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High-Dose Carmustine, Etoposide, and Cyclophosphamide Followed by Allogeneic Hematopoietic Cell Transplantation for Non-Hodgkin Lymphoma

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ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) has been shown to be curative in a group of patients with aggressive non-Hodgkin lymphoma (NHL). A previous study has demonstrated equivalent outcomes with a conditioning regimen based on total body irradiation and another not based on total body irradiation with preparative therapy using cyclophosphamide, carmustine, and etoposide (CBV) in autologous HCT. We investigated the safety and efficacy of using CBV in an allogeneic setting. Patients were required to have relapsed or be at high risk for subsequent relapse of NHL. All patients had a fully HLA-matched sibling donor. Patients received carmustine (15 mg/kg), etoposide (60 mg/kg), and cyclophosphamide (100 mg/kg) on days −6, −4, and −2, respectively, followed by allogeneic HCT. All patients were treated with cyclosporine and methylprednisolone as prophylaxis for graft-versus-host disease (GVHD). Thirty-one patients (median age, 46 years) who were felt to be inappropriate candidates for autologous transplantation were enrolled. Each subject had a median of 3 previous chemotherapy regimens. All patients engrafted. Fifteen of 31 patients are alive. Median follow-up time was 11.5 months (range, .4-126). There were 8 deaths due to relapse. Nonrelapse mortality (n = 8) included infection (n = 3), GVHD (n = 2), diffuse alveolar hemorrhage (n = 1), veno-occlusive disease in the setting of concurrent acute GVHD of the liver (n = 1), and leukoencephalopathy (n = 1). Probabilities of event-free survival and overall survival were, respectively, 44% (95% confidence interval, 26%-62%) and 51% (33%-69%) at 1 year and 44% (26%-62%) and 47% (29%-65%) at 5 years. Probability of relapse was 33% (15%-51%) at 1 year and 5 years. Probability of nonrelapse mortality was 31% (13%-49%) at 1 year and 5 years. Incidences were 29% for acute GVHD and 39% for chronic GVHD. None of the 12 patients who developed chronic GVHD has disease recurrence. Patients who had required >3 previous chemotherapy regimens before HCT had an increased probability of relapse. CBV is an effective preparative regimen for patients with aggressive NHL who undergo allogeneic HCT.

KEY WORDS

Cyclophosphamide, carmustine, and etoposide • Non-Hodgkin lymphoma • Allogeneic hematopoietic cell transplantation

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a malignant disease with increasing incidence [1]. With conventional chemotherapy, 40% to 50% of patients may be cured [2]; however, many patients relapse after initial chemotherapy. For those who relapse, high-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) has been shown to improve survival [3]. Despite such treatment, relapse remains the major cause of failure. Several potential reasons

for relapse can be identified. One possibility is that the hematopoietic cells that have been collected may contain clonogenic tumor cells, which could be reinfused during the HCT procedure. Two studies using sensitive molecular assays have found that the bone marrow is frequently contaminated with malignant cells in low- and intermediate-grade lymphomas [4,5].

High-dose chemotherapy with allogeneic HCT has been used extensively for myeloid and lymphoid leukemias with significant improvement in survival compared with standard chemotherapy [6-9]. The use of allogeneic HCT has been investigated in patients with refractory NHL and achieved results superior to that expected with standard chemotherapy regimens [10-12]. Its efficacy has been attributed to a graft-versus-lymphoma (GVL) effect and possibly to a graft that is free of tumor cells [13]. Various preparative regimens have been used in the allogeneic setting, with most being based on total body irradiation (TBI). We previously reported a study that demonstrated acceptable toxicity and survival equivalent to a non-TBI preparatory regimen of cyclophosphamide, carmustine (BCNU), and etoposide (VP-16; CBV) for patients with NHL who received autografts compared with a TBI-based regimen. This regimen has an outcome equivalent to those containing TBI with less toxicity [14]. In addition, we previously described our experience with allogeneic HCT using a regimen of TBI, VP-16, and cyclophosphamide for patients with advanced or refractory leukemias and lymphomas [15,16]. Because of the decreased toxicity of CBV compared with a TBI-based regimen and equivalent disease control in autografting, this study investigated the safety, toxicity, efficacy, and tolerability of this same regimen (CBV) in an allogeneic setting using cyclosporine (CSP) and methylprednisolone (PSE) as prophylaxis for graft-versus-host disease (GVHD) in patients who had relapsed or were at high risk for subsequent relapse of NHL.

MATERIALS AND METHODS

Patient Eligibility

Between February 1992 and March 2004, 31 adult patients with relapsed NHL or a high risk for subsequent relapse of NHL with fully HLA-matched related donors received allogeneic HCT at Stanford University (Stanford, Calif). The first 4 patients received bone marrow grafts. The subsequent 27 patients received granulocyte colony-stimulating factor (G-CSF), mobilized, allogeneic peripheral blood hematopoietic cells. No graft was manipulated.

Eligible patients were 18 to 60 years old with morphologically confirmed NHL. Exclusion criteria were (1) hepatic dysfunction that was defined by a serum transaminase level >2.5 times the normal value, (2) serum creatinine level >2 mg/dL or creatinine clearance <60 mL/min, (3) previous bone marrow transplantation procedure, (4) major organ dysfunction that might increase the risk of the transplantation procedure, or (5) severe psychological or medical illness. All patients and donors gave written informed consent as required by the institutional review board of Stanford University.

Study Definitions

Patients without clinical or radiologic evidence of disease or bone marrow involvement with lymphoma were defined as being in complete remission (CR), and patients with measurable residual disease were defined as being in partial remission (PR). Patients who did not respond to standard chemotherapy at initial presentation were classified as having induction failure (IF). Relapse was defined by evidence of radiographic or clinical progression in a new site or growth of disease in any previously involved sites.

Patients were considered to have bone marrow involvement if they had NHL demonstrated in the bone marrow at any time before allogeneic HCT. Nonrelapse mortality (NRM) included death from any cause except relapse. The day of allogeneic HCT was defined as day 0 for all survival and relapse analyses. Event-free survival (EFS) was calculated by scoring relapse or death from any cause as an event.

Patient Characteristics

Patient characteristics are listed in Table 1. Thirty-one patients were treated in this study. Of these, 21 were men and 10 were women, with a median age of 46 years. Histologic classification was based on the Working Formulation, which was the principal classification system in use during the period under study [17]. Patients were categorized into 4 groups according to histologic NHL subtype: low grade (n = 2), intermediate grade (n = 21), high grade (n = 3), and transformed (n = 5). Most patients had stage 4 disease at the time of transplantation (n = 24). Thirty-nine percent (12 of 31) of patients had bone marrow involvement and 58% (18 of 31) had extranodal disease. Among the 31 patients, 8 were in CR (3 in first CR and 5 in the second or subsequent CR), 15 were in PR, and 8 had IF. For those who had chemosensitive disease (CR and PR) at the time of transplant (n = 23), a large proportion had >1 relapse previously, with 5, 3, and 2 patients in their second, third, and fourth recurrences, respectively. Most patients were heavily pretreated before HCT, with 10 having had >3 previous regimens. Thirteen of the 31 patients had previous radiation, and 3 received radiation to the mediastinal area. Among the 21 patients with intermediate-grade histology, 5 had IFs and 5 had short disease-free intervals,

Table 1. *Patient and Donor Characteristics*

Patients, n	**31**
Age, y	
Median	**46**
Range	**20-60**
Gender	
Male	**21**
Female	**10**
Histology	
High grade	
Burkitt	**2**
T-cell lymphoblastic lymphoma	**1**
Intermediate	
Diffuse large B-cell cell	**10**
Mantle cell	**5**
NK T-Cell	**1**
T-cell rich B cell	**2**
Mixed histology	**3**
Low grade	
Follicular small cleaved	**1**
Marginal zone	**1**
Transformed	**5**
Stage at time of transplantation	
2	**1**
3	**6**
4	**24**
Bone marrow involvement	**12**
Extranodal involvement	**18**
B symptoms	**14**
Disease status at time of transplant	
First CR	**3**
Second or subsequent CR	**5**
First PR	**4**
Second or subsequent greater PR	**11**
IF	**8**
No. of relapses (first CR, first PR, and IF excluded)	
1	**6**
2	**5**
3	**3**
4	**2**
Prior chemotherapy regimens	
>3	**10**
≤3	**21**
Prior radiation	**13**
Prior mediastinal radiation	**13**
Donor age, y	
Median	**45**
Range	**17-64**
Donor gender	
Male	**21**
Female	**10**
Patient-donor pair sex mismatched	**16**
Patient-donor pair CMV-seronegative	**6**

with the time from first remission to first relapse being <6 months (range, 1-5).

Collection of Allogeneic Hematopoietic Cells

Patients were required to have a fully HLA-matched sibling donor. HLA compatibility was determined by serologic methods for HLA class I antigens and at least low-resolution molecular typing for HLA class II antigens. Bone marrow harvest was performed under anesthesia for the first 4 patients [18]. Beginning in July 1999, patients received G-CSF, "mobilized," allogeneic hematopoietic cells. HLA-matched donors received G-CSF at a dose of 16 μg/kg/d subcutaneously beginning on day −5. On day −1, the first apheresis collection began in the afternoon for a 3- to 4-hour apheresis procedure. The goal was 5×10^6 $CD34^+$ cells/kg of recipient weight. If this goal was not achieved in the first apheresis procedure, a second apheresis was performed on the morning of day 0. A minimum dose of 2×10^6 $CD34^+$ cells/kg of recipient weight was required for the allografting procedure. The hematopoietic cell products were not manipulated.

Preparative Regimen

The preparative regimen consisted of BCNU 15 mg/kg (maximum dose, 550 mg/m^2 actual body weight) on day −6 infused over 2 hours, etoposide 60 mg/kg on day −4 infused over 4 hours, and cyclophosphamide 100 mg/kg infused over 2 hours on day −2 [19]. All chemotherapy was based on adjusted ideal body weight.

Allogeneic Hematopoietic Cell Infusion

Hematopoietic cells from fully HLA-matched siblings were infused on day 0. Patients were premedicated with diphenhydramine 50 mg intravenously and hydrocortisone 100 mg intravenously before hematopoietic cell infusion. Fresh hematopoietic donor cells were administered from 30 minutes to 3 hours, depending on total volume.

Immunosuppression

Post-transplant immunosuppression was achieved by using intravenous CSP and PSE [20]. Intravenous CSP 3 mg/kg/d was given over 24 hours beginning on day −1. For patients who received bone marrow grafts, PSE was administered at .25 mg/kg 2 times a day beginning on day +7 and increased to .5 mg/kg 2 times a day on day +14. For patients who received allogeneic hematopoietic cells, intravenous PSE was administered at .5 mg/kg 2 times a day on day +7 through day +28. Beginning on day +29, all patients' PSE dose was decreased to .4 mg/kg 2 times a day, unless they were being treated for GVHD. Adjustment of CSP was based on serum, creatinine, and total bilirubin levels.

Supportive Care and Follow-up

All patients were housed in private rooms with high-efficiency particulate air filtration systems. Gut decontamination was attempted with nonabsorbable oral antibiotics or ciprofloxacin. *Pneumocystis carinii* (*P. jiroveci*) prophylaxis was instituted at the beginning of the preparatory regimen with trimethoprim/sulfamethoxazole for 4 days and reinstituted on day 42 through

discontinuation of immunosuppressive drugs. Patients received prophylactic acyclovir 5 mg/kg if the patient tested positive for herpes simplex virus beginning on day +1 and was discontinued when mucositis resolved. Antifungal therapy with fluconazole 400 mg was given on days +1 through +75. Vancomycin and broad-spectrum antibiotics were started when the patient developed febrile neutropenia. Growth factors were not routinely administered. Weekly quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) surveillance was done on days +21 through +100. Initiation of dihydroxyphenylglycol (ganciclovir) commenced with a single positive PCR of peripheral blood. Intravenous immunoglobulin 500 mg/kg was administered monthly from day −1 until day +100. All blood products were radiated with 2500 cGy and CMV-negative blood products were used for patients who were seronegative for CMV. Platelets were transfused to maintain a platelet count >10 000/μL, and red blood cells were transfused to maintain a hematocrit value >30%. Before November 2002, patients received low-dose heparin 100 U/kg/d by continuous infusion for prevention of hepatic veno-occlusive disease (VOD) and continued until white blood cell engraftment was detected. Subsequent to that date, patients received ursodeoxycholic 6 mg/kg/d as hepatic VOD prophylaxis until day +90.

Tumor staging using computed tomograms were performed at 3, 6, and 12 months after HCT and annually thereafter. Bone marrow biopsies were obtained routinely to assess engraftment and examined for lymphoma and donor chimerism on days 60, 100, 180, and 365 and at years 2, 3, 5, 7, and 10. A physician subsequently examined patients every 2 to 6 months, with chest radiographs performed at each visit and additional radiographic studies ordered as indicated.

Documentation of Hematopoietic Engraftment

The time required for white blood cell engraftment was defined by the first day on which the absolute granulocyte count reached .5 × 10^9/L. Platelet engraftment was defined as unsupported platelet counts >25 × 10^9/L. Engraftment of donor cells was also documented by cytogenetic analyses of recipient marrow cells after transplantation and amplification of highly variable DNA regions (short tandem repeats) of different sex-independent genes by PCR.

Definitions of Toxicity and Response

Early regimen-related toxicity was evaluated according to established transplantation-specific criteria [21]. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded according to consensus criteria [22]. Biopsies were obtained whenever required to confirm the diagnosis.

Statistical Methods

The final follow-up was completed on November 22, 2004, and EFS and overall survival (OS) were estimated with the method of Kaplan and Meier [23] and calculated as the day of bone marrow or peripheral blood hematopoietic cells infusion until the date of final follow-up examination. The relationships between clinical parameters and survival were evaluated using Cox univariate analysis.

RESULTS

Hematologic Reconstitution

All 31 patients engrafted. Median time to recovery of an absolute neutrophil count >.5 × 10^9/L was 11 days (range, 8-16). Similarly, median time to platelet recovery >25 × 10^9/L independent of transfusion in 30 patients who could be evaluated was 16 days (range, 13-27). Median number of days of hospitalization was 23 (range, 18-38).

Clinical Outcome

Outcomes for the 31 patients are listed in Tables 2 to 4. Twenty-one of 31 patients attained CR after HCT at their first evaluation, including 6 who had IFs and 8 who were in PR at the time of transplantation; 7 were in CR at time of transplantation and maintained at CR after HCT. As of November 2004, 15 (48%) were alive and 14 (45%) were without disease at median follow-ups of 11.5 months (.4-126) for all patients and 25.2 months (7.2-126) among the 15 surviving patients. Sixteen patients died. Fifty percent of deaths (n = 8) were due to relapse. The other causes of death included infectious complications (n = 3), GVHD (n = 2), organ toxicities (n = 2), and GVHD in combination with organ toxicity due to VOD (n = 1). Regimen-related toxicities included diffuse alveolar hemorrhage (n = 1), VOD (n = 1), and leukoencephalopathy (n = 1). Five patients died <100 days after transplantation, 10

Table 2. *Clinical Outcome After Allogeneic HCT in NHL by Disease Status*

Disease Status Before Transplantation	Disease Status After Transplantation at First Radiographic Evaluation	No. of Patients
IF	CR	6
PR	CR	8
CR	CR	7
PR	PR	1
PR	SD	1
PR	PD	5
IF	PD	2
CR	PD	1

SD indicates stable disease; PD, progressive disease.

died between day +100 and 1 year after transplantation, and 1 died 1 year after HCT. The most common cause of death at <100 days was organ toxicity (n = 3) and the most common cause of death in the first year after transplantation was relapse (n = 7).

Graft-versus-Host Disease

The actuarial incidence of grade II-IV aGVHD was 29% (2 with grade II, 3 with grade III, and 4 with grade IV). Four patients had gastrointestinal tract GVHD, 3 had involvement of the gastrointestinal tract and the skin, and 2 had liver GVHD. All patients were given CSP and steroids as GVHD prophylaxis and all cases of aGVHD developed while patients were on CSP. Patients who developed aGVHD received further immunosuppressive therapy. Two died of infectious complications. Both patients with liver GVHD died, 1 in the setting of a hepatitis C flare and 1 in the setting of concurrent VOD. One patient subsequently progressed to cGVHD of the lung and eventually died. The remaining 4 responded to treatment.

Twelve patients developed cGVHD (39%); aGVHD in 3 patients progressed to cGVHD and 9 developed de novo cGVHD. Among the 3 with progressive cGVHD, 1 had lung involvement and eventually died, 1 had extensive disease and is alive on active treatment, and 1 had limited disease and responded to local therapy. Among the 9 patients who developed de novo cGVHD, only 1 had extensive disease. The remaining patients (n = 8) had limited involvement. Sites that were involved among these 8 patients included the skin, eyes, mucosa, and pancreas.

Survival Analysis

Probabilities of OS estimated at 1 year and 5 years after allogeneic HCT as determined by the Kaplan-Meier method were 51% (95% confidence interval, 33%-69%) and 47% (29%-65%), respectively. The probability of EFS estimated at 1 year and 5 years was 44% (26%-62%; Figure 1, OS and EFS curves). A plateau in EFS was observed 1 year after HCT.

Among the 8 patients who relapsed and died, all had relapsed within the first 6 months after HCT. Seven died within the first year after transplantation and 1 died 1 year after transplantation. There were no late relapses. Among these 8 patients with early relapse, 3 had transformed NHL and 5 had heavily pretreated intermediate-grade NHL, with a median of 4 previous chemotherapy regimens before HCT.

There were 8 deaths due to nonrelapse causes: 3 from infection, 2 from GVHD, 1 from diffuse alveolar hemorrhage, 1 from VOD in the setting of concurrent liver aGVHD, and 1 from leukoencephalopathy. Probabilities of relapse and NRM were 33% (15%-51%) and 31% (13%-49%), respectively, at 1 year and 5 years (Figure 2, relapse and NRM curves).

Univariate analysis showed that patients who received >3 previous chemotherapy regimens had an increased probability of relapse (P = .004; relative risk, 10; 95% confidence interval, 2-52). All other analyzed clinical parameters (including gender, patient CMV status, donor CMV status, histology, bone marrow involvement, extranodal site involvement, B symptoms, previous radiation, disease status at transplantation, source of hematopoietic cells, and tumor chemosensitivity) were not found to be statistically significantly correlated with OS, EFS, or relapse.

Table 3. *Clinical Outcome by Subgroup Analysis*

	No. of Patients	No. of Relapses	Years to Relapse, Median (range)
Histology			
Low grade	2	0	—
Intermediate grade	21	6	.23 (.02-.34)
High grade	3	0	—
Transformed	5	3	.38 (.19-.48)
Disease status before transplantation			
CR	8	2	.32 (.26-.38)
PR	15	5	.29 (.02-.48)
IF	8	2	.18 (.16-.19)
Chemosensitivity to final treatment			
Chemosensitive	23	7	.29 (.02-.48)
Chemoresistant	8	2	.18 (.16-.19)

Table 4. *Clinical Outcome Based on Survival*

	Patients, n (%)
Alive	15 (48)
No evidence of disease	14
Relapse	1
Deceased	16 (52)
Relapse mortality	8 (26)
NRM	8 (26)
Infections	3
GVHD*	2
Diffuse alveolar hemorrahge	1
VOD and liver GVHD	1
Leukoencephalopathy	1
Early (<100 d after transplantation)	5 (16)
Infections	1
Toxicity†	3
Relapse	1
Day +100 to 1 y after transplantation)	10 (32)
Infections	2
GVHD	2
Relapse	6
Late (>1 y after transplantation)	1 (3)
Relapse	1

*Acute (grade III) in liver (n = 1), chronic in lung.
†Diffuse alveolar hemorrhage (n = 1), VOD with GVHD (n = 1), and leukoencephalopathy (n = 1).

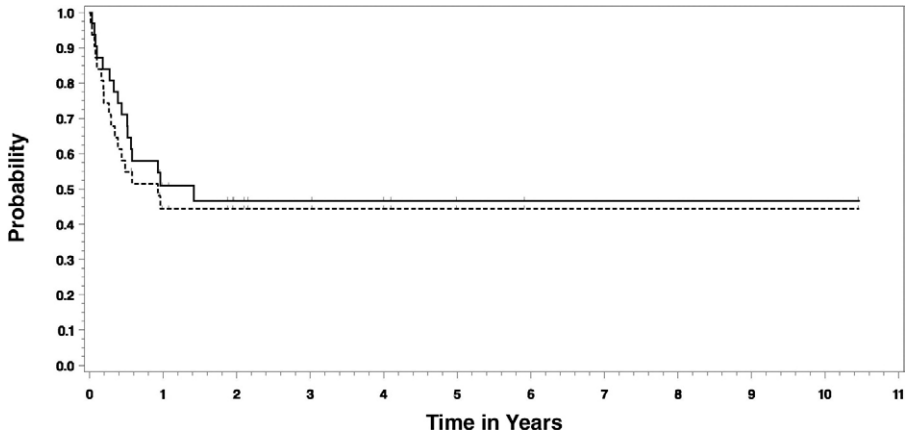

Figure 1. OS (solid line) and EFS (dashed line) probabilities for 31 patients treated with CBV followed by allogeneic HCT.

DISCUSSION

Autologous HCT is the standard of care for patients with chemotherapy-sensitive recurrent NHL [3]. However, for those with chemotherapy-resistant/refractory or high-grade aggressive disease, autologous HCT rarely produces durable remission. In this study, patients were selected for an allograft because of their high-risk NHL, with most having been heavily pretreated or having a short disease-free interval or IF or an autograft was judged to be insufficient to provide long-term remission and survival.

TBI-based regimens are commonly used as part of myeloablative preparative regimens in allogeneic bone marrow transplantation for patients with hematologic malignancies [15,24,25]. The nonradiation-based conditioning regimen with high-dose CBV was first reported in 1987 by Zander et al [26] to be successful in allowing durable engraftment in patients with acute leukemia who received allogeneic bone marrow transplants. In a comparative analysis, this chemotherapy-only preparatory regimen was found to be equivalent in outcome to TBI-based therapy in autotransplantation for NHL [14].

Allogeneic HCT for aggressive NHL has been assessed in several single-arm cohort studies. Most of these studies had small numbers of patients and comprised heterogeneous groups of patients with different histologies and stages of disease. In addition, there was a variety of preparative regimens, ranging from radiation based [27-29] to nonradiation based [30-34]. Doocey et al [29] recently reported similar EFS and OS values of 40%-50% after using a primarily TBI-based conditioning regimen in an allogeneic setting, although their patient cohorts were less heavily pretreated and had more interstitial pneumonitis than did those in our present report. CBV as a preparative regimen has also been reported by Demirer et al [30] and Rossi et al [33], with comparable results. Based on the results of these studies, it is apparent that a subset of patients achieve long-term disease-free survival with allogeneic HCT despite recurrent, refractory, or high-risk disease at the time of transplantation. This finding suggests the advantage of a tumor-free graft and potential GVL effectiveness.

Evidence of a GVL effect has been conflicting, primarily due to lack of randomized studies [35,36]. Different comparative trials have reported improved outcomes for patients who received an allogeneic

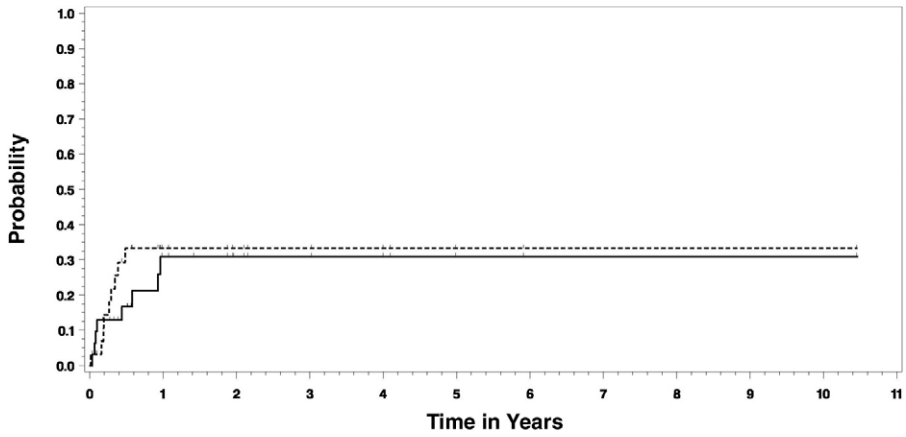

Figure 2. Probabilities of NRM (solid line) and relapse (dashed line) for 31 patients treated with CBV followed by allogeneic HCT.

HCT [12,37]. In a large retrospective analysis by the European Bone Marrow Transplantation Registry (EBMT), allogeneic transplantation was associated with a lower relapse rate than was autologous transplantation [37]. Further, lower relapse rates had been reported in the presence of GVHD [38]. In addition, disease response to withdrawal of immunosuppression and donor lymphocyte infusion has been reported [10,39]. Unfortunately, due to high procedure-related mortality with allogeneic transplants, the GVL effect has not been correlated with superior OS despite its association with a lower relapse rate, as demonstrated in the EBMT analysis [37]. Conversely, other small trials have not consistently demonstrated the correlation of decreased relapse rates with allogeneic HCT over autologous HCT [40]. A comparative analysis by Bierman et al [41] showed no difference in relapse rates after syngeneic HCT versus allogeneic HCT. In the analysis by Dhedin et al [10], there was no influence of GVHD on relapse.

In the present study, the GVL effect is supported by the finding that none of the 12 patients who developed cGVHD has recurrent disease. For those patients who relapsed, donor lymphocyte infusion was not performed due to rapidly progressive disease, although it may still have a curative role in patients whose disease is indolent in nature or when the relapse is aggressive but enters a minimal disease state after cytoreductive therapy.

The importance of chemosensitivity in determining outcome after allogeneic HCT has been shown in multiple studies [7,10,12,28,38,42]. In our study, no correlation was demonstrated between disease status and survival. Eight of the 31 patients in the present study had IF before transplantation. Of these 8 patients, 6 were converted to CR at the time of their first radiographic evaluation. One possible explanation for this finding is the potential effectiveness of our preparative regimen and the presumed GVL effect from the graft itself. Another explanation is that our patients were heterogeneous in histology and disease status such that a significant difference was not detected. Nevertheless, the initial success of being able to convert from IF to CR after allogeneic HCT can be further improved by post-transplant therapies such as early donor lymphocyte infusion, infusion of cytokine-induced killer cells [43], antibodies to CD20, or radiolabeled antibodies to anti-CD20 to decrease future relapse.

Myeloablative allogeneic HCT in NHL still has substantial morbidity and mortality. High NRM has been reported to be in the range of 20%-50% [10,28]. In the present trial, the NRM was 26%, with 10% of patients dying of treatment-related organ toxicity. Idiopathic pneumonitis can be a fatal complication after allogeneic HCT. For patients who received TBI-based therapy, development of idiopathic pneumonitis ranged from 9% to 23% [27-29]. For those who received non-TBI regimens, incidences from 6% to 16% have been reported [30,33]. In our study with CBV, none of our patients (including 3 who had previous chest radiation) developed documented idiopathic pneumonitis. This further supports CBV as an alternative to TBI-based regimens, especially for those who previously received mediastinal radiation.

Nonmyeloablative or decreased-intensity allogeneic hematopoietic transplants have been studied for NHL. Such preparative regimens result in low transplantation-related mortality and high 2-year OS of 62%-71% [44-50]. Faulkner et al [49] found the addition of anti-CD52 antibody (alemtuzumab) further decreased GVHD without increasing the risk of infection. A nonmyeloablative approach may be an alternative for patients with chemosensitive, low-bulk, stable disease at the time of transplantation.

In the present study, despite the incidences of relapse and NRM, it is important to note that most events occurred within the first year of transplantation. For those 8 patients who relapsed, 7 relapsed and died within the first year of transplantation. Moreover, for those who died of nonrelapse causes (n = 8), all died within the first year. This is evident in the plateau shown in the EFS curve in Figure 1. This finding suggests that the chance of relapse or other transplantation-related mortality is very minimal 1 year after HCT.

In conclusion, CBV as a preparative regimen for allogeneic transplantation in combination with CSP and PSE as GVHD prophylaxis has acceptable toxicity and is an effective therapy in patients with relapsed or high-risk NHL. A proportion of these patients achieve long-term survival despite an aggressive disease status before HCT. Further, this study further demonstrates evidence of a durable GVL effect. For patients with aggressive NHL, myeloablative HCT using CBV as conditioning therapy remains a viable option. Novel strategies are needed to further minimize regimen-related toxicity, GVHD, and relapse.

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