Yttrium-90 Ibritumomab Tiuxetan Doses Calculated to Deliver up to 15 Gy to Critical Organs May Be Safely Combined With High-Dose BEAM and Autologous Transplantation in Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

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ABSTRACT

Purpose

To determine the maximum-tolerated radiation-absorbed dose (RAD) to critical organs delivered by yttrium-90 (^{90}Y) ibritumomab tiuxetan in combination with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy with autologous transplantation.

Patients and Methods

Eligible patients had relapsed or refractory CD20+ non-Hodgkin's lymphoma (NHL). Individualized ^{90}Y activities were based on dosimetry and were calculated to deliver cohort-defined RAD (1 to 17 Gy) to critical organs with three to six patients per cohort. The therapeutic dose of ^{90}Y ibritumomab tiuxetan was followed by high-dose BEAM and autologous transplantation.

Results

Forty-four patients were treated. Thirty percent of patients had achieved less than a partial remission to their most recent therapy and would not have been eligible for autologous transplantation at most centers. The toxicity profile was similar to that associated with high-dose BEAM chemotherapy. Two dose-limiting toxicities occurred at the 17 Gy dose level, which made 15 Gy the recommended maximum-tolerated RAD. Although eight patients received at least twice the conventional dose of 0.4 mCi/kg, a weight-based strategy at 0.8 mCi/kg would have resulted in a wide range of RAD; nearly 25% of patient cases would have received 17 Gy or more, and many would have received less than 10 Gy. With a median follow-up of 33 months for all patients, the estimated 3-year progression-free and overall survivals were 43% and 60%, respectively.

Conclusion

Dose-escalated ^{90}Y ibritumomab tiuxetan may be safely combined with high-dose BEAM with autologous transplantation and has the potential to be more effective than standard-dose radioimmunotherapy. Careful dosimetry is required to avoid toxicity and undertreatment.

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INTRODUCTION

High-dose chemotherapy and autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) is curative in only a minority of patients who have relapsed or refractory non-Hodgkin's lymphoma (NHL).¹⁻⁴ The anti-CD20 radioimmunconjugates (RIC) yttrium-90 (^{90}Y) ibritumomab tiuxetan and iodine-131 (^{131}I) tositumomab produce durable remissions in previously treated patients who have relapsed or refractory, low-grade, follicular or transformed NHL.^{5,6} Because myelosuppression is the major toxicity of anti-CD20

RICs, they are ideal candidates for dose-escalation with stem cell support. Phase I/II studies have demonstrated that anti-CD20 RICs may be dose escalated with limited toxicity and that higher radiation doses are associated with improved clinical outcomes.⁷⁻⁹ Conventional, therapeutic-dose ^{131}I tositumomab or ^{90}Y ibritumomab tiuxetan has been added to the most commonly used high-dose chemotherapy program (ie, carmustine, etoposide, cytarabine, melphalan [BEAM]) to intensify the regimen,¹⁰⁻¹³ but the combination has not yet been shown to be superior to high-dose BEAM alone.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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In this phase I trial, ^{90}Y ibritumomab tiuxetan was combined with high-dose BEAM¹⁴ with the goal of administering the highest possible dose of RIC without increasing toxicity. The dose of RIC was patient-specific, was based on dosimetry, and was calculated to deliver cohort-defined radiation-absorbed doses (RADs) to critical organs. Fifteen Gy proved to be the maximum-tolerated RAD to critical organs and is the recommended dose for future study. When doses were calculated according to weight, there was considerable variability among patients, which justified the dosimetry-based approach.

PATIENTS AND METHODS

Eligibility

Patients 18 years and older who had relapsed or refractory B-cell NHL and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 were eligible. Biopsy before salvage chemotherapy was required to document recurrence, histology, and CD20 positivity. Only patients with adequate cardiac and pulmonary function—defined as a left ventricular ejection fraction of 45% or greater, a corrected diffusing capacity for carbon monoxide (DLCO_{cor}) of 70% or greater, and a forced expiratory volume in 1 second (FEV₁) or forced vital capacity (FVC) greater than 60% of the predicted value—were eligible. Additional requirements included a calculated creatinine clearance greater than 50 mL/min, transaminases less than two-fold the upper limit of normal, platelet count of 100,000/ μL or more, and absolute neutrophil count of 1,500/ μL . Patients with circulating malignant lymphoid cells or bone marrow involvement with lymphoma that constituted more than 25% of the cellular elements were ineligible. All patients signed informed consent documents approved by the institutional review board at the participating sites (ie, Northwestern University or Mayo Clinic) in accordance with the Declaration of Helsinki.

Clinical Trial Design

On day -22, patients were treated with rituximab 250 mg/m², which was followed immediately by a tracer dose of indium-111 (^{111}In) ibritumomab tiuxetan (5 mCi). Imaging of the tracer dose was performed immediately and at 4, 24, 72, and 144 hours postinjection. Dosimetry was performed on day -15. On day -14, patients were infused with rituximab 250 mg/m² followed by ^{90}Y ibritumomab tiuxetan at an initial activity calculated to deliver no more than 1 Gy to critical organs (ie, liver, lungs, kidney). The ^{90}Y activity of the RIC was individualized to deliver cohort-defined RAD (1, 3, 5, 7, 9, 11, 13, 15, 17 Gy) to critical organs.

On days -6 to -1, patients received the BEAM high-dose conditioning regimen intravenously on the basis of the adjusted ideal body weight (carmustine 300 mg/m² on day -6, etoposide 100 mg/m² and cytarabine 100 mg/m² twice daily on days -5, -4, -3, and -2, and melphalan 140 mg/m² on day -1). A peripheral blood sample was obtained on day 0 for measurement of radioactivity levels; this information was not used to determine the timing of reinfusion. A minimum of 2.0×10^6 CD34⁺ mobilized peripheral-blood progenitor cells per kilogram was infused on day 0. Beginning 2 hours after infusion of the autograft, granulocyte colony-stimulating factor 5 $\mu\text{g/kg}$ was administered subcutaneously daily until the absolute neutrophil count exceeded 1,500/ μL .

Dose-Limiting Toxicity

For purposes of this phase I trial, dose-limiting toxicity was defined as the following: any nonhematologic grade 4 toxicity, including stomatitis/pharyngitis, according to Common Toxicity Criteria, version 2.0, with the exception of fatigue, anorexia, dysphagia or vomiting; any nonhematologic grade 3 toxicity that did not resolve in 96 hours, with the exception of fatigue, anorexia, dysphagia, vomiting, stomatitis/pharyngitis, pulmonary toxicity (including hypoxia, dyspnea, pleural effusion, pneumonitis), sexual/reproductive dysfunction and hepatotoxicity; a requirement for oxygen support that persisted for greater than 10 days or a decline in DLCO_{cor} to less than 50% predicted,

corrected for hemoglobin; an increase in total bilirubin or alkaline phosphatase to greater than five-fold the upper limit of normal, or an increase in γ -glutamyltransferase, AST, or ALT to greater than 10-fold the upper limit of normal for more than 96 hours; a delay in recovery to an absolute neutrophil count of 500/ μL beyond day +21, or a requirement for platelet transfusions that persisted beyond 28 days; and veno-occlusive disease that did not resolve to a bilirubin less than three-fold the upper limit of normal within 30 days of transplantation.

Pretransplantation staging included computed tomography of the chest, abdomen, pelvis, and bone marrow examination. Gallium or fluorodeoxyglucose-positron emission tomography scans were obtained at the discretion of the investigator. Response was judged according to the consensus guidelines at 30 days, at 3 and 6 months post-transplantation, and yearly for 5 years thereafter.¹⁵ Pulmonary function testing, including DLCO_{cor}, was obtained at 30 days and at 3, 6 and 12 months post-transplantation. A repeat bone marrow was performed at 3 months if it was previously positive.

Dosimetry

This trial required patient-specific activities of ^{90}Y ibritumomab tiuxetan calculated to deliver cohort-defined RAD. The methodology for estimating the RAD from ^{90}Y was based on quantitative radionuclide imaging of a ^{111}In -radiolabeled ibritumomab tiuxetan pretreatment diagnostic tracer dose and MIRDose 3.0 model-based internal radionuclide dosimetry software (1994; Oak Ridge Associated Universities, Oak Ridge, Tennessee). The RAD estimates were corrected for critical organ mass that was calculated from computed tomography volume measurements.¹⁶

Measurement of Peripheral-Blood Radioactivity

Duplicate, 1.0-mL, whole-blood aliquots were obtained from the peripheral-blood sample drawn on day 0. A 1.0-mL ^{90}Y standard was prepared from a decayed, known, ^{90}Y activity sample prepared on day -14. Blood, standard, and background samples were each counted for 1 minute with a wide energy window in a thallium-doped sodium iodide crystal γ scintillation detector interfaced to a multichannel analyzer. After background correction, patient blood sample results were expressed as mean $\mu\text{Ci } ^{90}\text{Y/mL}$ whole blood.

Statistical Considerations

A modified 3 + 3 dose escalation design was applied in this study. To allow additional patients to begin protocol treatment before the required cohort of three at a given dose level were observed for the required 30 days for toxicity, a total of six patients at the previous dose level were permitted to be entered on study. Progression-free survival (PFS) was defined as the time from transplantation to relapse/disease progression or death. Overall survival (OS) was measured from the day of transplantation to death from any cause. PFS and OS were estimated by using the Kaplan-Meier method.¹⁷ Spearman correlation was used to relate blood radioactivity levels and time to neutrophil recovery.

RESULTS

Patient Characteristics

Forty-four patients were enrolled and treated on this phase I trial between May 2000 and April 2006, and their characteristics are listed in Table 1. Because this was a phase I trial, patients who were not responsive to salvage therapy were eligible; 30% of enrolled patients had achieved less than a partial remission to their most recent therapy and would not otherwise have been eligible for transplantation at most centers.

^{90}Y Ibritumomab Tiuxetan Dosing

One patient at the third dose level progressed before receiving treatment and was excluded from this analysis. All other patients who underwent dosimetry completed therapy. The critical organ was the

Table 1. Patient Characteristics

Characteristic	No.	%
Total No. of patients	44	
Sex		
Male	28	
Female	16	
Age, years		
Median	54	
Range	25-73	
Histologic subtype		
DLBCL	17	39
Mantle cell	7	16
Follicular	4	9
Transformed*	16	36
No. of prior chemotherapy regimens		
1	3	7
2	23	52
≥ 3	18	41
Prior therapy		
Rituximab	33	75
Radiation	7	16
Elevated LDH at study entry	20	45
Response to previous chemotherapy		
Primary refractory (no CR to frontline therapy)	19	43
< PR to salvage therapy (last treatment)	13	30
Never achieved CR	16	36

Abbreviations: DLBCL, diffuse, large B-cell lymphoma; LDH, lactate dehydrogenase; CR, complete response; PR, partial response.

*Transformation to diffuse, large B-cell lymphoma.

Fig 1. Weight-based activity doses of yttrium-90 ibritumomab tiuxetan that demonstrate the wide range in radioactivity normalized by patient weight for a defined radiation-absorbed dose to the critical normal organ.

liver in all but four patients, in whom it was the kidney. Patient-specific activity doses calculated to deliver a cohort-defined RAD to the critical organ varied widely (Table 2; Fig 1). For example, the ^{90}Y ibritumomab tiuxetan doses administered to deliver an estimated 15 Gy to the liver in six patients ranged from 0.50 to 1.39 mCi/kg. Although eight patients safely received doses of 0.8 mCi/kg or greater, a weight-based strategy at twice the conventional 0.4 mCi/kg dose would have resulted in a wide range of RAD (median, 13 Gy; range, 4 to 31); 10 of 44 would have received 17 Gy or more and three patients

would have received more than 24 Gy (Fig 2). Twelve patients would have received less than 10 Gy.

Safety

Grades 3 to 5 adverse events are listed in Table 3. Toxicities were similar to those typically seen in patients treated with high-dose BEAM alone and HSCT. Grade 3 stomatitis occurred more often at the higher dose levels.

There were two dose-limiting toxicities at the 17 Gy dose level. One patient death occurred on day +10 as a result of pneumonia and sepsis with subsequent acute renal failure, respiratory distress syndrome, and hypotension. A second patient at the 17 Gy dose level developed septic pulmonary emboli related to an infected intravenous catheter on day +13.

There were four additional patients who experienced grade 4 toxicities; one was infectious, one was genitourinary (ie, obstructive

Table 2. Yttrium-90-Ibritumomab Tiuxetan Dosing by Cohort

Radiation Absorbed Dose (Gy)	No. in Cohort	Activity Dose			
		Total (mCi)		mCi/kg	
		Median	Range	Median	Range
1	3	4.9	2.1-13.7	0.06	0.05 to 0.12
3*	7	21.6	14.2-56.7	0.26	0.18 to 0.64
5	6	30.9	16.1-48.1	0.40	0.13 to 0.64
7	6	36.3	25.9-55.0	0.39	0.27 to 0.73
9	3	27.8	26.9-36.5	0.32	0.29 to 0.45
11	5	51.4	29.4-65.5	0.57	0.50 to 0.75
13	5	61.4	38.5-98.2	0.77	0.41 to 1.06
15	6	73.1	51.3-99.3	0.95	0.50 to 1.39
17	3	97.5	81.9-104.2	1.16	0.95 to 1.20

*A patient assigned to the third cohort had an abnormally high uptake of indium-111 ibritumomab tiuxetan to the liver and was treated, therefore, at the second cohort level.

Fig 2. Calculated radiation-absorbed dose to the critical organ for each patient (N = 44) if dosed according to weight at 0.8 mCi/kg.

uropathy that required stenting), one was pulmonary (ie, pulmonary embolism on day -14), and one was hepatic. Reversible veno-occlusive disease with grade 4 edema developed in one patient at the 7 Gy dose level, which constituted a dose-limiting toxicity and necessitated the enrollment of three additional patients at that dose level.

Table 3. Adverse Events

Adverse Event	Grade			
	3		4 to 5*	
	No.	%	No.	%
Infection	24	55	3	7
Stomatitis	21	48	0	0
Hemorrhage	17	39	0	0
Fever	14	32	0	0
Nausea, vomiting, diarrhea	13	29	0	0
Hepatic	5	11	1	2
Transaminitis	2	5		
Hyperbilirubinemia	2	5		
γ -GT	1	2		
Cardiovascular	4	9	1	2
Pulmonary	4	9	3	7
Genitourinary	0	0	2	5
Neuropathy (sensory or motor)	2	5	0	0

NOTE. Total No. of patients = 44.

Abbreviation: γ -GT, γ -glutamyltransferase.

*As anticipated, all patients had grade 4 leukopenia, grades 3 to 4 thrombocytopenia, and grades 2 to 3 anemia.

One patient on cohort 7 (13 Gy) developed therapy-related myelodysplasia 9 months post-transplantation and subsequently died as a result of sepsis on day +483. This patient had follicular lymphoma that transformed and had received extensive prior alkylator therapy, which likely played a significant contributory role in the development of secondary myelodysplasia. The karyotype was complex and included 5q⁻, 7q⁻, and 8⁺.

Engraftment

Engraftment occurred at a median of 10 days (range, 8 to 18 days) for neutrophils and was defined as the first of three days with an absolute neutrophil count greater than 500/ μ L. Engraftment for platelets occurred at a median of 21 days (range, 11 to 40 days) and was defined as the first of three days with a platelet count of 20,000/ μ L without transfusion for 7 days. The median number of CD34⁺ cells infused per kilogram of patient weight was 5.0×10^6 (range, 2.7 to 14.3×10^6). A single patient in the second cohort (ie, 3 Gy) experienced a delay in platelet engraftment beyond 28 days. This patient received a total of 0.3 mCi/kg (total activity, 21.6 mCi); the autograft contained 4.6 million CD34⁺ cells/kg.

Residual Peripheral-Blood Radioactivity

The whole peripheral-blood μ Ci/mL (median, 0.012 μ Ci/mL; range, 0.001 to 0.062) on the day of transplantation before reinfusion of the autograft was related to both ⁹⁰Y activity and cohort-prescribed Gy level ($P = .004$ and $P = .007$, respectively by Spearman correlation analysis; $n = 37$). Residual peripheral-blood radioactivity was inversely related to time to neutrophil recovery ($P = .03$) but not to platelet recovery ($P = .4$).

Clinical Outcomes

Fifteen patients had a complete response (CR) to salvage therapy and entered the study without evidence of disease. Among the twenty-nine patients (66%) with active disease at study entry, eleven achieved CR, and six achieved partial remissions after protocol treatment. The median follow-up times were 33 months (range, 0.3 to 92 months) for all 44 patients and 50 months (range, 21 to 92 months) for the 27 patients alive at last follow-up. The estimated 3-year PFS and OS rates were 43% and 60%, respectively (Fig 3). The median time to progression was 20 months. When data were analyzed according to remission status at study entry, there was a trend in favor of those patients in CR (3-year PFS, 53% v 38% [$P = .41$]; 3-year OS, 79% v 50% [$P = .09$]). When PFS and OS were analyzed by histologic subset or according to dose (< 0.4 mCi/kg v ≥ 0.4 mCi/kg), there were no differences in clinical outcomes.

DISCUSSION

In this clinical trial, escalated doses of ⁹⁰Y ibritumomab tiuxetan calculated to expose critical normal organs to a maximum RAD of 15 Gy were safely combined with high-dose BEAM and autologous hematopoietic stem-cell transplantation with excellent clinical outcomes in this high-risk patient population. On the basis of dosimetry, individualized activity doses of radioimmunoconjugate were calculated to deliver cohort-defined RADs to critical organs. The weight-based activity doses (mCi/kg) varied considerably, which justified the dosimetry-based, rather than weight-based, strategy for dose escalation.

Fig 3. (A) Overall and (B) progression-free survival for all 44 treated patients from the time of transplantation.

The dosimetric approach to radioimmunotherapy was originally pioneered by Press et al⁷ on the basis of the observed, substantial variance of biodistribution of antibody from patient to patient. Press et al surmised that toxicity to normal organs would more likely correlate with RAD to critical normal organs than with activity doses calculated according to weight. In the Press et al trial, patients within the individual cohorts that were defined by target radiation dose to the critical normal organ had similar toxicity profiles, which is consistent with this concept. In our series, patient-specific doses calculated to deliver a cohort-prescribed RAD to the critical organ were highly variable. Among the six patients in the 15 Gy cohort, the weight-based activity dose varied nearly three-fold; this is consistent with the results of Ferrucci et al,¹⁸ who reported that RAD to normal target organs ranged as much as three- to eight-fold within weight-defined cohorts in their phase I trial of ⁹⁰Y ibritumomab tiuxetan as a single agent. Although eight patients safely received at least twice the conventional 0.4 mCi/kg dose in our series, a weight-based dose of 0.8 mCi/kg would have resulted in a wide range of RAD. One quarter of the 44 patients would have received 17 Gy or more, and three patients would

have received more than 24 Gy, which underscores the importance of careful systematic dosimetry. This variability may relate to tumor burden as well as to other individual differences that impact biodistribution. Although Devizzi et al¹⁹ reported treating 17 patients with 1.2 mCi/kg as a single agent without significant toxicity, the addition of radioimmunotherapy to the already toxic high-dose BEAM regimen requires caution and the precision of dosimetry to limit the potential for life-threatening toxicity. For many patients, the weight-based dose at 0.8 mCi/kg will deliver significantly less than the 15 Gy maximum-tolerated RAD to critical organs, which would possibly compromise its effectiveness. A dosimetric approach is recommended if the goal is to safely deliver the highest possible RAD.

Dosimetry that corrects the MIRDose model (Oak Ridge Associated Universities)-based RAD for actual organ mass requires expertise available only at specialized centers.²⁰ Mass correction is an important component of a patient-specific dosimetric approach, especially for a pure β -emitting radionuclide such as ⁹⁰Y, for which the RAD to a target organ that accumulates RIC is predominantly from activity within the target itself and not from other source organs (ie, self-dose). RAD is defined as the total energy deposited per unit mass, and the masses of critical organs (ie, liver, lung, kidney, and spleen) may vary substantially from the reference masses employed in the MIRDose model (Oak Ridge Associated Universities)-based RAD calculation. In an analysis of the first nine patients in this clinical trial who enrolled at Northwestern University, mass-corrected organ RAD estimates differed by $37.4\% \pm 28.3\%$ from those that were based on the reference masses.²¹

The toxicity profile of dose-escalated ⁹⁰Y-ibritumomab tiuxetan in combination with high-dose BEAM was similar to that associated with BEAM alone.¹⁴ Neither of the two dose-limiting toxicities that occurred at 17 Gy were unusual occurrences for patients undergoing high-dose chemotherapy and HSCT, and it is possible that higher RAD may be feasible. Severe hepatotoxicity occurred in only one patient case, although the liver was the critical dose-limiting organ in the majority of patient cases. Although the surrogate isotope ¹¹¹In has a greater tendency to localize in the liver than ⁹⁰Y, ¹¹¹In and ⁹⁰Y-radiolabeled ibritumomab have similar biodistribution in pre-clinical studies, which makes it unlikely that ¹¹¹In-based dosimetry overestimated the ⁹⁰Y liver RAD.^{22,23} One patient developed myelodysplasia that was likely related, at least in part, to extensive prior therapy with alkylators. Given the high rate of myelodysplasia/leukemia reported in patients with NHL who were undergoing autologous HSCT, this complication is not unexpected.²⁴ A recent analysis of secondary malignancies in patients treated with ⁹⁰Y-ibritumomab tiuxetan did not show evidence of an increased risk associated with radioimmunotherapy.²⁵

To avoid exposure of the autograft to toxic levels of radioactivity, reinfusion was scheduled 14 days after treatment with the RIC or more than five half-lives after treatment. Residual radioactivity in the peripheral blood correlated with the activity-administered and cohort-defined RAD to critical organs. Contrary to expectations, an inverse relationship between the measurement of residual radioactivity and myeloid, but not platelet, recovery was noted. Given the narrow window of myeloid engraftment (only one patient recovered their neutrophil count beyond day +13) and high number of CD34⁺ cells infused in all patient cases, this measurement is likely related to factors other than cell dose or the radioimmunotherapy.

Clinical outcomes for the high-risk patient population enrolled on this phase I trial are promising, and they provide the rationale for additional investigation of this strategy. The majority had active disease at study entry, and many had proven refractory to frontline therapy. Nearly one third had less than a partial response to salvage therapy and would have been ineligible for transplantation on this basis at many centers. With a median follow-up of 4 years, these results compare favorably and, in general, exceed those of other series that included similar high-risk patients with relapsed or refractory NHL who were treated with conventional transplantation regimens.²⁶⁻²⁸

Whether dose-escalated ⁹⁰Y-ibritumomab tiuxetan at the maximum-tolerated RAD of 15 Gy to critical organs will produce better outcomes than the conventional-activity 0.4 mCi/kg weight-based dose when combined with high-dose BEAM will require a head-to-head comparison. Promising results from trials that used a combination of conventional-activity dose ⁹⁰Y ibritumomab tiuxetan and high-dose BEAM in both relapsed and refractory patients^{11-13,29} have led to an Israeli-led, phase III, randomized, HSCT trial to compare ⁹⁰Y ibritumomab tiuxetan at the conventional 0.4 mCi/kg dose plus high-dose BEAM with high-dose BEAM alone. Similarly, the US Bone Marrow Transplant Clinical Trials Network is comparing conventional dose ¹³¹I tositumomab plus BEAM to rituximab plus BEAM in patients who have relapsed diffuse large B-cell lymphoma. Although dose-escalated ⁹⁰Y ibritumomab tiuxetan may be safely combined with high-dose BEAM followed by HSCT and has the potential to be more effective than standard-dose radioimmunotherapy in this setting, additional investigation of this approach is warranted, but it must be based on careful dosimetry to avoid toxicity and undertreatment.

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