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T-cell-depleted allogeneic transplant without donor leukocyte infusions results in excellent long-term survival in patients with multiply relapsed Lymphoma. Predictors for survival after transplant relapse

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Abstract

We analyzed 67 patients with lymphoma who received alemtuzumab-based conditioning regimens for allogeneic stem cell transplant and no post-transplant DLI. The median age was 54 (24–70), 43% had unrelated donors, 34% had chemotherapy refractory disease, and 25% had an elevated LDH. With a median follow-up for survivors of 35 months, the estimated 3-year progression-free survival (PFS) and overall survival (OS) were 30% and 47%, respectively. Chemosensitivity by CT and pre-transplant LDH were independent prognostic factors for both overall survival and progression-free survival. Patient age, performance status, donor type, lymphoma subtype, disease sensitivity by PET, and conditioning regimen did not correlate with PFS and OS. Patients who relapsed greater than 6 months after allogeneic transplant were frequently able to re-enter a subsequent durable remission. Our experience confirms the curative potential of alemtuzumab-containing RIC regimens for allogeneic HCT in patients with relapsed lymphoma without prophylactic DLI. An elevated pre-transplant LDH and chemorefractory disease prior to transplant confer a worse prognosis, while PET scan findings do not have this same implication. Patients who relapse greater than 6 months after their transplant are likely to achieve a subsequent remission with any of a variety of interventions, suggesting that GVL effects can be operative even after recurrence. Our outcomes challenge the utility of the common practice of prophylactic DLI after T-depleted transplant for lymphoma.

Keywords

Lymphoma; Alemtuzumab; Allogeneic HCT; LDH; Chemosensitivity

Introduction

Allogeneic hematopoietic stem cell transplant (allo-HCT) is an established treatment in the management of patients with relapsed lymphomas either as an alternative to autologous

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transplant or in patients who have failed prior autologous transplant. While some patients are cured after allo-HCT, disease recurrence, regimen related mortality, and graft-versus-host disease (GVHD) constitute ongoing obstacles, and there is a need for the development of safer and more effective transplant approaches [1–3].

This analysis evaluates the outcomes of 67 consecutive patients with relapsed Hodgkin and non-Hodgkin lymphomas treated at the University of Chicago between November 2001 and June 2009, using alemtuzumab-containing conditioning regimens. Alemtuzumab depletes recipient and incoming donor T cells; this has been shown to improve engraftment while significantly decreasing the risk for GVHD [4–7]. Our initial study used fludarabine, melphalan, and alemtuzumab [8]. In an effort to reduce recurrence rates, we also conducted consecutive prospective studies in which alemtuzumab was combined with busulfan and fludarabine or with clofarabine and melphalan. Others after similar conditioning have administered prophylactic donor lymphocyte infusion (DLI) for those with mixed chimerism, hoping for a beneficial graft-versus-leukemia (GVL) effect [9,10]. Since we have been unable to ascertain a consistent relationship between mixed chimerism and relapse, we did not use prophylactic DLI, although, like others, we routinely observe mixed chimerism after alemtuzumab-based conditioning [11]. We describe outcomes and predictors of outcome, and also report the further course in patients relapsing after an allo-HCT, a situation in which durable secondary remissions were often observed.

Patients and methods

Patient inclusion

All patients with a diagnosis of relapsed or refractory lymphoma who received an allo-HCT with an alemtuzumab-containing conditioning regimen at the University of Chicago between November 2001 and June 2009 were included. Conditioning regimens included FMC: fludarabine 30 mg/m² intravenously (IV) daily from day –7 to day –3, melphalan 140 mg/m² IV on day –2, and alemtuzumab [8]; CMC: clofarabine 30–40 mg/m² IV daily from day –7 to day –3, melphalan 140 mg/m² IV on day –2, and alemtuzumab [12]; FBC: fludarabine 25 mg/m² IV daily from day –7 to day –3, busulfan based on area under the curve (AUC), and alemtuzumab [13]; and TBCC: thiotepa 150–250 mg/m² IV daily from day –9 to day –7, busulfan 1 mg/kg orally every 6 h from day –6 to day –4, cyclophosphamide 60 mg/kg IV on days –3 and –2, and alemtuzumab [3]. The alemtuzumab dose was 20 mg daily from day –7 to day –3 in all patients. GVHD prophylaxis consisted of single-agent tacrolimus in all patients, routinely until day 100 in recipients of matched related transplant, and until day 180 in recipients of matched unrelated or mismatched graft. Fifty-five of the 67 patients participated in prospective studies. Twelve patients were treated off-protocol with FMC or TBCC, either for insurance reasons or because of comorbidities that precluded enrollment on the available clinical trials. Patients treated off-protocol provided informed consent for collecting and reporting their outcome data.

Donors were related or unrelated, with no more than a one-antigen mismatch after considering human leukocyte antigens HLA-A, -B, -C, and -DRB1. Patients and donors for unrelated donor transplant were typed for the HLA-A, -B, -C, and -DRB1 loci by molecular sequencing techniques.

Infection prophylaxis and supportive care

Patients who were cytomegalovirus (CMV) seropositive or had a CMV-seropositive donor were given ganciclovir 5 mg/kg from day –8 until day –3 followed by acyclovir 10 mg/kg IV every 8 h until discharge. At discharge, the vast majority of patients were given valacyclovir 2000 mg orally four times daily until day 210 [14]. CMV-negative donor/

recipient pairs received routine acyclovir prophylaxis. All patients were screened weekly for CMV viremia until day 120 and treated with ganciclovir or valganciclovir on detection of CMV viremia.

Definitions

Overall survival (OS) was defined as the time from transplant to death from any cause, with surviving patients censored at last follow-up. Progression-free survival (PFS) was defined as time from transplant to recurrence, progressive disease, or death, with surviving patients without disease progression censored at last follow-up. Both recurrence and progression were defined as disease progression, with non-relapse death considered as a competing event. Non-relapse mortality (NRM) was defined as death from any cause without previous disease progression, which was considered a competing event. Patients who died from transplant related causes were classified as NRM. Complete remission (CR) by computed tomography (CT) scan was defined as complete resolution of any prior evidence of lymphoma, while partial remission (PR) was defined as at least 50% improvement of the same [15]. Chemosensitive disease was defined as either a CR or a PR, while chemorefractory disease was anything less than this. Definitions of positive or negative positron emission tomography (PET) followed recommendations of the International Harmonization Project in Lymphoma [16].

Statistical analysis

The probabilities of PFS and OS were estimated from the time of transplant using Kaplan–Meier curves and compared using a two-tailed log-rank test. Relapse and non-relapse mortality were calculated using cumulative incidence estimates. STATA (version 10) and SPSS (version 17) were used for statistical analysis.

Variables examined included age, performance status, donor type, lymphoma subtype, pre-transplant lactate dehydrogenase (LDH), and disease responsiveness to salvage chemotherapy by CT and PET. In multivariate analysis, Cox proportional hazards models were used to confirm the significant variables.

Results

Patient characteristics

A summary of patient characteristics is listed in Table I. Median age was 54 years (range, 24–70 years). Thirty-six percent ($n=24$) were under the age of 50. Sixty-one percent ($n=41$) were male, and 39% ($n=26$) were female. Nine had Hodgkin lymphoma (HL), 23 low-grade B-cell NHL (LGL), 16 intermediate-grade B-cell NHL (IGL), one high-grade B-cell lymphoma (HGL), nine mantle cell lymphoma (MCL), and nine T-cell NHL (TCL). For analysis, LGL and MCL were grouped together, since outcomes were not significantly different when these two groups were evaluated separately.

Based on CT scan, 34% ($n=23$) had chemorefractory disease. Twenty-five percent ($n=17$) had an elevated LDH at the time of transplant. Pre-HCT PET (post-salvage chemotherapy) scans were performed in 46 patients and 29 (43% of total cohort) were PET positive. Performance status (PS) was 0 for 46 patients (69%), 1 for 20 patients (30%), and 2 for one patient. Nineteen patients (28%) had failed a prior autologous transplant.

Thirty-nine patients received FMC, 20 received CMC, and eight received busulfan–alemtuzumab based conditioning, either FBC ($n=5$) or TBCC ($n=3$). Donor type was related for 57% ($n=38$) and unrelated for 43% ($n=29$). Of the unrelated donors, 22 were 8/8 HLA matches, whereas seven had a single antigen/allele mismatch.

Progression-free survival and overall survival

With a median follow-up for survivors of 35 months, the estimated 3-year PFS and OS were 30% and 47%, respectively [Figures 1(A) and 1(B)].

Predictors of PFS and OS

Patient age, PS (0 vs. 1), donor type, and conditioning regimen did not correlate with outcome (Table II). Patients with low-grade B-cell NHL and mantle cell lymphoma as a group had a somewhat better PFS and OS than those with other types of lymphomas [Figures 2(A) and 2(B)], but the differences were not statistically significant.

Pre-transplant LDH and disease responsiveness to salvage chemotherapy prior to transplant (as determined by CT scan) were most predictive of outcome. Patients with an elevated pre-transplant LDH had a 3-year PFS of 16% (95% confidence interval [CI], 31–37) compared to 35% (95% CI, 22–49) for those with normal LDH ($p=0.009$). Similarly, 3-year OS was inferior at 35% (95% CI, 14–57) for those with elevated pre-transplant LDH compared to 52% (95% CI, 36–65) for those with normal LDH ($p=0.009$) [Figures 3(A) and 3(B)].

Patients with chemorefractory disease by CT scan had an estimated 3-year PFS of 15% (95% CI, 3–36) compared to 37% (95% CI, 23–52) for those with chemosensitive disease ($p=0.100$), and OS was 15% (95% CI, 3–36%) and 58% (95% CI, 42–71), respectively ($p=0.022$) [Figures 4(A) and 4(B)].

Interestingly, chemorefractory or chemosensitive disease by PET (positive vs. negative, respectively, assessed in 46 patients) did not correlate as strongly with OS or PFS ($p=0.35$ and 0.224 , respectively) [Figures 5(A) and 5(B)]. OS and PFS for patients who did not have a PET scan performed did not vary significantly from those with either negative or positive PET scans (data not shown).

Both LDH and chemosensitivity by CT remained significant in multivariate analyses for both OS ($p=0.002$ and 0.004 , respectively) and PFS ($p=0.004$ and 0.034 , respectively).

Toxicity and GVHD

Eleven patients had grade II–IV acute GVHD, and 11 patients had chronic GVHD (four limited, seven extensive). Twenty patients died of NRM. The most common cause of non-relapse death in patients was infection ($n=9$). Other causes included multiorgan failure ($n=3$), veno-occlusive disease ($n=1$), thrombotic thrombocytopenic purpura (TTP; $n=1$), GVHD ($n=2$), hypovolemic shock ($n=1$), respiratory failure ($n=1$), peritonitis ($n=1$), and therapy related leukemia in the single patient with graft failure followed by autologous reconstitution ($n=1$).

Relapse after allo-HCT

Twenty-seven patients (40%) have relapsed, of whom 16 have died, 12 from lymphoma and four in a subsequent remission from lung cancer, cardiomyopathy, DLI-induced GVHD, and complications of a second transplant. Six patients with a fulminant course at relapse did not receive any treatment and died rapidly. Nineteen patients have received combination chemotherapy regimens either with or without rituximab. In three patients salvage therapy was followed by DLI, and in four by a second allogeneic transplant. Two patients with indolent relapses have not yet required treatment.

Relapse within 6 months after transplant occurred commonly in those with aggressive lymphomas and was associated with a very poor prognosis. The median survival of patients relapsing within 6 months of allogeneic stem cell transplant was only 2.8 months following

relapse, and only two of 12 are long-term survivors. In contrast, relapse more than 6 months after transplant, which occurred in 15 patients, was associated with a median survival of 16.3 months ($p=0.002$, compared with outcome of relapse within 6 months). Nine of 15 remain alive, mostly in remission, and only two deaths are attributed to lymphoma [Figures 6(A) and 6(B)].

Discussion

Allogeneic HCT for relapsed lymphomas remains a high-risk and complex procedure. Novel reduced-intensity conditioning (RIC) regimens may have reduced toxicity, as have improvements in supportive care and donor selection. Still, relapse and mortality relating to GVHD remains a major complication of allo-HCT. Treatment related mortality is further exacerbated in patients with poor performance status, refractory disease, and multiple comorbidities [17], common problems in patients with lymphoma who are typically considered for allogeneic stem cell transplant after failing multiple other approaches.

Alemtuzumab-based conditioning for lymphoma has been studied primarily by groups in the UK, Europe, and South Africa, who have reported that by minimizing GVHD, these regimens may reduce allo-SCT related mortality, possibly with somewhat increased risks for opportunistic infections and disease recurrence [9,18–20]. Some centers have used prophylactic DLI in cases of mixed chimerism in an effort to reduce recurrence rates [9,10]. Similar to the Dana Farber group [21], we have not found that mixed chimerism predicts for disease recurrence [11], and have therefore not used this strategy.

Instead, in an effort to reduce recurrence rates, we have combined alemtuzumab with novel chemotherapy-based conditioning regimens. Here we present combined data on all 67 patients who underwent transplant using one of these regimens at our institution. Estimated 3-year PFS and OS were comparable to those found in patients with non-Hodgkin lymphoma treated with a similar conditioning regimen at 10 centers in the United Kingdom [9,19], those reported by the South African group using ‘Campath in the bag’ [18], or those of another UK group using BEAM (carmustine, etoposide, cytosine arabinoside, melphalan)-alemtuzumab [22]. We thus confirm that alemtuzumab-based conditioning regimens are associated with acceptable toxicity and can lead to durable responses even without the use of prophylactic DLI. This observation challenges the wisdom of the common practice of DLI in patients with mixed chimerism [9]. DLI may convert mixed to full donor chimerism, but at the risk of inducing GVHD.

Identifying simple predictors of response and duration of response is essential for improving treatment. We confirm that chemorefractory disease [23,24] as reflected by CT findings correlates with poor outcomes. In contrast, PET scan negativity did not correlate with outcomes. This contrasts with data of autologous transplant for lymphoma where PET scan has been shown to be predictive of outcome [25–27]. But it is consistent with a recent prospective study conducted at multiple centers in the UK using a fludarabine, melphalan, alemtuzumab conditioning regimen in which pre-transplant PET positivity was not associated with a worse PFS or OS [28]. The authors propose several explanations, including the possibility that PET scan findings may not have affected outcome due to the relatively low number of patients in each lymphoma subtype category, or the possibility that the conditioning regimen and/or the GVL effect associated with allogeneic HCT may have resulted in eradication of PET positive residual disease. In addition to these explanations, the inability to ‘standardize’ findings on a PET scan has recently been emphasized as a major limitation of this test [29,30].

Serum LDH, another simple and reproducible measure, was also found to be a powerful predictor of transplant outcome. This is consistent with data from the Dana Farber group, using a non-T-depleted conditioning regimen [21]. It has otherwise rarely been investigated in allogeneic transplant studies, because it is missing from most registry data sets. This is somewhat ironic, since it is a cheap and reproducible assay that has been repeatedly found to have major prognostic value in newly diagnosed and recurrent lymphoma.

Other established prognostic features such as reduction in performance status or disease histology were not confirmed in this analysis. This was probably due to the paucity of patients with PS of 2 and the relatively small number of cases within each histologic subgroup.

The fate and management of patients who relapse after allogeneic stem cell transplant is a final issue of major interest. There is considerable anecdotal evidence of the efficacy of DLI and of second transplant in lymphoma. The large majority of our relapsing patients, however, were treated with chemotherapy and/or monoclonal antibodies. Cellular therapies were used in only a few. Still, durable subsequent remissions were commonly observed particularly in those with late relapses (>6 months after transplant) and/or indolent lymphomas. Chemotherapeutic interventions are less commonly associated with GVHD than are cellular therapies, and may therefore be preferable as a first line of treatment. The frequent occurrence of durable responses to salvage after failure of multiple prior treatments is intriguing. We speculate that GVL effects of residual donor cells are potentiated by the chemotherapy, and that the combination of chemotherapeutic and cellular effects is instrumental in inducing these long-term remissions [31]. This hypothesis obviously warrants confirmation at both the clinical and experimental level.

In summary, we confirm the curative potential of alemtuzumab-containing RIC regimens for allogeneic HCT in patients with relapsed lymphoma, with low rates of GVHD and acceptable toxicity, and without the use of prophylactic DLI. An elevated pre-transplant LDH and chemorefractory disease prior to transplant confer a worse prognosis, while PET scan findings do not have this same implication. Finally, patients who relapse greater than 6 months after their transplant are likely to achieve a subsequent remission with any of a variety of interventions, suggesting that GVL effects can be operative even after recurrence. Based on our findings we question the routine use of prophylactic DLI for patients with mixed chimerism.

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Figure 1. Kaplan–Meier curves. (A) Progression-free survival; (B) overall survival.

Figure 2.
(A) Progression-free survival and (B) overall survival by lymphoma subtype.

Figure 3.
(A) Progression-free survival and (B) overall survival by pre-transplant LDH.

Figure 4.
(A) Progression-free survival and (B) overall survival by chemosensitivity by CT.

Figure 5.
(A) Progression-free survival and (B) overall survival by chemosensitivity by PET.

Figure 6.
Survival after relapse by (A) lymphoma subtype and (B) time to relapse.

Table I

Patient characteristics.

	<i>n</i> (%)
Age	
Median 54 (range 24–70)	
50 years	43 (64)
550 years	24 (36)
Gender	
Male	41 (61)
Female	26 (39)
Conditioning regimen	
Fludarabine/melphalan/alemtuzumab	39 (58)
Clofarabine/melphalan/alemtuzumab	20 (30)
Fludarabine/busulfan/alemtuzumab	5 (7)
Thiotepa/busulfan/cy/alemtuzumab	3 (4)
GVHD prophylaxis	
Tacrolimus	67 (100)
Lymphoma subtype	
HL	9 (13)
Low grade NHL	23 (34)
Intermediate grade NHL	16 (24)
High grade NHL	1 (1)
Mantle cell lymphoma	9 (13)
T-cell NHL	9 (13)
LDH prior to conditioning	
Elevated	17 (25)
Normal	50 (75)
Disease status at transplant by CT	
Chemosensitive	44 (66)
Chemorefractory	23 (34)
PET prior to transplant	
Positive	29 (43)
Negative	17 (25)
Not done	21 (31)
ECOG performance status (PS)	
PS 0	46 (69)
PS 1	20 (30)
PS 2	1 (1)
Donor type	
Related	38 (57)
Unrelated	29 (43)
Prior transplant	

	<i>n</i> (%)
Auto-HCT	19 (28)
Allo-HCT	4 (3)
None	44 (66)

cy, cyclophosphamide; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; LDH, lactate dehydrogenase; CT, computed tomography; PET, positron emission tomography; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic stem cell transplant.

Table II

Univariate analysis of PFS and OS.

	3-year PFS	<i>p</i> -Value (univariate)	3-year OS	<i>p</i> -Value (univariate)
Age				
50	29%	0.345	46%	0.333
<50	34%		50%	
Conditioning regimen				
Fludarabine/melphalan/alemtuzumab	33%	0.356	48%	0.344
Clofarabine/melphalan/alemtuzumab	42%		57%	
Busulfan-containing regimen/alemtuzumab	13%		25%	
Lymphoma subtype				
Hodgkin lymphoma	33%	0.826	33%	0.439
Low grade B-cell NHL/mantle cell	38%		62%	
Intermediate grade B-cell NHL	31%		38%	
T-cell NHL	30%		42%	
LDH				
Elevated	16%	0.009	35%	0.009
Normal	35%		52%	
Disease status at transplant by CT				
Chemosensitive	37%	0.1	58%	0.022
Chemorefractory	15%		29%	
PET prior to transplant				
Positive	26%	0.224	42%	0.35
Negative	45%		57%	
ECOG performance status (PS)				
PS 0	31%	0.617	50%	0.494
PS 1	34%		44%	
Donor type				
Related	26%	0.49	51%	0.28
Unrelated	36%		43%	

PFS, progression-free survival; OS, overall survival; NHL, non-Hodgkin lymphoma; LDH, lactate dehydrogenase; CT, computed tomography; PET, positron emission tomography; ECOG, Eastern Cooperative Oncology Group.