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Tositumomab and Iodine I 131 Tositumomab for Recurrent Indolent and Transformed B-Cell Non-Hodgkin's Lymphoma

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
An open-label phase II study was conducted at two centers to establish the efficacy and safety of tositumomab and iodine I 131 tositumomab at first or second recurrence of indolent or transformed indolent B-cell lymphoma.

Patients and Methods
A single dosimetric dose was followed at 7 to 14 days by the patient-specific administered radioactivity required to deliver a total body dose of 0.75 Gy (reduced to 0.65 Gy for patients with platelets counts of 100 to 149 $\times$ 10^9/L). Forty of 41 patients received both infusions.

Results
Thirty-one of 41 patients (76%) responded, with 20 patients (49%) achieving either a complete (CR) or unconfirmed complete remission [CR(u)] and 11 patients (27%) achieving a partial remission. Response rates were similar in both indolent (76%) and transformed disease (71%). The overall median duration of remission was 1.3 years. The median duration of remission has not yet been reached for those patients who achieved a CR or CR(u). Eleven patients continue in CR or CR(u) between 2.6+ and 5.2+ years after therapy. Therapy was well tolerated; hematologic toxicity was the principal adverse event. Grade 3 or 4 anemia, neutropenia, and thrombocytopenia were observed in 5%, 45%, and 32% of patients, respectively. Secondary myelodysplasia has occurred in one patient. Four patients developed human antimouse antibodies after therapy. Five of 38 assessable patients have developed an elevated thyroid-stimulating hormone; treatment with thyroxine has been initiated in one patient.

Conclusion
High overall and CR rates were observed after a single dose of tositumomab and iodine I 131 tositumomab in this patient group. Toxicity was modest and easily managed.

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INTRODUCTION

Follicular, small lymphocytic, and lymphoplasmacytoid lymphomas[1] together comprise a group of diseases characterized clinically by a propensity for advanced stage at presentation and longer median survival than other histologic subtypes of B-cell non-Hodgkin's lymphomas.[2-8] Typically, patients respond to therapy but the clinical course is of multiple episodes of recurrence culminating in death as a result of disease (irrespective of whether transformation to large B-cell pathology has occurred) or complications of therapy. Treatment options at recurrence are increasingly broad,[9,10] yet there has been little significant impact on survival.[11]

The CD20 antigen has become well established as a target for monoclonal antibody–directed therapy in B-cell lymphoma. This transmembrane phosphoprotein is expressed by more than 95% of B-cell lymphomas and is present on normal B cells except early progenitors and terminally differentiated plasma cells.[12,13] Because there is little shedding into the circulation, no inter-

nalization after antibody binding,[14,15] and no antigenic modulation, CD20 provides a [16]

After four weekly intravenous infusions of the chimeric anti-CD20 monoclonal antibody rituximab, responses are achieved in approximately 50% of patients. The complete remission (CR) rate, however, is low and the duration of response, in general, is short.[17,18] Given the sensitivity of these lymphomas to external-beam irradiation, radioimmunoconjugates directed against CD20 have been developed to overcome some of the deficiencies inherent in the use of cold antibodies.

The murine immunoglobulin G2a anti-B1 antibody tositumomab targets the CD20 antigen.[12] Covalently linked with iodine-131 (^{131}I), tositumomab and iodine I 131 tositumomab together comprise the BEXXAR therapeutic regimen (Corixa Corp, Seattle, WA, and GlaxoSmithKline, Philadelphia, PA). The dual-emission properties of ^{131}I result in delivery of high-energy beta particles over short distances, whereas measurements of gamma emissions may be made externally, allowing the determination of patient-specific pharmacokinetics. Encouraging results with tositumomab and ^{131}I tositumomab, hereafter referred to as ^{131}I tositumomab, have been achieved in a series of studies during the last decade. In a phase I/II, single-center, dose-escalation study of 59 patients with B-cell lymphomas, the overall response rate (ORR) was 71%.[19] A subsequent, multicenter, phase II trial of 47 heavily pretreated patients (median four prior therapies) with low-grade or transformed B-cell lymphoma reported an ORR of 57%, with 32% of patients achieving a CR.[20] These findings were subsequently confirmed in a large expanded-access program.[21] ^{131}I tositumomab is effective in chemotherapy-refractory patients (ie, those in whom treatment has failed or those who have experienced disease recurrence within 6 months from their last chemotherapy regimen). In this group the ORR was 65% (20% CR), in contrast with a response rate of only 28% and CR rate of 3% after their last regimen.[22] Most strikingly, 53% of patients had a longer remission duration after ^{131}I tositumomab than after their previous regimen.

On the basis of these promising results in a heavily pretreated population, this study was designed to investigate the safety and efficacy of ^{131}I tositumomab when administered earlier in the clinical course of indolent or transformed indolent B-cell lymphoma.

PATIENTS AND METHODS

^{131}I tositumomab in patients at first or second recurrence of indolent or transformed indolent B-cell non-Hodgkin's lymphoma. Duration of response, progression-free survival (PFS), safety, and survival were the secondary end points. The study was conducted at two centers in the United Kingdom. Local research ethics committee approval was granted at both sites and patients gave written informed consent before study entry.

Patient Eligibility

Adult patients with a histologically confirmed diagnosis of CD20-positive B-cell follicular (grade 1 or 2), small lymphocytic, lymphoplasmacytoid/immunocytoma, or unclassifiable low-grade B-cell lymphoma[1] were eligible for study entry. Patients with transformation from one of the above histologies to large B-cell lymphoma were also eligible. Histologic confirmation of transformation was documented before therapy. Patients were treated at first or second recurrence and had experienced disease progression after their last treatment. Patients were required to have a Karnofsky performance score ≥ 60, adequate renal and hepatic function, bidimensionally measurable disease ($\geq 2 \times 2$ cm by computed tomography scan), neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and no more than 25% of the intertrabecular bone marrow space infiltrated with lymphoma (determined by bone marrow trephine biopsy).

Patients were excluded if they had received cytotoxic chemotherapy, radiotherapy, or cytokine therapy within the previous 4 weeks or had experienced disease progression in a field previously irradiated with more than 35 Gy within 1 year. Systemic corticosteroids were discontinued at least 1 week before study entry. Patients were also excluded if they had previously received high-dose chemotherapy or radiotherapy with hematopoietic progenitor cell rescue; had prior exposure to either monoclonal or polyclonal antibodies, known HIV infection, active hydronephrosis, CNS lymphoma, or any other malignancy diagnosed within 5 years; or if they were pregnant or breastfeeding. Previous radioimmunotherapy and allergy to iodine were also exclusions to study entry.

Dosimetric and Therapeutic Doses

Tositumomab was centrally radiolabeled with ^{131}I (MDS Nordion Inc, Kanata, Canada) and shipped on a patient-specific basis. Administration was performed according to previously described methodology[20] (Fig 1). Patients received 120 mg potassium iodide daily, as thyroid blockade, from at least 24 hours before administration of the dosimetric dose until 14 days after the therapeutic administration. Before drug administrations, patients were premedicated with paracetamol 500 mg and chlorpheniramine 4 mg orally. After administration of the dosimetric dose, the effective half-life of total body clearance was calculated from gamma camera counts acquired at three time points. The patient-specific amount of radioactivity required to deliver the total-body therapeutic dose of 0.75 Gy was then calculated as previously described.[23] For patients with platelet counts between 100 and 149 $\times 10^9$/L, an attenuated total body dose of 0.65 Gy was administered, and for patients weighing more than 137% of their lean body mass, calculations were based on maximum effective mass. The therapeutic dose was administered 7 to 14 days after the dosimetric dose. Patients were hospitalized for this therapeutic phase and isolated in a dedicated facility until the total body activity was sufficiently low to permit discharge under current United Kingdom regulations.

Response Evaluation

The first response evaluation was performed 7 weeks after therapy and repeated at week 26 and every 3 months thereafter until disease progression or death. After 2 years, patients were observed every 6 months. A CR was defined as complete resolution of all disease-related radiologic abnormalities and the disappearance of all signs and symptoms related to the disease. Patients with bone marrow involvement at baseline were required to undergo a repeat bone marrow biopsy after therapy to confirm a CR. CR

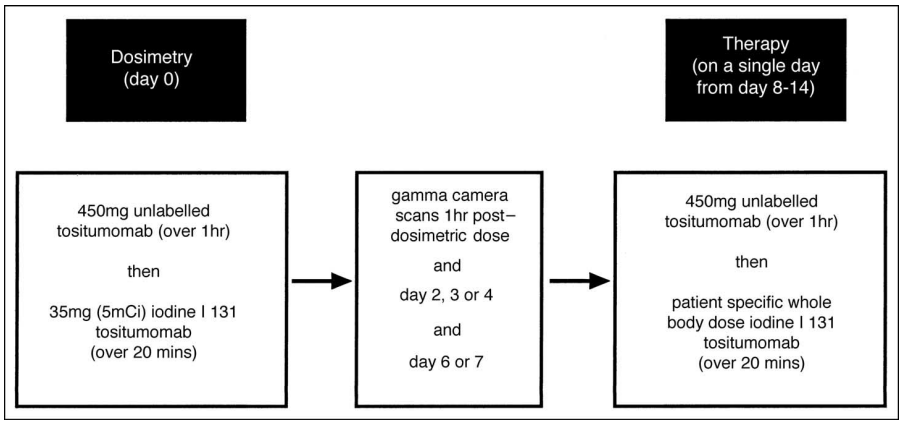

Fig 1. Drug administration. The desired total body dose was 0.75 Gy and attenuated to 0.65 Gy for patients with platelet counts 100 to 149 $\times$ 10^9/L.

unconfirmed [CR(u)] was defined as complete resolution of all disease-related symptoms but with residual focal abnormalities. Generally, these represented unchanging lesions of $\leq$ 2 cm diameter by radiologic evaluation. The study was initiated before publication of the International Workshop criteria,[24] resulting in some difference in definition. Partial remission was defined as a greater than 50% reduction in the sum of products of the longest perpendicular diameters of all measurable lesions (SPPD); stable disease was defined as a less than 25% increase or less than 50% decrease in the SPPD with no new lesions. Progressive disease was defined as a $\geq$ 25% increase of the SPPD from the nadir value. At disease progression, marker lesions were required to be more than 2 $\times$ 2 cm diameter by radiographic evaluation, or more than 1 cm diameter by physical examination. Progressive disease also included the appearance of any new lesion. Response was investigator assessed. Duration of response was defined as the length of time from the day of first evaluation with a response to the first day of documented progression. PFS was defined as the time from start of treatment (ie, the dosimetric dose) to first documented progression or death. Overall survival was defined from the date of start of therapy to death.

Evaluation of Toxicity and Safety

All adverse events from study entry through to week 13 were graded according to the National Cancer Institute Common Toxicity Criteria (version 1.0). Any adverse event occurring after this period considered to be possibly or probably related to study drug was also recorded. Full blood counts were performed weekly from week 3 until week 9, or until grade 0 toxicity had been reached, and blood counts were repeated at weeks 13 and 26, and every 3 months thereafter. The use of hematopoietic growth factors and blood products was at the discretion of the treating physician. History, physical examination, and hepatic, renal, and electrolyte studies were performed at weeks 3, 7, 13, and 26, and repeated every 3 months thereafter. Thyroid function tests (thyroid-stimulating hormone [TSH], free T4, and total T3) were performed at week 26 and repeated every 3 months thereafter. From 2 years onward, patients were evaluated every 6 months, and data were collected for disease status, diagnosis of secondary myelodysplasia or secondary acute myeloid leukemia, other secondary malignancy, thyroid dysfunction, and use of thyroid medication. Serum human antimouse antibody (HAMA) and thyroid function analyses were also performed at these times.

HAMA

Detection of HAMA on serum samples was performed at each site using the ImmuSTRIP HAMA immunoglobulin G enzyme-linked immunosorbent assay test kit (Immunomedics Inc, Morris Plain, NJ). Samples were taken at baseline and at day 5 and evaluated before the administration of the dosimetric and therapeutic doses, respectively. Patients with a positive HAMA at baseline or on day 5 did not receive subsequent ^{131}I tositumomab therapy. HAMA assessment was repeated at weeks 7, 13, and 26, and as part of long-term follow-up. Independent central analysis also was performed (Covance Central Laboratory Services Inc, Indianapolis, IN).

Statistical Analysis

Data were analyzed through November 2003 for all patients who had received any study drug. Hematologic toxicity was analyzed only for those patients who received a therapeutic dose. The level of significance for all comparative analyses was set at 0.05, with exact confidence limits calculated from binomial distributions. Analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC). Duration of response and survival data were analyzed using the censored data techniques of Kaplan-Meier.[25] Differences in response rates across patient subgroups were tested for statistical significance by χ^2 statistic (Yates corrected for two groups) and the log-rank test was used for duration of response by univariate analysis. The logistic regression model was used to perform multivariate analysis of response and the Cox proportional hazards model was used in multivariate analysis of PFS. Cumulative incidence estimates incorporating the presence of competing risk were used for the proportion of patients developing HAMA and hypothyroidism.[26]

RESULTS

Patient Characteristics

Forty-four patients were enrolled onto this phase II study at two institutions between July 2, 1998, and February 22, 2001. Three patients did not receive any study drug and are not included in the analysis (two patients had HAMA at baseline, in the absence of exposure to previous diagnostic or therapeutic murine proteins, and one patient withdrew consent before therapy). Thus, a total of 41 patients received a dosimetric dose of ^{131}I tositumomab. One patient

developed HAMA 12 days after dosimetry and did not receive the therapeutic dose. Clinical characteristics are documented in Table 1. The median age was 59 years (range, 36 to 90 years). Median follow-up of all patients is 3.0 years (3.6 years for responders). The median activity administered to deliver a total body dose of 0.65 or 0.75 Gy was 95.1 mCi (range, 49.2 to 145.3 mCi; median, 3,519 MBq [range, 1,820 to 5,372 MBq]).

Response to Treatment

A response was observed in 31 (76%) of 41 patients. Twenty patients (49%) achieved either a CR (37%) or CR(u) (12%). At the earliest time of assessment, 7 weeks after the dosimetric dose, CR or CR(u) was only documented in four of these 20 patients, indicating that time to maximal response may be slow. The median duration of remission for all responders was 1.3 years (95% CI, 0.7 years to not yet reached). For those in whom a CR or CR(u) was achieved, the median duration of remission has not yet been reached (95% CI, 1.1 year to not yet reached) but will exceed 2.5 years. Eleven (55%) of 20 patients continue in CR or CR(u) a median of 4.1 years (range, 2.6 to 5.2 years) after therapy. There was no difference in remission duration between CR and CR(u). The median PFS for all patients was 0.8 years (95% CI, 0.5 years to not yet reached); for responding patients, the median PFS was 1.7 years (95% CI, 0.8 to 2.5 years; Figs 2 and 3).

The highest overall response rate was seen in patients with follicular lymphoma (79%), with 59% achieving a CR or CR(u) (Table 2). The median duration of remission for patients with follicular lymphoma was 2.4 years (95% CI, 0.9 years to not yet reached); for those patients achieving CR or CR(u), the median duration of remission was 3.4 years (95% CI, 1.3 years to not yet reached). There was no significant difference in response rates between patients with disease transformation (71%) at the time of therapy and those without transformation (76%; $P = .999$); however, only seven patients were enrolled with transformed histology. Among the individuals with transformation, responders included patients with large tumor volumes and elevated lactate dehydrogenase levels (Table 3).

In univariate analysis, only lymph node diameter ≥ 5 cm was associated with a lower ORR and CR or CR(u) rate ($P = .011$; Table 4). A shorter duration of remission, however, was not observed in these patients. Thrombocytopenia at baseline (and therefore attenuation of total body dose; $P = .002$), elevated beta$_2$-microglobulin at study entry ($P = .004$), and two or more prior chemotherapy regimens ($P = .040$) were associated with a statistically shorter median duration of remission. In an analysis for shorter PFS, elevated beta$_2$-microglobulin ($P = .007$), receipt of two or more prior regimens ($P = .005$), and no response to last therapy ($P = .005$) were significant. In multivariate analysis, no variable significantly affected the ORR, CR or CR(u) rate, or PFS.

Table 1. Patient Characteristics (N = 41)

Characteristic	No. of Patients	%
Age, years		
Median	59	
Range	36-90	
No. aged > 60	16	39
Sex		
Male	20	49
Female	21	51
Karnofsky performance score		
Median	80	
Range	60-100	
Serum LDH		
Normal	36	88
Elevated	5	12
Beta$_2$-microglobulin		
Normal	23	58
Elevated	15	37
Not recorded	3	7
IPI		
0-1	20	49
2	13	32
3	6	15
4-5	2	5
Histology		
Follicular lymphoma	29	71
Small lymphocytic lymphoma	2	5
Lymphoplasmacytoid lymphoma	2	5
Low-grade B unclassifiable	1	2
Transformation to large B-cell lymphoma	7	17
Maximum tumor diameter, cm		
≥ 5	25	61
< 5	16	39
Bone marrow involvement		
Yes	22	54
No	19	46
Months from diagnosis to study entry		
Median	36	
Range	10-246	
Number of previous chemotherapy regimens		
1	23	66
2	17	41
> 2	1	2
Previous radiotherapy		
Yes	7	17
No	34	83
Response to last chemotherapy regimen		
CR or CR(u)	19	46
PR	17	41
SD	3	7
PD	2	5
Duration of response to most recent chemotherapy regimen, months		
Median	9	
Range	2-236	
Stage at study entry		
I or II	8	20
III or IV	33	80

Abbreviations: LDH, lactate dehydrogenase; IPI, International Prognostic Index; CR, complete remission; CR(u), unconfirmed complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

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