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⁹⁰Y-Ibritumomab tiuxetan followed by reduced-intensity conditioning and allogeneic stem-cell transplantation in patients with advanced follicular lymphoma

Karim E. Abou-Nassar¹, Kristen E. Stevenson², Joseph H. Antin¹, Kathleen McDermott¹, Vincent T. Ho¹, Corey S. Cutler¹, Ann S. LaCasce¹, Eric D. Jacobsen¹, David C. Fisher¹, Robert J. Soiffer¹, Edwin P. Alyea¹, John Koreth¹, and Arnold S. Freedman¹

¹ Department of Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts, USA, 02115

² Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts, USA, 02115

Abstract

RIC HSCT is a potentially curative therapeutic option for patients with advanced FL but disease relapse remains the most common cause of failure. Radioimmunoconjugates administered prior to RIC allogeneic HSCT may enhance cytoreduction and allow more time for graft versus lymphoma effect to develop without the associated toxicity of a myeloablative HSCT. We performed a retrospective study to describe the outcomes of patients with relapsed, refractory or transformed FL who received ⁹⁰Y ibritumomab tiuxetan followed by fludarabine and low-dose busulfan RIC allogeneic HSCT at the Dana-Farber Cancer Institute between 2006 and 2009, inclusively. Twelve patients were identified with a median age of 55 (40–66) years and a median number of lines of therapy of 5 (2–10). Two patients (17%) had transformed to a more aggressive histology and 5 (42%) had chemorefractory FL. Cumulative incidences of grade II–IV acute GVHD at 100 days were 17% (± 11%) and chronic GVHD at 12 months were 63% (±19%). Two-year non-relapse mortality was 18% (± 12%). Two-year OS and progression-free survival (PFS) were 83% (± 11%) and 74% (± 13%), respectively. This treatment is associated with favorable outcomes including acceptable rates of GVHD and relapse in advanced FL patients and warrants prospective studies.

Keywords

Follicular lymphoma; Allogeneic hematopoietic stem cell transplantation; Radioimmunotherapy; ⁹⁰Y-ibritumomab tiuxetan

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Address correspondence to: Arnold Freedman, MD, Associate Professor of Medicine, Harvard Medical School, Lymphoma Program, Dana-Farber Cancer Institute, 44 Binney Street, 617-632-4894 (office), 617-632-5168 (fax), Boston, MA, USA, 02115-6084, arnold_freedman@dfci.harvard.edu.

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INTRODUCTION

Follicular lymphoma (FL) is the most common indolent non Hodgkin lymphoma (NHL). Despite the advent of chemoimmunotherapy, FL remains incurable in the majority of cases with a median survival of 8–10 yrs [1]. During this period, 40–60% patients with advanced FL will relapse and require additional therapies. Although FL is often chemoresponsive in this setting, remissions become progressively shorter and the disease may become chemorefractory. Furthermore, FL will transform to a more aggressive histology at a rate of 3% per year, which is generally associated with a poor prognosis [2]. Improvements in the outcomes of patients with FL require effective treatment strategies for relapsed, refractory and transformed disease.

Although salvage chemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) is an option for the treatment of relapsed/refractory FL [3–5], studies have also highlighted issues of relapse, long-term toxicity, and secondary malignancies. Furthermore, not all patients are candidates for autologous HSCT, as many are heavily pretreated and unable to undergo stem-cell harvesting. Lastly, salvage chemotherapy followed by autologous HSCT may not be the optimal treatment strategy in high-risk transformed FL as it may eradicate the high grade component of the lymphoma, but the low grade component often recurs.

Allogeneic HSCT offers a potentially curative approach to the treatment of FL [6]. However, reduced intensity conditioning (RIC) regimens normally used in patients with FL often fail to provide sufficient cytoreduction in high-risk patients leading to higher relapse rates [7]. Furthermore, patients with transformed FL have either been excluded or present in low numbers in most series [6, 7]. Radiotherapy has been used extensively in the treatment of lymphomas in view of their inherently radiosensitive nature [8]. The anti-CD 20 radiolabeled immunoconjugates currently available include ⁹⁰Y-ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals, Irvine, CA, USA) and ¹³¹I-tositumomab (Bexxar, GlaxoSmithKline, Philadelphia, PA, USA). ⁹⁰Y-ibritumomab tiuxetan comprises the anti-CD20 monoclonal antibody, ibritumomab, conjugated via the tiuxetan chelator to the pure beta-emitting radioisotope yttrium-90 (⁹⁰Y). Prospective trials of this agent demonstrate response rates of 60 to 80 percent in previously treated disease [9–14] including patients who are refractory to rituximab.

Tumor load reduction using radioimmunoconjugates, termed radioimmunotherapy (RIT), followed by RIC allogeneic HSCT may enhance early cytoreduction, while allowing for long-term disease control through graft versus lymphoma effect (GVL) without the associated toxicity of a myeloablative HSCT in this older, often heavily pretreated patient population. Furthermore, the use of allogeneic donor stem cells renders the use of radioimmunoconjugates possible even in patients with pancytopenia or extensive bone marrow involvement. The use of RIT combined with RIC allogeneic HSCT has recently shown promising results in the management of acute myelogenous leukemia, myelodysplasia [15] and relapsed NHL [16, 17]. All series to date have reported on patients with heterogeneous histologies ranging from indolent to aggressive NHL. However, outcome is clearly related to histology [18] and the proportion of FL in prior studies was

small. It is therefore difficult to determine the true impact of RIT combined with RIC HSCT on patients with relapsed, refractory or transformed FL. In this report, we describe the baseline characteristics and outcomes of ^{90}Y ibritumomab tiuxetan followed by RIC allogeneic HSCT in patients with relapsed, refractory or transformed FL treated at the Dana-Farber Cancer Institute.

METHODS

Patients

We evaluated all consecutive patients with relapsed, refractory or transformed FL who received ^{90}Y ibritumomab tiuxetan followed by RIC allogeneic HSCT at the Dana-Farber Cancer Institute (Boston, MA, USA) between 2006 and 2009, inclusively. Only patients suspected of transformed FL on clinical grounds underwent repeat lymph node biopsy. Patients were selected to receive ^{90}Y ibritumomab tiuxetan prior to RIC allogeneic HSCT on the basis of refractoriness to other lines of therapy for FL including, chemoimmunotherapy and radiotherapy, as judged by the treating physician. Patients refractory to ^{90}Y ibritumomab tiuxetan did not proceed to allogeneic HSCT. The database was closed for analysis in May 2010 and chart review was performed for all data. This study was approved by the institutional review board was conducted in accordance with the principles of the Declaration of Helsinki.

Radioimmunotherapy

Patients received 0.4 mCi/kg of ^{90}Y -Ibritumomab tiuxetan prior to a planned RIC allogeneic HSCT. The radioimmunotherapy regimen was administered in two distinct steps. The first step involved an infusion of rituximab (250 mg/m^2) following premedication. Within 4 hours of rituximab, an infusion of ^{111}In ibritumomab tiuxetan (5 mCi over 10 minutes) was administered. A biodistribution assessment was performed 48 to 72 hr after ^{111}In ibritumomab tiuxetan. Seven days later patients with acceptable biodistribution received rituximab (250 mg/m^2) followed within 4 hours by ^{90}Y -Ibritumomab tiuxetan 0.4 mCi/kg (14.8 MBq/kg).

Reduced intensity conditioning

The conditioning regimen consisted of intravenous fludarabine and low-dose intravenous busulfan. Fludarabine (30 mg/m^2) was administered as an intravenous infusion over 30 minutes on days -5, -4, -3 and -2. Busulfan (0.8 mg/kg) was administered by intravenous infusion over 3 hours on days -5, -4, -3 and -2 for a total dose of 3.2 mg/kg based on actual body weight [19]. In one recipient of umbilical cord stem cells, the conditioning regimen consisted of fludarabine (30 mg/m^2) as an intravenous infusion over 30 minutes on days -8, -7, -6 and -5, -4, -3, melphalan (100 mg/m^2 on day -2) and anti-thymocyte globulin (1.5 mg/kg on days -7, -5, -3, -1).

Stem cell collection and administration

Patients received peripheral-blood stem cells or umbilical cord blood from matched or mismatched, related or unrelated donors. HLA-matched sibling or unrelated donors underwent filgrastim mobilization for 5 consecutive days from Day -4 pre-HSCT to Day 0.

Peripheral blood stem cells were collected by large volume apheresis. Unrelated donors were managed and mobilized following the procedures of the local donor centers. Plasma and red cell depletion were allowed for ABO incompatibility but no other form of graft manipulation was performed. A minimum dose of 2.0×10^6 CD34+ cells/kg was targeted.

GVHD prophylaxis and supportive care

Most patients received a graft-versus-host disease (GVHD) prophylaxis regimen consisting of tacrolimus \pm sirolimus starting on day -3 \pm low-dose methotrexate on days 1, 3, 6 as previously described [20]. In 3 patients, bortezomib was added to a tacrolimus-based GVHD prophylaxis regimen as part of a study protocol. Two patients received sirolimus and mycophenolate mofetil without a calcineurin inhibitor. Tacrolimus and sirolimus taper usually commenced between day 60 to 100, with the goal to be off all immune suppression by 6–9 months post transplant in the absence of GVHD. Acute GVHD (aGVHD) was graded according to the consensus scoring system [21]. Supportive care for all patients consisted of *Pneumocystis jiroveci* prophylaxis and varicella zoster virus/herpes simplex virus prophylaxis. Cytomegalovirus viral load was closely monitored by DNA-based assay and pre-emptive therapy was initiated in cases of reactivation.

Statistics

Overall survival (OS) was defined as the time from the date of allogeneic HSCT to the date of death from any cause; those alive or lost to follow-up were censored at the date last known alive. Progression-free survival (PFS) was defined as the time from the date of allogeneic HSCT to the date of relapse or death; those alive were censored at the date last known alive and relapse-free. OS and PFS were calculated using the Kaplan Meier (KM) method. Cumulative incidence curves for grade II–IV acute GVHD (aGVHD) and chronic GVHD (cGVHD) with death as a competing risk were also constructed and were calculated from the date of allogeneic HSCT.

RESULTS

Database search

Between 2006 and 2009, 41 patients underwent allogeneic HSCT at DFCI for FL. During this period, 13 were assessed to receive ^{90}Y ibritumomab tiuxetan followed by RIC allogeneic HSCT. One patient progressed despite ^{90}Y ibritumomab tiuxetan and did not undergo a planned HSCT. Of the 29 patients who did not receive ^{90}Y ibritumomab tiuxetan prior to conditioning, 3 underwent myeloablative allogeneic HSCT and the remainder (n=26) achieved good disease control with other agents prior to RIC allogeneic HSCT. The outcomes of the 12 patients who received ^{90}Y ibritumomab tiuxetan followed by RIC allogeneic HSCT are reported in this study.

Patient and Disease Characteristics

Baseline characteristics of the 12 patients included in this study are listed in table 1. The median age was 55 years (range: 40–66) and 6 patients (50%) were female. Ten patients (83%) had relapsed FL and two patients (17%) had transformed FL confirmed by lymph node biopsy findings. The median number of therapies was 5 (range: 2–10) and 1 patient

(8%) had undergone a prior autologous HSCT. Prior to receiving RIT, 7 (52%) patients were in PR and 5 (47%) were refractory to their last treatment. There were no cases of inadequate biodistribution and all patients received ^{90}Y -Ibritumomab tiuxetan 0.4 mCi/kg. The median time from RIT to allogeneic HSCT was 1 month (range: 0.4–5.8). Greater than 5 months separated RIT from allogeneic HSCT in 2 patients due to donor delays. Eight patients (67%) received their grafts from unrelated donors, 4 of which were antigen mismatched. One patient received double umbilical cord blood transplantation.

Engraftment and chimerism

The median (range) dose of CD34 cell dose infused was $6.42 (3.29 - 9.09) \times 10^6/\text{kg}$ (n=9). Ten patients (83%) had a nadir absolute neutrophil count (ANC) below 500 cells/mL, and 8 (67%) a platelet nadir below 20,000 cells/mL. All patients engrafted, with a median time to neutrophil recovery of 14 days (range: 11–35), and a median time to platelet recovery of 20 days (range: 11–163). Among 12 patients, 11 had chimerism measurements available at day 30, 9 at day 100 and 6 at day 365. The median (range) percentage donor whole blood chimerism achieved at these time points was 97% (88–100%), 98% (93–100%) and 100% (99–100%) (Table 2).

Toxicity and GVHD

Administration of the RIT was not associated with any grade 3–4 non-hematologic toxicity. The cumulative incidences of aGVHD (grade II–IV) and cGVHD are shown in Figures 1 and 2, respectively and table 2. The incidence of grade II–IV acute GVHD (SE) was 17% (11%) at 100 days and 25% (13%) at 200 days. Only one patient developed grade III–IV aGVHD. Seven patients developed cGVHD, one of which was severe. The 1-year cumulative incidence of cGVHD (SE) was 63% (19%). Two patients died of infectious causes, one of which as a direct consequence of severe aGVHD of the skin, resulting in a 2-year cumulative incidence (SE) of non-relapse mortality (NRM) of 18% (12%).

Treatment Response and Survival

The median follow-up for the 9 patients alive without relapse was 31 months (range 7–42). Outcomes are presented in table 2, Figures 3 and 4. Eight (67%) patients achieved CR after allogeneic HSCT. One patient relapsed 8 months after allogeneic HSCT. Treatment with bendamustine and rituximab and rapid taper of immunosuppression resulted in a GVHD flare followed by a CR. For the entire cohort, the 2-year PFS (SE) and OS (SE) were 74% (11%), and 83% (11%) respectively.

DISCUSSION

In the present study, the addition of the radioimmunoconjugate prior to allogeneic HSCT was associated with excellent OS and PFS with no apparent increase in NRM or GVHD compared with regimens that do not include RIT. The relapse rate appears to be low, although a precise estimate will depend on analysis of a larger cohort.

Conventional RIC allogeneic HSCT has the benefit of less immediate TRM than high dose conditioning regimens at the cost of a higher relapse rate. A CIBMTR report compared 88

RIC to 120 myeloablative matched sibling allogeneic HSCT in relapsed FL. Relapse rates with RIC were twice as high compared with myeloablative allogeneic HSCT (17% vs 8%) [7]. This result suggested that we could take advantage of the inherently radiosensitive nature of FL by using RIT to avoid the toxicities associated with the use of myeloablative regimens.

Radioimmunoconjugates have been used for over a decade in hematological malignancies and are potent drugs for the treatment of NHL. ^{90}Y -Ibritumomab tiuxetan was approved by the FDA in 2002 for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with rituximab refractory FL. In addition to antibody and complement-dependent cytotoxicity, radioimmunoconjugates exert a large part of their clinical activity through the radioisotope [10]. Because ^{90}Y does not emit gamma rays compared to ^{131}I used with tositumomab, radiation exposure to household members of patients treated with ^{90}Y -Ibritumomab tiuxetan is minimal, rendering outpatient administration feasible. Furthermore, ^{90}Y has a 5mm radiation path length compared to 0.8 mm for ^{131}I making ^{90}Y -Ibritumomab tiuxetan potentially better suited for bulky tumor load reduction. Through their unique mechanism of action, radioimmunoconjugates offer high response rates even in patients who are refractory to combination chemotherapy and rituximab [22, 12] with a limited toxicity profile. An integrated analysis of 250 patients with relapsed/refractory or transformed indolent NHL treated with ^{131}I -tositumomab revealed overall response (ORR) and complete response (CR) rates ranging from 47–68% and 20–38% respectively. Although in the majority of patients responses were not durable, among the 32% of patients who stayed in remission for 1 year, the median duration of response was an impressive 45.8 months [23]. Similar findings have also been reported with ^{90}Y -ibritumomab tiuxetan [9].

These promising results have led to the introduction of standard dose and high dose RIT as part of the conditioning regimen for ASCT in NHL with encouraging results [24–25]. Few studies have been published to date on RIT combined with RIC allogeneic HSCT in NHL. A recent German phase II prospective study evaluated the use of ^{90}Y -ibritumomab tiuxetan followed by RIC allogeneic HSCT using fludarabine and 2 Gy TBI as conditioning in 40 patients with relapse indolent NHL. The outcomes of 17 patients with FL were considerably superior to other histologies resulting in 2-year OS and PFS of 67% and 57% respectively compared to 51% and 43% respectively for the entire cohort [26]. Similarly, Shimoni and colleagues reported the outcomes of 12 patients with extensively treated advanced NHL of various histologies with active disease who underwent RIT combined with RIC HSCT. The conditioning regimen consisted of ^{90}Y -Ibritumomab tiuxetan and fludarabine combined with busulfan or melphalan followed by allogeneic HSCT. An ORR of 83% was observed along with a 2 year PFS of 33%. Only three patients had FL but all three were reported as long term survivors [17]. Our reported 2-year PFS and OS rates of 74% and 83% respectively are encouraging in this high risk, heavily pretreated FL patient population. These results compare favorably to previous reports of RIC allogeneic HSCT in FL with and without the use of radioimmunoconjugates [7, 18, 27]. Direct comparisons between these studies are limited by variations in patient and disease characteristics as well as conditioning regimens. Taken together, these results suggest that FL appears to be particularly amenable to the use

of RIT followed by RIC allogeneic HSCT compared to other indolent NHL histologies, although the reasons for this remain uncertain.

The use of RIT prior to RIC allogeneic HSCT in our study did not result in increased toxicity with a cumulative incidence of NRM at 2 years of 18%, similar to previous reports of RIC allogeneic HSCT in FL [7, 27]. Furthermore, engraftment was not delayed with a time to neutrophil and platelet recovery of 14 and 20 days respectively, similar to RIC allogeneic HSCTs our institution performed without RIT [18]. Moreover, no graft failures have been observed. GVHD remains a major cause of morbidity and mortality in RIC allogeneic HSCT. Previous reports of RIT followed by RIC allogeneic HSCT have highlighted a significant NRM attributable to such high rates of GVHD. Until now, published studies on RIT followed by RIC allogeneic HSCT in NHL reported high rates of aGVHD ranging from 43% to 67% leading to a 2-year NRM of 42% to 45% [17, 26]. The authors attributed this high rate of aGVHD to a combination of heavily pretreated patient population, unrelated mismatched donors, rapid achievement of complete chimerism and early withdrawal of immunosuppression. We observed a considerably lower cumulative incidence of Grade II–IV aGVHD (25%), which is comparable to previous reports of RIC allogeneic HSCT in indolent NHL [7, 18, 27]. Based on these findings, RIT prior to RIC allogeneic HSCT does not appear to be an important contributor to the development of aGVHD. Furthermore, a recent CIBMTR analysis revealed that exposure to anti-CD20 antibodies in the peri-transplant period may actually diminish the risk of acute GVHD [28]. Lastly, half of our patients received sirolimus plus tacrolimus, a combination which appears to result in a lower risk of aGVHD compared to a calcineurin inhibitor plus methotrexate [29].

This study has inherent limitations due to its retrospective nature. First, selection bias may limit the applicability of these results. However, our patient population consisted of high-risk heavily pretreated FL patients. Nearly half of them had either transformed to a more aggressive histology or become refractory to therapy. This accurately represents patients with relapsed/refractory or transformed FL undergoing allogeneic HSCT and whose expected outcomes are very poor [30]. Nevertheless, the outcomes of the 12 patients in this study were not different from those of 29 FL patients who underwent allogeneic HSCT at DFCI during the same period with less advanced and more chemosensitive disease (not shown). Only one of thirteen patients considered for this therapy failed to have an adequate response to ⁹⁰Y ibritumomab tiuxetan and hence did not proceed to RIC allogeneic HSCT. The use of RIT therefore allowed us to achieve adequate disease control in the vast majority of patients who had previously difficult to control FL. The outcome of this patient was not included in our KM curves as our intent was to describe the outcomes of patients successfully salvaged by RIT who were then consolidated by RIC allogeneic HSCT. Second, the uncontrolled nature of this study prevents us from drawing firm conclusions on the magnitude of the effect of adding RIT to a RIC allogeneic HSCT regimen in this patient population, as our results can only be compared to historical controls. As such, the potential impact of RIT on OS, PFS, rates of GVHD and NRM have to be interpreted with caution. Despite these limitations, combining RIT with RIC allogeneic HSCT for relapsed, refractory or transformed FL is well-tolerated and the outcomes are encouraging.

Although radioimmunoconjugates have well documented clinical efficacy and safety, they continue to be underutilized in the management of NHL. There is now growing evidence that these agents can play a role both as frontline and in relapse NHL. Furthermore, safety and efficacy data is becoming available to support their use in HSCT where they offer effective cytoreduction with low associated toxicity. In this study, we conclude that ^{90}Y ibritumomab tiuxetan followed by RIC allogeneic HSCT is associated with favorable outcomes including acceptable rates of GVHD and relapse in this high-risk relapsed, refractory or transformed FL patient population. Further validation through well designed prospective studies is warranted.

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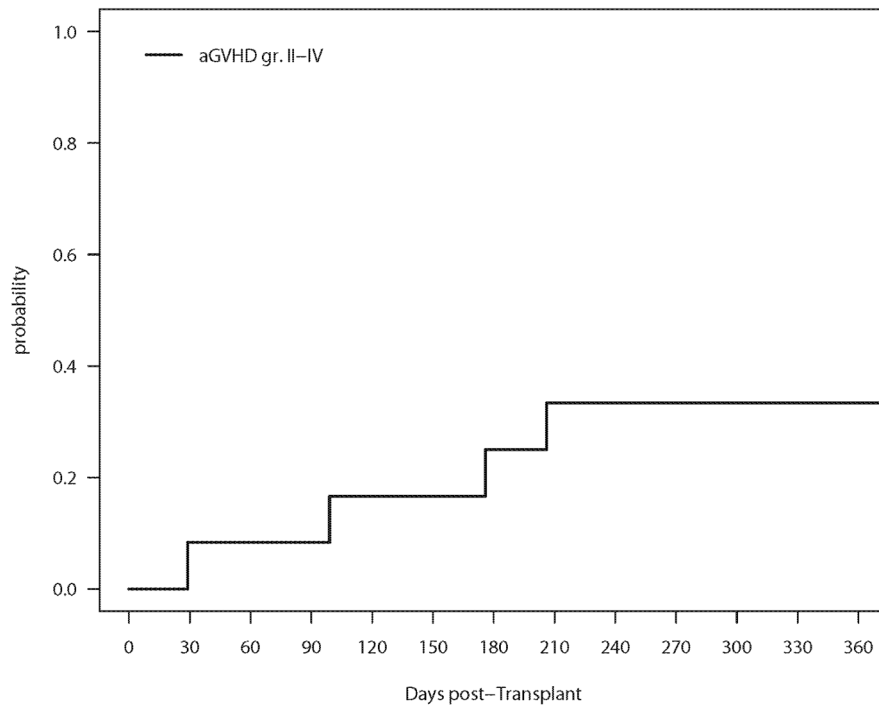


Figure 1.
Cumulative Incidence of Grade II-IV aGVHD

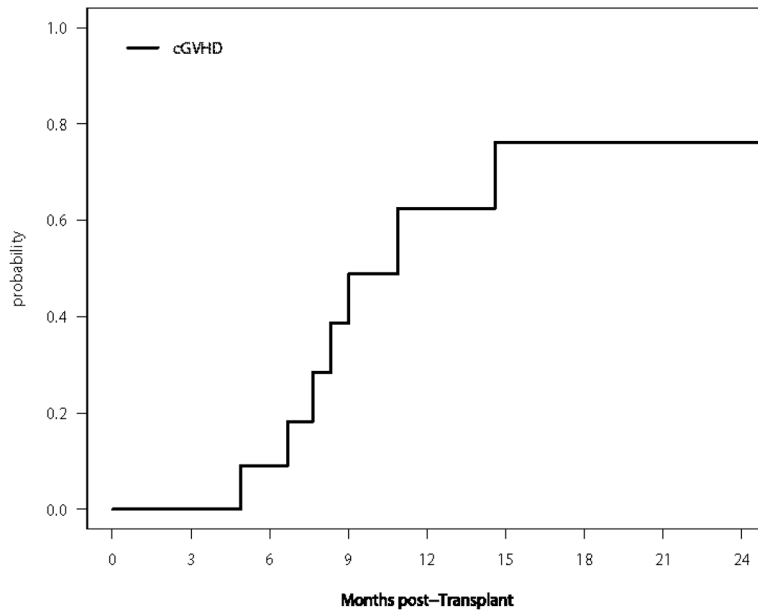


Figure 2.
Cumulative Incidence of cGVHD

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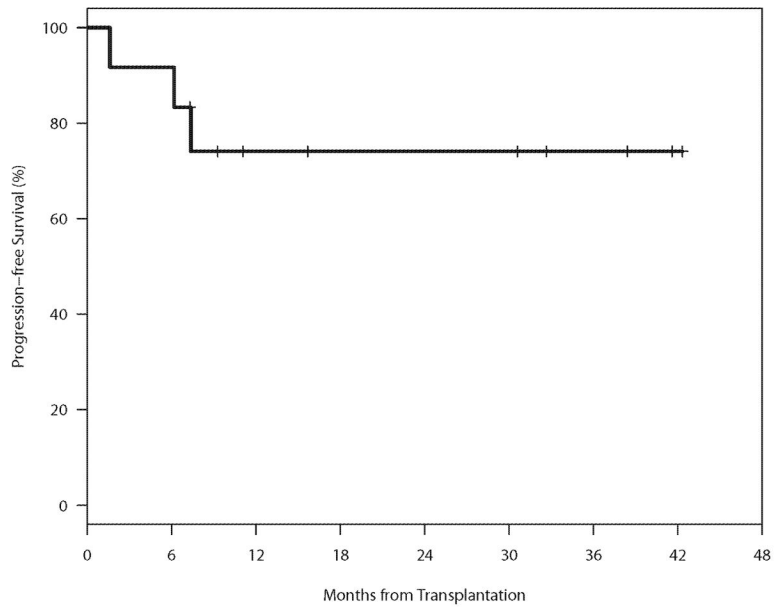


Figure 3.
Progression-free Survival (PFS)

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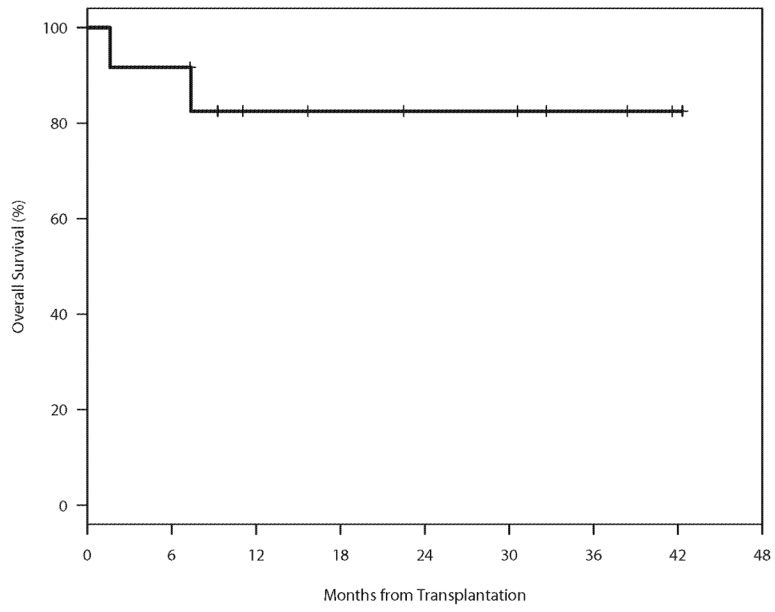


Figure 4.
Overall Survival (OS)

Table 1

Baseline characteristics

	N (%)
Number of Pts.	12
Age, median (range)	55 (40, 66)
Sex, Female	6 (50)
Type of Follicular Lymphoma	
Relapsed	10 (83)
Transformed	2 (17)
FL Stage at Diagnosis	
I	0 (0)
II	1 (8)
III	4 (33)
IV	7 (58)
FL Stage at Transplant	
I	0 (0)
II	1 (8)
III	4 (33)
IV	7 (58)
Status at Transplant Conditioning	
CR	0 (0)
PR	7 (58)
Refractory	5 (42)
No. of Prior Therapies before RIT, median (range)	5 (2, 10)
Prior Autologous Transplant	1 (8)
Karnofsky Performance Status	
70	2 (16)
80	5 (42)
90	4 (32)
100	1 (8)
Time from RIT to Allotransplant in mos., median (range)	1.0 (0.4, 5.8)
HLA Matched (A, B, DR)/Donor Type	
Matched Unrelated	4 (33)
Matched Related	3 (25)
Mismatched Unrelated*	4 (33)
Double umbilical cord blood	1(8)
CMV	
Donor -/Recipient -	4 (33)
Donor -/Recipient +	1 (8)
Donor +/Recipient -	4 (33)
Donor +/Recipient +	3 (25)
Stem Cell Source	

	N (%)
PBSC	11 (92)
Cord Blood	1 (8)
Type of Conditioning	
Busulfan/Fludarabine	11 (92)
Melphalan/Fludarabine/ATG	1 (8)
GVHD Prophylaxis	
Tacrolimus/mini-methotrexate	4 (33)
Tacrolimus/Sirolimus/mini-methotrexate	1 (8)
Tacrolimus/Sirolimus	2 (16)
Tacrolimus/Bortezomib/mini-methotrexate	3 (25)
Sirolimus/Mycophenolate mofetil	2 (16)
CD34 dose $\times 10^6$ /kg (median, range). n = 9	6.42 (5.81)

* Three patients had one antigen mismatch and one had two antigen mismatches

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Table 2**Patient Outcomes**

Outcome	N
No. of Pts. with ANC > 500	10
Time to Neutrophil Engraftment in days, median (range)	14 (11, 35)
No. of Pts. with Platelets > 20 000	8
Time to Platelet Engraftment in days, median (range)	20 (11, 163)
Day 30 donor chimerism % - median (range). n = 11	97 (12)
Day 100 donor chimerism % - median (range). n = 9	98 (7)
Day 365 donor chimerism % - median (range). n = 6	100 (1)
gr. II-IV aGVHD	4
gr. III-IV aGVHD	1
cGVHD	7
No. of Relapses	1
No. of Deaths	2
Sepsis/GVHD	1
Infection	1
Outcome	% Estimate (SE)
Cum. Inc. gr. II-IV aGVHD at 100 days	17% (11%)
Cum. Inc. gr. II-IV aGVHD at 200 days	25% (13%)
Cum. Inc. cGVHD at 12 months	63% (19%)
Cum. Inc. NRM at 12 months	18% (12 %)
PFS 2-year	74% (13 %)
OS 2-year	83% (11%)