Chapter 6

Autologous transplantation for transformed Non-Hodgkin Lymphoma using an Yttrium-^{90} ibritumumab tiuxetan conditioning regimen.

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Published in Biology of Blood and Marrow Transplantation, 2014 :20(12):2072-2075

Abstract

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 PFS rates ranging from 25-47%, 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. A total of 63 patients were treated from four institutions 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 wereexposed to rituximab. Disease status at ASCT was: 1^{st} complete remission (CR) (n=30), 1^{st} partial remission (PR) (n=11), 1^{st} relapse (n=14), and $\geq 2^{nd}$ CR (n=8). The median time from diagnosis of histological transformation to ASCT was 7.5 months (range 2.8-116 months). Two-year non-relapse mortality was 0 %. Median follow-up for living patients was 28 months (range 5-103). Two-year PFS was 68% (95% CI 58-75) and OS was 90% (95% CI: 80-95). 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 that have an indolent natural history. While 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-MALT marginal zone lymphoma (2). Although the majority of data in the literature revolves 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 following transformation have been poor, with one study showing a median survival after transformation of 1.2 years (3), but survival has improved significantly in the rituximab era (4).

Autologous stem cell transplantation (ASCT) is one treatment modality employed 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 to 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 to the high-dose BEAM (carmustine, etoposide, cytarabine, and 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 (11). This regimen has also been evaluated in a small prospective randomized trial in relapsed/refractory aggressive non-Hodgkin lymphoma patients, which confirmed its safety and showed a trend towards 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 four institutions. (City of Hope, VU University Medical Center, Chaim Sheba Medical Center, University Medical Center Gottingen).

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 histologic 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 grade 1 and 2 follicular lymphoma, marginal zone lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma. All patients were treated with at least one rituximab-containing regimen after transformation and prior to ASCT. Patients were >18 years of age, had < 25% marrow involvement at time of stem cell collection, and passed the institutional standard organ function criteria for autologous stem cell transplant. Patients were eligible if they achieved a partial or complete remission with conventional chemoimmunotherapy at either initial treatment or salvage therapy prior to ASCT.

Stem cell collection was performed with either G-CSF or chemo mobilization and Z-BEAM conditioning were 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 three days with an absolute neutrophil count (ANC) > 0.5 x10^9/L and the first seven days with an untransfused platelet count > 20x10^9/L. Toxicity post-ASCT was graded by the Bearman toxicity criteria (13). Disease response criteria were from the 1999 International Working Group (14). Complete response (CR) was defined as the complete resolution of all measurable disease, sustained for at least 4 weeks. Partial remission (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 three months post-ASCT for the first two years and then every 3-6 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 occurs first. Other outcomes examined included overall survival (OS) from the day of ASCT until death from any cause, and non-relapse 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, 95% confidence intervals 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. Non-relapse mortality (NRM) was measured from transplant to death from any cause other than disease relapse or disease progression.

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 (1CR, > 1CR), number of prior regimens (≤ 2, > 2), presence of marrow involvement at the time of ASCT (Yes, No), and center (CSMC, COH, UMCG, VUMC). All calculations were performed using SAS® version 9.2 (SAS Institute, Cary, NC). Generally, statistical significance was set at the $P<0.05$ level; all P values were two-sided. The data were locked for analysis on 03/04/2013 (analytic date).

Results

Sixty three patients who underwent ASCT between 2003 and 2011 were enrolled from four centers. Patient characteristics are listed in Table 1.

Table 1: Patient, disease and transplant characteristics

Variable	Median (range) or N (%)
Patient Gender	
Female	24 (38)
Male	39 (62)
Age at ASCT (years)	59.5 (36.4 - 69.0)
Time from Transformed DLBCL to SCT (months)	7.5 (2.8 - 116.0)
Disease Status from last therapy to SCT	
1st Complete Remission	30 (48)
1st Partial Remission	11 (17)
1st Relapse	14 (22)
2nd Complete Remission	6 (9)
2nd Relapse	1 (2)
≥3rd Complete Remission	1 (2)
Chemo Sensitivity	
Resistant	2 (3)
Sensitive	61 (97)
Bone Marrow Involvement at ASCT	
No	54 (86)
Yes	9 (14)
Prior Regimens	2 (1 – 6)
KPS at ASCT (n=57)	90 (70 – 100)
Treatment Center	
Chaim Sheba Medical Center (CSMC)	6 (9.5)
City of Hope Medical Center (COH)	20 (32)
University Medical Center Göttingen (UMG)	6 (9.5)
VU University Medical Center (VUMC)	31 (49)

Median age at ASCT was 59.5 (range 36-69 yrs). There were 24 females and 39 males. The median time from transformation to ASCT was 7.5 mo (range 2.8-116). Prior to ASCT, patients received a median of two regimens of chemotherapy (range 1-6), and all of them had received rituximab with at least one of these regimens. The distribution of disease status at ASCT was as follows: 1st CR n=30, 1st PR n=11, 1st relapse n=14, beyond 2nd CR n=8.

All patients demonstrated white cell engraftment at a median of 11 days (range, 8-33 days) post-stem cell infusion. The median time to platelet engraftment was 15 days (range, 3 – 71). Of the 63 patients, 21 (33) relapsed and 9 patients died. Median duration of follow-up was 31.3 months (7.1 - 103.4) for surviving patients, and the 2-year PFS was 68% (95%CI 58-75) and 2-year OS was 90% (95% CI: 80-95). On univariate analysis, only

disease status at ASCT proved to be significant with respect to PFS. Patients undergoing ASCT while in 1st CR had a longer 2-year PFS compared to patients undergoing ASCT with any other disease status (81.1% vs. 55.6%, p = 0.041, Figure 1). No variable was found to be significant with respect to OS (disease status could not be evaluated as an endpoint as there were no deaths in the patients received ASCT in 1CR). Multivariable analysis was not performed because no other factors were found to be statistically significant univariately.

Toxicity data were available for 57 of the 63 total patients enrolled. Aside from one grade 3 pulmonary toxicity, the only grade 3-4 toxicities reported were 14 infections. Notably there was no grade 3 stomatitis.

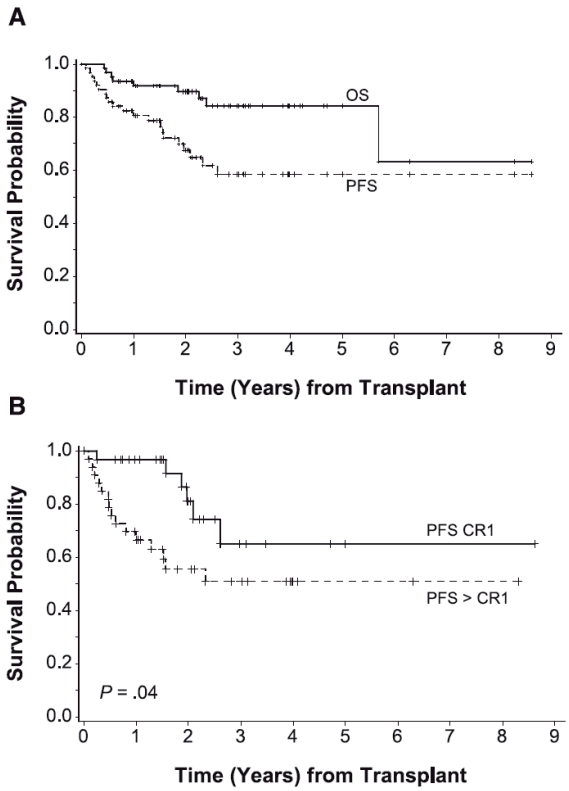

Figure 1: Overall and Progression-Free Survival. Overall survival (OS) is defined as time from date of stem cell infusion until death from any cause. Progression-free survival (PFS) is defined as time from stem cell infusion until disease relapse or progression or death from any cause, whichever comes first. Both OS and PFS are calculated by Kaplan-Meier method **A.** OS and PFS of all patients: the solid line indicates overall survival curve and the dashed line is progression-free survival. Median follow-up was 31.3 months (7.1 - 103.4) for surviving patients **B.** PFS stratified by disease status: the solid line includes patients that were in 1st CR at transplant and the dashed line includes patients that were beyond CR1. Median follow-up for surviving patients was 25.5 (7.1 - 103.4) months for patients in CR1, and 38.0 (11.7 - 99.6) for patients > CR1.

Discussion

Transformation of low grade lymphoma into an aggressive lymphoma, usually DLBCL, has traditionally heralded a poor prognosis with a median survival of one year after transformation (3), with ASCT used to improve upon these results. However, these statistics are derived from studies predating the rituximab era, and more recent literature indicates that outcomes have improved significantly since the advent of rituximab. For instance, Guirguis et al. report on a cohort of 317 DLBCL patients treated between 2002 and 2010 with R-CHOP, including 60 patients with transformed lymphoma who had never previously received R-CHOP prior to transformation (15).They found no difference in PFS or OS between patients with de novo or transformed DLBCL when treated with R-CHOP alone. Whether or not ASCT should be routinely performed for transformed lymphoma has been called into question (16). Interpretation of the available data is complicated by significant heterogeneity across studies with respect to clinical variables such as treatment history prior to transformation, regimens elected after transformation, rituximab use, and disease status at the time of transplantation. A large series from the Center for International Blood and Marrow Transplant Research (CIBMTR) reports on 108 patients with transformed follicular lymphoma treated with ASCT with a 5-yr OS of 50%, and 5-year PFS of 35%; however, only 30% of these patients had prior rituximab exposure (17). Nonetheless, two recent cohort studies have found benefit from ASCT in patients with transformed lymphoma (18,19). A Canadian retrospective study of 97 patients treated with autologous and 22 with allogeneic transplant, compared to 53 patients treated with rituximab-containing chemotherapy, finds that ASCT confers improved OS compared to rituximab-containing chemotherapy, whereas allogeneic transplant does not (18).

One of the most common conditioning regimens for ASCT in aggressive lymphoma is BEAM, and there has been interest in combining it with radioimmunotherapy to improve upon outcomes. We have previously shown that the combination of yttrium 90-ibritumomab tiuxetan and BEAM followed by ASCT is feasible and does not add significant toxicity when compared to BEAM alone (11). Further data have shown a promising response rate and PFS of this regimen both in patients with poor-risk de novo DLBCL (20), as well as in relapsed and refractory DLBCL (21), leading to interest in testing this regimen specifically in patients with transformed NHL. Here we report a 2-year PFS of 68% and OS of 90% with a median follow-up of over two years, results which compare favorably to other series involving patients with transformed lymphoma who have received prior rituximab. Only the disease status at the time of transplantation

proved to be a significant predictor of outcome, with patients transplanted while in 1st CR having a significantly improved PFS, presumably a marker for more chemosensitive disease. Moreover, both short and long-term toxicities of this regimen appear to be manageable in this group of patients. There was no non-relapse mortality, engraftment was not significantly delayed, and no patient experienced grade 3 mucositis, with the latter being an important result in light of a recent phase III trial showing that the addition of iodine-131 tositumumab, another CD20-directed radioimmunotherapy agent, to BEAM for ASCT conditioning resulted in significantly worse mucositis than did BEAM alone (22). Finally, albeit with limited follow-up, only one patient in this cohort developed a therapy-related myeloid neoplasm.

Our study has the advantage that all patients received rituximab in at least one of their regimens prior to transplant which makes the results more applicable to current practice. In addition, histological proof of transformation was required rather than simply clinical features suggestive of transformation. Limitations of the study include its retrospective single-arm design with the inherent biases associated with this type of analysis. To our knowledge this is the largest series of transformed NHL patients treated with this novel conditioning regimen. In summary, our data suggest that excellent therapeutic efficacy with acceptable toxicity are conferred by the addition of yttrium-90 ibritumomab tiuxetan to high-dose BEAM as a conditioning regimen for ASCT in patients with transformed non-Hodgkin lymphoma.

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