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Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM)—Campath Allogeneic Stem Cell Transplantation for Aggressive Non-Hodgkin Lymphoma: An Analysis of Outcomes from the British Society of Blood and Marrow Transplantation

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The role of allogeneic stem cell transplantation (SCT) in the management of aggressive non-Hodgkin lymphoma (NHL) remains to be defined, but the number of procedures performed continues to increase. We report here the outcomes of allogeneic SCT using carmustine, etoposide, cytarabine, and melphalan (BEAM)-Campath (Genzyme Corporation, Cambridge, MA) conditioning for aggressive NHL as reported to the British Society of Blood and Marrow Transplantation (BSBMT). This retrospective study identified 46 patients who reported to the BSBMT registry as having undergone BEAM-Campath conditioned allogeneic SCT for aggressive NHL between 1999 and 2010. Disease histology was diffuse large B cell lymphoma (DLBCL, n = 25), DLBCL/Burkitt lymphoma (n = 5), and T cell lymphoma (n = 16). At diagnosis, the median age was 42.5 (range, 17 to 59), 37 had advanced stage disease (Ann Arbor III/IV), 28 had 2 or more extra-nodal sites of disease, and 23 had elevated lactate dehydrogenase. International prognostic index was high or high/intermediate in 58%. The median number of prior therapies was 3 (range, 1 to 5) and 5 patients had previously undergone transplantation (4 autologous, 1 allogeneic). The median age at transplantation was 44.8 (range, 18 to 59), with 34 patients demonstrating chemo-sensitive disease and 22 undergoing transplantation in first response. Performance score was good in 40 patients and all engrafted with a median of 14 days (range, 11 to 27) to neutrophil recovery. At latest follow-up, 20 patients were alive with 17 in complete remission. Acute graft-versus-host disease (GVHD) developed in 7 patients and chronic GVHD developed in 13 (7 limited, 6 extensive). Five patients died from nonrelapse causes, with a cumulative incidence of nonrelapse mortality of 7% at 100 days and 11% at 3 and 5 years. Twenty-one patients died after lymphoma relapse, with a cumulative incidence of relapse/progression of 51% at 1 year and 53% at 5 years. Disease status at transplantation had no impact on relapse rate. Progression-free survival was 41% at 1 year and 36% at 5 years. Overall survival was 54% at 1 year and 42% at 5 years. Overall, BEAM-Campath–conditioned allogeneic SCT is well tolerated and able to deliver durable disease-free survival to a subset of patients with aggressive NHL. However, the high relapse rates indicate further investigation is needed to identify those patients most likely to benefit.

INTRODUCTION

Aggressive histology non-Hodgkin lymphoma (NHL) includes high-grade B cell lymphomas and peripheral T cell lymphomas (PTCL), which have the potential to be cured with combination chemotherapy.

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Although outcomes for patients with diffuse large B cell lymphoma (DLBCL) have improved with the addition of rituximab to initial chemotherapy [1,2], a significant minority of patients still experience relapse [3,4]. The role of high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) in relapsed disease was established in the pre-rituximab era [5]. However, those relapsing after or refractory to immuno-chemotherapy have a poor outcome with conventional salvage followed by HDT/ASCT [6].

PTCL comprise a heterogeneous group of NHL that tend to have more aggressive disease characteristics at presentation than their B cell counterparts. With the exception of anaplastic lymphoma kinase–positive anaplastic large cell lymphoma, the outcomes with anthracycline-based chemotherapy are worse than those for B NHL and the gold standard front-line combination chemotherapy remains to be defined [7-9]. The overall poor prognosis for patients with PTCL has led to use of HDT/ASCT to consolidate first responses [10-12], with more promising results.

The role of HDT/ASCT in the management of patients with aggressive NHL is clearly changing and alternative strategies are required in the management of some patients with high-risk features and those with relapsed disease. Although the optimal role for allogeneic stem cell transplantation (SCT) remains to be established in aggressive NHL, the number of procedures performed has significantly increased in recent years [13]. Allogeneic SCT offers the advantages of a tumor-free graft, the potential for a donor-derived immune cell–mediated graft-versus-lymphoma (GVL) effect, and a lower risk of relapse when compared with ASCT [14]. Concern over the risk of nonrelapse mortality (NRM) with conventional myeloablative regimens in aggressive NHL has led to the introduction of reduced-intensity conditioning (RIC) with variable success [15-17].

The less-intensive RIC regimens rely on the potential GVL effect for long-term disease control, but the evidence to support such an effect is less compelling in aggressive NHL than in low-grade disease [18]. Therefore, the antilymphoma efficacy of the conditioning chemotherapy is an important consideration in the development of such regimens. The BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen is widely used to condition ASCT with efficacy and acceptable toxicity and is more intensive than other RIC approaches with the potential for improved disease control [15]. In the United Kingdom, BEAM is commonly combined with the anti-CD52 monoclonal antibody Campath (Genzyme Corporation, Cambridge, MA), which is sufficiently immunosuppressive to allow donor stem cell engraftment, to condition patients with lymphoproliferative disease before allogeneic SCT [19,20]. We report here the outcome of patients with aggressive NHL conditioned with BEAM-Campath before allogeneic SCT as reported to the British Society of Blood and Marrow Transplantation (BSBMT).

METHODS

Data Collection and Study Population

The patients analyzed in this study were retrospectively identified from the BSBMT registry. The BSBMT is responsible for the collection and coordination of data submission on all transplantations performed by the 55 member centers in the United Kingdom and the Republic of Ireland each year and ensures that annual follow-up data on all patients are submitted to the registry. It is also responsible for the submission of data on all United Kingdom transplantations to the European Group for Blood and Marrow Transplantation.

The study population included all adult patients (>18 years) with a diagnosis of aggressive histology NHL who had received a BEAM-Campath–conditioned allogeneic SCT in a UK center as reported to the BSBMT between 1999 and 2010. The analysis identified 46 patients who underwent transplantation at 6 UK centers. All patients received carmustine (BCNU) 300 mg/m^2 on day −6, etoposide 200 mg/m^2 on days −5 to −2, cytarabine 400 mg/m^2 on days −5 to −2, and melphalan 140 mg/m^2 on day -1 together with Campath-1H (alemtuzumab) 10 mg (n = 44) or 20 mg (n = 2) on days −5 to −1. Cyclosporin was administered for 90 days after transplantation for graft-versus-host disease (GVHD) prophylaxis.

Endpoints and Definitions

The primary aim of this study was to report the outcomes of patients with aggressive NHL after BEAM-Campath–conditioned allogeneic SCT. The analysis included patient and disease characteristics; transplantation characteristics; time to neutrophil engraftment; and incidences of acute and chronic GVHD, NRM, relapse, progression-free survival (PFS), and overall survival (OS). Histologic diagnosis was based on local review, classified according to the World Health Organization criteria [21]. Disease status was defined according to International Workshop criteria for NHL [22]. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $\geq .5 \times 10^9$/L. Acute and chronic GVHD were defined and graded as per published criteria [23,24]. The incidence of chronic GVHD was calculated in patients surviving beyond 100 days and classified as none, limited, or extensive. NRM was defined as death from any cause without evidence of progression/relapse of lymphoma. Relapse was defined as disease progression after a complete remission (CR). PFS was measured from the time of transplantation to relapse (patients in CR), progression (patients in partial remission), death from any cause, or last follow-up. OS was defined as the time from transplantation to the date of death from any cause or last follow-up.

Statistical Analysis

Patient, disease, and transplantation characteristics (Tables 1, 2) were recorded with the median and range for continuous variables and percentage for categorical data. Cumulative incidence estimates were used for NRM and relapse. PFS and OS estimates were calculated using the Kaplan Meier method. Patient, disease, and transplantation characteristics were studied for associations with patient outcomes by univariate analysis and multivariate analysis using the log-rank test and Cox regression analysis respectively.

RESULTS

Patient and Transplantation Characteristics (Tables 1, 2)

The analysis identified 46 patients with a median age at diagnosis of 42.5 years. Disease histology included DLBCL, DLBCL/Burkitt's lymphoma, and PTCL with 13 patients

Table 1
Patient and Disease Characteristics

Characteristic	Value
No. of patients	46
Diagnosis	
DLBCL	25
DLBCL/Burkitt's lymphoma	5
Peripheral T cell lymphoma NOS	13
Anaplastic large cell lymphoma	2
Angioimmunoblastic T cell lymphoma	1
Sex (male/female)	27/19
Age at diagnosis, median (range), yr	42.5 (17-59)
Stage at diagnosis, n	
I/II	4
III/IV	37
Unknown	5
B symptoms	32
Prior lines of therapy, median (range)	2.5 (1-5)
Prior transplantation	5
Autologous	4
Allogeneic	1
Diagnosis to transplant, median (range), yr	.9 (.25-13.9)
Disease status at transplantation	
CR	15
Partial remission/VGPR	19
Primary refractory	4
Relapsed	7
Unknown	1

NOS indicates not otherwise specified; VGPR, very good partial remission.

Table 2
Transplantation Characteristics

Characteristics	Value
Age at transplantation, median (range), yr	44.8 (18-59)
Donor relationship	
Matched sibling	32
Matched unrelated donor	11
Mismatched unrelated	3
Stem cell source	
Peripheral blood stem cells	42
Bone marrow stem cells	4
Performance status at transplantation	
Karnofsky > 80	40
Karnofsky < 80	2
Unknown	4
CMV serostatus at transplantation, n (%)	
Recipient negative/donor negative	15 (33)
Recipient positive/donor negative	13 (28)
Recipient negative/donor positive	5 (11)
Recipient positive/donor positive	12 (26)
Unknown	1 (2)

having transformed from another subtype of lymphoma. Of the DLBCL/Burkitt's lymphoma patients, 1 was classified as Burkitt lymphoma and 4 as high-grade B cell lymphoma/Burkitt-like lymphoma, and all underwent transplantation at first relapse. At the time of diagnosis, 37 patients had advanced stage (Ann Arbor III/IV) disease, 28 had 2 or more extra-nodal sites of disease, and 23 elevated lactate dehydrogenase. The international prognostic index was high or high-intermediate in 58% of evaluable patients. A median of 2.5 prior lines of therapy had been received by the study population, with 11 of the 29 patients with B cell NHL having been previously exposed to rituximab. Five patients had undergone a prior transplantation procedure (4 autologous, 1 allogeneic).

The median age at the time of transplantation was 44.8 years, with a median time from diagnosis to transplantation of .9 years. At the time of allogeneic SCT, 34 patients demonstrated chemo-sensitive disease, with 22 undergoing the procedure in first response. The majority of patients in this study, 41 out of 46, underwent allogeneic SCT as their first transplantation procedure because they were considered to have a poor outlook with HDT/ASCT. All patients who underwent transplantation in first response were refractory to front-line therapy and those who underwent transplantation at first relapse had progressed early and/or been refractory to initial salvage therapy. The Karnofsky performance score was good (>80) in 40 of the 46 patients at transplantation. Peripheral blood stem cells were mobilized using granulocyte colony–stimulating factor from 42 donors, with the remaining 4 donors providing bone marrow stem cells. The donors were HLA-identical siblings (10/10), HLA-identical volunteer unrelated donors (VUD) (10/10), or HLA-mismatched VUD (9/10). No patient received a transplant from a donor with more than 1 antigen mismatch. Cytomegalovirus (CMV) status was matched between donor and recipient in 27 transplantations and was unknown in 1.

Engraftment, GVHD, and Toxicity

No patient experienced primary graft failure, with all 46 engrafting with a median time to neutrophil recovery of 14 days (range, 11 to 27). Donor lymphocyte infusion (DLI) was subsequently used in 10 patients; 4 received DLI for mixed chimerism, 5 for treatment failure, and 1 for an unknown indication. Eight patients experienced late graft failure; 4 received sibling donor cells and 4 VUD transplants, and 5 of these donors were male. Acute GVHD of grade II to IV occurred in 7 patients (15%) and was the primary cause of death in 1 patient. Chronic GVHD occurred in 13 of the 37 patients (35%) surviving beyond 100 days after transplantation and was limited in 7 patients and extensive in 6. There were 4 other transplantation-related deaths, with 3 due to infectious causes (1 bacterial and fungal, 1 fungal, and 1 viral) and 1 due to respiratory failure. CMV reactivation was identified in 7 patients. A total of 5 patients died of transplantation-related causes with the cumulative incidence of NRM of 7% at 100 days and 11% (95% confidence interval [CI], 2% to 20%) at 3 and 5 years after transplantation (Figure 1). The univariate analysis identified that NRM was significantly higher for those with a poor performance status, a VUD, a prior transplantation procedure, and for those exposed to 3 or more prior lines of therapy. The 3-year NRM for sibling donor transplant recipients was 3% versus 30% for VUD transplant recipients, $P = .042$ (Figure 2). Performance status and donor type remained significant in terms of NRM on the multivariate analysis (Table 3).

Relapse, PFS, and OS

At last follow-up, 20 patients were alive with 17 in CR. The remaining 26 patients had died: 21 after lymphoma relapse (20 from progressive lymphoma and 1 with viral encephalitis) and 5 from NRM. The cumulative incidence of lymphoma progression/relapse at 1 and 5 years after SCT was 51% and 53% (95% CI, 38% to 68%), respectively (Figure 3). Chimerism levels were available for 14 of the relapsing patients and did not predict relapse, with 8 having full donor chimerism and 6 having mixed chimerism. DLI was given to 5 of the patients with lymphoma relapse: 1 achieved a CR and the others did not respond.

Relapse was associated with use of a sibling donor in the univariate analysis (5-year relapse rate 63% versus 31%, $P = .047$) but not in the multivariate analysis. PFS was 41% and 36% at 1 and 5 years after SCT, respectively (Figure 4), with a trend towards longer PFS in patients < 45 years of age (5-year PFS, 51% versus 22%, $P = .06$). The 100-day mortality rate was 20% with OS of 54% at 1 year and 42% (95% CI, 28% to 56%) at 5 years (Figure 5). OS was improved in CMV-negative

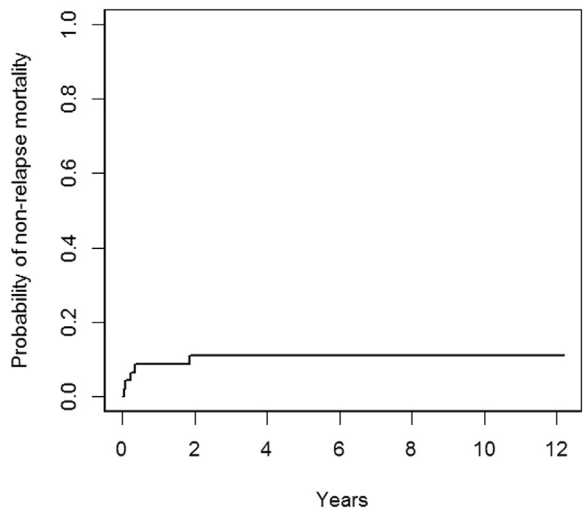

Figure 1. NRM after allogeneic transplantation with BEAM-alemtuzumab conditioning for NHL.

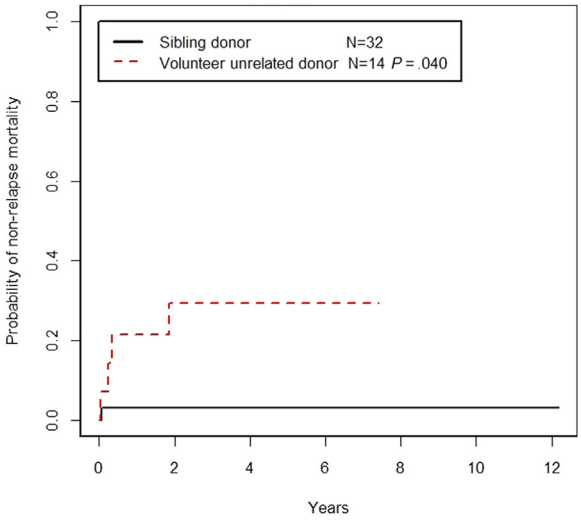

Figure 2. NRM after allogeneic transplantation with BEAM-alemtuzumab conditioning for NHL by type of donor.

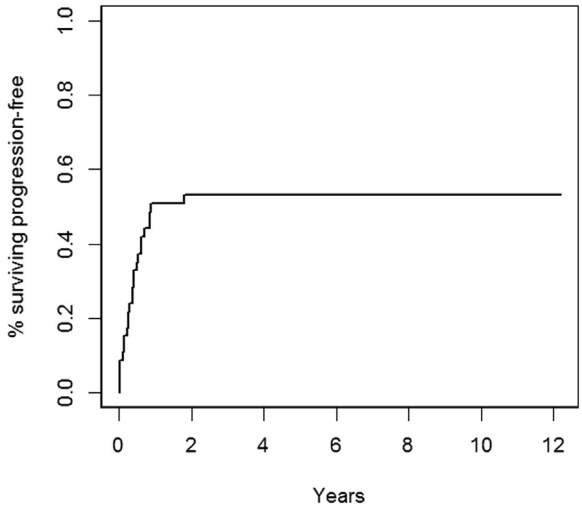

Figure 3. Relapse rate after allogeneic transplantation with BEAM-alemtuzumab conditioning for NHL.

patients with CMV-negative donors (5-year OS, 67% versus 31%, $P = .028$), but this lost significance in the multivariate analysis. Disease status at transplantation had no impact on relapse rate, PFS, or OS.

DISCUSSION

Allogeneic SCT is a potentially curative therapy in the management of aggressive NHL and the use of RIC regimens has increased the number of patients eligible for this approach. The BEAM regimen has been shown to be effective lymphoma therapy with low toxicity when used to condition both autologous and allogeneic SCT for lymphoproliferative disorders [19,20,25]. The addition of Campath in the allogeneic setting provides sufficient immunosuppression via T cell depletion to facilitate engraftment while reducing the risk of GVHD [16,19,20].

This retrospective analysis of the United Kingdom's experience of BEAM-Campath–conditioned allogeneic SCT for aggressive NHL confirms that the procedure is well tolerated with acceptable levels of toxicity. We included all patients with aggressive histology NHL, both B and T phenotype, as this is the patient population with high-grade lymphoproliferative disorders in whom the BEAM-Campath regimen is employed and historical data on allogeneic SCT has tended to analyze these histologies as a group. Overall, the outcome for the 46 patients identified in this analysis is a 5-year PFS of 36% and OS of 42%. These outcomes are comparable to those reported from other registry data as well as those from series of relapsed/refractory aggressive NHL patients, which included myeloablative transplantations [26-29]. The outcomes reported here also compare favorably with those reported for fludarabine-based RIC allogeneic SCT in aggressive NHL with 2 to 3-year OS ranging between 34% and 47% [15,16]. The main barrier to transplantation success in this cohort was relapsed disease, with a cumulative incidence of 53% at 5 years. High relapse rates have been a consistently reported feature with RIC regimens in aggressive NHL [15,16]. Lymphocyte recovery and, hence, immune reconstitution are delayed after T cell depletion with Campath-containing regimens [30]. This has resulted in concerns regarding the risk of relapse due to the likely negative impact on the potential for a GVL effect when T cell depletion is incorporated into RIC protocols [17]. Morris et al. identified disease status at transplantation as having a significant impact on outcome in transplantations incorporating T cell depletion [16]. RIC allogeneic SCT with T cell depletion places a greater emphasis on lymphoma control in the pretransplantation setting and after transplantation with the use of immunotherapeutic interventions. There is evidence to support a GVL

Table 3
Multivariate Analysis

Risk Factor	HR	95% CI	*P* Value
No. of prior lines	.964	.335-2.776	.946
Performance status at Tx	4.804	3.653-6.320	**.001**
Donor	∞	-	**.001**
Prior transplantation	5.267	.218-127.5	.307

HR indicates hazard ratio; Tx, treatment.
Bold indicates statistical significance.

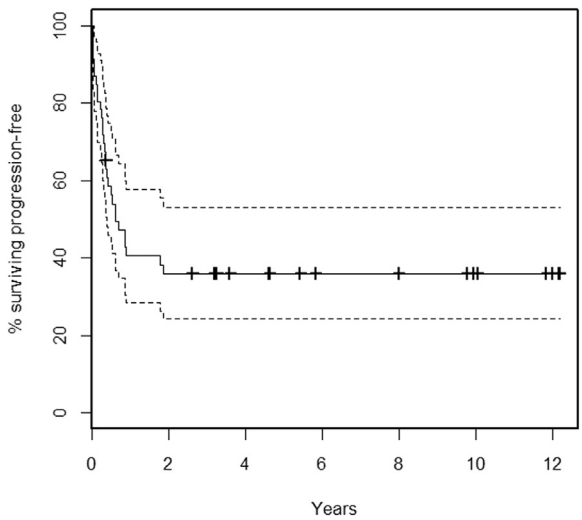

Figure 4. PFS after allogeneic transplantation with BEAM-alemtuzumab conditioning for NHL.

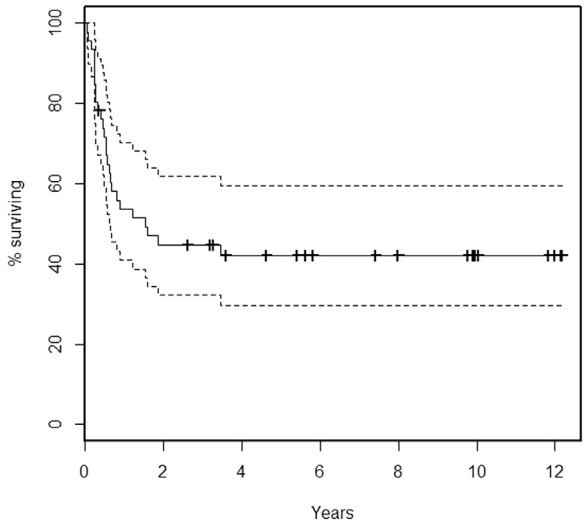

Figure 5. OS after allogeneic transplantation with BEAM-alemtuzumab conditioning for NHL.

effect in DLBCL with responses to reductions in immune suppression and DLI reported and long-term disease control achieved [14,31,32]. The observation that RIC allogeneic SCT can achieve durable disease control in patients who have relapsed after a previous ACST is further evidence of a GVL effect in aggressive NHL [33]. In this series, a complete response to DLI was seen in 1 of the 5 patients treated for relapse/progression. The rapid growth kinetics of aggressive NHL may allow the malignant clone to escape the potential GVL effect and, at least in part, explain the higher relapse rates seen after allograft when compared with indolent histologies [34].

Although relapse was problematic in this series, there was no association with disease status at transplantation, a finding consistent with a previous multi-center report of BEAM-Campath–conditioned transplantations [19]. In fact, no variable was found to be significantly associated with an increased relapse risk, with the association with use of a sibling donor losing significance in the multivariate analysis. This may reflect the impact of improved lymphoma control in a subset of patients exposed to BEAM, given that other series of reduced-intensity transplantations in aggressive NHL have consistently associated refractory disease at transplantation with inferior outcomes [35,36]. An alternative explanation, however, is that the number of patients is too small to enable identification of this effect. A prior autologous transplantation procedure has also been associated with increased risk of relapse and reduced OS in NHL patients undergoing allogeneic transplantation [37]. In the current series, only 4 patients had previously undergone HDT/ASCT, preventing any conclusions regarding the impact of prior transplantation on outcomes. In this cohort, there was a trend towards improved PFS in younger patients (<45 years) and OS in transplantation with a CMV-negative donor and recipient.

A previous study reported that T cell depletion did not influence the risk of infection or death from infection [15]. In the current series, we observed a low rate of infectious deaths. The NRM was 11% at 5 years, with infection implicated in 3 deaths from NRM and in 1 patient with encephalitis after relapse. CMV reactivation was documented in 7 patients. Poor performance status, as might be expected, and use of a VUD were associated with an increased risk of NRM. The increased risk associated with use of a VUD is not explained in this cohort by excessive GVHD. Acute GVHD (grade II to IV) occurred in 15% of patients and was the primary cause of death in 1. In keeping with other retrospective registry data, we failed to identify any correlation between GVHD and risk of relapse, PFS, or OS [18,38,39]. This could suggest that the GVL effect may exert lymphoma control independent of GVHD, or perhaps that, in some patients, the efficacy of the conditioning regimen is responsible for disease control. The unfavorable prognostic impact of T cell phenotype when compared with aggressive B cell NHL can be overcome by allogeneic SCT, with reduced relapse rates and comparable OS reported [17,40,41]. Such data provide support for the existence of GVL-mediated disease control in PTCL. We observed no difference in terms of outcome or relapse dependent on cell of origin seen in the current series.

As improvements in initial therapy for DLBCL have resulted in selection of more aggressive/chemo-resistant clones at relapse, allogeneic SCT may become increasingly important in the management of patients failing first-line therapy. Given the poor outcome of patients with DLBCL refractory to or progressing within 12 months of immunochemotherapy, eligible candidates are already considered for allogeneic SCT as their first transplantation procedure. Prospective trials comparing the outcome of autologous and allogeneic SCT in this setting are needed to allow conclusions to be drawn. There is also a need to better identify the subgroups of patients with high-risk disease who would benefit from an allogeneic procedure as their first transplantation, given that < 20% of those relapsing after an autologous transplantation actually receive an allogeneic SCT [18]. The role of allogeneic SCT in the first-line treatment of PTCL is currently being investigated in a large European prospective study (DSHNHL trial).

There remains a need to optimize conditioning regimens based on patient and disease characteristics to improve efficacy while minimizing toxicity. There is also a role for incorporation of novel agents and maintenance strategies after transplantation to reduce relapse risk before the emergence of a GVL effect.

The retrospective nature of this analysis of patients who underwent transplantation over a time period in which the role of transplantation in aggressive NHL has constantly evolved makes drawing firm conclusions difficult. Overall, the data presented here support BEAM-Campath conditioning before allogeneic SCT as a regimen that is well tolerated in patients with aggressive NHL and capable of delivering durable remissions in a subset of patients. The high relapse rate is indicative that further investigation is needed to allow identification of those patients most likely to benefit.

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