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Second Autologous Stem Cell Transplantation for Relapsed Lymphoma after a Prior Autologous Transplant

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ABSTRACT

We determined treatment-related mortality, progression-free survival (PFS), and overall survival (OS) after a second autologous HCT (HCT2) for patients with lymphoma relapse after a prior HCT (HCT1). Outcomes for patients with either Hodgkin lymphoma (HL, n = 21) or non-Hodgkin lymphoma (NHL, n = 19) receiving HCT2 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) were analyzed. The median age at HCT2 was 38 years (range: 16-61) and 22 (58%) patients had a Karnofsky performance score <90. HCT2 was performed >1 year after HCT1 in 82%. The probability of treatment-related mortality at day 100 was 11% (95% confidence interval [CI], 3%-22%). The 1-, 3-, and 5-year probabilities of PFS were 50% (95% CI, 34%-66%), 36% (95% CI, 21%-52%), and 30% (95% CI, 16%-46%), respectively. Corresponding probabilities of survival were 65% (95% CI, 50%-79%), 36% (95% CI, 22%-52%), and 30% (95% CI, 17%-46%), respectively. At a median follow-up of 72 months (range: 12-124 months) after HCT2, 29 patients (73%) have died, 18 (62%) secondary to relapsed lymphoma. The outcomes of patients with HL and NHL were similar. In summary, this series represents the largest reported group of patients with relapsed lymphomas undergoing SCT2 following failed SCT1, and with long-term follow-up. Our series suggests that SCT2 is feasible in patients relapsing after prior HCT1, with a lower treatment-related mortality than that reported for allogeneic transplant in this setting. HCT2 should be considered for patients with relapsed HL or NHL after HCT1 without alternative allogeneic stem cell transplant options.

KEY WORDS

Second autologous transplant • Non-Hodgkin lymphoma • Hodgkin lymphoma

INTRODUCTION

Aggressive lymphomas are inherently chemosensitive, and the successful use of high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HCT) supports the presence of a robust dose-response curve. HCT provides long-term disease

control in up to 50% of patients with relapsed chemosensitive disease [1], but therapeutic options for patients with non-Hodgkin (NHL) or Hodgkin (HL) lymphoma relapsing after an autologous stem cell transplant are limited. Allogeneic transplantation has been shown to be effective for some patients with recurrent lymphoma following an autologous HCT [2-4], but its widespread use is limited by factors such as comorbidities, a substantial risk of transplant-related mortality (TRM) and graft-versus-host disease (GVHD), and the lack of an appropriate donor. The use of allogeneic transplantation in lymphoma, as part of either ablative or reduced-intensity conditioning (RIC), appears quite dependent on histology, with aggressive histologic subtypes faring worse than indolent histologic counterparts [5,6].

We hypothesized that a second autologous HCT (HCT2) is a reasonable option for patients with relapsed lymphoma after a previous autologous HCT (HCT1) and either unwilling or unable to undergo an allogeneic transplant. Because most published reports of a second autologous HCT in patients with relapsed lymphoma are series from single institutions, we analyzed the characteristics and outcomes of this population from a large registry database.

PATIENTS AND METHODS

Data Sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a voluntary working group of over 500 transplant centers worldwide. Participating centers register basic information on consecutive transplants to a Statistical Center at the Medical College of Wisconsin. Detailed demographic and clinical data are collected on a representative sample of patients in the registry using a weighted randomization scheme. Participating centers are required to report all consecutive transplant data; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up.

The CIBMTR collects data at 2 levels: Registration and Research. Registration data includes disease type, age, sex, pretransplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow, peripheral blood, and cord blood-derived hematopoietic stem cells), conditioning regimen, posttransplant disease progression and survival, development of secondary cancers, and cause of death. Requests for data on progression or death for registered subjects are at 6-month intervals. All CIBMTR teams contribute registration data. Research data are collected on subsets of registered subjects, and includes comprehensive pre- and posttransplant clinical data. Computerized checks for errors, physician reviews of submitted data, and on-site audits of participating centers ensure the quality of data.

Patients

The study population includes all patients reported to the CIBMTR receiving a second autologous stem cell transplant (HCT2) between 1986 and 2003 for Hodgkin or non-Hodgkin lymphoma relapsing after a first autologous stem cell transplant (HCT1) and with at least 1 year of available follow-up. Median follow-up of survivors after HCT2 was 72 (range: 12-124) months.

Study Endpoints

The primary objectives were to determine the clinical outcomes of HCT2 for NHL and HL patients relapsing after HCT1. The secondary objectives were to describe patient-, disease-, and transplant-related variables associated with outcome after HCT2, including number of prior regimens, disease status prior to transplant (ie, chemosensitive versus chemoresistant), and histologic subtype.

Outcomes analyzed included TRM, progression/relapse, progression-free survival (PFS) and overall survival (OS). TRM was defined as death within 28 days posttransplant or death without lymphoma progression. Subjects with lymphoma progression were censored at the time of progression and a cumulative incidence estimate was derived with progression or relapse as the competing risk. Progression was defined as progressive lymphoma post transplant ($\geq$28 days) or lymphoma recurrence. It could follow a period of "stable" disease posttransplant, or a partial or complete remission. Progression represents new or larger areas of lymphoma ($\geq$25% increase in largest diameter) compared to the best posttransplant lymphoma state. Progression was summarized by the cumulative incidence estimate with TRM as the competing risk. For PFS, subjects were considered treatment failures at the time of lymphoma progression or death from any cause. Subjects alive without evidence of lymphoma progression were censored at last follow-up and the PFS event was summarized by a survival curve. The OS interval variable was defined as time from the date of transplant to the date of death or last contact and summarized by a survival curve.

Statistical Analysis

Univariate probabilities of engraftment, TRM, and lymphoma relapse/progression were calculated using cumulative incidence curves to accommodate corresponding competing risks [7]. Probabilities of 100-day mortality, OS, and PFS were calculated using Kaplan-Meier estimator [8]. Confidence intervals (CI) were calculated with a log-transformation.

Because of the small sample size, assessment of potential prognostic factors for the outcomes of interest was not evaluated in multivariate analysis. Analyses

were performed using SAS software, version 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient and Disease Characteristics

A total of 49 patients receiving HCT2 for relapsed lymphoma between 1986 and 2003 were reported to the CIBMTR. Four patients were excluded because the reason for retransplant was persistent disease and 4 because the HCT2 was part of a planned tandem transplant. An additional patient had insufficient information. During the same time period, 6,428 patients underwent HCT1 for relapsed HL or NHL; of this population 2,634 relapsed. The cumulative incidence of relapse after HCT1 at 3 years for all patients reported to the registry was 40% (CI: 39-41). Patient characteristics of the 40 patients included in the final analysis are listed in Table 1.

Twenty-one patients (53%) had HL and 19 (47%) had NHL (diffuse large B cell lymphoma, follicular large-cell lymphoma, and immunoblastic lymphoma). Twenty-three (58%) were male. Karnofsky performance status (KPS) was <90 in 13 (33%) and 22 (58%) at the time of HCT1 and HCT2, respectively. A comparison of patient and disease characteristics for HCT1 and HCT2 are listed Table 1. There was insufficient data to calculate the IPI (International Prognostic Index) for NHL patients prior to HCT1 and HCT2. Of the 21 patients with HL, 7 (35%) had extranodal involvement prior to transplant, only 1 had prior bone marrow involvement, 5 had pulmonary involvement prior to transplant, and 11 (55%) had B symptoms at diagnosis.

The median interval from diagnosis to HCT1 was 20 months (range: 4-162). The median time from HCT1 to relapse was 16 (range: 3-68) months. Nine (24%) patients relapsed within 6 months, 6 (16%) relapsed between 6 to 12 months, and 23 (60%) patients relapsed >12 months from HCT1. The median time from relapse to HCT2 was 6 (range: 1-40) months; only 5 (13%) patients underwent HCT2 >12 months from relapse. Overall, the time from HCT1 to HCT2 was ≤1 year in 7 (18%) patients and >1 year in 33 (82%) patients.

At the time of HCT1, 25 patients (64%) had received no more than 2 prior lines of salvage therapy, whereas 12 patients received 3 or more lines of salvage therapy. Thirty-three (87%) patients had chemosensitive disease, 4 (11%) had resistant disease, and 1 (2%) underwent HCT1 without prior salvage therapy. Disease status at HCT1 was complete remission (CR) in 16 (40%) patients, sensitive disease with primary induction failure or relapse in 13 (33%) patients, and resistant disease with primary induction failure and relapse in 3 (7%) patients. Most patients 27 (73%) had chemosensitive disease prior to HCT2, whereas 4 (11%) patients had resistant disease. Disease status at HCT2 was complete remission (CR) in 7 (18%)

Table 1. *Comparison of Patient and Disease Characteristics at Time of HCT1 and HCT2 for 40 Patients with Relapsed HL and NHL*

Variable	First Transplant	Second Transplant
Number of patients	40	
Age at transplant, median (range), years	35 (15-60)	38 (16-61)
Male sex	23 (58)	
Karnofsky score prior to transplant, <90	13 (33)	22 (58)
Missing	*1*	*2*
Histology		
Hodgkin lymphoma	21 (53)	
NHL-DLBCL/follicular large cell/immunoblastic	19 (47)	
Disease stage at diagnosis		
I-II	15 (41)	
III-IV	22 (59)	
Missing	*3*	
Bone marrow involvement at diagnosis	6 (16)	N/A
Missing	2	
Chemosensitive disease at transplant		
Sensitive	33 (87)	27 (73)
Resistant	4 (11)	4 (11)
Untreated	1 (2)	4 (11)
Not evaluable	0	2 (5)
Missing	*2*	*3*
Disease status at transplant		
CR1	10 (25)	0
CR2+	6 (15)	7 (18)
PIF/REL sensitive	13 (33)	16 (40)
PIF/REL resistant	3 (7)	5 (12)
Unknown/Missing	8 (20)	12 (30)
Interval from diagnosis to first transplant, median (range), months	20 (4-162)	
Time from first transplant to relapse (prior 2nd transplant), months		
<6	9 (24)	
6-12	6 (16)	
>12	23 (60)	
Missing relapse date	*2*	
Time from first transplant to relapse, median (range), months	16 (3-68)	
Missing relapse date	*2*	
Time from relapse (after 1st transplant) to second transplant, months		
<6	20 (53)	
6-12	13 (34)	
>12	5 (13)	
Missing relapse date	*2*	
Time from relapse to second transplant, median (range), months	6 (1-40)	
Missing relapse date	*2*	
Time from first to second transplant, years		
≤ 1	7 (18)	
>1	33 (82)	

CR indicates complete remission; NHL, non-Hodgkin's lymphoma; HCT, hematopoietic cell transplant.

patients, sensitive relapses in 16 (40%) patients, and resistant relapse in 5 (12%) patients; 12 (30%) of the patients had unknown or missing data regarding disease status at time of HCT2.

Transplant Characteristics

Transplant characteristics of both HCT1 and HCT2 are summarized in Table 2. Only 6 (15%) patients received stem cells collected from their initial harvest, whereas 34 (85%) patients required a second stem cell collection. The majority (83%) of preparative regimens for HCT1 were BCNU based, either as part of BEAM or CBV. At HCT2, BEAM was used in 19 (48%) of patients, CBV in 7 (17%) patients, and total-body irradiation (TBI)-based regimens in 8 (20%) of patients. Of note, only 1 patient received rituximab as part of either salvage or mobilization, perhaps reflecting the era studied.

We found prompt engraftment after HCT2 with median time to ANC $\geq 0.5 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L of 11 and 22 days, respectively. Eighty-seven percent (95% CI, 78%-97%) and 60% (95% CI, 44%-75%) of patients had ANC and platelet recovery, respectively, by day 28. 97% of patients had platelet recovery by day 48, and none of the patients became transfusion dependent. Following HCT2, a variety of planned adjunctive therapies were administered to 18 patients including chemotherapy, immunotherapy, radiation, or a combination of the 2; 22 (56%) patients did not have any planned treatment after HCT2.

Table 2. *Transplant Characteristics of 40 Patients with HL and NHL Relapsing after HCT1 and Undergoing HCT2*

Variable	First Transplant	Second Transplant
Conditioning regimen at transplant		
BEAM and similar	**8 (20)**	**19 (48)**
CBV or similar	**25 (63)**	**7 (17)**
TBI-based	**2 (5)**	**8 (20)**
Others	**5 (12)**	**4 (10)**
Unknown	**0**	**2 (5)**
Conditioning regimen used for first and second transplant		
Same	**10 (26)**	
Different	**29 (74)**	
PB CD34$^+$ cells infused		
$<4 \times 10^6$	**11 (39)**	**13 (93)**
$\geq 4 \times 10^6$	**2 (7)**	**1 (7)**
BM N/A	**15 (54)**	***10***
Missing	***12***	***16***
Graft type for		
BM	**15 (38)**	**10 (25)**
PBSC	**14 (35)**	**26 (65)**
BM + PBSC	**11 (27)**	**4 (10)**
Harvest		
Same cells used from harvest prior to HCT1	**6 (15)**	
Two different harvests	**34 (85)**	
Posttransplant planned treatment	**N/A**	
Chemotherapy + other		**1 (2)**
Immune only		**2 (5)**
Immune + other		**1 (3)**
Radiation only		**8 (20)**
Radiation + immune		**4 (6)**
Radiation + other		**1 (2)**
Other, not specified		**1 (2)**
None		**22 (56)**

PB indicates peripheral blood; BM, bone marrow; PBSC, peripheral blood stem cells; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; HCT, hematopoietic cell transplant.

Table 3. *Causes of Death for NHL and HL among Patients after HCT2*

	NHL		HL	
Causes of Death	**N eval**	**N (%)**	**N eval**	**N (%)**
Number of patients	**15**		**14**	
Primary disease		**10 (67)**		**8 (57)**
Interstitial pneumonia		**0**		**1 (7)**
Infection		**0**		**1 (7)**
Organ failure		**1 (7)**		**1 (7)**
New malignancy		**2 (13)**		**1 (7)**
Other, not specified		**2 (13)**		**2 (15)**

HCT indicates hematopoietic cell transplant.

Clinical Outcomes

Response following HCT2 includes a complete remission/unconfirmed (CR/CRu) in 23 (57%) patients, partial remission (PR) in 9 (23%) patients, and no response or progressive disease in the remaining 8 (20%) patients. With a median follow-up of 72 (range: 12-124) months following HCT2, 29 patients have died and 11 patients remain alive. The most common cause of death was primary disease in 18 (62%) patients. Three patients developed therapy-related myelodysplasia and died from this complication; other causes of death include interstitial pneumonia (n = 1), organ failure (n = 2), infection (n = 1), or not specified (n = 4). Causes of death by histology are shown in Table 3. The 3 year probability of PFS and OS was 36%. We found no difference in either PFS or OS based on histology (HL versus NHL) as shown in Figure 1.

Univariate probabilities of transplant outcomes after HCT2 are summarized in Table 4. The probability of TRM at day 100 following HCT2 was 15% (95% CI, 6%-28%). TRM was 18% (95% CI, 8%-32%), 30% (95% CI, 16%-45%), and 36% (95% CI, 21%-52%) at 1, 3, and 5 years, respectively.

In univariate analysis lymphoma relapse <12 months after HCT1 was associated with worse outcomes (Figures 2 and 3). The 5-year probabilities of PFS for patients relapsing <12 months and ≥12 months after HCT1 were 0% and 32%, respectively ($P = .001$). The 5-year probabilities of OS were 13% and 41%, respectively, for patients relapsing <12 months and ≥12 months after HCT1 ($P = .002$). For patients relapsing >3 years following HCT1, the PFS and OS at 5 years are 25% and 38%, respectively.

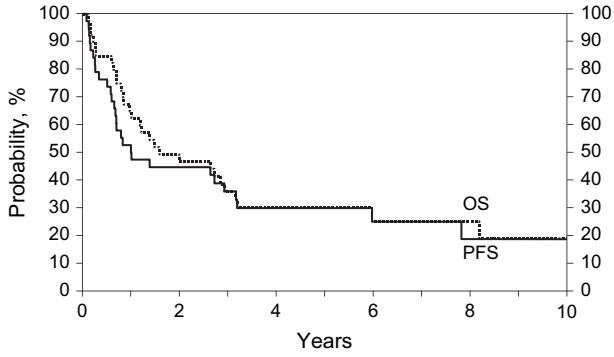

Figure 1. Probability of PFS and OS for patients following HCT2.

Patients with HL and NHL had similar PFS and OS. Chemosensitivity predicted for an improved outcome. The 5-year probabilities of PFS for patients with sensitive, resistant, and untreated lymphoma prior to HCT2 were 20%, 0%, and 50%, respectively (P = .006). Corresponding 5-year probabilities of OS for patients with sensitive, resistant, and untreated lymphoma were 32%, 0%, and 75%, respectively (P < .001).

Table 4. *Univariate Probabilities of Transplant Outcomes after HCT2*

Variable	N (%)
Best response posttransplant	
Continued complete remission (CCR)	**7 (17)**
Complete remission (CR)/Complete remission undetermined (CRU)	**16 (40)**
Partial remission (PR)	**9 (23)**
No response/progressive disease	**8 (20)**
Median follow-up of survivors after second transplant, months	**72 (12-124)**

Outcome event	N	Prob (95% CI)
100 day mortality	**40**	**15 (6-28)**
ANC>0.5 x 10^9/L	**37**	
@ 28 days		**87 (78-97)**
@ 100 days		**97 (90-100)**
Platelet recovery ≥ 20 × 10^9/L	**31**	
@ 28 days		**60 (44-75)**
@ 100 days		**86 (72-95)**
TRM	**38**	
@ 1 year		**18 (8-32)**
@ 3 years		**30 (16-45)**
@ 5 years		**36 (21-52)**
Progression/relapse	**38**	
@ 1 year		**32 (18-47)**
@ 3 years		**34 (20-50)**
@ 5 years		**34 (20-50)**
PFS	**38**	
@ 1 year		**50 (34-66)**
@ 3 years		**36 (21-52)**
@ 5 years		**30 (16-46)**
Overall survival	**40**	
@ 1 year		**65 (50-79)**
@ 3 years		**36 (22-52)**
@ 5 years		**30 (17-46)**

CI indicates confidence interval; ANC, absolute neutrophil count; PFS, progression-free survival; TRM, transplant-related mortality; HCT, hematopoietic cell transplant.

DISCUSSION

Patients with lymphoma relapse following an autologous stem cell transplant (HCT1) have a median survival of only 7 to 8 months for NHL and 10 months for HL [9-11]. Although a second autologous transplant (HCT2) is feasible in some of these patients, the published literature is largely limited to small series from single institutions. This study is the largest series describing the outcomes of patients after HCT2 with relapsed HL or NHL following HCT1.

In our series, the patients were relatively young, with a median age at HCT2 of 38 years, and histology was nearly evenly split between relapsed HL and aggressive NHL. The NHL patients in our series had an aggressive histology, suggesting that in practice HCT2 is perhaps not being considered for indolent subtypes. HCT2 for patients relapsing after HCT1 was feasible and showed encouraging outcomes, with 30% PFS and OS at 5 years. Eighty-five percent of our patients successfully underwent a second stem cell collection for HCT2 despite prior high-dose chemotherapy. Although this may indicate the inherent selection bias of a retrospective study, mobilization and collection of an autologous graft is feasible in a proportion of patients after prior HCT1. Neutrophil and platelet engraftment after HCT2 was prompt, and TRM was 11% at day 100, lower than that reported with allogeneic stem cell transplant performed in this setting [12]. However, we did note an increase in late non-relapse mortality that could be due to late regimen-related events. Although the major cause for failure was lymphoma relapse, patients surviving beyond 1 year in remission appear to have a favorable outcome without further late relapses. There were no observed differences in outcome between HL and NHL.

The strongest predictor of outcome was time to relapse following HCT1. Patients relapsing within 6 months of HCT1 fared particularly poorly after HCT2, with PFS and OS at 1 year of only 11% and 22%, respectively. In comparison, patients relapsing >12 months following HCT1 enjoyed a better PFS and OS of 64% and 78% at 1 year, and those patients with very late relapses >18 months 53% and 72% at 1 year. Although the number of patients with very late relapses following HCT1 is small, our data is consistent with other reports. Of 6 patients described by the Memorial Sloan Kettering Cancer Center (MSKCC), those relapsing beyond 12 months from HCT1 and subsequently undergoing HCT2 did quite well with a median survival that had not been reached at 26 months of follow-up [9].

Our series is 1 of the largest thus far reported of HCT2 for patients with relapsed lymphomas after

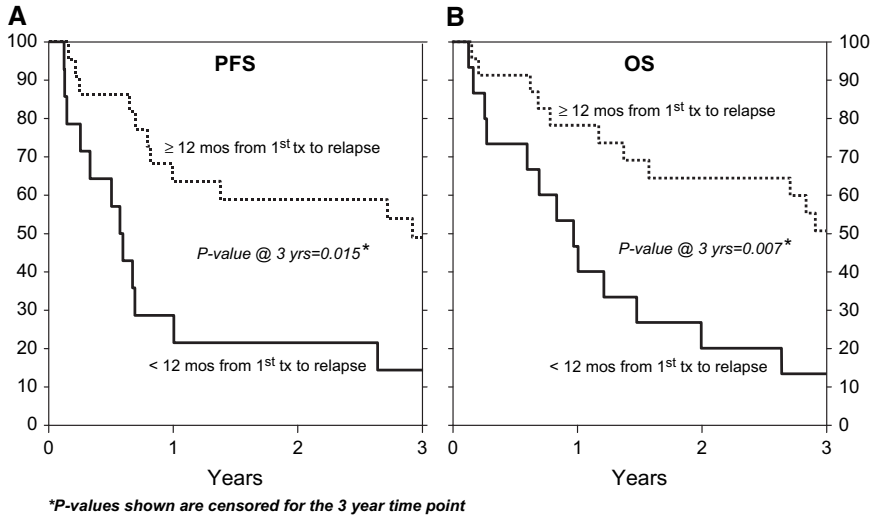

Figure 2. (A) Probability of PFS by time to relapse from HCT1. (B) Probability of OS by time to relapse from HCT1.

HCT1. In addition to the MSKCC series already mentioned [9], the M.D. Anderson Cancer Center (MDACC) [13] and The Ohio State group [14] each reported on 4 such patients. Two other retrospective studies with differing patient groups were recently reported as well [15,16]. A retrospective French study described 18 patients with a median age of 41 years, including 6 with indolent and 12 with a variety of aggressive histologies, including mantle cell lymphoma, T cell lymphoma, and transformed lymphomas. With a median follow-up of 42 months from HCT2, they report a median PFS and OS of 13 and 37 months, respectively. The median time to granulocyte recovery was identical to our group, but TRM for HCT2 was higher at 22%. The European Group for Blood and Marrow Transplantation (EBMT) reported on 34 lymphoma patients undergoing HCT2 after HCT1, although their population differs from ours in several important ways. First, they included patients with a planned tandem transplant, which was an exclusion criterion in our investigation. Second, the EBMT series included 8 patients failing to achieve a PR following HCT1, and therefore proceeding to HCT2 prior to relapsing. These 2 populations may be better risk patients overall, likely contributing to their optimistic finding of 42% and 48% PFS and OS, respectively, at 2 years [16]. On the other hand, they also included 5 patients with indolent lymphomas who had a dismal outcome, with no long-term survivors.

For HL, the number of planned tandem transplants reported outweighs reports of patients undergoing for HCT2 for relapse following HCT1, making comparisons between our study and others difficult. The City of Hope group reported 5 year PFS and OS of 49% and

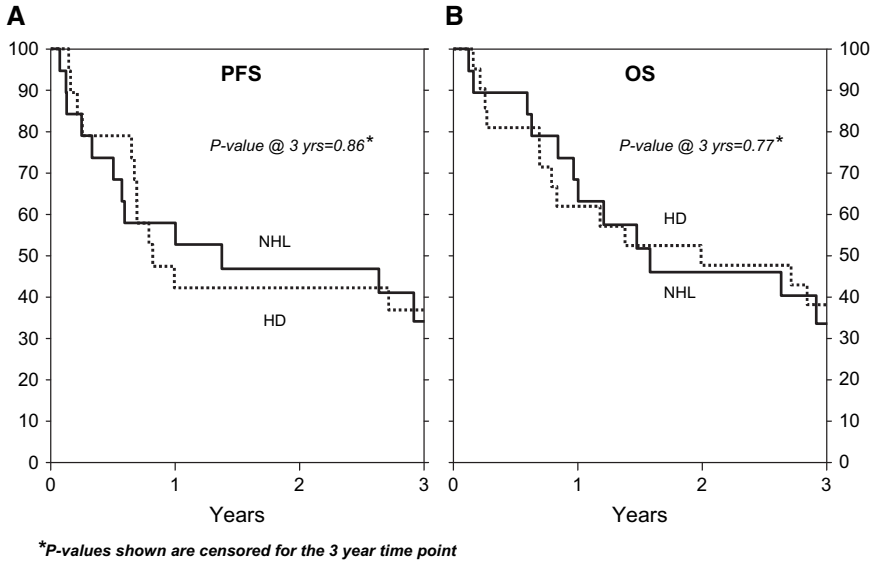

Figure 3. (A) Probability of PFS histology. (B) Probability of OS histology.

54%, respectively, for patients with relapsed and refractory HL undergoing tandem autologous transplantation [17]. In several small case series evaluating HCT2 following failure of HCT1, the ability to demonstrate chemosensitivity appears to be an important prognostic feature [14,18,19]. It should be noted that TRM appears to be much higher for HL patients than might be expected for other lymphoma populations. Lin and colleagues [14] found a very high rate of pulmonary toxicity, likely reflecting the prevalent use of mantle irradiation coupled with busulfan or BCNU containing preparative regimens, and perhaps the use of front-line bleomycin-containing regimens as well.

The application of allogeneic stem cell transplantation, particularly for aggressive lymphoma remains controversial. Conventional myeloablative allogeneic transplants are associated with high TRM rates of 25% to 41% [3,20-22]. Other series, including a large CIBMTR analysis, failed to show long-term disease control in patients with aggressive NHL, with 5-year PFS of only 5% [12]. Patients relapsing after a prior autologous HCT may also be particularly vulnerable to toxicity from fully ablative allogeneic regimens. Reduced-intensity conditioning (RIC) regimens were developed to reduce TRM, but there is limited data on the use of RIC in patients relapsing after a prior autologous HCT, especially for aggressive histologies. The most optimistic report is from MDACC on 20 NHL patients with minimal disease burden relapsing after a prior autologous HCT, including 10 with diffuse large B cell lymphoma [23]. Using fludarabine, cyclophosphamide, and rituximab, the authors show an encouraging 95% 3-year PFS and minimal toxicity, with a median follow-up time of 25 months. These results are tempered, however, by other studies of RIC of patients relapsing following prior autologous HCT [24]. The Fred Hutchinson Cancer Research Center reported a 3-year PFS and OS of 28% and 31%, respectively, with no plateau in terms of relapse in a group of 147 patients (including 24 with aggressive NHL) treated with fludarabine/TBI conditioning [25]. An EBMT study identified 62 patients with aggressive NHL undergoing RIC allogeneic transplants (50% after a failed a prior autologous HCT) and found a dismal 13% PFS with corresponding 37% TRM at 2 years [6]. Thus, although RIC may be capable of providing occasional durable remissions for some aggressive lymphoma patients failing a prior autologous HCT, its application and timing need further clarification.

More than half our population had HL. The lack of clearly defined alternative options for patients with HL relapsing after HCT1 may have prompted physicians to consider HCT2 over allogeneic stem cell transplant approaches. Contrary to NHL, demonstration of strong graft-versus-lymphoma (GVL) effects in HL has been elusive, with few prospective studies. Fully myeloablative transplants are highly toxic in this group of patients, with TRM rates up to 60% and disappointing PFS rates of 15% to 26% [22,26,27]. RIC regimens with modern supportive care may offer an improvement, but consistent demonstration of efficacy remains challenging. A Spanish cooperative group showed a 2-year PFS of 32% for 40 patients, primarily undergoing matched related donor RIC transplants [28]. A cooperative group study from the United Kingdom and a study from the MD Anderson Cancer Center report PFS rates of approximately 30% using fludarabine and alkylating agent-based regimens [29,30]. Overall survival in these three studies approximate 50%, and TRM rates are substantially better than fully ablative regimens at 12-20%. Despite the signals of graft-versus-HL effects, large comparative studies show inferior disease control for HL patients undergoing RIC compared to other lymphoproliferative disorders, and its role remains to be defined [25,31].

There are several important limitations to our data. First, as a registry analysis, we do not have an adequate comparison group of patients with relapsed HL/NHL following HCT1 who do not proceed to HCT2. Conceivably, these patients might have been further treated with palliative care, chemotherapy (with or without monoclonal antibodies) alone, or an allogeneic stem cell transplant using a variety of donors and preparative regimens. In the absence of an appropriate comparison group, we do not know whether or not our results are superior to any of these options, and the group studied is likely a highly selected population. Furthermore, only one patient is reported to have received rituximab prior to HCT2, and current advances in management that include rituximab as part of the salvage and/or preparative regimen could influence outcome. As discussed above, our data compares favorably to the published literature on patients undergoing allogeneic HCT, particularly in terms of TRM and OS. Another major limitation is that we do not know how many patients were considered for HCT2, but were unable to mobilize sufficient stem cells or otherwise unable to proceed to HCT2. This information is critical to understand the limitations to the widespread application of HCT2. However, the emergence of newer mobilizing agents such as AMD3100 may lead to successful remobilization of stem cells prior to HCT2 [32]. Finally, the heterogeneity of preparative regimens used in this population precludes any comparison of efficacy. Conditioning regimens selected are likely based on physician preference, and the majority of regimens for HCT2 was different from the original regimen used for HCT1. Finally, we were unable to calculate an IPI (International Prognostic Index) score prior to either HCT1 or HCT2. Given the prognostic significance of the second line IPI shown by several groups, this could have helped to better identify patients appropriate

for HCT2 [33,34]. Nevertheless, our data are promising in that, until other effective treatments are described, HCT2 appears to be a reasonable option for selected young patients relapsing at least 12 months after HCT1 with chemosensitive disease and with available PBSC collections.

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