Allogeneic and autologous stem cell transplantation with busulfan, cyclophosphamide, and etoposide conditioning therapy for relapsed/refractory non-Hodgkin lymphoma

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ABSTRACT

The optimal stem cell transplantation (SCT) conditioning therapy for relapsed/refractory non-Hodgkin lymphoma (NHL) is not clearly defined. In a retrospective analysis, we examined 25 patients with "high risk" relapsed/refractory NHL who received busulfan, cyclophosphamide, and etoposide (Bu/Cy/VP16) conditioning with autologous or allogeneic SCT. The majority of patients had aggressive histology and 52% had primary refractory NHL. Furthermore, 48% of patients had chemotherapy-resistant disease at the time of SCT. Fifty-six percent of patients underwent allogeneic SCT, while 44% had autologous SCT. The median engraftment time for neutrophils and platelets was 13.5 and 14 days, respectively. The 100-day treatment-related mortality (TRM) was 16%, while the 2-year non-relapse mortality (NRM) rate was also 16%. At a median follow-up of 15 months, the estimated 2-year disease-free survival (DFS) rate was 64% (95% confidence interval (CI): 36% - 82%) and the estimated 2-year overall survival (OS) was 69% (95% CI: 40% - 86%). Furthermore, the 2-year disease-specific survival (DSS) rate was 73% (95% CI: 40% - 90%). Using Cox proportional hazard modeling, the International Prognostic Index at time of relapse predicted DFS and OS. Altogether, Bu/Cy/VP16 was associated with early TRM; however, late toxicities (including NRM) were uncommon resulting in relatively good survival rates in a high-risk relapsed/refractory NHL population.

Keywords: Stem Cell Transplantation; Busulfan; Cyclophosphamide; Etoposide; Non-Hodgkin Lymphoma

1. INTRODUCTION

Stem cell transplantation (SCT) is an effective therapeutic modality for patients with relapsed or refractory non-Hodgkin lymphoma (NHL) [1-5]. The timing and type of SCT (*i.e.*, autologous or allogeneic) depends in part on disease histology, disease status (*i.e.*, relapsed vs. refractory), patient physical condition, and disease-specific prognostic and other risk factors. A number of SCT chemotherapy conditioning regimens have been studied in relapsed/refractory NHL; however, the optimal conditioning regimen is not clearly defined.

Busulfan, cyclophosphamide, and etoposide (Bu/Cy/VP16) have been investigated as a SCT conditioning regimen [6-12]. The outcomes of prior studies, however, have been quite variable with 3-year progression-free survival (PFS) rates ranging from 39% to 70% and 3-year overall survival (OS) rates ranging from 43% to 72% [8,10]. Furthermore, there are few Bu/Cy/VP16 studies that have been reported in the past 5 - 10 years as supportive care treatments, and understanding of SCT has improved over the past decade. Also, an improved

understanding of the complications associated with Bu/Cy/VP-16 is needed, especially as the early treatment-related mortality (TRM) with this regimen may be as high as 46% [13].

We analyzed the Northwestern experience with utilizing Bu/Cy/VP16 conditioning therapy for patients with relapsed/refractory NHL. Notably, this conditioning regimen was reserved at our institution for patients with high-risk disease (e.g., short initial remission, high IPI at relapse, chemotherapy-resistant disease at SCT, etc.). We examined detailed patient and disease characteristics, patient outcomes, and analyzed potential prognostic factors that predicted survival with Bu/Cy/VP16 SCT.

2. MATERIALS AND METHODS

2.1. Study Design

We performed a retrospective analysis of all relapsed/refractory NHL patients who received stem cell transplantation with Bu/Cy/VP16 conditioning chemotherapy at the Northwestern University Robert H. Lurie Comprehensive Cancer Center from 3/2003 to 6/2011. This study was approved by the Northwestern University Institutional Review Board. Relapsed disease was defined as disease that recurred following a response to initial therapy (lasting >6 months), while refractory disease was defined as disease that did not respond to therapy or relapsed within 6 months of remission. Patients who had received prior SCT were excluded from the analysis. Detailed patient characteristics were collected including patient age, gender, co-morbidities, baseline pulmonary (diffusing capacity for carbon monoxide (DLCO) and presence of obstructive or restrictive defects on pulmonary function testing), liver (liver enzymes), and cardiac function (ejection fraction and diastolic function on echocardiographic evaluation), and performance status. Furthermore, detailed disease characteristics at the time of relapse prior to SCT were examined including disease histology, chemotherapy sensitivity, number of extranodal sites, disease stage, number of prior chemotherapy regimens, history of prior radiation, LDH immediately before transplant after salvage therapy (pre-SCT LDH), presence of bulk disease (>10 cm), International Prognostic Index (IPI), and disease status at time of SCT.

2.2. Preparative Regimen

Busulfan was dosed at 3.2 mg/kg intravenous (IV) daily for 4 days on days -8 to -5, etoposide was dosed at 20 - 40 mg/kg (most commonly 30 mg/kg) IV for one day on day -4, and cyclophosphamide was dosed at 50 mg/kg IV daily for 2 days on days -3 and -2 (all based on ideal body weight). Granulocyte colony stimulating factor (G-CSF), dosed at 5 µg/kg, was started on day 5 for autologous SCTs. Dilantin seizure prophylaxis was given

with chemotherapy infusion and all patients received ciprofloxacin for prophylaxis prior to conditioning therapy, and bactrim, acyclovir, and diflucan prophylaxis on discharge after transplant. Patients who received allogeneic SCT received graft versus host disease (GVHD) prophylaxis with a calcineurin inhibitor and methotrexate.

2.3. Statistical Analysis

Engraftment time was defined as the time to an absolute neutrophil count (ANC) > 500/µL for 3 consecutive days and a platelet count > 20,000/µL post-SCT without requiring a transfusion. Toxicity post transplant was graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC) scale. Early toxicity was defined as adverse events occurring less than 100 days post-transplant, whereas late toxicity was defined as adverse events occurring ≥ 100 days post-transplant. Allogeneic SCT patients were also evaluated for the presence of GVHD in the acute (<100 days) and chronic (≥100 days) post-SCT period.

Overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) curves were constructed using the Kaplan-Meier method. OS was defined as survival after transplant. DFS was defined as survival in complete remission (complete clinical and radiographic resolution of tumor). DSS was defined as survival from disease post SCT. Univariate proportional hazard modeling was performed to determine which patient and disease characteristics as described above might be associated with survival outcomes. Logrank tests were used to compare survival rates and the Wald chi-square test was used to determine the significance of model coefficients from the Cox regression, which was in turn used to determine the effect of various factors on survival. Fisher's exact test was used to examine the association between toxicity outcomes and categorical patient and disease characteristics, while the Wilcoxon rank-sum test was used to examine the association between toxicity outcomes and continuous patient and disease characteristics. For all analyses, $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Patient Demographics

Twenty-five patients with relapsed or refractory NHL underwent SCT with Bu/Cy/VP16 conditioning from 3/2003 to 6/2011. The demographics of the study population and the associated disease characteristics are summarized in **Table 1**.

The majority of patients (76%) had aggressive NHL histology. All patients had relapsed or refractory disease.

Furthermore, 52% of patients had primary refractory lymphoma. The median number of prior regimens was 3. In terms of disease status at time of SCT (*i.e.*, response to salvage therapy), 52% of patients had chemotherapy sensitive disease (n = 11 complete remission and n = 2 partial remission), while 48% had chemotherapy resistant disease (n = 12 progressive disease).

3.2. Engraftment, Toxicity, and Transplant Related Mortality (TRM)

The median engraftment time for neutrophils and platelets were 13.5 and 14 days, respectively. In terms of SCT-related toxicity, 92% patients experienced grade 3 or 4 hematologic toxicity. The most common grade 3 or 4 non-hematologic toxicities were neutropenic fever (92%), infection (68%), pneumonitis (28%), intubation (16%), and altered mental status/stroke (12%) in the early post-transplant period (**Table 2**). In the late post-transplant period, 44% of patients experienced pneumonitis (**Table 2**). The most common grade 1 - 2 toxicities in the early post-transplant period were elevated liver enzymes (72%) and mucositis (64%) followed by renal failure (8%), hypersensitivity reaction (8%), and thromboembolism (4%).

In the initial post-transplant period (*i.e.*, <100 days), 4 of 25 patients died from hypoxemic respiratory failure (3) and sepsis (1) yielding a TRM of 16%. Two of these patients had allogeneic SCT (diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic lymphoma), while the other two had received autologous SCT (both DLBCL) yielding TRM rates of 14% and 18% for allogeneic and autologous patients, respectively.

Among patients who received allogeneic SCT, 11/14 (79%) experienced acute GVHD, with skin and liver involvement being the most frequent organs involved. After 100 days post-SCT, 6/11 (55%) patients experienced chronic GVHD most commonly affecting the skin. Notably, there were no non-relapse deaths that occurred after 100 days post-SCT in either the autologous or allogeneic population; thus, the 2-year NRM for all patients was 16% with all of these deaths occurring <100 days.

3.3. Survival

The median follow-up time for all patients was 15 months (range: 2 - 96 months). The 1-year and 2-year DFS rates for all patients (**Figure 1**) were 73% (95% confidence interval (CI): 64% - 87%) and 64% (95% CI: 36% - 82%), respectively, while the 1-year and 2-year OS rates were 79% (95% CI: 57-91%) and 69% (95% CI: 40% - 86%), respectively (**Figure 1**). Of note, only 2 of 25 (8%) patients died due to NHL. This resulted in a 2-year disease-specific survival (DSS) for all patients of
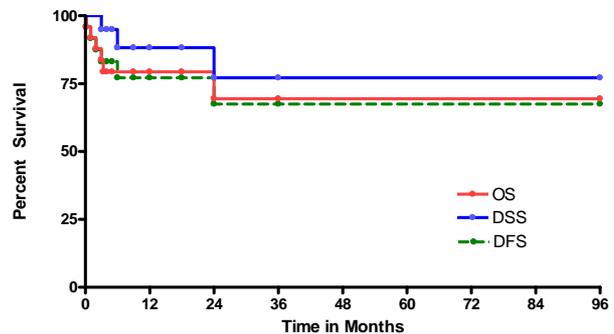

Figure 1. Overall Survival (OS), Disease Specific Survival (DSS) and Disease Free Survival (DFS). The 1 year rate of OS was 79% (95% CI: 57 - 91%) and the 2 year rate of OS was 69% (95% CI: 40% - 86%). The 1 year rate of DSS was 83% (95% CI: 56 - 94%) and the 2 year rate of DSS was 73% (95% CI: 40% - 90%). The 1 year rate of DFS was 73% (95% CI: 64% - 87%) and the 2 year rate of DFS was 64% (95% CI: 36% - 82%).

73% (95% CI: 40% - 90%) (**Figure 1**). For allogeneic patients, OS was 86% at 1 year and 75% at 2 years, whereas for autologous patients, OS was 72% at 1 year (OS could not be calculated at 2 years due to the follow-up period).

3.4. Prognostic Factors

Proportional hazard modeling of multiple patient characteristics and disease factors were examined for all patients to identify potential factors that predicted survival using a univariate analysis (**Table 3**). We identified that elevated pre-SCT LDH (hazard ratio (HR) 8.1, 95% CI: 1.4 - 45.2, p = 0.02) and IPI at time of relapse prior to SCT (HR 3.0, 95% CI 1.1 - 7.9, p = 0.03) portended inferior DFS, while increasing age (HR 1.1, 95% CI: 1.0 - 1.1, p = 0.06), chemotherapy-resistant disease (HR 7.73, 95% CI: 0.93 - 64.5, p = 0.07), and performance status prior to SCT (HR 6.5, 95% CI: 0.8 - 53.8, p = 0.08) were of borderline significance. Elevated pre-SCT LDH (HR 15.0, 95% CI: 1.6 - 138.1, p = 0.02) and IPI (HR 4.4, 95% CI: 1.5 - 13.1, p = 0.008) also predicted inferior OS, while worse performance status (HR 3.74, 95% CI: 0.99 - 14.0, p = 0.05), age (HR 1.1, 95% CI 1.0 - 1.2, p = 0.06), and chemotherapy-resistant disease (HR 6.54, 95% CI: 0.76 - 56.3, p = 0.09) were borderline.

Fisher's exact test and Wilcoxon rank sum test analysis were performed to examine patient and disease characteristics that correlated with late toxicity. The strongest predictors of post-SCT late toxicity were pre-transplant LDH (p = 0.057) and IPI (p = 0.11). Finally, late toxicity was more likely to be associated with aggressive NHL disease histology (61%) compared with low grade (31%) or mixed histologies (8%).

Table 1. Patient demographics and disease characteristics.

Criteria	Description
Age	Median: 49
	Range: 27 - 71
Sex	Male: 16/25 (64%)
	Female: 9/25 (36%)
Histology	Low grade (5 FL and 1 MZL 6/25 (24%)
	Aggressive (9 DLBCL, 3 MCL, 2 transformed DLBCL), 1 Richter's transformation (*i.e.*, CLL to DLBCL), 1 precursor B-cell ALL): 16/25 (64%)
	Mixed histology (*i.e.*, 2 NHL and HL and 1 DLBCL and FL): 3/25 (12%)
Extra-nodal sites	Median: 2
	Range: 0 - 7
Disease stage	Median: 4
	Range: 2 - 4
	Stage 2: 3/25 (12%)
	Stage 3: 7/25 (28%)
	Stage 4: 15/25 (60%)
Disease status[*]	Primary refractory: 13/25 (52%)
	Relapsed disease: 12/25 (48%)
Remission period prior to SCT (for those patients in remission)	Median: 4 months
	Range: 2 - 12 months
Performance Status	Median: 1
	Range: 0 - 2
LDH immediately prior to SCT (pre-SCT LDH)	Normal: 16/25 (64%)
	1 - 3 times normal: 8/25 (32%)
	$\geq$3 times normal: 1/25 (4%)
IPI	0:1/25 (4%)
	1: 2/25 (8%)
	2: 13/25 (52%)
	3: 6/25 (24%)
	4: 3/25 (12%)
	Median: 2
Prior regimens	Median: 3
	Range: 1 - 7
Prior radiation	Yes: 4/25 (16%)
	No: 21/25 (84%)
Bulky adenopathy	Yes: 4/25 (16%)
	No: 21/25 (84%)

Continued

Comorbidities	Yes: 22/25 (88%)
	No: 3/25 (12%)
	Number of patients with various comorbidities:
	Cardiac disease: 2/25 (8%)
	Diabetes: 4/25 (16%)
	Hyperlipidemia: 3/25 (12%)
	Hypertension: 10/25 (40%)
	Prior cancer: 6/25 (24%)
	Pulmonary disease: 5/25 (20%)
	Psychiatric: 8/25 (32%)
	Renal disease: 4/25 (16%)
	Thromboembolism: 3/25 (12%)
	Other including rheumatologic/neurologic disease: 12/25 (48%)
Baseline pulmonary status	Normal: 12/25 (48%)
	Decreased DLCO or obstructive/restrictive defect: 13/25 (52%)
Baseline liver function	Normal: 19/25 (76%)
	Elevated liver function tests: 6/25 (24%)
Baseline cardiac function	Normal: 13/25 (52%)
	Depressed EF (<50%) or diastolic dysfunction: 12/25 (48%)
Disease/chemotherapy sensitivity (at time of SCT)	Sensitive: 13/25 (52%)
	Resistant: 12/25 (48%)
Type of SCT	Allogeneic: 14/25 (56%)
	Autologous: 11/25 (44%)

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, Non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; IPI, International Prognostic Index; DLCO, diffusing capacity for carbon monoxide; EF, ejection fraction; SCT, stem cell transplant. *Primary refractory disease indicates no remission to prior therapy or remission duration < 6 months.

Table 2. Early and late SCT-related grade 3 and 4 toxicities.

Toxicity	Early*	Late*
Neutropenic fever	23/25 (92%)	None
Infection	17/25 (68%)	3/18 (17%)
Pneumonitis	7/25 (28%)	8/18 (44%)
Intubation	4/25 (16%)	None
Altered mental status or stroke	3/25 (12%)	1/18 (5.6%)
Renal failure	2/25 (8%)	None
Cardiac complication	2/25 (8%)	None

*Early indicates 1 - 99 days post-SCT, while late indicates ≥ 100 days post-SCT.

4. DISCUSSION

Stem cell transplantation has become a treatment option for NHL patients including those with relapsed/ refractory disease, low, intermediate or high grade NHL, and aggressive NHL [1-6,9-10,12,14-19]. For relapsed/ refractory NHL, Bu/Cy/VP-16 has been investigated as a conditioning regimen. We retrospectively analyzed the efficacy and toxicity of this regimen at the Northwestern University Robert H. Lurie Comprehensive Cancer Center for patients with "high risk" relapsed or refractory NHL.

Results of our study support data from prior studies suggesting that Bu/Cy/VP-16 is an effective conditioning regimen prior to SCT in patients with relapsed/refractory NHL. We noted a 2-year OS rate of 69% and 2-year DFS rate of 64% in a relatively high risk NHL patient population. These data are similar to results obtained by Kim *et al.* [10] who estimated the 3-year OS and PFS for relapsed/refractory or high-risk NHL patients transplanted with Bu/Cy/VP-16 to be 72% and 70%, respectively, with 61% of patients in complete remission and 39% of patients in partial remission prior to transplant. Escalon *et al.* [8] noted a 3-year OS of 43% and progression-free survival of 39%, with 60% of patients in complete

Table 3. Proportional hazard modeling of prognostic factors affecting survival.

Prognostic Factors	OS			DFS		
	HR	95% CI	P	HR	95% CI	P
Allogeneic vs. autologous	0.52	0.09 - 3.11	0.47	0.66	0.13 - 3.36	0.62
Stage						
III vs. II	0.3	0.02 - 4.92	0.4	0.3	0.02 - 4.96	0.4
IV vs. II	0.64	0.07 - 5.97	0.69	0.75	0.09 - 6.69	0.8
III/IV vs. II	0.52	0.06 - 4.67	0.56	0.6	0.07 - 5.20	0.65
Chemotherapy-resistant disease	6.54	0.76 - 56.3	0.09	7.73	0.93 - 64.5	0.07
IPI (continuous)	4.39	1.48 - 13.1	0.008	3.01	1.15 - 7.92	0.03
Bulky disease	0.97	0.11 - 8.34	0.98	0.77	0.09 - 6.45	0.81
Age (continuous)	1.07	1.00 - 1.15	0.06	1.06	1.00 - 1.13	0.06
Gender: Male vs. Female	1.08	0.20 - 5.92	0.93	1.3	0.25 - 6.72	0.75
Number of extra nodal sites >3	2.47	0.45 - 13.57	0.3	2.03	0.39 - 10.51	0.4
Number of prior regimens >3	0.51	0.09 - 2.84	0.45	0.41	0.08 - 2.13	0.29
Performance status 2 - 4	3.74	0.99 - 14.0	0.05	6.5	0.8 - 53.8	0.08
Baseline liver function[*]	1.55	0.28 - 8.62	0.62	2.29	0.50 - 10.34	0.29
Baseline cardiac function[*]	0.55	0.10 - 2.99	0.49	0.47	0.09 - 2.41	0.36
Baseline pulmonary function[*]	1.42	0.28 - 7.24	0.67	1.05	0.23 - 4.79	0.95
Pre-SCT LDH						
1 - 3 normal	15.03	1.64 - 138.08	0.02	8.05	1.44 - 45.18	0.02
≥3 normal	114.45	4.00 - 3277.54	0.01	69.22	3.23 - 1480.45	0.01

Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; P, p-value; IPI, International Prognostic Index; Pre-SCT LDH, LDH immediately prior to transplant. [*]Analysis involved comparing abnormal versus normal status.

remission/complete remission unconfirmed and 30% of patients with partial remission prior to transplant, while Copelan *et al.* [7] noted a 3-year progression free survival of 47%, with 41% of patients in sensitive-first relapse.

The majority of our patients in the current series had aggressive disease, which was noted by Copelan *et al.* [7] to be an adverse prognostic factor. Weaver *et al.* [20] showed that disease stage may be an important determinant of survival outcomes. While disease stage alone did not have a statistically significant impact on survival outcomes in our study, it was factored into the calculated IPI, which we identified as a predictive factor for survival. In addition, several studies have shown that disease status at time of SCT is a critical factor that predicts survival [21,22]. Stiff *et al.* [22] found that the 3-year OS and PFS of patients with chemotherapy-resistant disease was statistically inferior (p = 0.009) at 29% and 22%, respectively, in comparison with chemo-sensitive disease

patients whose 3-year OS and PFS were 55% and 42%, respectively. Gulati *et al.* [21] found that the DFS of patients who were in complete remission prior to transplant was 80% in comparison with 11% for those patients who had progressive disease. Nearly 50% of patients in our series had chemotherapy-resistant disease at time of SCT. Despite these high-risk features of patients herein, Bu/Cy/VP-16 appeared to mitigate this adverse prognostic factor.

Our study was limited by sample size and follow-up. Other investigators have estimated the 4 - 5 years survival of patients with NHL to be approximately 50% [6,15,23], although Zhang *et al.* [24] noted a 5-year survival rate of 64%, so further longitudinal analysis of our population is needed to determine whether the pre-transplant characteristics we have identified (lower baseline IPI and normal pre-transplant LDH) continue to confer a survival advantage in the long-term. This will be critical not only for observation of potential disease relapse, but also re-

garding the development of late effects, in particular the second malignancies/leukemia.

The early TRM with Bu/Cy/VP-16 in our study was 16%. This overall result compares favorably with the 46% TRM noted by Vaughan *et al.* [13]. The majority of patients in our series with TRM died due to sepsis and/or hypoxemic respiratory failure, which has been described [8,23]. Mucositis also occurred frequently in the early post-transplant period, which has been noted by other authors [7-9,25]. Hepatic toxicity was commonly seen in the initial pre-transplant period, which was also noted by Kim *et al.* [10] and Copelan *et al.* [7]. However, veno-occlusive disease was rare in our population (n = 1); although more cases have been noted in the literature [10, 13]. This may be due to intravenous administration of etoposide as opposed to oral dosing, as suggested by Kayshap *et al.* [26].

Pneumonitis was a common late toxicity, which has previously been described with this regimen [9,27]. Crilley *et al.* [28] noted significant pulmonary toxicity with this regimen in patients who had received prior radiation, but Spitzer *et al.* [29] found no difference in pulmonary toxicity between patients receiving total body irradiation and busulfan in combination with etoposide; the pulmonary toxicity noted in our population may therefore be a consequence of busulfan [30]. Given the prevalence of this toxicity, alternative regimens may be considered in those patients with poor baseline pulmonary function, given the risk of long-term disabling pulmonary consequences. Nevertheless, despite these toxicities, there were no late non-relapse fatal events noted (*i.e.* >100 days). Additionally, there were no secondary malignancies or myelodysplasia seen in contrast with Vaughan *et al.* [13]. This may be due in part to our follow-up time period, and further longitudinal study of our patient population is needed.

Altogether, we conclude that Bu/Cy/VP-16 may serve as an effective conditioning regimen for patients with relapsed/refractory NHL. This includes patients with chemotherapy-resistant NHL, including active disease at time of SCT. However, additional analysis and continued refinement of this conditioning regimen are warranted in order to decrease the transplant-related mortality associated with this therapy.

5. ACKNOWLEDGEMENTS

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