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Matched-Cohort Analysis of Autologous Hematopoietic Cell Transplantation with Radioimmunotherapy versus Total Body Irradiation–Based Conditioning for Poor-Risk Diffuse Large Cell Lymphoma

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We conducted a matched-cohort analysis of autologous transplant conditioning regimens for diffuse large cell lymphoma in 92 patients treated with either radioimmunotherapy (RIT) or total body irradiation (TBI)–based conditioning regimens. The RIT regimen consisted of 0.4 mCi/kg of ^{90}Y-ibritumomab tiuxetan plus BEAM (BCNU, etoposide, cytarabine, melphalan). The TBI-based regimen combined fractionated TBI at 1200 cGy, with etoposide and cyclophosphamide. Five factors were matched between 46 patient pairs: age at transplant ±5 years, disease status at salvage, number of prior regimens, year of diagnosis ±5 years, and year of transplantation ±5 years. Patients in the TBI group had higher rates of cardiac toxicity and mucositis, whereas Z-BEAM patients had a higher incidence of pulmonary toxicity. Overall survival at 4 years was 81.0% for the Z-BEAM and 52.7% for the TBI group ($P = .01$). The 4-year cumulative incidence of relapse/progression was 40.4% and 42.1% for Z-BEAM and TBI, respectively ($P = .63$). Nonrelapse mortality was superior in the Z-BEAM group: 0% compared with 15.8% for TBI at 4 years ($P < .01$). Our data demonstrate that RIT-based conditioning had a similar relapse incidence to TBI, with lower toxicity, resulting in improved overall survival, particularly in patients with ≥2 prior regimens.

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KEY WORDS: Radioimmunotherapy, Diffuse large cell lymphoma, Autologous hematopoietic cell transplantation, BEAM, TBI, DLCL

INTRODUCTION

Although the Parma trial established the use of high-dose chemotherapy with autologous hematopoietic cell transplantation (AHCT) as superior to conventional chemotherapy for relapsed chemotherapy-sensitive diffuse large cell lymphoma (DLCL) [1], relapsed disease remains the most common cause of treatment failure. To address this problem, various strategies have been used to reduce relapse rates, including the use of novel conditioning regimens and posttransplantation immunotherapy with rituximab [2]. The regimens that have been studied as part of prospective clinical trials include: total body irradiation (TBI) plus combination chemotherapy with etoposide and cyclophosphamide [3], high-dose BEAM (BCNU, etoposide, cytarabine, melphalan) [4], BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) [1], and cyclophosphamide, BCNU, etoposide [5]. In a comparative study of TBI/etoposide/cyclophosphamide versus cyclophosphamide, BCNU, etoposide, the relapse rate is lower in patients treated with the TBI-containing regimen [6]. An inverse relationship between recurrence rates and radiation doses is demonstrated in a phase III trial of 12-Gy TBI versus 15.75-Gy TBI; the relapse rate is lower in the higher dose radiation cohort, but also results in higher treatment-related mortality [7]. In addition, the toxicity associated with a TBI-based conditioning regimen often precludes its use in older patients and even in some younger patients, as TBI is associated with substantial morbidity. A GEL/TAMO cooperative study of DLCL patients treated with a TBI-containing regimen shows

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a 2.5-fold higher (hazard) risk of death compared with those treated with chemotherapy alone [8].

Radioimmunotherapy (RIT) has been explored as a means of harnessing the antitumor effects of radiation while potentially reducing toxicity compared with fractionated TBI. The use of targeted antibodies to deliver radiation directly to the tumor and its microenvironment is intended to spare critical organs, thereby allowing treatment of older and more heavily pretreated patients. Two different radiolabeled anti-CD20 antibodies have been used to treat B cell lymphomas: iodine-131 (I^{131})-tositumomab (Bexxar®) and yttrium-90 (Y^{90})-ibritumomab tiuxetan (Zevalin®). We previously reported the results of a phase I/II trial demonstrating the safety of combining standard dose ^{90}Y-ibritumomab with high-dose BEAM followed by autologous transplantation (Z-BEAM) [9]. The toxicity profile was similar to high-dose BEAM alone and the overall survival (OS) at 2 years was a promising 89.7% in the 20 DLCL patients. A randomized phase II comparison of BEAM versus Z-BEAM conditioning before autologous transplantation for DLCL, reported at the 2010 American Society of Hematology Meeting, suggests improvements in both OS and progression-free survival (PFS) in the Z-BEAM arm [10]. However, often assumed, it has never been demonstrated that outcomes for autologous transplantation with the ^{90}Y-ibritumomab Z-BEAM regimen are superior to TBI-based autologous conditioning regimens. In this study, we performed a comparative analysis of a consecutive case-series of DLCL patients prospectively treated with Z-BEAM, who were matched to patients receiving a TBI-based conditioning regimen. The goal of this retrospective study was to evaluate the impact of RIT-based conditioning on OS and PFS.

PATIENTS AND METHODS

Patients

From January 1997 to January 2009, a matched series of 92 patients with DLCL (46 patients for each conditioning regimen) underwent AHCT at the City of Hope (COH); Z-BEAM patients were transplanted from 2002 to 2009, TBI patients were transplanted from 1997 to 2008. All DLCL patients treated on 2 phase I/II RIT trials with myeloablative BEAM plus standard dose ^{90}Y-ibritumomab tiuxetan (Zevalin®) were included in the analysis as part of the Z-BEAM treatment group. DLCL TBI patients were identified and paired/selected for analysis from a prospective observational research transplant database and were all treated based on a standard institutional operating procedure for cyclophosphamide (Cy)-TBI-VP-16 autologous transplantation. In situations where more than 1 potential TBI patient was identified as a potential pair for a Z-BEAM patient, the best-matched patient was selected. Patients were matched on age (±5 years), disease status at the time of salvage, number of prior regimens, year of diagnosis (±5 years), and year of transplantation (±5 years). The COH institutional review board approved the analysis of these data. All pathology specimens were reviewed by the COH Department of Hematopathology to confirm diagnosis before transplantation. Disease status was confirmed by clinical assessment, including physical examination, laboratory evaluation, imaging by computed tomography (CT) scans and nuclear imaging, and bone marrow biopsies, as per COH patient care standard operating procedures. Chemosensitivity was defined as at least a partial remission (PR) to salvage treatment, as determined by CT scanning, and resolution of all disease-related symptoms, which was maintained for at least 4 weeks. The international prognostic index score was calculated as per the International non-Hodgkin Lymphoma Prognostic Factors Project [11]. Patients in both treatment groups were managed similarly with respect to organ function screening, disease status assessments, and follow-up. All patients were enrolled on prospective observational and long-term follow-up protocols.

Eligibility Criteria

All patients

Patients with histologically confirmed $CD20^+$ DLCL were eligible if they met any of the following conditions: (1) DLCL that required at least 2 different induction regimens to achieve either complete or partial remission, (2) high or high-intermediate age-adjusted international prognostic index score at diagnosis, or (3) experienced a relapse event after initial response.

Z-BEAM

Patient exclusion criteria included: prior RIT, prior irradiation of >10 Gy to the liver or lung, and/or active chronic hepatitis B or C. Organ function criteria was standard for AHCT. In addition, patients had to have <10% lymphomatous marrow involvement at the time of stem cell collection. After the initial trial consent and screening, patients were also determined to be ineligible if they were human anti-Zevalin antibody positive or if they had unfavorable biodistribution on pre-Zevalin imaging.

TBI

Patients between the ages of 18 and 65 years were eligible. The minimum organ function criteria followed institutional treatment guidelines for AHCT. Patient exclusion was primarily based on performance status, age, extent of prior radiation, and other comorbid conditions.

Debulking, Mobilization, and Conditioning Regimens

All patients

Salvage chemotherapy was given to debulk disease and to determine chemosensitivity before AHCT. Chemosensitivity was defined as at least a PR to salvage treatment and resolution of all disease-related symptoms (based on CT scan), which was maintained for at least 4 weeks. Some patients received 1.5 to 2 g/m^2 Cy as part of mobilization, followed by filgrastim 10 μg/kg. Other patients were mobilized with filgrastim following debulking chemotherapy.

Z-BEAM

On day −21, patients were given an infusion of rituximab 250 mg/m^2 followed by Indium-111-labeled ibritumomab tiuxetan 185 MBq. Starting in May 2008, patients were administered 250 mg/m^2 cold rituximab only if their serum rituximab levels were below 10 μg/mL before administration of either the imaging or treatment dose of radiolabeled antibody. Ten of 46 patients were accrued after May 2008 and had rituximab levels drawn; 2 of those 10 received rituximab 250 mg/m^2 before the imaging dose, and 0 of 10 needed it before the therapeutic dose. Imaging studies were performed at 2, 24, 48, and 72 hours to determine the biodistribution of the Indium-111-labeled antibody. On day −14, patients with favorable imaging were given rituximab 250 mg/m^2 (except for those accrued after May 2008), followed by ^{90}Y-ibritumomab tiuxetan 14.8 MBq (0.4 mCi/kg); the dose was capped at 40 mCi. One week later, patients were admitted to the transplant unit and received BEAM: BCNU 150 mg/m^2 on days −7 and −6, etoposide 100 mg/m^2 and cytarabine 100 mg/m^2 twice a day on days −5 through −2, and melphalan 140 mg/m^2 on day −1. On day 0, autologous stem cells were infused per institutional standard operating procedures and followed by filgrastim on day +5. All Z-BEAM patients with the exception of 1 (n = 45) received rituximab therapy before transplantation.

TBI

For all patients, peripheral blood progenitor cells were mobilized with filgrastim 10 μg/kg with either Cy or debulking chemotherapy. Radiation was delivered as 3 daily fractions starting on day −8 to a total dose of 1200 cGy. This was generally performed as an outpatient. On day −4, patients were admitted to the transplant unit and received etoposide 40 mg/kg, followed by Cy 100 mg/kg on day −2. Stem cells were infused on day 0 followed by filgrastim on day +5. All patients received antibacterial, antiviral, and antifungal prophylaxis as per institutional standard operating procedures. Just over one-half, 67% (n = 31), of the TBI patients received prior rituximab therapy.

Disease Assessment

Response criteria for this analysis were from the International Working Group [12]. Complete response (CR) was defined as the complete resolution of all measurable disease, sustained for at least 4 weeks. PR was defined as a 50% or more reduction in the sum of the products of the diameters of all measurable lesions. Induction failure was defined as failure to achieve at least a PR with first-line therapy, or progression from a CR or PR within 4 weeks of first-line treatment. Relapse was defined as a clinical or radiologic progression at least 4 weeks after an initial CR or PR to first-line therapy.

Staging was performed at salvage chemotherapy, before AHCT and posttransplantation at 100 days, 6 months, 12 months, 18 months, 24 months, and then every year thereafter or as clinically indicated. Staging included physical examination, complete blood counts, basic biochemical profile including renal and liver function tests, lactate dehydrogenase, chest X-ray, CTs of the chest, abdomen, and pelvis, and unilateral or bilateral bone marrow biopsy if indicated.

Statistical Analysis

The primary endpoints were OS and PFS; secondary endpoints included: early/late toxicities/complications, nonrelapse mortality (NRM), and relapse/progression (RP) incidence. Survival estimates were calculated based on the Kaplan-Meier product-limit method; 95% confidence intervals (CIs) were calculated using the logit transformation and the Greenwood variance estimate [13]. Differences between Kaplan-Meier curves were assessed by the log-rank test. Patients who were alive at the time of analysis were censored at the last contact date. OS was measured from transplantation to death from any cause. PFS was defined as time from transplantation to recurrence, progression, or death. RP incidence was defined as time from transplantation to recurrence or progression. NRM was measured from transplantation to death from any cause other than disease relapse or disease progression. Cumulative incidence curves were generated for NRM and RP in the competing risks setting, given that death and RP events were in competition. The cumulative incidence of NRM and RP were calculated using the method described by Gooley et al. [14]; differences between cumulative incidence curves in the presence of a competing risk were tested using the Gray method [15]. The significance of demographic and treatment features was assessed using stratified survival analysis and univariate, multivariable Cox proportional hazards regression analysis, or the corresponding hazard analysis for competing risks [16,17].

Univariate and multivariable Cox regression models were used to assess the impact of patient, disease, and treatment factors on OS and PFS. The

factors studied were: disease status at the time of salvage (1 CR/PR; induction failure, equal to or greater than first relapse), bulky disease at diagnosis (≥5 cm, yes/no), bone marrow involvement at AHCT (yes/no), number of prior regimens (>2, ≤2), CD34 count (< or ≥5.2 × 10^6 cell dose), treatment regimen (RIT or TBI), and chemosensitive disease (yes/no). All calculations were performed using SAS® version 9.2 (SAS Institute, Cary, NC) or R 2.11.1. Generally, statistical significance was set at the $P < .05$ level; all P values were 2 sided. For multivariable Cox regression, factors shown to be significant at the $P < .10$ level univariately were included in the analysis. The data were locked for analysis on March 31, 2010, (analytic date). Modification of treatment-related effects by number of regimens received before AHCT (≤2, >2) and chemosensitivity status (sensitive, resistant) were evaluated by including interaction terms/stratification factors in the regression model [18].

RESULTS

Treatment Group Matching

Patient, disease, and treatment characteristics are shown in Table 1. The median age of the Z-BEAM cohort was 56 years (range: 19-78) and 53 years (range: 21-62) for TBI patients. Although the groups showed no statistical differences on the match factors: age at transplantation (±5 years), disease status at salvage, number of prior regimens, year of diagnosis (±5 years), and year of transplantation (±5 years); the 2 groups did show slight differences (not statistically significant) in prevalence of the following features: gender, chemosensitivity, bulky disease at transplantation, median time from diagnosis to transplantation, and median time from first-line therapy to transplantation. Prior rituximab therapy in the Z-BEAM group was significantly higher than in the TBI group ($P < .01$). Among the 92 patients, 76 patients had received prior rituximab: 45 Z-BEAM patients and 31 TBI patients. Of those patients receiving prior rituximab, we further stratified into those patients who received ritumab for salvage therapy only and those who received rituximab as part of induction therapy (± salvage therapy as well). In addition, 30 patients in the Z-BEAM and 20 in the TBI groups had failed rituximab induction (relapsed within 1 year of diagnosis). The breakdown of previous rituximab treatments is displayed in Table 1.

Table 1. Patient Characteristics

Variable	Z-BEAM (N = 46) n (%) or Median (Range)	TBI (N = 46) n (%) or Median (Range)
Patient gender, n (%)		
Female	17 (37)	21 (46)
Male	29 (63)	25 (54)
Age at transplant (years),* median (range)	56.5 (19-78)	53 (21-62)
Months from Dx to HCT, median (range)	16.4 (0.6-130)	12.8 (3.7-104)
Months from first-line therapy to HCT	14.9 (5.7-125)	12.1 (3.6-54)
Year of transplant,* median (range)	2005 (2002-2009)	2001 (1997-2008)
Disease status at time of salvage, n (%)		
First CR	6 (13)	7 (15)
Frist PR	7 (15)	5 (11)
Induction failure	10 (22)	12 (26)
≥1st Relapse	23 (50)	22 (48)
Chemosensitivity, n (%)		
Resistant	14 (30)	8 (17)
Sensitive	32 (70)	38 (83)
Bone marrow involvement at Dx, n (%)		
No	33 (72)	35 (76)
Yes	9 (19)	10 (22)
Not available	4 (9)	1 (2)
Bulky disease at Dx, n (%)		
No	11 (24)	4 (9)
Yes	26 (57)	28 (61)
Not available	9 (19)	14 (30)
CD34 Cell dose median (range)	5.4 (2.5-37)	5.1 (1.3-30)
Number of prior regimens,* median (range)	2 (1-7)	2 (1-5)
Prior rituximab		
No	1 (2)	15 (33)
Yes	45 (98)	31 (67)
Salvage only	5 (11)	7 (15)
Induction†	40 (87)	24 (52)
Failed rituximab at induction‡	30 (65)	20 (43)

Z-BEAM indicates BCNU, etoposide, cytarabine, melphalan; TBI, total-body irradiation; Dx, diagnosis; HCT, hematopoietic cell transplantation; CR, complete remission; PR, partial remission.

*Matched factors.

†Induction group indicates that all patients had rituximab induction, and may also have had rituximab during salvage therapy.

‡Failed rituximab at induction includes all patients who failed induction or relapsed within 1 year of diagnosis, and also had rituximab at induction.

Toxicity

Toxicity data for the first 100 days posttransplantation are illustrated in Figure 1. There was notably more cardiac toxicity in the TBI group, specifically ventricular and supraventricular arrhythmias, as well as more deaths attributable to cardiac disease. There were 8 episodes of documented bacterial infection in the Z-BEAM group and 11 in the TBI group. The 100-day mortality was 0% in the Z-BEAM group and 8.7% in the TBI group (4 of 46); of the 4 deaths in the TBI group, 3 were attributable to disease progression and 1 to infection. Patients continue to be followed for other long-term complications, including myelodysplasia and secondary malignancies as shown in Table 2. There was 1 case of myelodysplasia in the Z-BEAM group, and there were 2 cases of acute myelogenous leukemia in the TBI group.

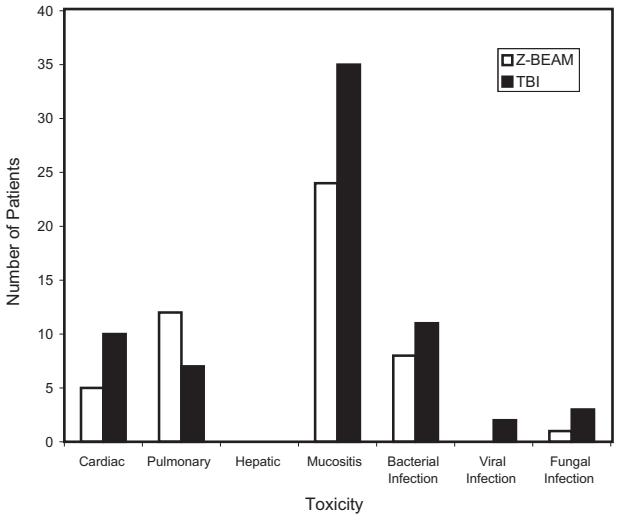

Figure 1. Toxicities ≤100 days. The number of patients with grade 3 and above toxicity in the first 100 days is graphically depicted. Z-BEAM patients are white bars, and TBI patients are black bars. Toxicities are NCI CTC v3.0.

Outcomes

The median length of follow-up was 59.9 months (range: 11.3-128.7) for all surviving patients (n = 60). The median follow-up for the 37 Z-BEAM patients was 51.0 months (range: 11.3-88.0) and 81.9 months (12.5-128.7) for the 23 TBI patients. As of the analytic date, there were 17 RP events in the Z-BEAM group and 19 in the TBI group. In the Z-BEAM group, there were 9 total deaths and 23 in the TBI group; causes of death are listed in Table 3. OS for the Z-BEAM group was significantly improved; 81% (95% CI: 68.8-88.8) for Z-BEAM versus 52.7% (95% CI: 44.6-60.2) for the TBI group at 4 years ($P = .01$) (Figure 2A). There was a trend toward improved PFS in the Z-BEAM group 59.6% versus 42% for the TBI group ($P = .10$) (Figure 2B). Results to date show that a plateau in PFS appears to have been achieved for both groups: at 2.6 years in the Z-BEAM group and 3.9 years for the TBI group. The poorer OS probability for the TBI cohort was primarily because of toxicity, with a 4-year cumulative incidence of NRM of 0% for Z-BEAM and 15.8% (95% CI: 8.0-31.3) for TBI ($P < .009$) (Figure 2C). The 4-year cumulative incidence of RP was very similar for both groups, as seen in Figure 2D, with 40.4 (95% CI: 27.7-59.0) for Z-BEAM and 42.1 (95% CI: 29.8-59.4) for TBI.

Because the incidence of RP was similar for the 2 regimens, we decided to look at subsequent treatments and outcomes in the patients who relapsed following autologous transplantation. In the Z-BEAM group, 8 of 17 relapsed patients were living (4 of the 8 survivng more than 3 years since relapse), whereas in the TBI group, only 3 of 19 were still alive at the analytic date. In the relapsed Z-BEAM (n = 17) versus TBI patients (n = 19), use of rituximab for salvage posttransplantation was proportionally similar in the 2 groups: 8 of 17 for Z-BEAM and 9 of 19 for TBI. A higher proportion of Z-BEAM patients were salvaged postautologous relapse with agents such as gemcitabine (5 of 17 versus 3 of 19), lenalidomide (3 of 17 versus 0 of 19), bendamustine (2 of 17 versus 0 of 19), and bortezomib (2 of 17 versus 0 of 19), with several receiving more than 1 of the above-listed agents. Two of the Z-BEAM patients were salvaged postautologous relapse using allogeneic transplantation (both died), and 2 of the TBI patients were also salvaged postautologous relapse with allogeneic transplantation (1 died).

Predictors of Improved Survival: Multivariable Analysis

Using Cox regression modeling, we further evaluated the independent effect of treatment group and

Table 2. Long-Term Toxicities >100 Days Posttransplantation

Event	Z-BEAM (N = 46) n (%)	TBI (N = 46) n (%)
Grade ≥3		
Overall*	18 (39)*	32 (70)*
Cardiac	3	4
Pulmonary	5	3
Hepatic	0	1
Mucositis	0	4
Infection	1	5
Bacterial	1	4
Viral	0	0
Fungal	0	1
Secondary malignancy		
Acute myelogenous leukemia	0	2
Basal cell carcinoma	1	0
Myelodysplasia	1	0
Squamous cell carcinoma	2	0

Z-BEAM indicates BCNU, etoposide, cytarabine, melphalan; TBI, total body irradiation.
All toxicities are NCI CTC v3.0.
*Fisher exact test, $P = .006$.

Table 3. Relapse and Death Events

Variable	Z-BEAM (N = 46) n (%)	TBI (N = 46) n (%)
Number of relapse/progression events	17 (37)	19 (41)
Number of death events	9 (20)	23 (50)
Cause of death		
Relapse/disease progression	9	16
Infection	0	2
Chronic heart failure, chronic renal insufficiency	0	1
Therapy-induced AML-related CNS bleed	0	1
Hypertensive hypertrophic cardiomyopathy with diastolic dysfunction	0	1
Left hemispheric infarct, autoimmune hemolytic anemia, pneumonia	0	1
Unknown	0	1

Z-BEAM indicates BCNU, etoposide, cytarabine, melphalan; TBI, total body irradiation; AML, acute myelogenous leukemia; CNS, central nervous system.

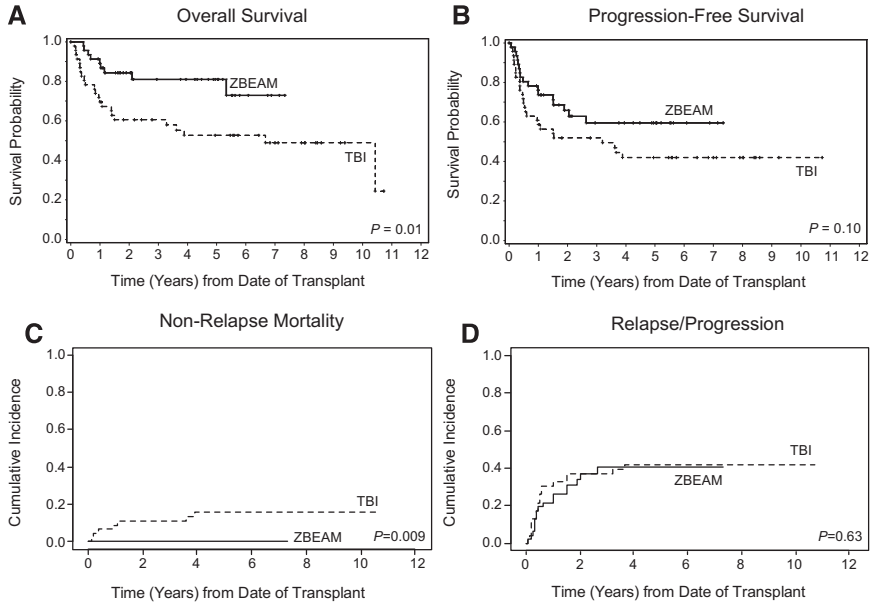

Figure 2. Survival outcomes stratified by treatment regimen. For all curves, solid lines represent Z-BEAM patients (N = 46) and dashed lines represent TBI patients (N = 46). Panel A shows the Kaplan-Meier estimate of overall survival probability. Panel B shows progression-free survival, defined as time from stem cell infusion to recurrence, progression, or death from any cause, whichever occurred first. Panel C shows the cumulative incidence of nonrelapse mortality, and panel D shows the cumulative incidence of relapse or progression. RP and nonrelapse mortality were calculated as competing risks.

other risk factors on OS and PFS, analyzing factors that were identified as predictive in the univariate analysis at the $P \leq .10$ level. For OS, the factors found to be predictive by univariate analysis were: treatment type (2-fold increase in risk for TBI patients), disease status at salvage (4- to 8-fold increase in risk for patients beyond 1 CR/PR), number of prior regimens (2-fold increase in risk for patients who received more than 2 regimens before AHCT), and prior rituximab therapy (2-fold increase in risk for patients who did not receive prior rituximab). Generally, the same list of risk factors was identified for PFS, with the addition of chemosensitivity status. Patients with resistant disease showed a 2-fold increase in RP or death when compared with patients with sensitive disease.

In our univariate and initial multivariable analysis, an interesting phenomenon occurred in which the impact of treatment arm on hazard risk did not attain significance in the univariate setting but was significant in the multivariable analysis. This uncharacteristic result prompted us to revise the Cox regression model to include an interaction term, which tested for possible interactions between treatment arm and other factors in the analysis. A significant interaction effect was seen between the variables of treatment arm and number of prior regimens ($P < .01$) for both OS and PFS. This interaction relationship was identified after stratified analyses revealed that the effect of 1 of the variables differed depending on the level of the other variable. As shown in Figure 3A and B, patients treated with more than 2 prior regimens who underwent AHCT using a TBI-based regimen had significantly poorer PFS when compared with TBI patients who received 2 or fewer regimens ($P < .01$). This difference was not seen in the Z-BEAM group. A similar interaction trend ($P = .07$) was seen between the variables of treatment regimen and chemosensitivity status, for PFS but not for OS. When assessing the impact of treatment in the context of patient chemosensitivity status, the results showed that Z-BEAM patients who were chemosensitive had improved PFS outcomes when compared with those who were resistant ($P = .02$) (Figure 3C). Among TBI patients, however, this was not the case ($P = .17$) (Figure 3D); patients who were chemosensitive did not show significantly improved PFS over chemoresistant patients.

For OS, the multivariable model showed that, after controlling for the relationship between transplantation conditioning regimen and number of prior regimens, TBI patients who received more than 2 regimens before AHCT were at a significantly increased risk for death posttransplantation (hazard ratio [HR]: 3.46; 95% CI: 1.23-9.79) ($P = .02$) (Table 4). Patients who were classified as induction failures at AHCT were found to have a significant increase in risk of death posttransplantation compared with those in first CR or PR (HR: 6.66; 95% CI: 1.81-24.53) ($P < .01$); this remained true after adjusting for the impact of treatment group and number of prior regimens. For PFS, the multivariable results trended similar to OS (Table 4). The multivariable model showed that, after controlling for the relationship between treatment group and number of prior regimens, TBI patients who received more than 2 regimens before AHCT had a trend toward increased

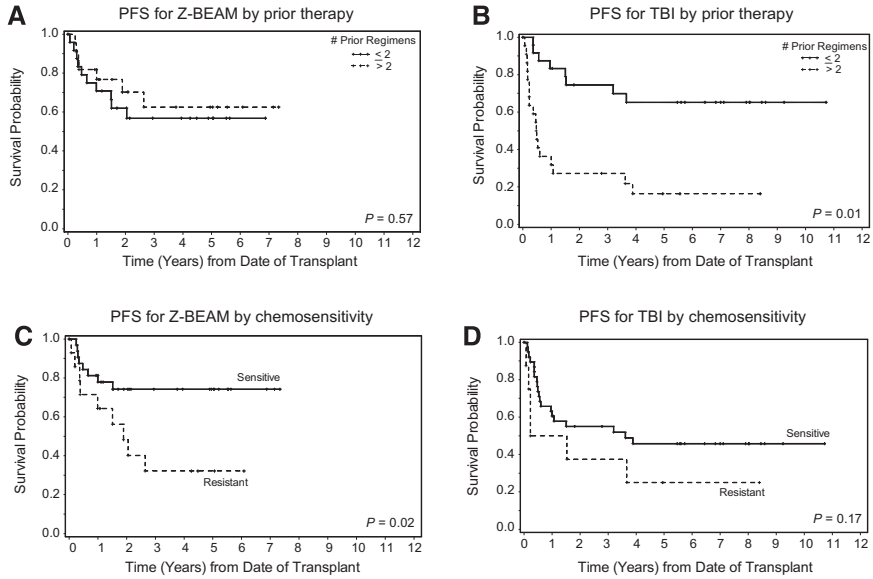

Figure 3. Factors interacting with treatment regimen for progression-free survival (PFS). Panel A shows the PFS for the 46 Z-BEAM patients stratified by the number of prior regimens. Panel B shows the PFS for the 46 TBI patients stratified by the number of prior regimens. Panel C shows the PFS for the 46 Z-BEAM patients stratified by sensitivity to chemotherapy. Panel D shows the PFS for the 46 TBI patients stratified by sensitivity to chemotherapy.

risk for RP or death posttransplantation (HR: 1.89; 95% CI: 0.84-4.29) ($P < .13$). Patients who were classified as induction failures at AHCT were found to have a significant increase in risk of death or RP posttransplantation compared with those in first CR or PR (HR: 5.08; 955% CI: 1.69-15.31) ($P < .01$); this remained true after adjusting for the impact of treatment group and number of prior regimens.

DISCUSSION

The last 20 years has seen a shift in research emphasis from standard radiotherapy and chemotherapy regimens toward inclusion of less toxic biologic, immunologic, and targeted therapies. RIT combines the potency of radiotherapy in the treatment of lymphoma, with the targeting capability and immunologic potency of cell-type specific monoclonal antibodies. ^{90}Y-ibritumomab tiuxetan is more effective as a single-agent therapy than its unlabeled, monoclonal antibody counterpart, rituximab, for the treatment of B cell lymphoma [19], and also increases the response rate when combined with cyclophosphamide, Oncovin, and prednisone or prednisolone (CHOP) chemotherapy [20]. RIT agents utilizing yttrium-90 as opposed to iodine-131 have potential advantages based on: (1) the longer path length of the β-particle emission, allowing for cross-fire killing of nonantigen bearing cells in the tumor microenvironment, and (2) the lack of γ-particle emissions that necessitate shielding of the patient from family members and friends. Standard-dose ^{90}Y-ibritumomab tiuxetan can be administered in the outpatient setting, and its ease of

Table 4. Multivariable Analysis: OS and PFS

	Overall Survival			Progression-Free Survival		
Variable	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Treatment * prior regimens						
RIT * ≤2 regimens	1.00	—	—	1.00	—	—
RIT * >2 regimens	0.62	0.16-2.38	.49	0.46	0.17-1.26	.13
TBI * ≤2 regimens	0.92	0.28-3.09	.90	0.62	0.24-1.62	.33
TBI * >2 regimens	3.46	1.23-9.79	.02	1.89	0.84-4.29	.13
Disease status at HCT						
First CR/first PR	1.00	—	—	1.00	—	—
≥1st relapse	3.20	0.87-11.72	.08	3.57	1.28-9.90	.01
Induction failure	6.66	1.81-24.53	<.01	5.08	1.69-15.31	<.01
Chemosensitive status						
Sensitive	NA	NA	NA	1.00	—	—
Resistant	NA	NA	NA	1.51	0.78-2.92	.22

OS indicates overall survival; PFS, progression-free survival; CI, confidence interval; RIT, radioimmunotherapy; TBI, total body irradiation; CR, complete remission; PR, partial remission. NA, not analyzed.
*Indicates interaction between terms.

use and exportability has made yttrium the isotope of choice for RIT at COH.

Addition of rituximab to front-line treatment regimens for DLCL has drastically improved responses and survival [21,22], raising the 5-year event-free survival from 29% for CHOP to 47% for R-CHOP. Those selected DLCL patients who do fail rituximab-containing front-line therapy have poorer outcomes following salvage therapy with autologous transplantation than patients who have never been exposed to rituximab [23]. One potential method of improving response and survival rates for autologous transplantation in relapsed DLCL patients is incorporation of radioimmunotherapy into the conditioning regimen.

Z-BEAM, the radioimmunotherapy plus chemotherapy conditioning regimen combining ^{90}Y-ibritumomab tiuxetan plus high-dose BEAM, is demonstrated to be well tolerated and efficacious in the initial phase I/II studies [9,24]. Median engraftment times in the initial trials are similar to conventional conditioning regimens. Rates of pulmonary and hepatic toxicity are also low: 12% grade 3 hepatic and 7% pulmonary toxicity [9]. Based on this initial data, we have performed subsequent trials targeting pre-RIT serum blood rituximab and have analyzed efficacy in various histologies such as mantle cell, follicular, and DLCL. Based on preliminary data in DLCL patients, RIT-based conditioning had a particular benefit for DLCL patients, whose response to salvage BEAM plus autologous transplantation is reduced in the post-rituximab era [23].

Our matched cohort analysis of DLCL patients supports the efficacy of RIT-based conditioning with Z-BEAM. The PFS (4-year 60%) and OS (4-year 81%) of Z-BEAM were similar to other RIT high-dose therapy regimens. For instance, a phase II study from the Nebraska group of 40 chemosensitive DLCL patients yielded a 3-year PFS of 70% and OS of 81% [25]. The toxicity profile was favorable, especially considering that the cohort included older patients.

Nonetheless, a major concern regarding novel conditioning regimens is whether efficacy has been sacrificed in the name of minimizing toxicity. Historically, radiation has been extensively used in lymphoma conditioning, because of the radiosensitivity of the disease. Use of fractionated radiation greatly reduced toxicity, allowing the delivery of higher radiation dosing in the context of TBI. However, pulmonary toxicity, especially in older patients, remains a concern. Overall, the incidence of pneumonitis after TBI-based conditioning for lymphoma is 22% [26]. The long-term toxicity of therapy-related myelodysplasia is also an ongoing issue, as radiation is a known risk factor for transplantation-related myodysplastic syndrome [27]. In many centers, such as our own, TBI has fallen out of favor because of these toxicities, and numerous novel therapies are under exploration. Nonetheless, radiation-based conditioning remains a treatment modality for young, high-risk patients in many transplant centers, because of its long-term record of efficacy.

This matched comparative analysis suggests that the toxicity profile of TBI-based conditioning for autologous transplantation may outweigh its purported benefits. Cardiac toxicity was a major factor in the TBI-treated group; given the relatively older age of non-Hodgkin lymphoma patients, this is a major concern. Considering the fact that pre-HCT chest irradiation is a known risk factor for cardiovascular complications [28], the lower cardiac toxicity in the Z-BEAM population is particularly desirable. There were a higher number of pulmonary events in the Z-BEAM group, but most were not clinically significant as they included coughing in 4 patients and temporary hypoxia during stem cell infusion in 6; 2 patients had pneumonia and 1 pneumonitis that could be attributable to the conditioning regimen. Despite a higher incidence of fever and neutropenia in the Z-BEAM-treated group, survival was not affected. It is possible the higher fever/neutropenia incidence was because of discontinuation of levofloxacin prophylaxis in 2005. Relapse and progression incidence was also not significantly different between the 2 groups, suggesting that RIT conditioning had equal disease control to TBI. Because follow-up on the TBI group is longer than for the Z-BEAM group, it is possible that the higher proportion of surviving relapsed patients in Z-BEAM compared with TBI (8 of 17 versus 3 of 19) may theoretically still die, bringing the OS curves closer together. However, of the 8 surviving relapsed patients in the Z-BEAM group, 4 of them have survived beyond 3 years postrelapse and are therefore beyond the high-risk period for disease recurrence. Thus, the use of RIT-based conditioning harnesses the efficacy of radiation while greatly reducing toxicity; NRM was significantly lower for Z-BEAM at 0% compared with 15.8% for TBI ($P < .009$).

Our analysis of the interaction between treatment type (Z-BEAM versus TBI) and number of regimens before AHCT also highlights the potential efficacy of Z-BEAM conditioning. Most striking were the vastly better results in Z-BEAM patients treated with multiple prior chemotherapy regimens (>2) compared with similar patients treated with TBI. Although the number of prior regimens did not impact OS for Z-BEAM-treated patients, the TBI patients with extensive prior therapy had significantly worse outcomes. This difference is likely attributable to the superior NRM of the RIT conditioning regimen. If these results are confirmed, patients with multiple prior regimens may derive benefit from Z-BEAM autologous transplantation and be spared the toxicity of allogeneic transplantion. On the other hand, when patients were

stratified as chemosensitive versus resistant, PFS was significantly different in the RIT group compared with no difference in the TBI group. This suggests an improved efficacy of Z-BEAM in chemosensitive patients; that is, the chemosensitive patients did strikingly well, whereas for TBI-treated patients, one could say both chemosensitive and chemoresistant patients did poorly.

We are aware that this study has some caveats related to its nonrandomized nature; however, very few physicians would be likely to enroll such high-risk patients to a randomized comparison of these 2 regimens. One major difference in the treatment groups is related to an imbalance in the use of rituximab pretransplantation in the 2 treatment arms. Prior rituximab treatment was far more prevalent in the Z-BEAM arm (45 patients) compared with the rituximab arm (31 patients). Of those who received prior rituximab, there were 30 patients in the Z-BEAM arm who failed rituximab-containing induction therapy, and 20 patients in the TBI arm. Despite the negative prognostic impact of rituximab failure indicated by the CORAL study [23], the OS was better for Z-BEAM. Although more patients in the Z-BEAM arm received prior rituximab compared with the TBI arm (98% versus 67%), which would appear to favor prognosis in the Z-BEAM group, a larger percentage of the Z-BEAM patients (65%) had failed rituximab induction compared with TBI patients (43%), which puts the Z-BEAM arm at a prognostic disadvantage. It is possible that if there had been fewer rituximab failures in the Z-BEAM arm, it would have had an even greater survival advantage over TBI.

We have attempted to equalize as many variables as possible through factor matching, but there are some apparent differences (all nonsignificant except for rituximab-related) between the 2 treatment arms that may confound our results. For instance, some chemotherapy agents in the TBI arm, specifically Cy, were not used in the RIT arm, and could therefore contribute to the higher toxicity rates. Also, because TBI has been less frequently used in the past 5 years, the cases tend to be separated based on time, although we have limited this difference to 5 years in matched cases. In addition, the Z-BEAM patients were all treated on protocol, whereas the TBI patients were not. However, our review of supportive care standard operating procedures over the years included in the study does not reveal significant differences, with 2 exceptions. First was the cessation of routine levofloxacin prophylaxis in the Z-BEAM group, which may account for the higher rate of febrile neutropenia in that group. Second, many of the patients in the TBI arm were staged using only a CT scan, whereas all Z-BEAM patients were staged pretransplantation using a PET scan. Despite these issues, this study is as well controlled as possible and, we believe, affirms the assumption that RIT provides radiotherapy as effectively as TBI with less morbidity.

The small randomized phase II study comparing Zevalin®-BEAM to BEAM shows a trend toward improved PFS in the RIT arm based on a preliminary report of the data [10]. Updates of this abstract, presented orally at the American Society of Hematology meeting, showed improvement in both OS and PFS for the Z-BEAM arm by multivariable analysis, providing support for a potential phase III study. Our comparison of Z-BEAM with TBI conditioning is another step toward the establishment of RIT conditioning as a new standard of care for AHCT conditioning for non-Hodgkin lymphoma. We demonstrate comparable efficacy of the 2 regimens, as evidenced by similar relapse incidence, with decreased toxicity and NRM for Z-BEAM.

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AUTHORSHIP STATEMENT

A.K. and J.P. designed the study, analyzed the data, and wrote the manuscript. N.T. and J.S. collected and analyzed the data. S.T. assisted with data review and manuscript preparation. A.N., A.R., and S.J.F. offered critical review of study design and manuscript writing. All authors reviewed and approved the final version of the manuscript.

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