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¹³¹I-Tositumomab Therapy as Initial Treatment for Follicular Lymphoma

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ABSTRACT

BACKGROUND

Advanced-stage follicular B-cell lymphoma is considered incurable. Anti-CD20 radioimmunotherapy is effective in patients who have had a relapse after chemotherapy or who have refractory follicular lymphoma, but it has not been tested in previously untreated patients.

METHODS

Seventy-six patients with stage III or IV follicular lymphoma received as initial therapy a single course of treatment with ¹³¹I-tositumomab therapy (registered as Tositumomab and Iodine I 131 Tositumomab [the Bexxar therapeutic regimen]). This consisted of a dosimetric dose of tositumomab and ¹³¹I-labeled tositumomab followed one week later by a therapeutic dose, delivering 75 cGy of radiation to the total body.

RESULTS

Ninety-five percent of the patients had any response, and 75 percent had a complete response. The use of polymerase chain reaction (PCR) to detect rearrangement of the *BCL2* gene showed molecular responses in 80 percent of assessable patients who had a clinical complete response. After a median follow-up of 5.1 years, the actuarial 5-year progression-free survival for all patients was 59 percent, with a median progression-free survival of 6.1 years. The annualized rate of relapse progressively decreased over time: 25 percent, 13 percent, and 12 percent during the first, second, and third years, respectively, and 4.4 percent per year after three years. Of 57 patients who had a complete response, 40 remained in remission for 4.3 to 7.7 years. Hematologic toxicity was moderate, with no patient requiring transfusions or hematopoietic growth factors. No cases of myelodysplastic syndrome have been observed.

CONCLUSIONS

A single one-week course of ¹³¹I-tositumomab therapy as initial treatment can induce prolonged clinical and molecular remissions in patients with advanced follicular lymphoma.

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APPROXIMATELY 90 PERCENT OF PATIENTS with follicular lymphoma present with disseminated disease, which is considered incurable with standard treatment. The localized form of the disease (stage I or II), however, may be curable with external-beam radiation therapy to involved sites.^{1,2} Although standard radiation fields cannot encompass stage III and IV follicular lymphoma, monoclonal antibodies labeled with radionuclides and given systemically can potentially deliver cytotoxic doses of radiation to all sites of disseminated disease.

Tositumomab is a murine IgG2a monoclonal antibody that selectively binds to CD20 on the surface of normal and malignant B cells. It can be labeled with iodine-131 to yield ¹³¹I-labeled tositumomab. The actions of tositumomab and ¹³¹I-labeled tositumomab (registered as Tositumomab and Iodine I 131 Tositumomab [the Bexxar therapeutic regimen, Corixa and GlaxoSmithKline]) probably depend on ionizing radiation from the decaying iodine-131 and on antibody-mediated effects.³⁻⁶ Overall response rates of 47 to 68 percent and complete response rates of 20 to 38 percent in patients who had a relapse after extensive chemotherapy or whose disease was refractory to chemotherapy or the anti-CD20 antibody rituximab have been reported.⁷⁻¹² Approximately 30 percent of such patients had remissions lasting 1 to 10 years (median, 60 months) after treatment with ¹³¹I-tositumomab therapy.¹³ Given these encouraging results, we evaluated ¹³¹I-tositumomab therapy as initial treatment for advanced follicular lymphoma.

METHODS

PATIENTS

In this phase 2, single-group, open-label, single-center study, we enrolled 76 consecutive, previously untreated patients to receive the study drug between June 1996 and April 1999. Eligibility criteria were as follows: low-grade, B-cell lymphoma (World Health Organization classification, follicular grade 1 or 2)¹⁴; an age of at least 18 years; no prior therapy; Ann Arbor stage III or IV; involvement of 25 percent or less of the marrow by lymphoma on trephine biopsy; an absolute neutrophil count of more than 1500 per cubic millimeter; and a platelet count greater than 100,000 per cubic millimeter. Patients had stable or progressive disease with at least one lesion measuring at least 2 by 2 cm. The institutional review board at the University of Michi-

gan approved the study. Written informed consent was obtained from all the patients.

DRUG ADMINISTRATION AND DOSIMETRY

The details of the administration of ¹³¹I-tositumomab therapy have been described elsewhere.^{10,15-18} The regimen consists of two steps (Fig. 1). In step 1, on day 0, patients receive a 1-hour intravenous infusion of 450 mg of tositumomab, followed by a 20-minute infusion of 35 mg of tositumomab labeled with 5 mCi of iodine-131, for dosimetric purposes. In step 2, which is 7 to 14 days after step 1, patients receive a 1-hour infusion of 450 mg of tositumomab, followed by a 20-minute infusion of 35 mg of tositumomab labeled with an amount (in millicuries) of iodine-131 calculated from serial total-body gamma-camera counts after the dosimetric dose to deliver a dose of total-body radiation of 75 cGy.

CLINICAL RESPONSE CRITERIA AND EVALUATION

A complete response was defined as the disappearance of all disease for at least one month or an absence of change in minimal residual radiographic abnormalities for at least six months. A clinical complete response was defined as complete resolution of all disease-related symptoms for at least one month. A stable or diminishing residual focus of 2 cm or less was considered to be only scar tissue. A partial response was defined as a reduction by at least 50 percent in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least one month. Progressive disease was defined as an increase of at least 25 percent in the sum of the products of the largest perpendicular diameters from nadir, or a new lesion larger than 2 cm as revealed by radiography or 1 cm according to physical examination, or involvement of the bone marrow in a patient who had had a complete response or a clinical complete response.

Disease status was determined by physical examination; computed tomography (CT) of the neck, chest, abdomen, and pelvis; and bilateral bone marrow biopsies of the iliac crest if the bone marrow was positive for lymphoma at baseline. Physical examinations and CT imaging were performed at baseline and 6 and 12 weeks after therapy, then every 3 months until 2 years after treatment, and every 6 months thereafter. Bilateral bone marrow biopsies for purposes of restaging were performed 6 and 12 months after treatment and then yearly.

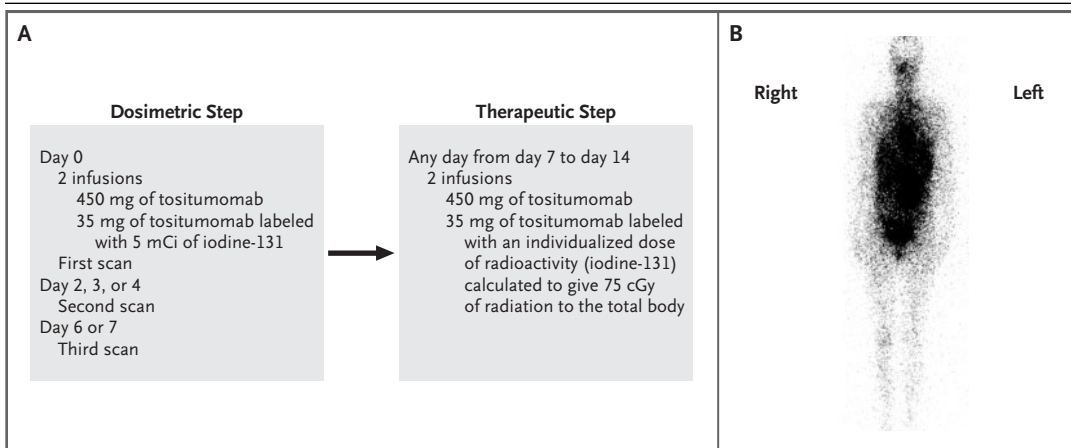


Figure 1. Treatment Regimen.

Panel A shows the schedule of infusions and gamma-camera scans. The therapeutic step is administered on a single day between day 7 and day 14; 97 percent of the patients in this study received the therapeutic dose on day 7 or 8. Panel B shows an anterior view of a gamma-camera image of one of the patients on day 7 with ¹³¹I-labeled tositumomab targeting a large abdominal mass.

MOLECULAR RESPONSE

Bone marrow cells were assayed at baseline with the use of a nested polymerase-chain-reaction (PCR) assay for t(14;18) translocations in which the *BCL2* gene is juxtaposed with the immunoglobulin heavy-chain locus. Subsequent samples for this analysis were obtained at 6, 12, and 25 weeks. DNA from positive bands was sequenced to verify identity with each patient's baseline sample.

SURVEILLANCE FOR MYELODYSPLASTIC SYNDROME AND SECONDARY ACUTE LEUKEMIA

The serial bone marrow biopsy specimens and aspirates obtained from patients in remission were examined microscopically for evidence of myelodysplastic syndrome. Karyotype analyses were performed serially by Genzyme Genetics with the use of standard metaphase techniques. For patients with disease progression, medical records and patients' reports obtained every six months were used for surveillance.

TOXICITY

Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute, version 1, with a grade of 1 indicating mild adverse events, a grade of 2 moderate adverse events, a grade of 3 severe adverse events, and a grade of 4 life-threatening adverse events. An adverse event was considered to be infusion-related if

its onset was on the day of an infusion. Peripheral blood B and T cells (CD19+ and CD3+, respectively) were enumerated by flow cytometry⁷ at baseline, 6 and 12 weeks after treatment, and then every 3 months until B-cell counts returned to normal.

HUMAN ANTIMOUSE ANTIBODIES

Serum samples were assessed before the dosimetric dose was administered; two days before the therapeutic dose was administered; at weeks 2, 6, 12, and 25; then every six months for two years; and yearly thereafter with the use of a previously described enzyme-linked immunosorbent assay¹⁵ and the Immustrip enzyme-linked immunosorbent assay for detecting human antimouse antibody (Immunomedics).

STATISTICAL ANALYSIS

Data collected from June 20, 1996, through March 1, 2004, were analyzed. For analyses of complete responses, complete and clinically complete responses were combined. The level of significance for comparative analyses was set at 0.05, with exact confidence limits calculated from binomial distributions. All reported P values are two-sided. No interim analysis for early stopping was performed. Duration of response and progression-free survival were analyzed with the use of Kaplan-Meier techniques.¹⁹ Univariate analyses of the factors listed in Table 1 were performed with the use of chi-

Table 1. Characteristics of the 76 Patients According to the Clinical Outcome after Treatment with ¹³¹I-Tositumomab Therapy.

Characteristic	Number of Patients	Five-Year Progression-free Survival	
		Complete Response	% of patients
Age			
≤60 yr	69	74	56
>60 yr	7	86	86
Sex			
Male	41	68	56
Female	35	83	63
Months from diagnosis to study entry			
≤12	46	74	61
>12	30	77	56
Stage of follicular lymphoma at study entry			
III	23	87	82
IV	53	70	49*
Histologic classification			
Grade 1 follicular center-cell lymphoma	53	72	59
Grade 2 follicular center-cell lymphoma	22	82	58
Mantle-cell lymphoma†	1	100	0
Bone marrow involvement			
None	27	89	81
1% to 25%	49	67‡	47‡
Serum lactate dehydrogenase§			
Normal	52	77	58
Elevated (>1× normal)	23	70	60
Bulky disease (maximal nodal diameter)			
<5 cm	43	88	63
≥5 cm	33	58¶	54
International Prognostic Index score§			
1	42	83	60
2 or 3	33	64	57
B symptoms at study entry 			
Present	11	91	73
Absent	65	72	57
Positive for t(14;18) major breakpoint translocation involving the BCL2 gene			
Unknown†	3		
Yes	39	77	51
No	34	76	70

* In a univariate analysis, $P < 0.05$ for the comparison with stage III follicular lymphoma.

† The patient with mantle-cell lymphoma and the three patients whose t(14;18) major breakpoint translocation was unknown were excluded from the analyses.

‡ In multivariate and univariate analyses, $P < 0.05$ for the comparison with an absence of bone marrow involvement.

§ The information was not available for one patient.

¶ In multivariate and univariate analyses, $P < 0.05$ for the comparison with a significant maximal nodal diameter of less than 5 cm.

|| B symptoms are weight loss, night sweats, and fever.

square and log-rank tests.²⁰ Multivariate analyses of response rates were performed with the use of a logistic-regression model, and multivariate analyses of the duration of responses were performed with the use of a Cox proportional-hazards model.²¹

Drs. Kaminski and Wahl designed the study. Data were collected and recorded by personnel at the University of Michigan. Statistical analyses were performed by Mr. Kroll at Corixa, who worked in conjunction with the investigators. All authors had access to and involvement in the interpretation of the data, as well as input into and control over the manuscript, which was written primarily by Dr. Kaminski.

RESULTS

PATIENTS

The median age of the patients was 49 years (range, 23 to 69), and the median time from the diagnosis of lymphoma to treatment was 8 months. Of the 76 patients, 70 percent had histologic grade 1 follicular lymphoma, 29 percent had grade 2, and 1 had mantle-cell lymphoma (Table 1). Sixty-four percent had bone marrow involvement, and 43 percent had at least one tumor with a diameter of at least 5 cm.

RESPONSE

Responses were observed in 72 of the 76 patients, most of whom reported regression of palpable tumor within two weeks. Complete responses were observed in 57 of 76 patients (Table 1), with a median time to an evaluated complete response of 202 days (range, 55 to 693).

The five-year rate of progression-free survival for all patients was estimated at 59 percent (95 percent confidence interval, 49 to 71) (Fig. 2). The median progression-free survival was 6.1 years (95 percent confidence interval, 3.0 years to [upper confidence level not reached]), with a median follow-up of 5.1 years. The 5-year progression-free survival for patients with a complete response was 77 percent (95 percent confidence interval, 67 to 89); 40 of the 57 patients (70 percent) who had a complete response (53 percent of the entire study population) remained in complete remission for 4.3 to 7.7 years after treatment (Fig. 3). All patients with a partial response had disease progression, with a median time to progression of 0.6 year. The annualized rate of relapse for all patients decreased from 25 percent per year during the first year to 13

percent per year the second year, 12 percent per year the third year, and 4.4 percent per year after three years. Only four relapses occurred after five years. In three of these four cases, the relapse was isolated in a single site, which was treated with local radiation therapy.

The five-year rate of overall survival was 89 percent (95 percent confidence interval, 83 to 97) (Fig. 2). Of the 76 patients, 9 (12 percent) died; no deaths were thought to be directly related to the treatment. Six patients died from progressive lymphoma, one from complications of an unrelated surgery, one from septic shock after receiving an allogeneic transplant, and one from neurologic complications of an allogeneic transplant. One patient was withdrawn from the study at one year and one patient at four years because of an inability to comply with the schedule of evaluations. We continue to follow all the other patients.

A maximal nodal diameter of at least 5 cm at baseline was associated with a significantly decreased complete-response rate, as compared with a maximal nodal diameter of less than 5 cm (odds ratio, 0.17). Likewise, bone marrow involvement at baseline was associated with a significantly decreased complete-response rate, as compared with no bone marrow involvement (odds ratio, 0.24). However, among patients who had a complete remission, neither bulky disease nor bone marrow involvement was clinically important: the rate of progression-free survival did not differ significantly between patients with and those without bulky disease ($P=0.39$) or between patients with and those without bone marrow involvement ($P=0.09$). Overall, bone marrow involvement and disease stage had a significant effect on progression-free survival in univariate analyses (Table 1), but in multivariate analyses, only bone marrow involvement had a significant effect.

MOLECULAR RESPONSE

PCR assays for *BCL2* gene rearrangement were performed at baseline in 73 of the 76 patients; the results were positive in 39 of 73. A second analysis, performed after the B-cell count had returned to normal (six months after treatment) in 36 of these 39 patients, showed that 34 patients had become negative for the *BCL2* gene rearrangement. Of 20 patients who had the rearrangement at baseline and were in complete remission at six months, 16 had negative PCR results, and 13 of them remained in complete remission after a median follow-up of

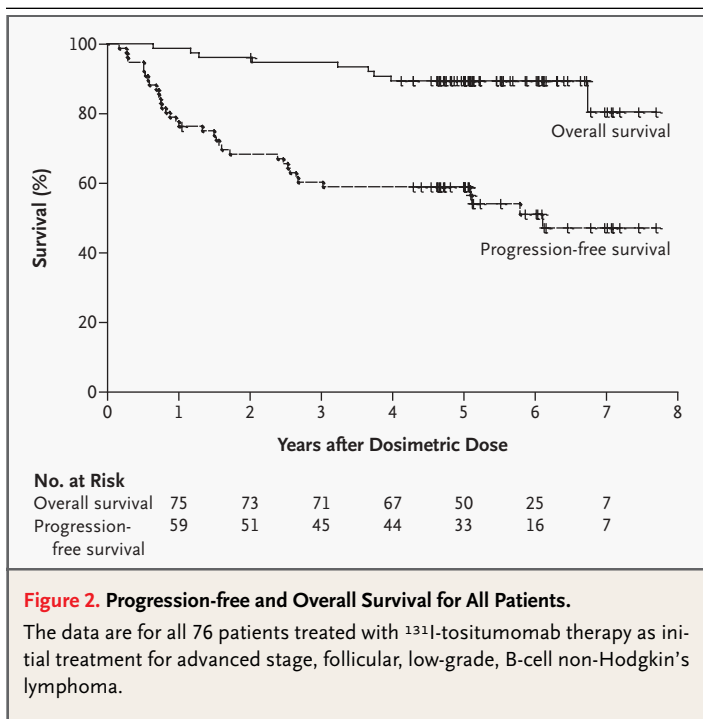


Figure 2. Progression-free and Overall Survival for All Patients.

The data are for all 76 patients treated with ¹³¹I-tositumomab therapy as initial treatment for advanced stage, follicular, low-grade, B-cell non-Hodgkin's lymphoma.

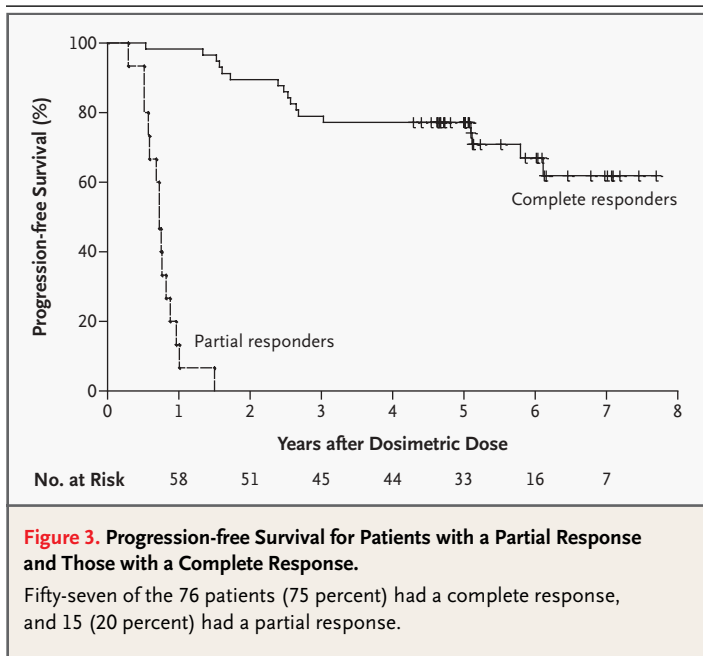
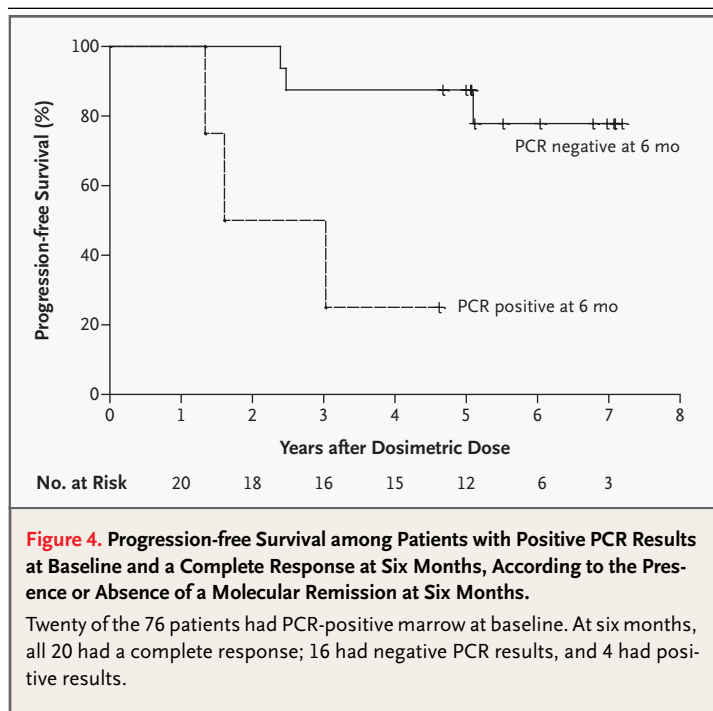


Figure 3. Progression-free Survival for Patients with a Partial Response and Those with a Complete Response.

Fifty-seven of the 76 patients (75 percent) had a complete response, and 15 (20 percent) had a partial response.

more than five years (Fig. 4); in contrast, three of four patients with a complete remission but positive PCR results for marrow at six months have had relapses ($P=0.003$ for the difference in progression-free survival).



TOXICITY

Adjustments to the rate of infusion were required for three doses in the dosimetric step but for no doses in the therapeutic step. Adverse events were reported in 46 percent of patients with the dosimetric dose and 21 percent of patients with the therapeutic dose. All infusion-related adverse events were grade 1 or 2 except for one grade 3 headache. Sixteen patients (21 percent) had a drug-related grade 3 or 4 nonhematologic adverse events, the most common of which were arthralgia (in 8 percent of the 76 patients), headache (5 percent), and myalgia (5 percent).

Hematologic toxicity was common but usually moderate (Table 2); four patients had grade 4 neutropenia, and none had grade 4 thrombocytopenia. By week 12, the absolute neutrophil count had risen to at least 1000 cells per cubic millimeter and the hemoglobin concentration to at least 11 g per deciliter in all patients, and in all but one patient the platelet count had risen to at least 100,000 per cubic millimeter. No patient received blood-product transfusions or hematopoietic growth factors related to treatment. There were no cases of febrile neutropenia, and no patients were hospitalized for infection. One case each of localized herpes zoster and herpes simplex was reported within the first 12 weeks.

B-CELL DEPLETION

At week 7, B-cell counts had dropped by 95 percent on average. The median time until B-cell counts returned to the normal range was six months. No reductions in serum immunoglobulin levels were observed.

HUMAN ANTIMOUSE ANTIBODIES

Antimouse antibodies were detected in 48 of the 76 patients at a median of 3.3 weeks (range, 1.7 to 39.0) after the dosimetric dose. These antibodies remained detectable for a median of 5.5 months (range, 1.1 to 25.1). There was no relation between these antibodies and progression-free survival ($P=0.28$). However, among 23 patients in whom antibody levels were more than five times the lowest level of detection within the first seven weeks, post hoc analysis showed that the five-year rate of progression-free survival was 35 percent, as compared with 70 percent for the remaining 53 patients ($P=0.003$).

Grade 2 or higher fever, myalgia, arthralgia, or rash developed in 26 percent of the patients within the first two weeks after the therapeutic dose. This influenza-like syndrome resolved in three to four days without recurrence or apparent sequelae. A post hoc analysis showed that 65 percent of patients with the syndrome were in the subgroup of 23 patients with antimouse antibody titers that were more than five times the level of detection within the first seven weeks, as compared with 18 percent of patients without the syndrome ($P<0.001$).

MYELODYSPLASTIC SYNDROME AND BONE MARROW CYTOGENETIC FINDINGS

No cases of myelodysplastic syndrome or acute leukemia were observed after a median follow-up of 5.1 years. The upper limit of the 95 percent confidence interval for the annual incidence of myelodysplastic syndrome was 0.8 percent. Karyotype analyses in 53 patients, with a median of 4 analyses per patient (range, 1 to 10) during a median follow-up of 20 months (range, 2 to 55), revealed clonal cytogenetic abnormalities in 2 patients, but these abnormalities were not confirmed by fluorescence in situ hybridization and did not persist on later testing.

THYROID FUNCTION

Nine of the 76 patients had had an elevated level of thyroid-stimulating hormone or had used thyroid medication before therapy began. Of the remain-

ing 67 patients, 9 were found to have an elevated level of thyroid-stimulating hormone and 4 began thyroid medication after therapy. Estimates of the two-year and five-year cumulative incidence rates for an elevated level of thyroid-stimulating hormone or the start of thyroid supplementation were 8 percent and 13 percent, respectively.

SECOND CANCERS

After 399 person-years of follow-up, basal-cell carcinoma was diagnosed in one patient at 7 months, breast cancer in two patients at 24 and 43 months, prostate cancer in one patient at 46 months, and ductal carcinoma in situ of the breast in one patient at 49 months.

DISCUSSION

In our study of radioimmunotherapy as initial treatment for follicular lymphoma, we found that a single course of ¹³¹I-tositumomab therapy resulted in a 95 percent overall response rate and a 75 percent complete-response rate. An estimated 77 percent of patients with a complete remission remained disease-free at five years. Moreover, a molecular remission (undetectable *BCL2* translocation) was achieved in 80 percent of assessable patients who had a complete response at six months. The treatment was associated with moderate and reversible hematologic toxicity, and no cases of myelodysplastic syndrome or acute myeloid leukemia were observed during a median follow-up of just over five years.

The rates of overall and complete responses in our study were higher than the rates observed with ¹³¹I-tositumomab therapy in previously treated patients. The reason for this difference is unclear, but regardless of the mechanism, our results favor using radioimmunotherapy early in the course of follicular lymphoma rather than reserving this treatment for chemotherapy-resistant disease.

Our results compare favorably with the best published results of studies of any type of initial therapy, including monoclonal anti-CD20 antibody (rituximab) alone,^{22,23} intensive chemotherapy,²⁴⁻²⁷ or chemotherapy combined with rituximab.^{28,29} For example, the arduous and toxic regimen of alternating triple therapy (often referred to as the ATT regimen) resulted in a median failure-free survival of five years.²⁷ In another study, 38 patients given rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemothera-

Table 2. Hematologic Toxicity in 76 Patients.*

Variable	Absolute Neutrophil Count	Hemoglobin	Platelet Count
Median nadir value	1300 per mm ³	12.2 g/dl	83,000 per mm ³
Median time to nadir (days)	47	44	29
Toxicity (%)†			
Grade 3 or 4	34	0	17
Grade 4	5	0	0
Median duration of toxicity (days)‡			
Grade 3 or 4	22	NA	22
Grade 4	22	NA	NA
Median time to return to baseline grade (days)	60	56	43

* NA denotes not applicable.

† Common Toxicity Criteria of the National Cancer Institute define a grade 3 absolute neutrophil count as 500 to less than 1000 per cubic millimeter and a grade 4 count as less than 500 per cubic millimeter, a grade 3 hemoglobin level as 6.5 to less than 8.0 g per deciliter and a grade 4 level as less than 6.5 g per deciliter, and a grade 3 platelet count as 10,000 to less than 50,000 per cubic millimeter and a grade 4 count as less than 10,000 per cubic millimeter.

‡ The duration of grade 3 or 4 toxicity was defined as the number of days from the last count before grade 3 or 4 toxicity to the first day of the documented return to grade 2 toxicity.

py had an overall response rate of 100 percent, a complete-response rate of 58 percent,²⁸ and a median time to disease progression of 6.9 years.²⁹ Considering the toxicity of this therapy and the time required to complete it (12 infusions over a span of 20 weeks), the results we obtained with only 2 infusions 1 week apart are notable. The flattening of the disease-progression curve after three years is encouraging, but longer follow-up is needed because of the long natural history of the disease.

Interpretation of molecular responses in follicular lymphoma can be difficult because of differences in PCR methods and disease status.³⁰ Nevertheless, we found that negative PCR results correlated well with clinical remission and predicted a durable complete remission. Indeed, we found that 81 percent of patients who had both a complete remission and a molecular response had a progression-free survival of five years, suggesting that such patients may not benefit from additional or more intensive treatment. Furthermore, we did not find a difference in outcome between patients who had baseline t(14;18) rearrangements and those who did not, a finding that differs from the results reported with other treatments.³¹

The only pretreatment factors that influenced

the complete remission rate were tumor bulk and bone marrow involvement, whereas only bone marrow involvement was associated with decreased progression-free survival in multivariate analyses. Still, even with bone marrow involvement, the five-year rate of progression-free survival was 47 percent. Recently, chemotherapy followed by a course of ^{131}I -tositumomab therapy has yielded promising results as initial treatment.^{32,33} It is not clear, however, whether it is best to give the radiolabeled antibody before or after chemotherapy. Currently, a prospective, randomized phase 3 study is being conducted by the Southwest Oncology Group and the Cancer and Leukemia Group B, in which treatment with concomitant rituximab and CHOP is compared with CHOP followed by ^{131}I -tositumomab therapy. Our results with the radiolabeled antibody alone suggest that additional prospective, randomized phase 3 studies may need to be performed to determine whether the combined therapy approach represents an improvement over treatment with the radiolabeled antibody alone.

Another factor that seemed to influence the outcome in our study was the development of anti-mouse antibodies. Such antibodies developed in 10 percent of patients previously treated with chemotherapy,^{7,9-11,15} whereas in our study these antibodies appeared in 63 percent of patients. Presumably, patients with previously treated lymphoma are less immunocompetent than those who have not received previous treatment, possibly because of immunosuppression from chemotherapy. The effect of the antibodies on the clinical outcome was apparent in only 23 patients in our study, who had high titers of anti-mouse antibodies soon after completion of the treatment. Use of a human, humanized, or chimeric anti-CD20 antibody as the carrier for the radionuclide might reduce the likelihood that anti-mouse antibodies will develop, but it is possible that such radiolabeled antibodies could also deliver additional radiation to normal organs because of prolonged serum clearance of the antibodies.

The principal toxicity we observed was hematologic, which was less severe than the hematologic toxicity seen with this regimen in previously treated patients. Temporary B-cell depletion occurred, but with no apparent clinical consequences. Serum immunoglobulin levels did not fall appreciably, a finding that matches the results previously reported for the patients initially enrolled in this study.³⁴ About one quarter of the patients had an influenza-like syndrome, the development of which was highly correlated with the development of anti-mouse antibodies. Hypothyroidism was uncommon (occurring in 13 percent of patients) and was managed with thyroid hormone replacement. No cases of myelodysplastic syndrome or acute myeloid leukemia, which are possible consequences of radiation therapy, were observed.³⁵

In conclusion, a single one-week treatment with ^{131}I -tositumomab therapy induced complete remissions lasting more than five years in most patients who had previously untreated follicular lymphoma. Our data support the use of this regimen early in the course of treatment of this disease. However, the ideal sequence of the various available therapies is not known and will require phase 3 randomized, comparative trials.

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Drs. Kaminski and Wahl, Ms. Estes, and Ms. Regan report having received consulting and lecture fees from Corixa and GlaxoSmithKline. Ms. Tuck reports having received consulting fees from Corixa and having equity and stock options in Corixa. Mr. Kroll is an employee of Corixa and reports having equity and stock options in Corixa. Drs. Kaminski and Wahl report having received grant support from Corixa. In addition, they receive royalties from patents they jointly hold on anti-CD20 radioimmunotherapy for lymphoma, and they have been expert witnesses in defending these patents. Dr. Zasadny reports holding a patent licensed to Corixa.

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