Published in final edited form as:

Leuk Lymphoma. 2014 December ; 55(12): 2739–2747. doi:10.3109/10428194.2014.894185.

A Prospective Study of an Alemtuzumab Containing Reduced-intensity Allogeneic Stem Cell Transplantation Program in Patients with Poor-Risk and Advanced Lymphoid Malignancies

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Abstract

Reduced-intensity conditioning (RIC) regimens for allogeneic stem cell transplantation (allo-SCT) have used alemtuzumab to abrogate the risk of graft-versus-host disease (GVHD). Thirty-eight advanced lymphoma patients underwent a prospective phase II study of melphalan, fludarabine and alemtuzumab containing RIC allo-SCT from 20 matched related and 18 unrelated donors with cyclosporin-A as GVHD prophylaxis. The cumulative incidence of grade II-IV acute GVHD at 3 months was 10.5% and three evaluable patients experienced chronic GVHD. Progression-free (PFS) and overall (OS) survival at 5 years is 25% (95% CI: 13-40) and 44% (95% CI: 28-59%) respectively. Previous high-dose therapy and autologous stem cell transplantation (HDT-ASCT) and elevated LDH at the time of allo-SCT resulted in inferior OS. Within this cohort of high-risk lymphoma patients, alemtuzumab containing RIC resulted in a low risk of GVHD and a high incidence of POD, especially in those with poor-risk features defined by elevated LDH pre-allo-SCT and previous HDT-ASCT.

Keywords

Reduced-intensity; allogeneic transplantation; alemtuzumab; lymphoma

Introduction

Patients with indolent histology B-NHL, and those with aggressive histology B-NHL who have failed high-dose therapy and autologous stem cell transplantation (HDT-ASCT), are considered incurable with combination chemotherapy. While HDT-ASCT remains the standard of care for relapsed and refractory diffuse large B-cell lymphoma (DLBCL)[1], a

recent multi-center prospective study reported that the majority of patients either fail to undergo, or relapse following HDT-ASCT by intent-to-treat[2]. Additionally, while HDT-ASCT has provided prolonged remissions for patients with mantle-cell lymphoma (MCL) [3, 4] and follicular lymphoma (FL) [5], it is still considered non-curative, and concerns of additive toxicity, including myelodysplasia, remain [6].

Previously, allo-SCT with myeloablative conditioning (MAC) and unmodified grafts had demonstrated favorable NHL disease control at the expense of increased transplant-related mortality (TRM) [7, 8]. More recently, unmodified non-myeloablative (NMA) and RIC conditioned allo-SCT have offered favorable NHL control, attributable to graft-versus-lymphoma (GVL) effect [9, 10] and reduced TRM [11-19]. Despite this, graft-versus-host disease (GVHD) remains the largest contributor to transplant-related mortality (TRM) in addition to its negative impact on quality of life. To abrogate this GVHD risk, RIC regimens have incorporated *in-vivo* lymphoid depletion with alemtuzumab [20]. Concerns with T-cell depletion, *in-vivo* or *ex-vivo*, have included risk of progression of disease (POD) and infectious risks post-allo-SCT. Herein, we present results of advanced Hodgkin (HL) and non-Hodgkin (NHL) lymphoma patients treated on a prospective phase II study investigating the integration of alemtuzumab into RIC with fludarabine and melphalan followed by allo-SCT from HLA-matched or mismatched related and unrelated donors.

Materials and Methods

Patients

MSKCC IRB #01-092 was a single center, non-randomized, prospective phase II clinical trial of a RIC regimen of melphalan, fludarabine, and alemtuzumab followed by an unmodified hematopoietic peripheral blood (PBSCT) or bone marrow (BM) allo-SCT from an HLA compatible related or unrelated donor for the treatment of lymphohematopoietic malignancies. We analyzed thirty-eight patients with lymphoid malignancies enrolled on MSKCC IRB # 01-092 for this report. Eligibility criteria for the clinical trial included relapsed or primary refractory non-Hodgkin (NHL) or Hodgkin (HL) lymphoma not otherwise eligible for an allo-SCT with MAC due to: advanced age, poor performance status, end-organ insufficiency, significant comorbidities, or recent HDT-ASCT. Patients with aggressive histology NHL by WHO criteria were required to demonstrate chemosensitivity to salvage therapy prior to allo-HCT or stable disease with ineligibility to proceed to autologous stem cell transplantation because of disease involving bone marrow. Patients were 18-70 years of age and had a fully matched or single HLA-disparate related or unrelated donor at 6-loci (HLA-A, HLA-B and HLA-DR β 1). Eligibility also required: creatinine clearance ≥ 30 cc/minute, total bilirubin ≤ 2.5 mg/dL, AST and ALT $\leq 3 \times$ upper limit of normal, resting left ventricular ejection fraction of $\geq 30\%$, diffusion capacity of carbon monoxide adjusted for hemoglobin of $\geq 40\%$ and a Karnofsky performance status ≥ 40 . There was no limit to number of prior lines of therapy, which included any combination of chemotherapy, immunotherapy, and/or radiation therapy with the intent of inducing remission. Consolidation therapy, such as: monoclonal antibody maintenance, involved-field radiation therapy (IFRT) and/or HDT-ASCT did not comprise previous line of therapy in the analysis.

All patients were required to undergo disease restaging with bone marrow aspiration and biopsy as well as computed tomography cross-sectional imaging of the chest, abdomen, and pelvis within 30 days of beginning conditioning. Disease was assessed per standard International Working Group (IWG) criteria [21] as well as additional criteria for chronic lymphocytic leukemia [22]. The hematopoietic comorbidity index (HCT-CI) was applied to each patient for analysis purposes [23]. Pre-admission lactate dehydrogenase (LDH) and Karnofsky performance status (KPS) were also obtained for analysis purposes

Conditioning and Transplantation Procedure

Alemtuzumab 20 mg and fludarabine 25 mg/m² were administered intravenously daily from day -8 to day -5 for a total dose of 80 mg and 100 mg/m² respectively. Patients with HLA-matched related grafts received melphalan 50 mg/m², while patients with HLA-matched unrelated or HLA-single allele disparate grafts received melphalan 70 mg/m², intravenously daily from day -3 to day -2. Healthy donors underwent G-CSF mobilization at 16 mcg/kg daily for at least 5 days with a targeted CD34+ cell collection of 5×10^6 /kg of recipient body weight. Bone marrow harvests targeted mononuclear cell dose of 2.5×10^8 /kg of recipient body weight.

GVHD Prophylaxis and Supportive Care

GVHD prophylaxis, in addition to alemtuzumab within the conditioning regimen, consisted of cyclosporine-A (CsA) initiated day -1 at a dose of 1.5 mg/kg intravenously every 12 hours with a target trough serum level of 200-300 ng/ml. CsA transitioned to oral formulation by day +30 as tolerated and continued until at least day +100 followed by a rate according to physician discretion. Patients were managed clinically according to MSKCC standard guidelines, including infection prophylaxis. *Pneumocystis carinii* prophylaxis consisted of trimethoprim-sulfamethoxazole or pentamidine if hematopoiesis was compromised. Herpesviridae prophylaxis consisted of acyclovir 400-800 mg/day in divided doses. Fungal prophylaxis routinely consisted of fluconazole 200-400 mg/day and single or divided doses for 30-60 days post-allo-SCT per treating physician. In addition, atovaquone or trimethoprim-sulfamethoxazole was prescribed for prevention of toxoplasmosis infections after transplantation in seropositive patients or those with seropositive donors. Patients received no cytomegalovirus (CMV) specific prophylaxis with ganciclovir or valganciclovir, but CMV seronegative patients received seronegative blood products regardless of the donor's serologic status. CMV reactivation by CMV pp65 antigenemia assay of peripheral blood was monitored regularly through day +100 when either the patient or donor was CMV seropositive. Patients with documented CMV viremia received pre-emptive therapy. All patients were in a single HEPA-filtered isolation room. Patients that experienced severe mucositis were eligible for total parenteral nutrition no earlier than day +2. Donor/host chimerism was routinely performed every 3 months for the first year post transplantation using short-tandem repeat (STR) amplified by polymerase chain reaction (PCR). Chimerism was not routinely assessed in patients that experience progression of disease. Mixed chimerism was defined as <90% donor chimerism of all nucleated cell populations in bone marrow.

Infectious endpoints

Serious infections were accrued prospectively and classified as described [24] with the exception that invasive fungal infections (IFI) without clinical compromise were not deemed life-threatening. CMV or EBV viremias without end organ disease were not scored as severe infections. Severe infections included infections requiring intravenous therapy and/or hospitalization. Life-threatening infections required vasopressors and/or intubation, and included any viral end-organ disease, EBV-post-transplantation lymphoproliferative disorder (EBV-PTLD) or *Toxoplasmosis gondii* infections. Lethal infections were defined as those either causing death, or contributing to death even if the primary cause of death according to the algorithm of Copelan et al [25] was due to GVHD or organ failure. Mild or moderate infections, and positive blood cultures with *coagulase negative Staphylococcus* thought to be a contaminant were excluded. Recurrence intervals were defined for viruses and IFIs as described [24]. Patients were censored from analysis after day 30, if they had graft failure, and at time of disease progression.

Statistical Analysis

This study was designed as a single center, non-randomized phase II trial to investigate the feasibility and safety of a non-myeloablative conditioning regimen plus an unmodified peripheral blood stem cell transplant in patients with hematologic malignancies who are not candidates for myeloablative conditioning by virtue of age, prior organ toxicity or intensity of prior therapy. The trial enrolled a total of 51 patients. This analysis applies to the 38 patients enrolled with lymphoid malignancies. Endpoints of the study were overall survival (OS), progression-free survival (PFS), transplant-related mortality (TRM), engraftment, cumulative incidence of infection and GVHD. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) $>500/\mu\text{L}$ on 3 consecutive measurements. Platelet recovery was defined as 3 consecutive measurements of $>20,000/\mu\text{L}$ unsupported by transfusion. Patients who engrafted were evaluable for acute GVHD (aGVHD), and patients surviving at least 100 days were evaluable for chronic GVHD (cGVHD). aGVHD was graded based upon IBMTR criteria[26], wherein grade A=I, B=II, C=III and D=IV in this manuscript henceforth. cGVHD was based upon historic criteria[27]. Disease was reevaluated per protocol at day +100, 6 months, 12 months, 18 months, 24 months and yearly thereafter. OS and PFS were estimated using the KM method. OS was defined as time from transplant to death from all causes. PFS was defined as time from transplant to progression of disease or death. Cause of death was lymphoid malignancy in cases of progression of disease following transplantation. TRM comprised all cases of death without progression of disease. Attribution to TRM was assessed by previously published criteria [25]. TRM, time to first infection, time to GVHD were estimated using the cumulative incidence function. Gray's test was used to examine whether time to GVHD differed by donor source.

Results

Thirty-eight patients with lymphoid malignancy consented and underwent allo-SCT on MSKCC IRB protocol 01-092 from October 2001 to May 2006. Two patients received BM grafts, while the remaining patients received PBSCT. Patient demographics are detailed in Table I.

Engraftment and GVHD

The median total nucleated cell-dose (TNC) and CD34+ cell dose were $13.2 \times 10^8/\text{kg}$ (range 1.9-35.0) and $9.9 \times 10^6/\text{kg}$ (range 1.1-31.7) respectively. CD34+ cell dose data were not available on two patients. All evaluable patients (n=37) engrafted neutrophils at a median time of 15 days (range 10-25). One patient died at day +8 post-transplant before engraftment. Median time to platelet engraftment was 12 days (range 6-40). Full donor chimerism was achieved in all evaluable patients by 3 months posttransplant. Subsequently, mixed chimerism was observed in 14% of evaluable patients at 6 months and 12% of patients at one-year status post transplant.

GVHD

Eight of 37 engrafted patients developed grade II-IV aGVHD independently of any donor leukocyte infusions (DLI). The cumulative incidence of grade II-IV aGVHD at 3 months was 10.5%. Four patients experienced severe (grade III-IV) aGVHD at a median of 3.3 months post-allo-SCT, 3 from unrelated donors. There was a trend toward an increased cumulative incidence in aGVHD in unrelated compared with related donors ($p=0.18$) (Figure 1). Of the thirty evaluable patients, 3 experienced cGVHD, 1 limited and 2 extensive.

Infections

Thirteen of the 38 patients experienced 48 severe, life-threatening or lethal infections. Table II characterizes the infections based upon time period experienced post-allo-HCT and degree of severity. Four patients experienced adenoviral enteritis, one with concurrent cystitis, all requiring intravenous cidofovir treatment. Eleven of 22 (50%) at risk patients (patient and/or donor CMV seropositive) reactivated CMV, including a patient with CMV pneumonitis. Twelve infections caused or contributed to death in 4 patients, all of which were bacterial in etiology with the exception of one IFI. With the exception of one bacterial sepsis and multi-organ failure on day +4 in a patient before engraftment and one proven IFI [28] followed by gram-negative sepsis in a patient with delayed engraftment, all lethal infections occurred in the setting of GVHD. Six of these lethal infections occurred from 6-12 months post-allo-HCT.

Survival

As of February 2012, 14 of 38 patients were alive with a median follow-up of 7.4 years. PFS was 36% (95% CI: 22%-51%), 30% (95% CI: 17%-45%), and 25% (95% CI: 13%-40%) at 1, 3, and 5-years post-allo-SCT respectively; while OS was 66% (95% CI: 48%-78%), 50% (95% CI: 33%-64) and 44% (95% CI: 28-59%) at 1, 3 and 5-years post-allo-SCT respectively (Figure 2). Cumulative incidence (CI) for POD was 16% (95% CI: 4-30%) and 24% (95% CI: 10-38%) at one and two-years respectively. There was no demonstrable plateau on the POD CI curve (Figure 3). TRM at one year post-allo-SCT was 19% (95% CI: 6-31%) (Figure 3). Pre-allo-SCT factors were analyzed for PFS and OS including: WHO histology (indolent, aggressive, HL), number of lines of therapy, previous IFRT donor, previous HDT-ASCT, HCT-CI, chemosensitivity, KPS and LDH pre-allo-SCT. Previous HDT-ASCT demonstrated significantly lower PFS and OS while elevated LDH portended

worse OS with a trend toward lower PFS ($p=0.06$) at one-year post-allo-SCT in univariate analysis (Table III). There was a trend toward worse OS in patients with HCT-CI 3 ($p=0.1$).

Donor Leukocyte Infusions

Fifteen patients received DLI as summarized in Table IV, with 6 of the 15 still alive. Three patients received DLI for mixed chimerism, while the majority of DLI infusions were for progressive or persistent lymphoma. Three of 12 patients (25%) achieved a sustained CR after DLI. Two of these patients received anti-lymphoma therapy before DLI. Seven of fifteen patients experienced GVHD after DLI, including 33% of the patients experiencing either severe grade III/IV aGVHD and/or extensive cGVHD post-DLI.

Discussion

These data represent a single-center experience with RIC allo-SCT for advanced and poor-risk lymphoid malignancies as part of a prospective phase II study for hematologic malignancies. We observed a five-year OS of 44% with prolonged median follow-up of >7 years for survivors. Nearly 2/3 of patients failed the treatment program experiencing POD or death from any cause at one year post-allo-SCT. The predominant failure event was the continuously observed cumulative incidence of POD. The low PFS and OS data are likely due to inclusion of a heavily pre-treated and co-morbid population of poor-risk patients, the majority of which had historically poor prognostic features including either aggressive histologic disease [17, 29, 30] (HL and DLBCL) and/or were chemorefractory prior to RIC allo-SCT [17, 30, 31]. Additionally, aggressive histology lymphoma has demonstrated a higher risk of non-relapse mortality following alemtuzumab containing RIC allo-SCT [18]. This may be attributable to consequence of compounded immune suppression with more proximal intensive salvage chemotherapy including HDT-ASCT. The enrichment of these characteristics in our series likely limited the power to detect other pre-allo-SCT prognostic factors. In univariate analysis, prior HDT-ASCT negatively impacted OS and PFS, elevated LDH at time of allo-SCT was prognostic for OS, and patients with HCT-CI 3 trended toward reduced OS and PFS ($p=0.1$). LDH above normal prior to allo-SCT has been previously identified by others to be a poor-prognostic feature in both alemtuzumab containing [32] and non-*in vivo* T cell depleted RIC allo-SCT [29]. HCT-CI 3 has reached prognostic significance in other RIC allo-SCT series for patients with lymphoid malignancies [33, 34]. The small number of patients limits the power to detect a statistically significant difference in outcomes according to HCT-CI, though a strong trend was appreciated ($p=0.1$). Lastly, we observed no difference in outcomes according to allo-SCT from related or unrelated; and, in turn by trial design, lower (100 mg/m^2) versus higher (140 mg/m^2) dose of melphalan in the conditioning regimen. A previously reported randomized study demonstrated no benefit in dose differences of melphalan in a non-alemtuzumab containing RIC allo-SCT of melphalan and fludarabine for multiple myeloma [35]. Given the association of infectious related mortality with GVHD in our series, we speculate that any benefit from increased dose melphalan in terms of lymphoma control could have been potentially countered by the risk of early GVHD related events in the unrelated cohort, given

the trend toward increased acute GVHD (see Figure 1). Again, these conclusions are limited by small numbers.

While early experience with myeloablative allo-SCT generally yielded poor results secondary to prohibitively high TRM, RIC has abrogated the risk of TRM, translating into improved outcomes for allogeneic transplanted patients with lymphoid malignancies[36]. Despite the lowered systemic toxicity with RIC relative to MAC programs, the incidence of GVHD; especially cGVHD, and its impact on TRM, has remained a challenge [37]. With the intent of abrogating the risk of GVHD, the anti-CD52 pan-lymphoid depleting antibody alemtuzumab was introduced into fludarabine-based RIC programs with an early signal toward this goal [20]. Shortly thereafter, in a prospective comparison with non-alemtuzumab containing fludarabine-based RIC, alemtuzumab-containing RIC demonstrated reduction of both aGVHD and cGVHD incidence, increased risk of CMV reactivation, and no difference in EFS and OS compared with the non-alemtuzumab containing group[38]. Our data corroborate the contributing immune suppressive effect of this treatment program as manifested by an extremely low-incidence of both aGVHD (10.5% grade II-IV at 3 months post-all-SCT) and cGVHD, along with a concomitantly large infectious burden. The deleterious impact of alemtuzumab incorporation into conditioning programs on infection incidence has been previously reported [39, 40]. Interestingly, despite the cell-mediated immune suppressive properties of alemtuzumab, < 50% of the infections within the first 120 days were of viral etiology, either reactivation or acquired *de novo*. The majority of the viral infections were reactivation of CMV (65%) with one of eleven resulting in end-organ disease. It is important to highlight that no CMV specific prophylaxis in the form of ganciclovir or valganciclovir was instituted. Success has been met with such prophylactic strategies in allo-SCT platforms at high-risk for CMV reactivation including alemtuzumab RIC [41] and umbilical cord blood transplantation [42]. Twelve infections caused or contributed to death in four patients within the first year post-transplantation. The majority of these infections occurred within the setting of GVHD and all were of bacterial or fungal etiology. None of these infections occurred following either POD or DLI. This is likely owing to the compounded functional immune compromised state of GVHD in conjunction with the immune suppression therapy for this condition. It is important to note that supportive care of the patients on this study pre-dates implementation of contemporary prophylaxis against both bacterial[43] and invasive fungal infection[44] within our institutional guidelines.

An additional consequence of *in vivo* T cell depletion with alemtuzumab includes potential contribution to the incidence of POD in our series of heavily pre-treated patients, with the majority being chemorefractory pre-SCT. The cumulative incidence of POD in our series continuously increased without plateau reaching approximately 50% at 7 years. While the GVL effect has been previously called into question in lymphoma [45], a large registry series with RIC has recently demonstrated a reduced-risk of both acute and chronic GVHD at the expense of a significantly increased risk of relapse in hematologic malignancies following T-cell depletion *in vivo* with either anti-thymocyte globulin (ATG) or alemtuzumab [46]. Histologies, such as acute leukemias, were included in this registry series wherein GVL effects are considered not as potent relative to lymphoid malignancies,

especially those of indolent histology. Many other series in various lymphoid malignancies have demonstrated an increased risk of POD with *in vivo* T-cell depletion with either ATG or alemtuzumab compared to T-replete grafts in RIC, including indolent NHL histologies such as: MCL [19], CLL/SLL [16] and FL [47]. Additionally, several series' with RIC allo-SCT for various lymphoid malignancies have reported a decreased risk of POD with the incidence of cGVHD [48-50]; again, serving as a surrogate of likely GVL effects and protection from POD with GVHD. Despite this, POD rates in aggressive histology lymphoma such as DLBCL [8, 11, 17, 51] and HL [52, 53] often exceed 30-40% post-RIC allo-SCT and appear to not be greatly affected by the incorporation of alemtuzumab [54, 55]. This suggests relatively less prognostic impact of GVL on aggressive histology disease.

DLI following relapsed CML post-*ex vivo* T-cell depleted allo-SCT was met with initial success [56], providing rationale for treatment of progressive lymphoma following *in vivo* T-cell depletion with alemtuzumab. In our series, of the 13 patients that received DLI for persistent or progressive lymphoma, 3 are alive with durable remissions. Two of the 3 patients had preceding lymphoma therapy prior to DLI. Of the 15 total patients to receive DLI, 5 (33%) experienced either severe grade III-IV aGVHD and/or extensive cGVHD. Demonstrable GVL effects following DLI for HL was initially described by Peggs and Mackinnon et al with 56% response rate to DLI following POD of HL post-allo RIC SCT conditioned with melphalan, fludarabine and alemtuzumab [57]. This same group has reported the most extensive experience with DLI for POD post-alemtuzumab containing allo-SCT for various lymphoma histologies including: FL [14], DLBCL [54], CLL [58] and HL [55, 57, 59]. Their relative success with this program is potentially a result of precise risk-adaptive strategies, akin to the previous model of T-cell depleted allo-SCT in the initial CML experience [56], with pre-emptive DLI for: early findings on functional-imaging [60], minimal residual bone marrow positive disease by PCR [58] and correcting T-cell mixed-chimerism [14, 58, 59]. Others have found no relapse reducing benefit to DLI in patients with mixed T-cell chimerism post-alemtuzumab conditioned allo-SCT, while observing a reduced incidence of GVHD in patients that sustain mixed T-cell chimerism [61, 62]. This latter observation suggests a mechanism of immune tolerance contributing to reduced GVHD risk in patients with mixed T-cell chimerism. These two studies contain a majority of patients with myeloid diseases and varying conditioning programs. Well controlled, prospective studies would need to be done to confirm or deny these retrospective findings.

In summary, while our prospective experience with RIC allo-SCT utilizing T-cell depletion *in-vivo* with alemtuzumab resulted in a low incidence of GVHD, many early failures related to TRM and POD were demonstrated, in addition to a continuously increasing cumulative incidence of the latter with long-term follow-up. Selection of a heavily pre-treated patient population, of which the majority possessed poor-risk chemorefractory and/or aggressive histology lymphoma prior to allo-SCT, likely contributed to these results. Despite our discouraging results, success has been met by others with this approach as previously mentioned. Going forward, given the low incidence of GVHD, perhaps elements of T-cell depletion *in-vivo* can be integrated at more risk-adjusted doses based upon patients' characteristics. Lower doses of both alemtuzumab [63, 64], as well as ATG [65], have been successfully applied with desired effect of lowering GVHD risk while potentially lowering

risk of untoward effects such as POD or infections. Moreover, harnessing the potent GVHD preventive effects of *in-vivo* T-cell depletion may permit easier administration of post-allo-SCT lymphoma therapy in a maintenance fashion until a GVL effect takes hold.

Prospectively designed studies of risk-adapted dosing of *in-vivo* T-cell depleting antibodies in more finitely defined patient risk groups would need to be conducted on a large, multi-institutional level.

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Figure 1. Cumulative Incidence of aGVHD According to Donor Source

Figure 2. Kaplan-Meier OS and PFS

Figure 3. Cumulative Incidence of TRM and POD

Table I

Patient characteristics

Variable	N=38	%
Age at transplant, years, median	45	(range 24-67)
WHO histology		
indolent NHL	16	42
MCL	6	
FL	6	
CLL/SLL	2	
WM	2	
aggressive NHL	6	16
DLBCL	5	
gamma/delta T-cell NHL	1	
Hodgkin lymphoma	16	42
Median No. Previous Lines of Therapy	4	(range 1-6)
Previous Monoclonal Antibody	24	63
Previous Involved-Field Radiotherapy	24	63
Previous ASCT		
No	23	61
Yes	15	39
HCT-CI, median	2	(range 0-7)
0-2	21	57
3-7	17	43
Graft		
Matched related donor	20	53
Matched unrelated donor	11	29
mismatched donor	7	18
Pre-Allo-SCT Lymphoma Status		
CR	10	26
PR	3	8
SD	20	53
PD	5	13
Chemosensitive		
No	25	66
Yes	13	34
Pre-allo-SCT LDH		
normal	23	61
elevated	15	39
KPS		
70	8	21

Variable	N=38	%
> 70	30	79

Allo-SCT: allogeneic stem cell transplant, ASCT: autologous stem cell transplant, CLL: chronic lymphocytic leukemia, CR: complete remission, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, HCT-CI: hematopoietic cell transplantation comorbidity index, KPS: Karnofsky performance status, LDH: lactate dehydrogenase, MCL: mantle cell lymphoma, NHL: non-Hodgkin lymphoma, PD: progression of disease, PR: partial remission, SD: stable disease, SLL: small lymphocytic lymphoma, WHO: world health organization, WM: Waldenstrom's macroglobulinemia

Table II
Severe Infections Post-Allo SCT

Time	N	Type of Infection	Severity
Admit-30 (N=38 evaluable)	14	1 Adenovirus	1 severe
		1 RSV	1 severe
		12 Bacterial	9 severe; 3 lethal
31-60 (N=37 evaluable)	9	1 Adenovirus	1 severe
		1 Toxoplasmosis	1 life-threatening
		7 Bacterial	5 severe, 1 life-threatening, 1 lethal
61-120 (N=36 evaluable)	9	1 Adenovirus	1 severe
		1 EBV-PTLD.	1 life-threatening
		5 Bacterial.	4 severe, 1 lethal
		2 Fungal	1 life-threatening, 1 lethal
121-180 (N=32 evaluable)	7	1 CMV	1 life-threatening
		1 Adenovirus.	1 severe
		5 Bacterial	3 severe, 2 lethal
180-1 yr (N=30 evaluable)	9	8 Bacterial	2 severe, 2 life-threatening, 4 lethal
		1 Fungal	1 life threatening

CMV: cytomegalovirus, EBV-PTLD: Epstein-Barr virus post-transplant lymphoproliferative disorder, RSV: respiratory syncytial virus

Table III
Univariate OS and PFS

Variable	N=38	Univariate OS p-value	Univariate PFS p-value
Age at transplant, yrs	45	0.27	0.45
WHO histology		0.42	0.34
indolent NHL	16		
aggressive NHL	6		
Hodgkin lymphoma	16		
No. of Previous Lines of Therapy		0.87	0.91
<4	16		
4	22		
Previous ASCT		0.01	0.003
No	20		
Yes	18		
Chemosensitive		0.35	0.50
NO (SD+PD)	25		
Yes (CR+PR)	13		
HCT-CI		0.10	0.11
0-2	21		
3-7	17		
Graft		0.06	0.32
Matched related donor	20		
Matched unrelated donor	11		
mismatched donor	7		
Melphalan Dose		0.44	0.68
Low Dose	20		
High dose	18		
Pt donor CMV		0.88	0.85
Negative	21		
Positive	16		
Pre-allo LDH		0.03	0.06
normal	23		
elevated	15		
KPS		0.28	0.41
70	8		
> 70	30		

Allo-SCT: allogeneic stem cell transplant, ASCT: autologous stem cell transplant, CMV: cytomegalovirus, CR: complete remission, HCT-CI: hematopoietic cell transplantation comorbidity index, KPS: Karnofsky performance status, LDH: lactate dehydrogenase, NHL: non-Hodgkin lymphoma, PD: progression of disease, PR: partial remission, SD: stable disease, WHO: world health organization

Table IV

Donor Lymphocyte Infusions (DLI) post-allo SCT

Disease	Donor	Indication for DLI	Treatment before DLI	Maximum dose CD3(+) $1 \times 10^6/\text{kg}$ DLI	Response post-DLI	GvHD post-DLI	Current Status	Months status post DLI
CLL	MRD	PD	R-CVP	500	CR	aGVHD grade 1, extensive cGVHD	Alive CR	75
DLBCL	MRD	PD	none	1	Initial PD, CR following rituximab	aGVHD grade 3	Dead	92
HL	MRD	PD	gemcitabine	10	NE	none	Dead	1
HL (CD 20+)	MMRD	PD	rituximab	0.05	PD	none	Dead	12
HL	MUD	MC	none	1	FD	aGVHD grade 2, limited cGVHD	Alive	58
DLBCL	MRD	PD	Rituximab, IFRT	10	CR	none	Alive CR	82
MCL	MUD	SD	Bortezomib, thalidomide, rituximab, cyclophosphamide	10	PD	none	Dead	2
HL	MRD	1) EBV-PTLD 2) PD	1) concurrent rituximab 2) GND	1) 1 2) 500	1) CR 2) PD	1) none 2) aGVHD grade III	Dead	50
HL	MRD	PD	GND	100	PD	aGVHD grade II	Dead	13
FL	MRD	PD	none	6	CR	none	Alive	35
MCL	MRD	PD	FCR	10	SD	aGVHD grade III	Dead	5
FL	MRD	MC	none	10	MC	none	Alive	29
HL	MUD	PD	GN	50	SD	cGVHD extensive	Dead	56
CLL/SLL	MRD	PD/MC	rituximab	50	SD/MC	none	Dead	4
$\gamma\delta$ T cell NHL	MRD	PD	ICE	10	SD	none	Alive	24

acute graft-versus-host disease (aGVHD); chronic graft-versus-host disease (cGVHD); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); complete remission (CR); cyclophosphamide, vincristine, prednisone (CVP); diffuse large B-cell lymphoma (DLBCL); Epstein-Barr virus post-transplantation lymphoproliferative disorder (EBV-PTLD); fludarabine, cyclophosphamide, rituximab (FCR); gemcitabine, vinorelbine, liposomal doxorubicin (GND); Hodgkin lymphoma (HL); involved-field radiation therapy (IFRT); mantle cell lymphoma (MCL); matched related donor (MRD); matched unrelated donor (MUD); mismatched unrelated donor (MMUD); mixed chimerism (MC); non-Hodgkin lymphoma (NHL); progression of disease (POD); rituximab (R); stable disease (SD).