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Allogeneic Stem Cell Transplantation Provides Durable Remission in Patients with Primary Mediastinal Large B Cell Lymphoma

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Standard therapy for relapsed or refractory (rel/ref) primary mediastinal large B cell lymphoma (PMBCL) is salvage therapy followed by autologous (auto) hematopoietic stem cell transplantation (HSCT). However, many patients have refractory disease and are unable to undergo autoHSCT, and a sizeable proportion of patients will relapse after autoHSCT. By analogy to diffuse large B cell lymphoma, these patients may be treated with allogeneic (allo) HSCT with curative intent, but at the risk of significant morbidity and mortality. Given the advent of effective immunotherapy approaches for rel/ref PMBCL, it is important to better understand the toxicity and efficacy of alloHSCT in these patients, to which these new approaches could be an alternative. Therefore, we retrospectively studied the outcomes of alloHSCT in a multicenter cohort of 28 patients with rel/ref PMBCL who underwent transplantation at 4 centers. Most patients (79%) were sensitive to pretransplantation therapy and 86% received reduced-intensity conditioning. The overall progression-free survival (PFS), overall survival (OS), and cumulative incidences of nonrelapse mortality and relapse in the cohort at 5 years were 34%, 45%, 32%, and 33%, respectively. Outcomes were significantly better in patients with pretransplantation responsive disease (2-year PFS and OS of 50% and 58%, respectively) compared with refractory patients (2-year PFS and OS of 0%). In our multicenter retrospective study, alloHSCT produced durable remissions in a proportion of patients with treatment-sensitive disease before transplantation (5-year PFS of 44%) and should be considered in the treatment of patients with rel/ref PMBCL.

INTRODUCTION

Primary mediastinal large cell lymphoma (PMBCL) is a subset of aggressive B cell non-Hodgkin lymphoma (B-NHL) with distinct biological and clinical features [1,2]. Standard initial therapy for PMBCL includes anthracycline-based chemoimmunotherapy with or without radiation therapy (RT) [3-9]. Although the majority of patients will be cured with frontline therapy, up to 10% to 25% of patients will experience relapsed or refractory (rel/ref) PMBCL [3-9]. Standard treatment of rel/ref PMBCL is similar to that of other aggressive B-NHLs, usually with salvage therapy and autologous (auto) hematopoietic stem cell transplantation (HSCT) in chemosensitive patients [10-12].

Patients with rel/ref PMBCL who are ineligible for or fail autoHSCT have a poor prognosis [10,12]. Recently, immunotherapy with blockade of the programmed death-1 receptor (PD-1) or chimeric antigen receptor modified (CAR) T cells have proven to be effective in rel/ref PMBCL, with some patients exhibiting remission in excess of 1 to 2 years [13-15]. Nevertheless, although many patients with PMBCL treated with PD-1 blockade or CAR T cells will achieve a complete remission (as high as 71% with CAR T cells and 21% to 33% with PD-1 blockade), fewer than one-half of patients treated with either modality will have a durable remission [13-16]. Therefore, allogeneic (allo) HSCT retains an important potential therapeutic role, producing sustained remission in patients with other

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advanced aggressive B-NHLs [17,18]. In the setting of novel and effective immunotherapy options for rel/ref PMBCL, an understanding of the toxicities and efficacy of alloHSCT is necessary to inform treatment decisions about its potential use. However, there are scant modern data on alloHSCT outcomes in patients with PMBCL, limited to case reports or small series [10,19,20]. Therefore, we performed a multicenter retrospective study to evaluate alloHSCT outcomes in patients with rel/ref PMBCL.

METHODS

We performed a retrospective, multicenter study of consecutive adult patients with rel/ref PMBCL who underwent alloHSCT at Dana-Farber Cancer Institute/Brigham and Women's Hospital, Fred Hutchinson Cancer Center, Massachusetts General Hospital, and City of Hope between January 2000 and September 2015. Confirmation of the histological diagnosis was performed before transplantation at each center. Patients with gray zone lymphoma were excluded. Disease response before transplantation was determined according to the treating physician using the contemporaneous standard imaging modality and lymphoma response criteria at the time of transplantation (eg, Cheson criteria, Lugano classification). Patients underwent alloHSCT according to institutional practice.

Patient baseline and transplantation characteristics are reported descriptively. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Acute and chronic graft-versus-host disease (GVHD) were graded using standard criteria [21,22]. GVHD data were abstracted from each site's Center for International Blood and Marrow Transplant Research database; therefore, staging information according to the National Institutes of Health consensus criteria are not available. The cumulative incidence of nonrelapse mortality (NRM) and the cumulative incidence of relapse/progression were calculated using competing risk analysis. Cumulative incidences of acute and chronic GVHD were calculated using competing risk analysis, with relapse/death as a competing risk. The log-rank test was used to compare PFS and OS between subgroups, and the Gray test was used to compare NRM and GVHD incidences. P values were 2-sided, with a significance level of .05. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). The study was approved by the Institutional Review Board at each participating center.

RESULTS

At the participating centers, 28 patients with rel/ref PMBCL underwent alloHSCT during the study period and composed the study cohort. The patients' baseline and transplantation characteristics are summarized in Table 1. The median age at transplantation was 35 years (range, 17 to 57 years); 54% of the cohort was female; the median number of previous therapies was 4 (range, 2 to 7); 57% of the patients were refractory to frontline therapy (only 1 patient received R-EPOCH; the other patients received R-CHOP or similar anthracycline-based combination regimens with or without radiation therapy [RT]); 86% had received previous RT, with 6 patients (21%) receiving RT as the most recent pretransplantation salvage therapy; and 71% had undergone previous autoHSCT. The 8 patients who had not undergone previous autoHSCT were chemorefractory, and one-half were refractory to all therapies and proceeded to alloHSCT immediately after salvage radiation. At the time of alloHSCT, 1 patient (4%) was in complete response (CR), 21 patients (75%) were in partial response (PR), and 6 (21%) were refractory to pretransplantation therapy.

Of the 28 patients, 18 had their pretransplantation response assessed by positron emission tomography (PET), and 10 were assessed using computed tomography (CT) scans. Among the 6 patients who received RT as the most recent pretransplantation salvage therapy, the response to RT was CR in 1 patient, PR in 3 patients, and stable disease in 2 patients. No patients had received previous PD-1 blockade or CAR T cell therapy. Most patients (86%) received a reduced-intensity conditioning (RIC) regimen. Fifteen patients (54%) had a matched (8/8) related donor, 8 (29%) had a matched (8/8) unrelated donor, 2 had a mismatched (7/8) unrelated donor, and 3 had an umbilical cord donor. All patients received peripheral blood stem cell grafts except for the 3 umbilical cord blood recipients. One patient received antithymocyte globulin as part of their GVHD prophylaxis regimen. One patient received rituximab as part of the HSCT conditioning regimen, and another received rituximab as chronic GVHD prophylaxis after alloHSCT as part of a clinical trial.

Table 1
Patient Baseline and Transplantation Characteristics

Characteristic	Value
Total patients, n (%)	28 (100)
Age, yr, median (range)	35 (17-57)
Female sex, n (%)	15 (54)
Previous lines of therapy, median (range)	4 (2-7)
Previous rituximab exposure, n (%)	28 (100)
Previous radiation therapy, n (%)	24 (86)
Primary refractory to frontline therapy, n (%)	16 (57)
Previous autologous HSCT, n (%)	20 (71)
Disease status at transplantation, n (%)*	
CR	1 (4)
PR	21 (75)
Refractory	6 (21)
Donor type, n (%)	
Matched related	15 (54)
Matched unrelated	8 (29)
Mismatched unrelated	2 (7)
Umbilical cord	3 (11)
Conditioning intensity, n (%)	
Reduced intensity	24 (86)
Myeloablative	4 (14)
Conditioning regimen, n (%)	
Flu/Mel ± ATG or Zevalin	7 (25)
Flu/TBI 200 ± rituximab	7 (25)
Flu/Bu (RIC)	4 (14)
Flu/Cy/TBI	3 (11)
TBI 200	3 (11)
MAC regimens (Bu/Cy, Cy/TBI, BEAM)	4 (14)
GVHD prophylaxis, n (%)	
CNI/MMF	12 (43)
CNI/sirolimus ± MTX	8 (29)
CNI/MTX	4 (14)
Other	4 (14)
Follow-up time in survivors, yr, median (range)	5.0 (.5-14.0)

Flu indicates fludarabine; Mel, melphalan; ATG, antithymocyte globulin; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, and melphalan; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate.

In the study cohort, the median duration of follow-up in survivors was 5.0 years (range, .5 to 14.0 years). The cumulative incidences of grade II-IV and III-IV acute GVHD at day +100 were 39% and 4%, respectively. The cumulative incidence of chronic GVHD at 1 year was 21% (18% extensive). The incidence of chronic GVHD in patients with matched related donors was lower at 7%, compared with 38% in patients with all other donor types ($P = .065$). The 1 patient who received rituximab after HSCT developed extensive chronic GVHD. The overall PFS, OS, and cumulative incidences of NRM and relapse in the cohort at 2 years were 39% (95% confidence interval [CI], 21% to 56%), 45% (95% CI, 26% to 63%), 32% (95% CI, 16% to 50%), and 29% (95% CI, 13% to 47%), respectively (Figure 1). The NRM in patients who received RIC was 29%, compared with 50% in patients who received a myeloablative conditioning

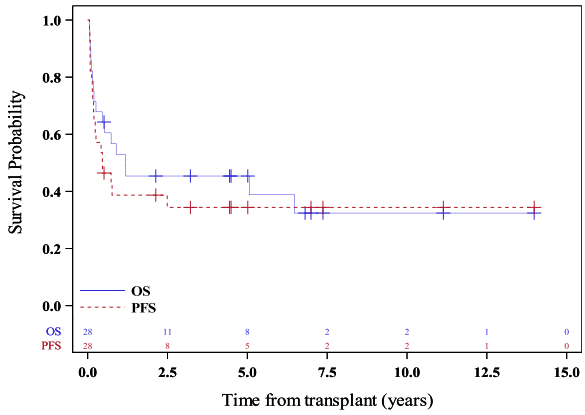

Figure 1. PFS and OS after alloHSCT in patients with rel/ref PMBCL.

(MAC) regimen (P = .36). The overall PFS, OS, NRM, and cumulative incidence of relapse in the cohort at 5 years were 34% (95% CI, 17% to 52%), 45% (95% CI, 26% to 63%), 32% (95% CI, 16% to 50%), and 33% (95% CI, 16% to 51%), respectively. The causes of death in the patients with NRM were due to pneumonia/sepsis (n = 4), cardiogenic shock (n = 1), GVHD (with or without infection; n = 2), or unknown causes (n = 2), and all occurred within 1 year of HSCT. Of note, 1 patient received post-transplantation lenalidomide as maintenance therapy and remained in durable remission. The 1 patient who received antithymocyte globulin as part of the transplantation regimen did not relapse.

Outcomes were significantly better in patients who had CR or PR before alloHSCT with a 2-year PFS of 50% and 2-year OS of 58% (5-year PFS and OS of 44% and 58%, respectively), compared with a 2-year PFS and OS of 0% in patients who were refractory to pretransplantation therapy (P = .0463 for PFS; P = .0144 for OS) (Figure 2). Patients who were primary refractory to initial therapy (n = 16) did not have significantly different PFS than patients who had a CR with upfront therapy (2-year PFS, 44% versus 31%; P= .33). There was also no significant difference in PFS according to conditioning intensity (P = .47); however, the comparison was limited by the small number of patients (n = 4) who received an MAC conditioning regimen and 2 early NRM events in the MAC group. In the group of 8 patients who proceeded directly to alloHSCT without previous autoHSCT (6 receiving an RIC regimen), 5 had early NRM, 1 relapsed within 5 months after alloHSCT, and 2 patients remained in durable remission (1 chemorefractory with salvage RT before transplantation, the other in PR to third salvage RT before transplantation).

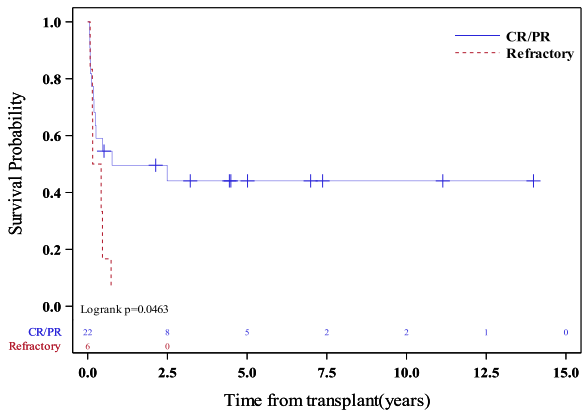

Figure 2. PFS in patients with sensitive versus refractory PMBCL at alloHSCT.

Nine patients (32%) relapsed or progressed after alloHSCT. In these 9 patients, the 2-year OS from the time of relapse/progression was 33%. Out of 4 patients who were receiving immunosuppression at the time of relapse, 3 exhibited a reduction in disease burden with immunosuppression taper. Of the 5 patients treated with systemic therapy after relapse, 4 had an objective response to a postrelapse regimen. One patient had a short-lived response to rituximab, and another patient had a CR to bendamustine with rituximab followed by donor lymphocyte infusion (DLI) and then a CR to brentuximab vedotin after a relapse. A third patient had rituximab with gemcitabine and oxaliplatin and sequential DLI followed by proton beam radiation, all in rapid sequence, resulting in a CR that lasted approximately 1 year and followed by a sustained CR to brentuximab vedotin. One patient had a brief response to high-dose methotrexate for central nervous system relapse and then progressed. One patient received post-relapse RT but did not respond. As mentioned above, 2 patients underwent DLI after relapse, and both developed subsequent GVHD. The patient who received sequential chemotherapy, DLI, and RT achieved a CR that lasted for approximately 1 year, whereas the other patient received DLI in CR and ultimately progressed within 4 months. Three patients who relapsed died without receiving subsequent therapy. No patients received PD-1 blockade or CAR T cell therapy at the time of data retrieval.

DISCUSSION

In our retrospective, multicenter study, to our knowledge the largest study published to date evaluating alloHSCT outcomes in patients with PMBCL, alloHSCT produced durable remission in a subset of heavily treated patients with rel/ref PMBCL. As commonly observed in the setting of transplantation, patients with refractory disease at the time of alloHSCT had dismal outcomes (0% PFS and OS at 2 years), whereas patients with sensitive disease had significantly better PFS and OS (2-year and 5-year PFS/OS of 50%/58% and 44%/58%, respectively). Based on these findings, patients with rel/ref PMBCL who do not exhibit an objective response to salvage therapies do not appear to be appropriate candidates for alloHSCT. Of note, some patients with refractory disease who never proceeded to or relapsed after autoHSCT but were ultimately responsive to salvage therapy and later underwent alloHSCT did achieve long-term remission.

In addition to the sizeable proportion of patients with treatment-sensitive PMBCL who remained in durable remission after alloHSCT, a number of observations from this analysis speak to the potential utility of alloHSCT in these patients. Among the patients who underwent transplantation after responding to pretransplantation therapy and despite the use of PET to evaluate most patients, 21 patients were only in PR at the time of transplantation compared with only 1 who was in CR. Although it can be difficult to discern between residual disease and inflammation and fibrosis in patients with PMBCL [23-25], our findings suggest that alloHSCT as a therapeutic strategy need not be limited to patients with PMBCL in CR. The great majority of patients in our cohort underwent RIC alloHSCT, and all of the patients who achieved durable remission were in only PR at the time of transplantation, supporting the idea of a graft-versus-lymphoma (GVL) effect in PMBCL. In addition, the reductions in tumor burden after immunosuppression taper in patients with post-transplantation relapse as well as the response observed with concurrent GVHD after DLI provide further support that there is GVL in PMBCL. However, it should be noted that this patient received sequential chemotherapy, RT, and DLI, making it difficult to ascertain which

therapy led to the response. Aside from the possible GVL effects that we observed, the responses produced by systemic therapies following post-transplantation relapse and the relatively favorable survival observed in PMBCL patients with post-transplantation relapse were notable and may indicate that the prognosis associated with post-alloHSCT relapse might not be as poor as with other aggressive hematologic malignancies.

Our study has some limitations, including its retrospective nature and the small number of patients included in the analysis. We report outcomes of alloHSCT in patients who underwent transplantation over a long period that resulted in heterogeneity in transplantation practices and precludes an in-depth subgroup analysis of prognostic factors for HSCT outcomes. Nevertheless, although the number of patients who received a MAC regimen in our cohort was small, owing to the higher NRM observed and favorable outcomes observed in patients who received an RIC regimen, there does not appear to be a role for MAC in patients with PMBCL. The rate of NRM in this study was higher than would be expected in a mostly RIC cohort. The deaths due to GVHD would be expected after alloHSCT; however, the deaths due to pneumonia with associated respiratory failure may be related to the disease site and type of treatment received by these patients (eg, mediastinal RT). Based on the time period in which most patients included in this study underwent transplantation, this analysis did not include any patients who underwent haploidentical alloHSCT, which in recent years has become the donor source in a sizeable proportion of patients undergoing alloHSCT. It should be noted that our cohort also did not include any patients who received previous PD-1 blockade or CAR T cells, which are being increasingly incorporated into the treatment of patients with PMBCL. In the future, it will be important to study the potential impact of those therapies on the outcomes of patients who subsequently undergo allogeneic HSCT.

In recent years, with the growing evidence supporting PD-1 blockade and CAR T cells as effective treatment options for PMBCL, the treatment paradigm for patients with rel/ref PMBCL is in flux. Although follow-up times are relatively short in the available data on the use of these agents for PMBCL, there is a strong suggestion that a sizeable proportion of patients will experience a durable remission. Roughly 30% to 40% of patients with PMBCL who receive CAR T cell therapy remain in ongoing response at a median follow-up of >2 years, whereas 21% to 33% of patients with PMBCL treated with PD-1 blockade will achieve CR and at a median follow-up of 29 months, all patients with CR have remained in remission [13,16]. In our cohort, approximately one-half of the patients who had treatment-sensitive rel/ref PMBCL were cured with alloHSCT.

In clinical practice, it will be challenging to decide how to sequence these effective novel agents and how to incorporate potentially curative alloHSCT in the treatment of patients with rel/ref PMBCL. Although many patients will enter remission with CAR T cell or PD-1 blockade therapy, only a minority of patients with rel/ref PMBCL treated with either therapy will experience a sustained remission. Data on outcomes in patients with PMBCL who relapse after CAR T-cells or PD-1 blockade are limited; in these patients, it might not be possible to achieve another remission to ultimately proceed to alloHSCT. Further investigation is necessary to determine the optimal timing for alloHSCT in the setting of novel therapies for PMBCL, either as consolidation in remission after the receipt of novel therapies or as part of a post-novel therapy relapse strategy. Nevertheless, our findings may help guide decision making in individual patients with rel/ref PMBCL who achieve remission with salvage therapies, including PD-1 blockade or CAR T cells.

Based on the sizeable proportion of patients in our cohort who experienced sustained remission, alloHSCT should be considered in the management of eligible patients with rel/ref PMBCL who are unable to proceed to or fail autoHSCT and are sensitive to salvage therapies. Likewise, due to the dismal outcomes in patients with stable or refractory disease to pretransplantation salvage therapy observed in our study, patients who do not have an objective response to salvage therapies should be considered for novel therapeutic options rather than alloHSCT.

DECLARATION OF COMPETING INTEREST

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