at least 1 month with iodine ^{131}I tositumomab than the last chemotherapy, whereas only 10 had a longer remission with the last chemotherapy.

Early adverse experiences

Infusions were well tolerated, and only 2 (1.1%) of 177 infusions were interrupted or rate-adjusted. The most common nonhematologic adverse events were fever, asthenia, nausea, and chills (Table 3). Fevers and chills generally occurred around the time of the dosimetric dose, and asthenia and nausea occurred more often after the therapeutic dose. The great majority of events were grade I in severity, and grade II events were rare. There were no grade IV events. The incidence and severity of adverse events among the re-treated patients were similar to those after initial treatment. No substantive changes were observed in serum electrolytes, liver enzymes, renal function tests, or immunoglobulin levels.

As expected, the dose-limiting toxicity was hematologic. In the phase I dose-escalation part of the study, the MTD was established as 75 cGy in 25 patients who had not undergone a prior ASCT.[24] Fourteen additional patients were then treated with this MTD in the phase II segment of the study. The MTD for patients who had a prior ASCT was determined in 13 patients to be 45 cGy. For 20 patients who had not had a prior ASCT and received the 75-cGy MTD, the median time to nadir for platelet and neutrophil counts was 35 days and 43 days, respectively (Table 4). The median time from treatment to recovery to baseline hematologic grade for these blood components was 51 and 64 days, respectively. Four (20%) patients experienced grade IV platelet or neutrophil nadirs lasting a median of 19 and 11.5 days, respectively. Two of the 20 patients were given granulocyte colony-stimulating factor, and 3 patients received a platelet and/or a red blood cell transfusion. The hematologic toxicity profile for patients who were re-dosed or re-treated was similar to that observed after initial treatment.

A depletion of or substantial drop in CD20-positive peripheral blood cells was observed in 47 of the 59 patients shortly after treatment. The median time to B-cell recovery (defined as a return to the normal range of the absolute number of CD20-expressing cells) was 3.6 months (95% CI: 3.2-6.6). No significant effect on T-cell counts was observed.

Late adverse experiences

An elevation of TSH following the therapeutic dose was noted in 5 patients at 3 to 29 months following initial therapy or re-treatment. None of these patients were symptomatic and 2 patients were placed on thyroid hormone supplementation.

Five patients were diagnosed with myelodysplasia (MDS) 1.2 to 7.5 years after iodine ^{131}I tositumomab treatment; 1 patient subsequently developed acute myeloid leukemia. These patients had previously received a median of 4 prior chemotherapies (range 2-8) and all had previously received alkylating agents. Bone marrow cytogenetic analysis at the time of diagnosis of MDS was performed in 4 cases, and, in each case, clonal abnormalities of chromosomes 5 and/or 7 were observed.

Three patients were diagnosed with solid tumors after RIT; 2 with superficial transitional-cell bladder cancer and 1 with squamous cell carcinoma of the rectum. Both patients with bladder cancer had been previously exposed to cyclophosphamide, a risk factor for the development of bladder cancer.[36] One of these patients had findings suggestive of bladder cancer prior to RIT and the other was diagnosed with bladder cancer 6 months after RIT.

Table 3. Nonhematologic adverse events

Event	All patients (n = 59)		Unknown		Grade I		Grade II		Grade III		Grade IV	
	N	%	N	%	N	%	N	%	N	%	N	%
Fever	31	53	0	0	11	19	20	34	0	0	0	0
Asthenia	20	34	0	0	19	32	1	2	0	0	0	0
Nausea	20	34	0	0	18	31	1	2	1	2	0	0
Chills	17	29	0	0	10	17	3	5	4	7	0	0
Infection	13	22	2	3	9	15	2	3	0	0	0	0
Arthralgia	13	22	1	2	11	19	1	2	0	0	0	0
Rash	11	19	1	2	7	12	3	5	0	0	0	0
Pain	9	15	0	0	9	15	0	0	0	0	0	0
Vomiting	8	14	0	0	6	10	1	2	1	2	0	0
Urticaria	8	14	0	0	3	5	5	8	0	0	0	0
Headache	7	12	0	0	6	10	1	2	0	0	0	0
Myalgia	7	12	1	2	6	10	0	0	0	0	0	0
Diarrhea	6	10	0	0	5	8	0	0	1	2	0	0
Pharyngitis	6	10	0	0	6	10	0	0	0	0	0	0
Pruritus	6	10	0	0	5	8	1	2	0	0	0	0
Dizziness	5	8	1	2	3	5	0	0	1	2	0	0
Urinary tract infection	5	8	0	0	3	5	2	3	0	0	0	0
Abdominal pain	4	7	0	0	4	7	0	0	0	0	0	0
Serum sickness	4	7	1	2	0	0	0	0	3	5	0	0
Anorexia	4	7	1	2	3	5	0	0	0	0	0	0
Injection site reaction	3	5	1	2	1	2	1	2	0	0	0	0
Constipation	3	5	0	0	3	5	0	0	0	0	0	0
Gastritis	3	5	0	0	2	3	1	2	0	0	0	0
Hypothyroidism	3	5	0	0	0	0	3	5	0	0	0	0
Paresthesia	3	5	3	5	0	0	0	0	0	0	0	0
Cough increased	3	5	0	0	3	5	0	0	0	0	0	0
Rhinitis	3	5	0	0	2	3	1	2	0	0	0	0
Sweating	3	5	0	0	1	2	2	3	0	0	0	0
Conjunctivitis	3	5	0	0	3	5	0	0	0	0	0	0

All adverse events that occurred in at least 5% of patients.

HAMA

Ten (17%) patients developed HAMA following either initial treatment[9] or re-treatment.[1] Five patients were part of the initial cohort of patients who received more than one dosimetric dose with their first treatment. No patient who received only one dosimetric dose was prevented from receiving a therapeutic dose because of HAMA. The median time to first HAMA detection was 15 days after first exposure to antibody (range, 12-194).

Table 4. Hematologic toxicity in 20 patients receiving a 75-cGy whole-body dose

	Absolute neutrophil count	Platelets	Hemoglobin
Time to nadir (days)			
Median	43	35	41
95% confidence interval	41-55	33-37	33-48
Range	22-106	29-45	6-78
Time to recovery to baseline (days)			
Median	64	51	50
95% confidence interval	58-84	48-55	37-62
Range	29-159	37-405	9-9
Maximum toxicity			
Grade III	35%	20%	5%
Grade IV	20%	20%	5%
Median duration of grade IV (days)	11.5	19	2
Range	10-22	2-85+	2-2
Supportive care			
Any supportive care	4 (20%)		
G-CSF	2 (10%)		
GM-CSF	0 (0%)		
Erythropoietin	0 (0%)		
Platelet transfusion	3 (15%)		
RBC transfusion	3 (15%)		

G-CSF indicates granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; RBC, red blood cell.

Discussion

This report summarizes the updated results of the first phase I/II study of anti-CD20 radioimmunotherapy for NHL using nonmyeloablative doses. Initial reports of this study, as it was accruing patients, strongly suggested promising results.[23-25] A larger patient cohort with extended follow-up has now allowed us (1) to better define clinical response rates and the durability of remissions; (2) to analyze the impact of various factors on response, response duration, and survival; (3) to establish the MTD for patients who have undergone ASCT; (4) to evaluate the feasibility and utility of re-treatment; and (5) to better characterize short-term and long-term safety.

This study demonstrates that a single course of iodine ^{131}I tositumomab resulted in a high rate of tumor responses of considerable duration. On an intent-to-treat basis, responses were observed in 42 (71%) of 59 patients and CRs in 20 (34%) of 59 patients. The PFS was 12 months for all responders and 20.3 months for those who achieved a CR. In long-term follow-up, 7 of the 20 CRs have remained disease-free from 3 to almost 6 years. Four of these 7 patients had relapsed after ASCT.

These results are particularly noteworthy, given the generally poor prognosis of the patients entered in the study. These patients had received a median of 4 prior therapeutic interventions for their NHL, and about half had no response to their most recent chemotherapy treatment. Many patients had high tumor burdens and elevated LDH values. Fourteen patients had relapsed after ASCT. Indeed, patients with the poor prognostic factors of high tumor burdens, elevated LDH, relapse after ASCT, or no response to the last administered chemotherapy had response rates of more than 50%.

A multivariate analysis demonstrated that only tumor histology was an independent predictor of PFS after iodine ^{131}I tositumomab therapy. Patients with low-grade histologies and transformed histologies had significantly higher response rates and a longer PFS than patients with de novo intermediate- or high-grade histologies. Indeed, the 4-year overall survival and PFS for patients with low-grade or transformed NHL was 62% and 20%, respectively. The response rate was as high as 92% for the 24 patients with low-grade NHL and 79% for the 14 with transformed NHL who actually received a therapeutic dose of iodine ^{131}I tositumomab. Twenty (53%) of these 38 patients achieved a CR. In the 15 de novo higher-grade patients who received a therapeutic dose, 7 PRs were observed. It should be noted, however, that patients with various histologies and clinical characteristics were represented in the group with de novo higher-grade NHL, including 4 patients with mantle-cell NHL, 5 patients who relapsed after ASCT, and 8 who received a whole-body dose of 55 cGy or less. Additional studies of this treatment are thus warranted in the higher-grade histologies.

In contrast to an expected decline in response rate and duration with each subsequent treatment for patients with low-grade and transformed low-grade NHL, iodine ^{131}I tositumomab produced a significantly higher response rate (83%) than the immediately preceding chemotherapy (50%) in these patients. Indeed, 17 (81%) of 21 patients responded to RIT but not to their most recent chemotherapy. Also, the number of patients who had a longer response with iodine ^{131}I tositumomab was nearly triple the number who had a longer response to chemotherapy. This finding suggests an independent mechanism of action from chemotherapy and the potential role of this radiolabeled antibody in chemotherapy-relapsed or refractory disease.

Another encouraging finding was that patients who relapsed after achieving a response to iodine ^{131}I tositumomab could achieve another remission with re-treatment in 56% of the cases. The opportunity to re-induce remissions was afforded by several factors. First, this treatment was very well tolerated. Interruption or slowing of infusions for adverse reactions was rarely required. Although myelosuppression was dose-limiting, this toxicity was generally moderate, predictable, reversible, and seldom required supportive intervention, even in post-ASCT patients. This factor may be a result of the individualized dosing scheme based on dosimetric dose clearance rates and the restriction on the level of bone marrow involvement by NHL for study entry. Second, relapsing tumors continued to express CD20. All 6 patients who underwent a tumor biopsy prior to re-treatment had immunohistochemical evidence of CD20 expression by the tumor, and all re-treated patients had clearly detectable tumor targeting by gamma camera imaging. Third, the rate of HAMA development was low after the first treatment. Although the usual time of follow-up for the development of HAMA was 12 weeks (thus possibly missing the detection of later development of HAMA in some patients), HAMA developed in only 1 of 16 patients after re-treatment. These data support the notion that the incidence of HAMA is low in this patient population and that it may be possible to re-treat patients multiple times.

In terms of late adverse events, the incidence of elevated TSH levels was low and no patient had symptoms of hypothyroidism. This finding indicates that the protection of the thyroid from free ^{131}I by the administration of SSKI is adequate for the millicurie dose range given in this study.

In long-term follow-up, 5 cases of MDS were diagnosed. Each of the 5 patients had received multiple prior chemotherapy regimens (median of 4), at least 1 of which included an alkylating agent. Chromosomal analysis was performed on 4 cases, and all 4 cases had abnormalities involving chromosomes 5 and/or 7. These specific abnormalities are commonly associated with exposure to alkylators, but they have also been reported following radiotherapy.[37] With the limited number of cases in our study, it is not presently possible to determine the contribution of the RIT to the development of MDS.

A number of other studies of RIT in NHL—including those using antibodies directed against antigens other than CD20 as well as CD20, labeled with either ^{131}I or other radioisotopes using nonmyeloablative doses or myeloablative doses with stem cell support—have shown promising results.[38-51] Differing patient characteristics and selection criteria make comparisons of these studies difficult, and thus questions about the relative merits of different isotopes for use in RIT in NHL remain. The short pathlength of ^{131}I beta particles may provide an advantage over those from other isotopes in targeting smaller tumors and micrometastases while minimizing exposure of surrounding normal tissue. In addition, because of gamma emissions, ^{131}I can be used for imaging and dosimetric purposes to noninvasively assess radiation clearance on an individual basis and thus permit patient-specific dosing. Moreover, under new U.S. Nuclear Regulatory Commission guidelines, the risk of caregiver exposure to gamma emissions is sufficiently low to allow outpatient ^{131}I treatment.[52,53]

Another issue is the incremental value of the radionuclide. Part of the therapeutic advantage of the radionuclide is believed derived from the fact that the emitted beta particles can cause irradiation of many tumor cells in the vicinity of the decaying atom. This creates a situation in which cells within a tumor are caught in a crossfire of beta particles, including cells to which antibody has not penetrated or bound and cells lacking expression of the target antigen. The higher response rates we achieved following a higher TBD support this hypothesis. However, unlabeled tositumomab, especially at the 475-mg dose, appeared to have antitumor activity in some patients after a dosimetric dose in our study.[23,24] Although, this study was not designed to separately assess the response rate of the unlabeled antibody, an ongoing, multicenter, randomized trial comparing iodine ^{131}I tositumomab with unlabeled tositumomab should help resolve this issue.

As a result of the promising data obtained during the progress of our study, several multicenter trials of iodine ^{131}I tositumomab have either recently been completed or are in progress. Phase II and III studies in patients with relapsed/refractory low-grade and transformed NHL appear to have confirmed the response rates we obtained.[54,55] An ongoing phase II trial is being conducted by our group to assess efficacy and safety of iodine ^{131}I tositumomab in previously untreated patients with advanced-stage low-grade NHL.[56] These studies, along with future clinical trials, will help clarify the role of this new therapeutic approach in the treatment of NHL.

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References

1. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med. 1993;328:1023-1030.
2. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol. 1993;20(S):75-88.
3. Gallagher CJ, Gregory WM, Jones AE, et al. Follicular lymphoma: prognostic factors for response and survival. J Clin Oncol. 1986;4:1470-1480.
4. Morrison VA, Peterson BA. High-dose therapy and transplantation in non-Hodgkin's lymphoma. Semin Oncol. 1999;26:84-98.
5. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med. 1987;316:1493-1498.
6. Appelbaum FR, Sullivan KM, Buckner CD, et al. Treatment of malignant lymphoma in 100 patients with chemotherapy, total body irradiation, and marrow transplantation. J Clin Oncol. 1987;5:1340-1347.
7. Meeker TC, Lowder J, Maloney DG, et al. A clinical trial of anti-idiotype therapy for B cell malignancy. Blood. 1985;65:1349-1363.
8. Brown SL, Miller RA, Horning SJ, et al. Treatment of B-cell lymphomas with anti-idiotype antibodies alone and in combination with alpha interferon. Blood. 1989;73:651-661.
9. Nadler LM, Stashenko P, Hardy R, et al. Serotherapy of a patient with a monoclonal antibody directed against a human lymphoma-associated antigen. Cancer Res. 1980;40:3147-3154.
10. Press OW, Appelbaum F, Ledbetter JA, et al. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. Blood. 1987;69:584-591.
11. Dyer MJ, Hale G, Hayhoe FG, Waldmann H. Effects of CAMPATH-1 antibodies in vivo in patients with lymphoid malignancies: influence of antibody isotype. Blood. 1989;73:1431-1439.
12. McLauglin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825-2833.
13. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. J Immunol. 1980;125:1678-1685.
14. Einfeld DA, Brown JP, Valentine MA, et al. Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. EMBO J. 1988;7:711-717.
15. Press OW, Farr AG, Borroz I, et al. Endocytosis and degradation of monoclonal antibodies targeting human B-cell malignancies. Cancer Res. 1989;49:4906-4912.
16. Press OW, Howell-Clark J, Anderson DK. Retention of B-cell specific monoclonal antibodies by human lymphoma cells. Blood. 1994;83:1390-1397.
17. Tedder TF, Forsgren A, Boyd AW, Nadler LM, Schlossman SF. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Eur J Immunol. 1986;16:881-887.
18. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. Immunol Today. 1994;15:450-454.
19. Buchsbaum DJ, Wahl RL, Normolle DP, Kaminski MS. Therapy with unlabeled and I-131-labeled pan B-cell monoclonal antibodies in nude mice bearing Raji Burkitt lymphoma xenografts. Cancer Res. 1992;52:6476-6481.
20. Maloney D, Smith B, Appelbaum F. The anti-tumor effect of monoclonal anti-CD20 antibody therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma cell lines [abstract]. Blood. 1996;88(10s):637a.
21. Shan D, Ledbetter JA, Press OW. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. Blood. 1998;91:1644-1652.
22. Kolstad A, Tuck MK, Kaminski MS. Characterization of the apoptotic process initiated by ligation of CD20 by the mouse monoclonal antibody Anti-B1 in the Burkitt's lymphoma cell line Ramos [abstract]. Blood. 1999;94(10s):87a.
23. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [Iodine-131]anti-B1 (anti-CD20) antibody. N Engl J Med. 1993;329:459-465.
24. Kaminski MS, Zasadny KR, Francis IR, et al. I-131-Anti-B1 radioimmunotherapy for B-cell lymphoma. J Clin Oncol. 1996;14:1974-1981.
25. Wahl RL, Zasadny KR, MacFarlane D, et al. Iodine-131 Anti-B1 Antibody for B-cell lymphoma: an update on the Michigan Phase I experience. J Nuc Med. 1998;39(8s):21s–27s.
26. Fraker PJ, Speck JC Jr. Protein and cell membrane iodinations with a sparingly soluble chloramide, 1,2,3,6-tetrachloro-3a,6a-diphrenylglycoluril. Biochem Biophys Res Commun. 1978;80:849-857.
27. Wahl RL, Wissing J, del Rosario R, Zasadny KR. Inhibition of autoradiolysis of radiolabeled monoclonal antibodies by cryopreservation. J Nucl Med. 1990;31:84-89.
28. Kaminski MS, Fig LM, Zasadny KR, et al. Imaging, dosimetry, and radioimmunotherapy with iodine 131-labeled anti-CD37 antibody in B-cell lymphoma. J Clin Oncol. 1992;10:1696-1711.
29. Wahl RL, Kroll S, Zasadny KR. Patient-specific whole body dosimetry: principles and a simplified method for clinical implementation. J Nucl Med. 1998;39(8):14s–20s.
30. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-491.
31. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966;50:163-170.
32. Cox DR. Regression models and life tables. J R Stat Soc. 1972;B34:187.
33. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika. 1947;12:153-157.
34. Armitage P. The comparison of survival curves. J Royal Stat Soc A. 1959;122:279-292.
35. Rosenberg S, Berard C, Brown J, et al. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage: The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer. 1982;49:2112-2135.
36. Travis LB, Curtis RE, Boice JD Jr, Fraumeni JF. Bladder cancer after chemotherapy for non-Hodgkin's lymphoma. N Engl J Med. 1989;321:544-545.
37. Le Beau MM, Albain KS, Larson RA, et al. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol. 1986;4:325-345.
38. Rosen ST, Zimmer AM, Goldman-Leiken R, et al. Radioimmunodetection and radioimmunotherapy of cutaneous T cell lymphomas using an I-131 labeled monoclonal antibody: an Illinois Cancer Council study. J Clin Oncol. 1987;5:562-573.
39. DeNardo GL, DeNardo SJ, O'Grady LF, et al. Fractionated radioimmunotherapy of B-cell malignancies with I-131 Lym-1 monoclonal antibodies. Cancer Res. 1990;50(3s):1014s–1016s.
40. DeNardo GL, Lamborn KR, Goldstein DS, et al. Increased survival associated with radiolabeled Lym-1 therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Cancer. 1997;80(12s):2706-2711.
41. DeNardo GL, DeNardo SJ, Goldstein DS, et al. Maximum-tolerated dose, toxicity, and efficacy of I-131 Lym-1 antibody for fractionated radioimmunotherapy of non-Hodgkin's lymphoma. J Clin Oncol. 1998;16:3246-3256.
42. Kuzel T, Rosen ST, Zimmer AM, et al. A phase I escalating-dose safety, dosimetry, and efficacy study of radiolabeled monoclonal antibody Lym-1. Cancer Biother. 1993;8:3-16.
43. Goldenberg DM, Horowitz JA, Sharkey RM, et al. Targeting, dosimetry, and radioimmunotherapy of B-cell lymphomas with iodine-131-labeled LL2 monoclonal antibody. J Clin Oncol. 1991;9:548-564.
44. Juweid M, Sharkey RM, Markowitz A, et al. Treatment of non-Hodgkin's lymphoma with radiolabeled murine, chimeric or humanized LL2, an anti-CD22 monoclonal antibody. Cancer Res. 1995;55(23s):5899s–5907s.
45. Czuczman MS, Strauss DJ, Divgi CR, et al. Phase I dose-escalation trial of iodine 131-labeled monoclonal antibody OKB7 in patients with non-Hodgkin's lymphoma. J Clin Oncol. 1993;11:2021-2029.
46. White CA, Halpern SE, Parker BA, et al. Radioimmunotherapy of relapsed B-cell lymphoma with Yttrium 90 anti-idiotype monoclonal antibodies. Blood. 1996;87:3640-3649.
47. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled antibody therapy of B-cell lymphoma with autologous bone marrow support. N Engl J Med. 1993;329:1219-1224.
48. Press OW, Eary JF, Appelbaum FR, et al. Phase II trial of Iodine-131-B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. Lancet. 1995;346:336-340.
49. Liu SY, Eary JF, Petersdorf SH, et al. Follow-up of relapsed B-cell lymphoma patients treated with iodine-131-labeled anti-CD20 antibody and autologous stem-cell rescue. J Clin Oncol. 1998;16:3270-3278.
50. Knox SJ, Goris ML, Trisler K, et al. Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. Clin Cancer Res. 1996;2:457-470.
51. Wiseman GA, White CA, Stabin M, et al. Therapeutic index of IDEC-Y2B8 radioimmunotherapy: up to 850 fold greater radiation dose to tumor than to normal organs [abstract]. Proc Am Soc Clin Oncol. 1999;18:4a.
52. Siegel JA. Revised Nuclear Regulatory Commission regulations for release of patients administered radioactive materials: outpatient iodine-131 anti-B1 therapy. J Nucl Med. 1998;39(8s):28s–33s.
53. Gates VL, Carey JE, Siegel JA, Kaminski MS, Wahl RL. Nonmyeloablative iodine-131 anti-B1 radioimmunotherapy as outpatient therapy. J Nucl Med. 1998;39:1230-1236.
54. Kaminski MS, Vose J, Saleh M, et al. A multicenter phase II study of Iodine-131 anti-B1 antibody (Bexxar) in patients with chemotherapy-relapsed/refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphoma [abstract]. Blood. 1997;90(10):509a.
55. Kaminski MS, Zelenetz AD, Press O, et al. Multicenter, phase III study of iodine-131 tositumomab (Anti-B1 Antibody) for chemotherapy-refractory low-grade or transformed low-grade non-Hodgkin's lymphoma [abstract]. Blood. 1998;92:316a.
56. Kaminski MS, Estes J, Regan D, et al. Front-line treatment of advanced B-cell low-grade lymphoma with radiolabeled anti-B1 antibody: initial experience [abstract]. Am Soc Clin Oncol. 1997;16:51a.