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Allogeneic hematopoietic cell transplantation after failed autologous transplant for lymphoma using total lymphoid irradiation and anti-thymocyte globulin conditioning

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Abstract

We describe 47 patients with lymphoma and failed prior autologous hematopoietic cell transplantation (HCT) who received TLI-ATG conditioning followed by allogeneic HCT. Thirty-two patients had non-Hodgkin lymphoma (NHL; diffuse large B cell lymphoma [n=19], T-cell NHL [n=6], mantle cell lymphoma [n= 4], or other B-cell subtypes [n=3]), and 15 had Hodgkin lymphoma. The median follow-up was 4.9 (range, 2.1–11.9) years. The cumulative incidence of grade II–IV acute GVHD at day +100 was 12%, and the cumulative incidence of extensive chronic GVHD at 1 year was 36%. The 3-year cumulative incidences of overall survival, progression-free survival (PFS), and non-relapse mortality (NRM) were 81%, 44%, and 7%, respectively. Fifteen patients died (relapse, n=10; NRM, n=5). Among the 25 patients with relapse after allogeneic HCT, 11 (44%) achieved durable (>1 year) complete remissions following donor lymphocyte infusion or chemoradiotherapy. The majority of surviving patients (75%; n=24) were able to discontinue all immunosuppression. For patients with relapsed lymphoma after autologous HCT, allogeneic HCT using TLI-ATG conditioning is a well-tolerated, predominantly outpatient therapy with low NRM (7% at 3 years), a low incidence of GVHD, durable disease control, and excellent overall survival (81% at 3 years).

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INTRODUCTION

For patients with relapsed non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) after initial chemotherapy, autologous hematopoietic cell transplantation (HCT) can cure between 20–60% of patients [1–3]. Relapse after autologous HCT is a common occurrence, and is associated with a poor prognosis and limited therapeutic options [4].

Allogeneic HCT is a potentially curative therapy for refractory hematologic malignancies, including for lymphomas which have relapsed after autologous HCT [5–9]. This approach relies primarily on immunologic graft-vs.-tumor (GVT) effects to eradicate residual malignant cells. High-dose conditioning regimens confer cytoreduction in addition to GVT effects, but these regimens are associated with high non-relapse mortality (NRM, 30–50%) even in highly selected younger patients [10–15]. Treatment-related mortality with myeloablative conditioning can be particularly significant in lymphoma patients with prior failed autologous HCT (NRM >75%) [16, 17]. Thus, reduced-intensity conditioning regimens are preferred in this patient population [18–23].

As previously reported, we developed a reduced-intensity conditioning regimen for allogeneic HCT consisting of total lymphoid irradiation combined with rabbit anti-thymocyte globulin (TLI-ATG) [24, 25]. Here we report outcomes of patients undergoing allogeneic HCT with TLI-ATG for relapsed lymphoma after failed autologous HCT.

METHODS

Patient Population

The study cohort consists of 47 consecutive adult patients with relapsed or progressive lymphoma after autologous HCT who underwent allogeneic HCT with TLI-ATG conditioning between December 2001 and April 2011 in the Blood & Marrow Transplant program at Stanford University Medical Center. Twenty-seven of these patients were included in previous published analyses from our group [25]. All patients provided informed consent in accordance with the Declaration of Helsinki and were enrolled on transplant protocols approved by the Institutional Review Board. Data were analyzed as of May 2, 2014, allowing a minimum follow-up of 2 years for all patients. Exclusion criteria included corrected pulmonary diffusion capacity <35% predicted, cardiac ejection fraction <30%, Karnofsky performance status (KPS) < 50%, decompensated liver disease, and pregnancy. Disease status at the time of enrollment and responsiveness to chemotherapy were not exclusion criteria. Disease status was evaluated according to established guidelines [26]. Donors and recipients underwent high-resolution human leukocyte antigen (HLA) typing for class-I (HLA - A, - B, - Cw) and class II (HLA - DRB1, - DQB1) molecules.

Transplant Regimen

The TLI-ATG conditioning regimen was administered as previously described [24, 25]. In brief, rabbit ATG (Thymoglobulin®; Genzyme, Cambridge, MA) was infused intravenously at 1.5 mg/kg/day for 5 consecutive days, beginning on day -11 before HCT. TLI was administered at a dose of 0.8 Gy/day from day -11 through day -7, inclusive, and from day -4 through day -2, inclusive, with 2 additional fractions of 0.8 Gy delivered on day -1 for a

total dose of 8 Gy. Due to a protocol amendment, the 15 patients treated after May 2009 received 1.2 Gy (rather than 0.8 Gy) fractions, scheduled as above, for a total dose of 12 Gy. The radiation fields used have been previously described [24, 27]. All patients received unmanipulated granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cells (G-PBMC) on day 0. Post-grafting immunosuppression consisted of cyclosporine (CSA) and mycophenolate mofetil (MMF). For patients with HLA-identical sibling donors, CSA was tapered to discontinuation between days +56 and +180, while MMF was stopped on day +28. For patients with unrelated-donor grafts, CSA was tapered to discontinuation between days +100 and +180, and MMF was tapered to discontinuation between days +42 and +96 [24, 25].

All patients were monitored for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) with serum polymerase chain reaction assays, and all patients received bacterial, viral, and fungal prophylaxis according to institutional standard practice. EBV was monitored by plasma PCR every other week between day +14 and day +100 after allogeneic HCT, and pre-emptive rituximab therapy was given for patients with an EBV copy number of >10,000/mL, or at physician discretion for lower levels of viremia. Evaluation for relapse/progression commenced at day +90 (unless clinically indicated sooner) and was repeated at 6, 12, 18 and 24 months after allogeneic HCT and annually thereafter.

Evaluation of donor chimerism

DNA genotyping of polymorphic markers encoding short tandem repeats (STR) was used to quantify donor chimerism in all patients [28]. Donor chimerism was evaluated in whole blood and in cell subsets using immunomagnetic beads (Dynal Biotech/Invitrogen) coated with monoclonal antibodies against CD3, CD15, CD19 and CD56. Full donor chimerism was defined as the achievement, at any time point, of at least 95% donor $CD3^+$ chimerism in the peripheral blood. Primary graft failure was defined as failure to surpass 5% donor $CD3^+$ chimerism [25], while mixed chimerism was defined as donor $CD3^+$ chimerism ranging from 5–95% [29]. Donor lymphocyte infusions were given at the discretion of the attending physician to treat overt relapse or impending graft rejection, but were not used to convert stable mixed chimerism.

Study Definitions

The study endpoints included progression-free and overall survival (PFS and OS, respectively) and the incidences of lymphoma relapse, NRM, and acute and chronic GVHD. GVHD was graded using current consensus criteria for acute, late acute, and chronic GVHD [30, 31]. NRM was defined as death from any cause in the absence of lymphoma progression or relapse. OS was defined as the time to death from any cause after the date of transplant. PFS was defined by the first observation of relapse/progression, or by death, whichever came first. The study definition of relapse included progressive disease for those who had measurable disease at allogeneic HCT, and relapsed disease for those in complete remission (CR) at allogeneic HCT.

Statistical Analysis

Descriptive statistical analyses were performed to create actuarial PFS and OS estimates using the Kaplan-Meier method, with 2-sided 95% confidence intervals (CI) from Greenwood's formula. The cumulative incidences of grade II-IV acute GVHD, extensive chronic GVHD, and NRM were estimated using a competing-risk model. The cumulative incidence of GVHD was calculated with competing risks of relapse, death, or primary graft failure. The cumulative incidence of NRM was calculated with the competing risk of relapse. Multivariate regression analyses of correlation between variables (age, diagnosis, pre-transplant disease status, time from autologous HCT to allogeneic HCT, donor type, and donor chimerism status) and relapse were performed using a Cox proportional-hazards model. The point of no effect signifying the null hypothesis was 0. A two-tailed Fisher's exact test was performed to determine correlation between diagnosis/disease status/extra-nodal disease/donor type and likelihood of achieving full donor chimerism. The same approach was used to test the correlation between likelihood of achieving very high donor $CD3^+$ chimerism (≥99%) and the likelihood of relapse. All *P*-values are two tailed and a value of <0.05 was considered significant. Statistical analysis was performed using R (www.r-project.org), except for Fisher's exact test, which was calculated with GraphPad (San Diego, CA).

RESULTS

Patient Characteristics

The baseline characteristics of the 47 study patients are described in Table 1. All patients had progressive lymphoma after autologous HCT requiring salvage chemotherapy prior to allogeneic HCT. The median age was 46 years (range, 22–64 years) and men comprised 51% of the cohort. Twenty-six patients had a diagnosis of B-cell NHL, most of whom had aggressive histologies. Six patients had T-cell NHL and 15 had Hodgkin lymphoma (HL). Thirty-three patients (70%) had advanced-stage disease, defined as beyond 2^{nd} remission or progressive disease at allogeneic HCT. Of the 20 patients (43%) with residual lymphoma at allogeneic HCT, the maximum disease volume was <2 cm in 6 patients, 2–5 cm in 7 patients, and bulky (>5 cm) in 7 patients. Twenty-five patients (53%) had HLA-identical sibling donors, while the remainder had unrelated donors (HLA-matched unrelated donor, n=19; HLA-allele-mismatched unrelated donor, n=3). The median number of prior lines of therapy before allogeneic HCT was 5 (range, 4–9). All patients with B-cell non-Hodgkin lymphoma (n=26) had received prior rituximab therapy before allogeneic HCT. The median follow-up for surviving patients was 4.9 years (range, 2.1–11.9 years), and all surviving patients had at least 2 years of follow-up after allotransplantation.

Engraftment and Chimerism

At day +90 after allogeneic HCT, full donor chimerism was achieved in 29 patients (62%) and stable mixed chimerism was achieved in 16 patients (34%). Two patients (4%) had primary graft failure. At evaluation between day +80 and day +100, the median levels of peripheral-blood donor chimerism in the $CD3^+$, $CD15^+$, $CD19^+$, and $CD56^+$ lineages were 96%, 99%, 99%, and 95%, respectively. Achievement of full donor T-cell chimerism was not significantly associated with disease status at the time of allogeneic HCT,

chemosensitivity, diagnosis (NHL vs. HL), extra-nodal disease, or donor type (related vs. unrelated; $P > 0.1$ for all comparisons). The median $CD34^+$ cell dose administered was 7.3 (range, 1.8–19.0) $\times 10^6$ $CD34^+$ cells/kg recipient weight. Only one patient received a $CD34^+$ cell dose of $<2 \times 10^6$ cells/kg, and that patient had stable mixed chimerism at day +90 after allogeneic HCT.

Tolerability of TLI and ATG

Ninety-eight percent (n=46) of patients received their hematopoietic cell infusions as outpatients. Thirteen patients (28%) required admission to the hospital in the first 100 days after allogeneic HCT, with a median hospital length of stay of 5 days (Table 2). All patients readmitted for non-relapse causes (n=12) within the first 100 days after allogeneic HCT were treated successfully and discharged from the hospital, with the exception of one patient who expired on day +101 after allogeneic HCT due to bacterial sepsis in the setting of ganciclovir-related neutropenia and line infection. Post-transplant cytopenias were limited; neutropenia (absolute neutrophil count $<0.5 \times 10^9$/L) occurred in 13 patients (28%) and severe thrombocytopenia (platelet count $<10{,}000 \times 10^9$/L) occurred in 4 patients (9%) during the first 100 days after allogeneic HCT. Fifteen patients (33%) required packed red blood cell (PRBC) transfusions in the first 100 days after allogeneic HCT.

Eighty-three percent of patients (n=39) were at high risk for CMV reactivation by virtue of donor or recipient seropositivity and 51% (n=24) developed CMV viremia requiring pre-emptive therapy; 1 patient had documented CMV organ disease. EBV viremia requiring treatment occurred in 15% of patients (n=7), including 1 case of biopsy-proven polymorphic PTLD. All seven cases of EBV viremia/PTLD were treated to resolution with rituximab.

Graft-Vs.-Host Disease

The cumulative incidence of acute GVHD grades II-IV at day +100 was 12% (95% CI, 2%–23%; Figure 1). One patient had grade III acute GVHD and none had grade IV acute GVHD; no deaths were attributable to acute GVHD. The onset of acute GVHD occurred at a median of day +66 after allogeneic HCT (range, 29–265). One patient developed late-onset acute GVHD after DLI. The cumulative incidences of extensive chronic GVHD at 1 year and at 3 years were 36% (95% CI, 22–51%) and 50% (95% CI, 32–68%), respectively (Figure 1). The median time to chronic GVHD onset was 398 days (range, 119–1706 days), a figure which includes 7 patients who developed chronic GVHD after DLI. Two deaths were attributed to complications of chronic GVHD. In surviving patients (n=32), 75% (n=24) had discontinued all immunosuppressive therapy at last follow-up.

Survival and Non-relapse Mortality

Cumulative incidence estimates of 3-year OS and PFS were 81% (95% CI, 65%–90%) and 44% (95% CI, 24%–55%), respectively (Figure 2). For patients with NHL (n=32), 3-year OS and PFS were 78% and 46%, respectively. For patients with Hodgkin lymphoma (n=15), 3-year OS and PFS were 86% and 40%, respectively. At last follow-up, 68% (n=32) of the original cohort were alive with a minimum follow up of 2 years from allogeneic HCT (Table 4). Among surviving patients, 97% (n=31) were in CR at last follow-up (30 with durable CR lasting ≥1 year). Thirty-one of the surviving patients (97%) had KPS of ≥80 and 24 (75%)

had successfully discontinued all immunosuppressive therapy, including patients who had developed GVHD after DLI (Figure 3).

Of the 15 deaths in the study cohort, 5 were due to NRM. The 1-year and 3-year cumulative incidences of NRM were 4% (95% CI, 0%–11%) and 7% (95% CI, 0%–16%), respectively. Causes of NRM included chronic GVHD in two patients and sepsis, secondary malignancy (lung sarcoma) and suicide in one patient each (Table 4).

Relapse and Management

Twenty-five patients (53%) had evidence of lymphoma relapse or progression after allogeneic HCT at a median of 296 (range, 3–1,387) days after transplant. The cumulative incidences of relapse at 1 year and 3 years after allogeneic transplant were 33% (95% CI, 20%–47%) and 55% (95% CI, 38%–72%), respectively. In multivariate regression analysis, relapse risk was significantly increased in patients with chemoresistant lymphoma at allogeneic HCT (n=7; p=0.008) and with low $CD3^+$ donor chimerism at day +90 after allogeneic HCT (p=0.01). Peak donor $CD3^+$ chimerism through day +180 was significantly lower in patients who relapsed as opposed to those who remained in complete remission (p=0.007, Figure 4). Age, diagnosis, time from autologous HCT to allogeneic HCT, and donor type were not significantly associated with relapse risk (p>0.1 for all comparisons).

The characteristics and management of patients who relapsed after allogeneic HCT are detailed in Table 3. Therapeutic strategies in this setting included DLI (n=11; as sole therapy in 5 patients, and in combination with chemotherapy in 6 patients), chemotherapy and/or radiation (n=11), or no treatment (n=3). Of the 11 patients who were treated with DLI, 5 had Hodgkin lymphoma, 3 had DLBCL, and 1 each had follicular lymphoma, mantle cell lymphoma, and angioimmunoblastic T-cell lymphoma. The median dose of DLI was 1.0 (range, 0.7–6.0) × 10^7 $CD3^+$ cells/kg recipient weight. Following DLI, extensive chronic GVHD occurred in 6 patients, but caused no deaths (the 2 deaths after DLI were caused by progressive lymphoma). Eight of the eleven DLI recipients (73%) are alive at last follow-up and 7 remain in CR, with median $CD3^+$ donor chimerisms of 100% (range; 90%–100%). Among the 25 patients who relapsed, 10 died of progressive disease, including the 3 patients who received no further treatment. Fourteen of the patients with post-transplant relapse (56%) were alive at last follow-up; 13 were in CR (8 post-DLI and 5 with other treatment) and 1 had progressive disease. At last follow-up, 31 patients were alive and in CR, for a current progression-free survival of 66%.

DISCUSSION

This study evaluated 47 patients with relapsed lymphoma and a history of failed autologous HCT treated uniformly with TLI-ATG conditioning followed by allogeneic HCT. In this cohort, TLI-ATG conditioning and allogeneic HCT led to an overall survival of 81% at 3 years, with 97% of surviving patients in complete remission at last follow-up. Despite heavy pre-treatment, non-relapse mortality was only 7% at 3 years after allogeneic HCT, and 75% of surviving patients were able to discontinue all immunosuppression. Most patients in this study had aggressive NHL or relapsed Hodgkin lymphoma after failed autologous HCT, and thus had very poor prognoses with conventional therapies. The low NRM and high overall

survival seen in this study strongly suggest that allogeneic HCT should be offered to eligible patients in this setting. Additionally, many patients with post-transplant relapse were treated successfully back into CR with chemotherapy and/or DLI. This report builds on previously published data with TLI-ATG conditioning [24, 25] and adds new observations regarding long-term outcomes, duration of immunosuppressive therapy for chronic GVHD, and successful treatment of post-transplant relapse with cellular therapy.

The cumulative incidence of acute GVHD in our study (12%) is considerably lower than the incidences of 30–65% reported in several single and multicenter studies of reduced-intensity conditioning and allogeneic HCT for relapsed lymphoma [7, 8, 12, 13, 32–34]. Two single-institution studies from the United Kingdom utilizing alemtuzumab-based conditioning noted cumulative incidences of acute GVHD grades II–IV of 15–17% [9, 20]. Similarly, Khouri et al. reported an incidence of acute GVHD grades II–IV of 11% in patients with follicular lymphoma conditioned with fludarabine, cyclophosphamide, and rituximab, although virtually all patients in that study received allografts from HLA-identical siblings [6, 35]. In our study, in which approximately half of patients received unrelated-donor allografts, the cumulative incidence of acute GVHD grades II–IV was 12% and there were no deaths related to acute GVHD. The combination of T-cell depletion via thymoglobulin and protective conditioning with TLI likely contributed to the low incidence and severity of acute GVHD with our approach. The cumulative risk of extensive chronic GVHD is comparable to that reported in similar patient cohorts in the literature [7, 8, 12, 32, 33, 36], and included 7 patients who developed extensive chronic GVHD after DLI. Other groups have reported lower incidences of chronic GVHD of 10–20% [9, 13, 34], possibly due in part to the use of bone marrow rather than G-PBMC allografts. As morbidity and mortality in chronic GVHD is closely linked to the duration of immunosuppression, it is important to note that the majority of surviving patients in our study (75%) were able to completely discontinue all immunosuppression at last follow-up.

Non-relapse mortality after TLI-ATG conditioning (4% at 1 year and 7% at 3 years) was substantially lower than that reported by other groups [7–9, 12, 13, 32–34, 37]. This conditioning regimen is well-tolerated even in this high-risk patient group where all patients had failed prior high-dose chemotherapy and autologous HCT [32, 33]. Neutropenia and severe thrombocytopenia were uncommon, occurring in 28% and 9% of patients respectively, and only 28% of patients required hospital admission during the first 100 days after allogeneic HCT. Viral reactivation is often a concern with thymoglobulin-containing conditioning regimens, but its impact was limited in our study: 51% of patients required pre-emptive antiviral therapy for CMV reactivation but only 1 developed CMV disease, and the three cases of EBV-driven PTLD were all treated to resolution with rituximab.

Relapse or disease progression after allogeneic HCT was noted in 25 patients in our cohort (53%). Low donor $CD3^+$ chimerism and pre-transplant chemoresistance significantly increased the risk of relapse in multivariate analysis. The relapse rate reported in this study is comparable to that seen in other trials of reduced-intensity conditioning and allogeneic HCT for aggressive lymphoma [7, 8, 12, 13, 37, 38], and likely reflects in part the fact that 43% of patients in this study entered allogeneic HCT with residual lymphoma. Importantly, because of the low rates of acute GVHD and toxicity with TLI-ATG, salvage therapy with

DLI was a viable salvage option for many patients and led to CR in >50% of patients with post-allotransplant relapse. There were 10 deaths related to lymphoma relapse, and at last follow-up 30 of the 32 surviving patients (94%) had been in CR for >1 year. We view the 3-year OS of 81% in this study is an excellent result in a setting where lymphoma is rapidly and commonly fatal with conventional therapy, particularly since patients who relapse after TLI-ATG can often be treated back into durable remission with DLI.

This report has several limitations. The sample size, while consistent with other published reports of allogeneic HCT for lymphoma [8, 9, 35], is relatively small. The disease mix described here is heterogeneous and the diseases may have different degrees of sensitivity to GVL effects. Additionally, while the TLI-ATG regimen has been validated by other groups in a multi-institutional setting [39, 40], we describe a single-center experience here. Finally, 27 of the 47 patients described in this report were included in previous summaries of clinical results with TLI-ATG conditioning [25]; this manuscript adds a substantial number of new patients and extends the follow-up for approximately 3 years beyond that of previously published reports.

In conclusion, this study demonstrates that TLI-ATG conditioning followed by allogeneic HCT is a well-tolerated therapy which produces excellent overall survival for patients with relapsed lymphoma after failed autologous HCT. Rates of NRM, acute GVHD, and hospitalization are low. The relapse rate should be interpreted in the context of the effectiveness of post-relapse treatment with DLI, which led to high rates of sustained CR and overall survival. While prospective comparative trials are needed to determine the ideal transplant regimen in this setting, TLI-ATG conditioning is an excellent therapeutic option for this patient population, which otherwise fares poorly with conventional therapy. We and others have found that increased donor T-cell chimerism associates with a lower risk of relapse after allogeneic HCT. Taken together with the success of DLI reported in this manuscript, these findings point to a potential role for post-transplant infusion of selected T-cell subsets to increase donor T-cell chimerism, augment GVT effects, and reduce relapse rate [41]. The incorporation of novel targeted agents, such as ibrutinib in B-cell malignancies, may provide another avenue to decrease relapse rates after allogeneic HCT for lymphoma.

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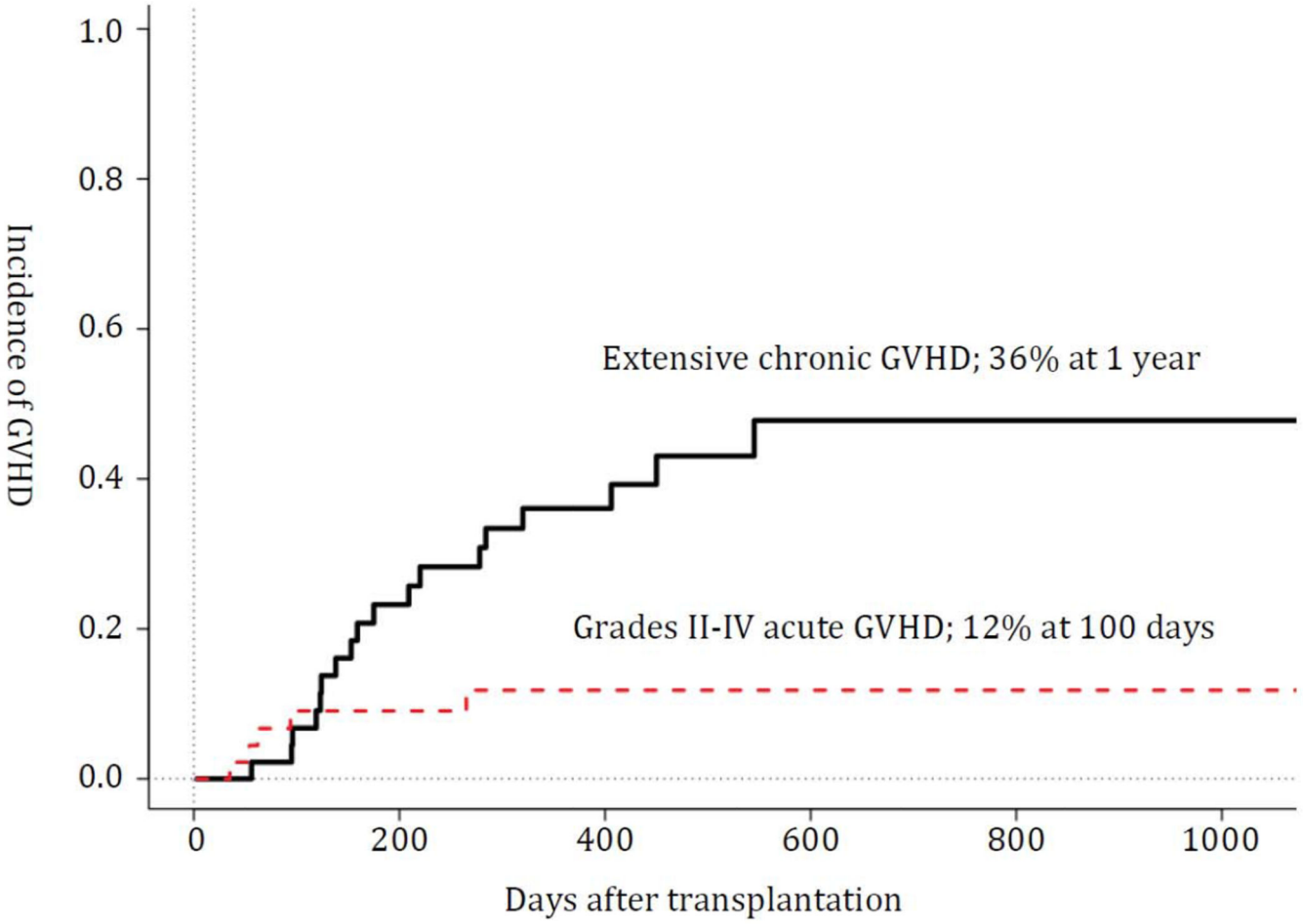

Figure 1.
Cumulative incidences of acute GVHD grades II–IV (red dotted line) and extensive chronic GVHD (solid line). Abbreviation: GVHD, graft-vs.-host disease.

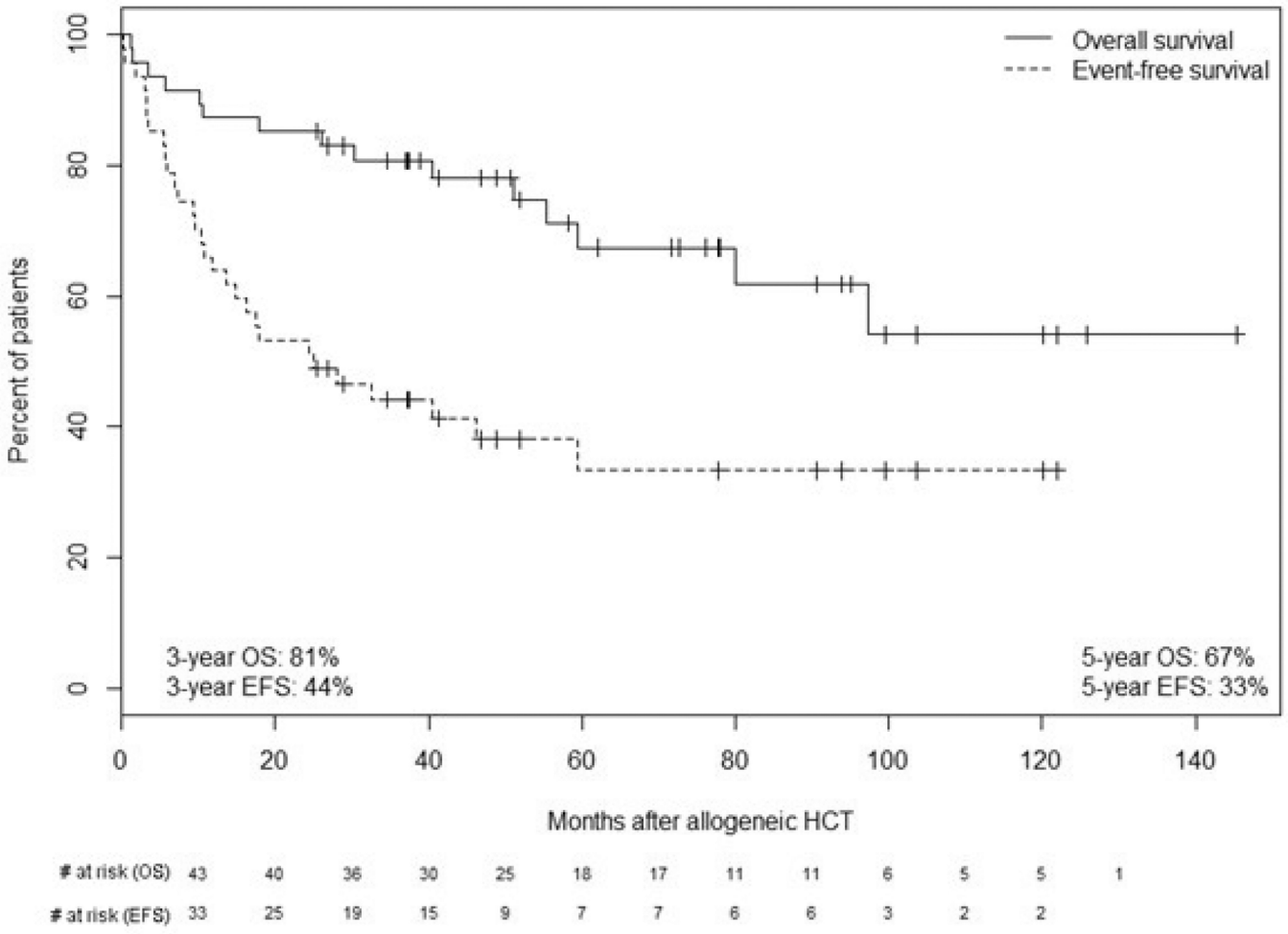

Figure 2.

Kaplan-Meier estimates of overall survival (solid line) and progression-free survival (dotted line). Abbreviations: HCT, hematopoietic cell transplantation; OS, overall survival; PFS, progression-free survival.

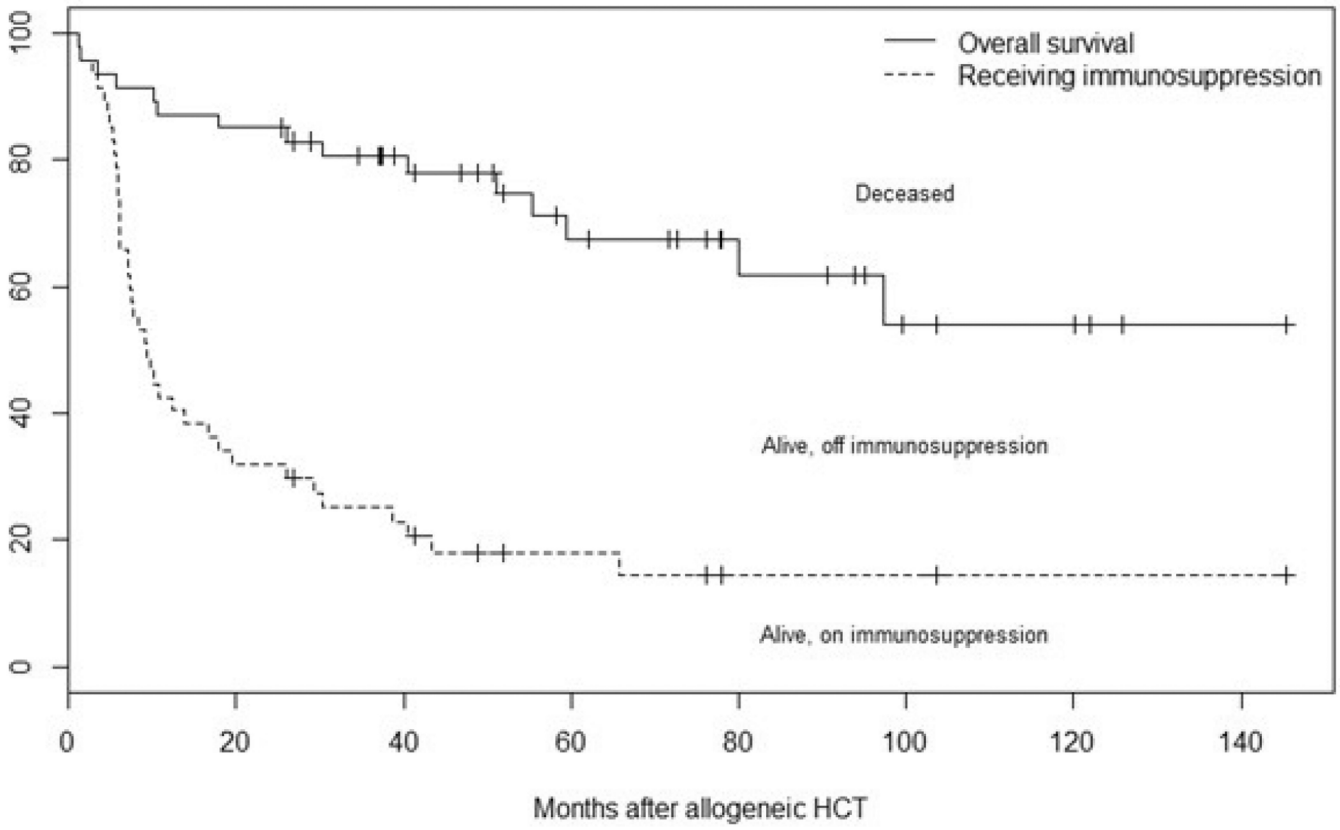

Figure 3.

Proportion of patients requiring systemic immunosuppression over time. Abbreviations: HCT, hematopoietic cell transplantation.

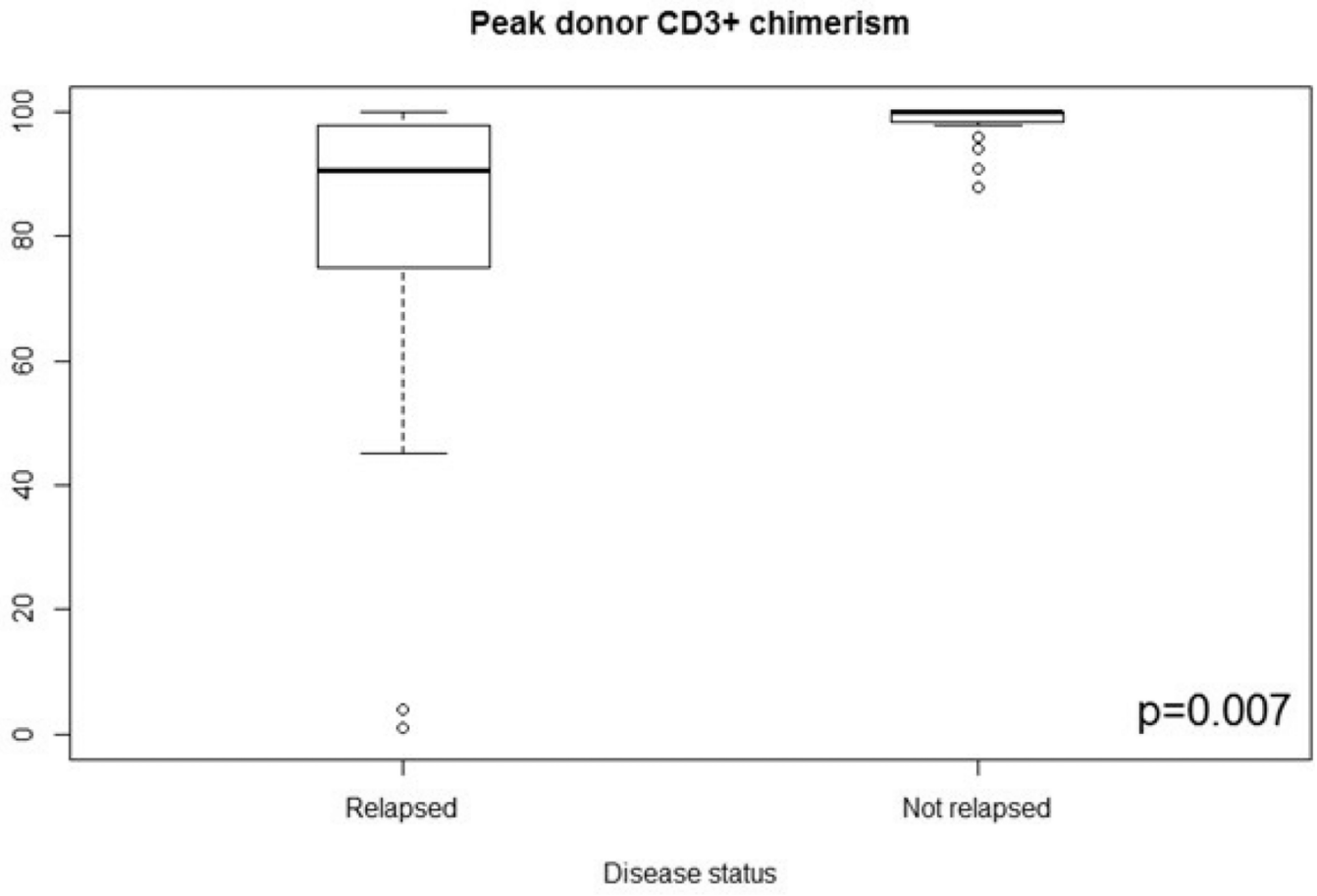

Figure 4.

Peak donor $CD3^+$ peripheral-blood chimerism through day +180 in patients with and without disease relapse. Dark horizontal line indicates median; box indicates 25^{th} and 75^{th} percentile ranges; whiskers represent range with outliers shown as hollow circles. By day +180, 29 patients (62%) had achieved full donor chimerism, 16 patients (34%) had mixed chimerism, and 2 patients (4%) had primary graft failure.

Table 1

Patient and disease characteristics.

Patient and Disease Characteristics	No. of patients (n=47)
Median age in years, (range)	46 (22 – 64)
Sex, no. (%)	
Male	24 (51)
Female	23 (49)
Diagnosis, no. (%)	
Non-Hodgkin lymphoma	32 (68)
B-cell type	26 (55)
Diffuse large B-cell lymphoma	19 (40)
Mantle cell lymphoma	4 (9)
Follicular lymphoma	2 (4)
Lymphoplasmacytic lymphoma	1 (2)
T-cell type	6 (13)
Angioimmunoblastic T-cell lymphoma	3 (6)
NK/T cell neoplasm	2 (4)
Anaplastic large cell lymphoma	1 (2)
Hodgkin lymphoma	15 (32)
B-cell neoplasm who received prior rituximab, n (%)	26 (100)
Disease status at the time of transplant, no. (%)	
Chemosensitive disease	40 (85)
Chemoresistant disease	7 (15)
Extranodal disease involvement*, n (%)	25 (53)
Advanced disease at transplant†, no. (%)	33 (70)
Number of prior therapies§, median (range)	5 (4 – 9)
Time from autologous to allogeneic HCT, median (range)	20 (6 – 115)
< 18 months	19 (40%)
≥ 18 months	28 (60%)
Donor, no. (%)	
Sibling	25 (53)
Unrelated	22 (47)
Degree of HLA match	
Matched	44 (94)
Mismatched ‡	3 (6)
Donor – recipient cytomegalovirus status, no. (%)	

Patient and Disease Characteristics	No. of patients (n=47)
Donor and/or recipient seropositive	39 (83)
Donor and recipient seronegative	8 (17)

[*] At any time before allogeneic HCT.

[†] Lymphoma beyond second complete/partial remission and progressive disease.

[§] Not including single-agent rituximab or local radiotherapy.

[‡] All were unrelated and had single HLA-allele mismatches.

Abbreviations: NK, natural killer cell; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen.

Table 2

Post-transplant outcomes. At last follow-up, 32 patients were alive and 15 had died.

Post-transplant Outcomes	No. of patients (n=47)
Median follow-up*, years (range)	4.9 (2.1–11.9)
Re-admission within 100 days, n (%)	13 (28%)
Median hospital stay§, days (range)	5 (1–20)
Cause of readmission§ (n=13)	
Neutropenic fever	3
Non-neutropenic fever	3
CMV reactivation	2
CSA toxicity	1
Others †	4
Post-HCT cytopenias in first 100 days §, n (%)	
Patients with neutrophil nadir ≤ 0.5×10^9/L	13 (28%)
Patients with platelet nadir ≤ 10×10^9/L	4 (9%)
Patients with no blood product transfusions	15 (33%)
Post-transplant PRBC transfusions, mean	2.7
Cytomegalovirus in first 100 days, n (%)	
Reactivation (viremia only)	24 (51%)
Organ disease ¢	1 (2%)
EBV reactivation ‡	9 (19%)
Cause of death (n=15)	
Disease progression/relapse	10
Chronic GVHD	2
Sepsis	1
Secondary malignancy	1
Suicide	1
Treatment for relapse (n=25)	
DLI +/− additional therapy	11/25 (44%)
Chemoimmunotherapy and/or radiotherapy	11/25 (44%)
No additional therapy	3/25 (12%)
Outcomes after relapse (n=25)	
Death	10/25 (40%)
Alive	15/25 (60%)
Returned to complete remission	14
Progressive disease	1

*Of surviving patients.

[§] Among patients re-admitted within the first 100 days after HCT.

[†] Other causes of readmission included one case each of syncope, bacteremia, relapse, and post-transplant lymphoproliferative disorder.

[¢] Biopsy or shell-vial positive.

Table 3

Characteristics and outcomes in patients with post-transplant relapse (n=25).

Time to relapse in days, median (range)	296 (3–1387)
Treatment for relapse, n (%)	
DLI	11 (44%)
DLI alone	5
Chemotherapy + DLI	6
Chemo-immunotherapy and/or radiotherapy	11 (44%)
No additional therapy	3 (12%)
Outcomes after relapse, n (%)	
Death	10 (40%)
Alive	15 (60%)
Returned to complete remission[§]	14
Progressive disease	1

[§]Seven after donor lymphocyte infusion.

Abbreviations: HCT, hematopoietic cell transplantation; DLI, donor lymphocyte infusion.