Autologous Transplantation for Transformed Non-Hodgkin Lymphoma Using an Yttrium-90 Ibritumomab Tiuxetan Conditioning Regimen

Matthew Mei [1], Marielle J. Wondergem [2], Joycelynne M. Palmer [3], Avichai Shimoni [4], Justin Hasenkamp [5], Ni-Chun Tsai [2], Jennifer Simpson [6], Auayporn Nademanee [1], Andrew Raubitschek [6], Stephen J. Forman [1], Amrita Y. Krishnan [1,*]

[1] Department of Hematology/HCT, City of Hope, Duarte, California
[2] Department of Haematology, VU University Medical Centre, Amsterdam, The Netherlands
[3] Department of Biostatistics, City of Hope, Duarte, California
[4] Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel Aviv, Israel
[5] Department of Hematology and Oncology, University Medical Center Göttingen, Göttingen, Germany
[6] Department of Radiation Oncology, City of Hope, Duarte, California

Article history:
Received 15 May 2014
Accepted 25 July 2014

Key Words:
Radioimmunotherapy
Zevalin
Z-BEAM

A B S T R A C T

Transformation from indolent non-Hodgkin lymphoma (NHL) to diffuse large B cell lymphoma (DLBCL) has historically been associated with a poor prognosis. A small series of autologous stem cell transplantation (ASCT) studies using conventional conditioning regimens has demonstrated durable progression-free survival (PFS) rates ranging from 25% to 47%, but data in the rituximab era are lacking. Here we report the results of a multicenter retrospective trial evaluating ASCT in patients with transformed lymphoma using the Z-BEAM conditioning regimen, which combines yttrium-90–labeled ibritumomab tiuxetan (Zevalin) with high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) chemotherapy. Sixty-three patients from 4 institutions were treated between 2003 and 2011. Histological confirmation of transformation was required and defined as a diagnosis of DLBCL in patients with either a prior history or concomitant diagnosis of low-grade B cell NHL. Median patient age at ASCT was 59.5 years, median number of prior regimens was 2, and all patients were exposed to rituximab. Disease status at ASCT was as follows: first complete remission (CR) (n = 30), first partial remission (n = 11), first relapse (n = 14), and at least second CR (n = 8). The median time from diagnosis of histological transformation to ASCT was 7.5 months (range, 2.8 to 116). Two-year nonrelapse mortality was 0%. Median follow-up for living patients was 28 months (range, 5 to 103). Two-year PFS was 68% (95% confidence interval, 58% to 75%), and overall survival was 90% (95% confidence interval, 80% to 95%). In conclusion, the Z-BEAM conditioning regimen for ASCT is well tolerated by patients with transformed lymphoma and demonstrates encouraging clinical outcomes.

INTRODUCTION

The low-grade B cell lymphomas are a collective group of diseases with an indolent natural history. Although long remissions with therapy are very common, relapses tend to be the rule rather than the exception, and transformation to a higher grade lymphoma can occur at a rate of approximately 3% per year in the case of follicular lymphoma [1] and perhaps as high as 16% in the case of non–mucosa-associated lymphoid tissue marginal zone lymphoma [2]. Although most data in the literature revolve around the transformation of follicular lymphoma into diffuse large B cell lymphoma, other indolent B cell lymphomas, such as small lymphocytic lymphoma and marginal zone lymphoma, are also known to transform into higher grade disease. Historically, long-term outcomes after transformation have been poor, with 1 study showing a median survival after transformation of 1.2 years [3]. However, survival has improved significantly in the rituximab era [4].

Autologous stem cell transplantation (ASCT) is a treatment modality used to overcome the poor prognosis associated with transformed lymphoma. A number of small series consistently show that many patients with transformed lymphoma who undergo ASCT can enjoy prolonged remissions [5-7]. One of the few prospective trials evaluating the outcomes of ASCT in transformed lymphoma demonstrates a median progression-free survival (PFS) and overall survival (OS) of 26 months and 47 months, respectively, with 2-year and 5-year OS of 73% and 47%, respectively [8]. Whether these results are applicable in the context of prior rituximab is not clear; however, a limited but growing body of literature suggests that overall clinical outcomes in the rituximab era are also significantly improved by ASCT compared with historical controls, with 2-year survival exceeding 80% [9,10].

Despite the positive trend in overall outcomes with rituximab, the major cause of mortality in this population remains disease progression, and improvement in available therapies is still needed. One potential avenue is modification of the ASCT conditioning regimen. The addition of the radiolabeled antibody yttrium-90 ibritumomab tiuxetan (Zevalin) to the high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) chemotherapy regimen (Z-BEAM) has been shown to have a similar toxicity profile as BEAM alone in historical control patients with relapsed/refractory non-Hodgkin lymphoma (NHL) [11]. This regimen has also been

Financial disclosure: See Acknowledgments on page 2074.

* Correspondence and reprint requests: Amrita Y. Krishnan, Department of Hematology and Hematopoietic Cell Transplantation, 1500 E. Duarte Rd., Duarte, CA 91010.
E-mail address: akrishnan@coh.org (A.Y. Krishnan).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.07.028

evaluated in a small prospective randomized trial in relapsed/refractory aggressive NHL patients, which confirmed its safety and showed a trend toward improved outcomes [12]. Given these promising results, we present the outcomes of transformed lymphoma treated with ASCT conditioned with Z-BEAM in a retrospectives series of patients from 4 institutions (City of Hope, VU University Medical Center, Chaim Sheba Medical Center, and University Medical Center Göttingen).

METHODS

Physicians at the selected institutions received a standardized electronic spreadsheet specifying the required data fields. After local institutional review board clearance, researchers retrospectively reviewed institutional databases for patients meeting the specified eligibility criteria.

Major eligibility included a diagnosis of transformed NHL, with histological diagnosis confirmed at the treating institution. Transformed NHL was defined as initial biopsy-proven indolent lymphoma with subsequent occurrence of biopsy-proven diffuse large B cell lymphoma (DLBCL). The initial indolent subtypes included grades 1 and 2 follicular lymphoma, marginal zone lymphoma, and mucosa-associated lymphoid tissue lymphoma. All patients were treated with at least 1 rituximab-containing regimen after transformation and before ASCT. Data on patient characteristics at the time of transformation, such as extent of disease, stage, and lactate dehydrogenase, were not available for many patients because initial treatment was often delivered by community hospitals, with patients referred to the participating transplant centers only after transformation. Patients were older than 18 years of age, had less than 25% marrow involvement at time of stem cell collection, and passed the institutional standard organ function criteria for ASCT. Patients were eligible if they achieved a partial remission (PR) or complete remission (CR) with conventional chemoimmunotherapy at either initial treatment or salvage therapy before ASCT.

Stem cell collection was performed with either granulocyte colony-stimulating factor or chemomobilization, and Z-BEAM conditioning was administered as previously described [11,12]. Post-transplant transfusional support and infectious prophylaxis was as per institutional standard practice. Neutrophil and platelet engraftment were defined as the first of 3 days with an absolute neutrophil count $>.5 \times 10^9$/L and the first 7 days with an untransfused platelet count $>20 \times 10^9$/L. Toxicity post-ASCT was graded by the Bearman et al. toxicity criteria [13]. Disease response criteria were from the 1999 International Working Group [14]. 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. Relapse was defined as a clinical or radiological progression at least 4 weeks after an initial CR or PR to first-line therapy. Response was evaluated approximately every 3 months post-ASCT for the first 2 years and then every 3 to 6 months or as clinically indicated.

Statistical Methods

The primary outcome of the study was progression-free survival (PFS), defined as the time from ASCT to date of disease relapse, progression, or death from any cause, whichever occurred first. Other outcomes examined included overall survival (OS), measured from the day of ASCT until death from any cause, and nonrelapse mortality (NRM), measured from transplant to death from any cause other than disease relapse or disease progression. Survival estimates were calculated based on the Kaplan-Meier product-limit method, and 95% confidence intervals (CIs) were calculated using the logit transformation and the Greenwood variance estimate. 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.

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. Univariate analysis was performed to evaluate the significance of the following factors: sex (female, male), age at the time of ASCT (<59.5, ≥ 59.5), time from diagnosis of transformation to ASCT (<7.5, ≥ 7.5), disease status at ASCT (1 CR, >1 CR), number of prior regimens (≤ 2, >2), presence of marrow involvement at the time of ASCT (yes, no), and center (City of Hope, VU University Medical Center, Chaim Sheba Medical Center, and University Medical Center Göttingen). All calculations were performed using SAS version 9.2 (SAS Institute, Cary, NC). Generally, statistical significance was set at the $P < .05$ level; all P values were 2-sided. The data were locked for analysis on March 4, 2013 (analytic date).

RESULTS

Sixty-three patients (24 women and 39 men) who underwent ASCT between 2003 and 2011 were enrolled from 4 centers. Patient characteristics are listed in Table 1. Median age at ASCT was 59.5 years (range, 36 to 69). The median time from transformation to ASCT was 7.5 months (range, 2.8 to 116). Before ASCT, patients received a median of 2 regimens of chemotherapy (range, 1 to 6), and all had received rituximab with at least 1 of these regimens. The distribution of disease status at ASCT was as follows: first CR (n = 30), first PR (n = 11), first relapse (n = 14), and beyond second CR (n = 8). Disease stage at ASCT was II to IV in 35 patients (56%), and lactate dehydrogenase was above the upper range of normal in 20 patients (32%).

All patients demonstrated WBC engraftment at a median of 11 days (range, 8 to 33) after stem cell infusion. The median time to platelet engraftment was 15 days (range, 3 to 71). Of the 63 patients, 21 relapsed and 9 patients died. Median duration of follow-up was 31.3 months (range, 7.1 to 103.4) for surviving patients, and the 2-year PFS was 68% (95% CI, 58% to 75%) and 2-year OS 90% (95% CI, 80% to 95%). On univariate analysis, only disease status at ASCT proved to be significant with respect to PFS. Patients undergoing ASCT while in first CR had a longer 2-year PFS compared with patients undergoing ASCT with any other disease status (81.1% versus 55.6%, $P = .041$, Figure 1). No variable was found to be significant with respect to OS (disease status could not be evaluated as an endpoint because no deaths occurred in patients receiving ASCT in first CR). Multivariable analysis was not performed because no other factors were found to be statistically significant univariately.

Toxicity data were available for 57 of 63 patients. Aside from 1 grade 3 pulmonary toxicity, the only grades 3 to 4

Table 1
Patient, Disease, and Transplant Characteristics

Variable	Value
Patient gender	
Female	24 (38)
Male	39 (62)
Median age at ASCT, yr (range)	59.5 (36.4-69.0)
Disease stage at ASCT	
Stages 0-II	19
Stages III-IV	35
Not applicable	9
Lactate dehydrogenase at ASCT	
≤ Normal range	42
> Normal range	20
No data	1
Median time from transformed DLBCL to ASCT, mo (range)	7.5 (2.8-116.0)
Disease status from last therapy to ASCT	
First CR	30 (48)
First PR	11 (17)
First relapse	14 (22)
Second CR	6 (9)
Second relapse	1 (2)
At least third CR	1 (2)
Chemosensitivity at ASCT	
Resistant	2 (3)
Sensitive	61 (97)
Bone marrow involvement at ASCT	
No	54 (86)
Yes	9 (14)
Number of prior regimens (range)	2 (1-6)
KPS score at ASCT (n = 57) (range)	90 (70-100)
Treatment center	
Chaim Sheba Medical Center	6 (9.5)
City of Hope Medical Center	20 (32)
University Medical Center Göttingen	6 (9.5)
VU University Medical Center	31 (49)

KPS indicates Karnofsky Performance Status.
Values are number of cases with percents in parentheses, unless otherwise noted.