

Allogeneic Bone Marrow Transplantation in Patients With Sensitive Low-Grade Lymphoma or Mantle Cell Lymphoma

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ABSTRACT

Purpose: To report survival outcomes of allogeneic BMT in patients with low-grade lymphoma or mantle cell lymphoma (MCL).

Patients and Methods: Thirty-five patients with low-grade lymphoma (48%), chronic lymphocytic leukemia (26%), or MCL (26%) underwent myeloablative allogeneic BMT from HLA-identical siblings at the Johns Hopkins Oncology Center. Patients had a median age of 46 years, a median of 2 prior treatments, and 31% were in complete remission at the time of transplantation. The preparative regimen was cyclophosphamide/total body irradiation for most patients. All grafts were T-cell depleted by counter flow centrifugal elutriation with CD34⁺ augmentation.

Results: The incidence of acute GVHD grade >2 was 6% and of grades 1 to 2 was 37%. The incidence of chronic GVHD was 6%. The median follow-up time was 25 months. The rate of event-free survival (EFS) was 50% (95% confidence interval [CI], 33%-66%). Only 1 patient relapsed. The transplantation-related mortality (TRM) was 46% for all patients. The TRM was 86% for patients with resistant disease and 14% for patients with sensitive disease and <2 prior treatments; rates of EFS were 0% (95% CI, 0%-0%) and 79% (95% CI, 47%-93%), respectively.

Conclusion: These data show that, with T-cell depletion, the TRM and relapse rates are modest for patients with sensitive disease and <2 prior treatment courses. Thus, if there is a role for allogeneic BMT in the management of patients with these tumors, it is early in the course of the disease.

KEY WORDS

AlloBMT • Mantle cell lymphoma • Event-free survival • Transplantation-related morbidity
• Graft-versus-lymphoma effect • Chronic lymphocytic leukemia • Follicular lymphoma

INTRODUCTION

Low-grade lymphoma and chronic lymphocytic leukemia (CLL) are indolent lymphoproliferative disorders with median survival times of 7 to 10 years [1-4]. Despite this indolent course, patients with higher stages of the disease, as well as those refractory to initial treatments have median survival times of less than 2 to 4 years [4,5]. There are many available therapies for these disorders, but relapse almost inevitably occurs [4]. Mantle cell lymphoma (MCL) is also incurable with standard chemotherapies but has a more aggressive course, with a median survival of 3 years [4,6].

High-dose therapy with autologous blood or bone marrow transplantation (BMT) has been performed successfully,

and the toxicity observed is comparable to that observed in other diseases with this procedure. Several investigators have reported on their results of durable remissions [7-14]. However, many of these studies with longer follow-up times report a continuous relapse rate, suggesting that autologous BMT is similar to other chemotherapy modalities in its failure to cure these diseases [11,12,15-17]. In addition, myelodysplasia is emerging as an important problem, occurring in up to 20% of patients in some series [18-20].

Allogeneic BMT offers several potential advantages over autologous transplantation: it has graft-versus-lymphoma (GVL) effect; it is a source of stem cells free of neoplastic cells; and the marrow has not been exposed to chemotherapy

mutagens. Although the use of allogeneic transplantation in cases of low-grade lymphomas and CLL has been reported from many centers [15,17,21-37], the median older age of the patient population, the high rates of graft-versus-host disease (GVHD), and associated high transplantation-related mortality (TRM) have limited the use of this approach. We report the results of 35 consecutive patients with low-grade lymphoma, CLL, or MCL who underwent T cell-depleted allogeneic BMT by elutriation at the Johns Hopkins Oncology Center.

PATIENTS AND METHODS

Patients

Thirty-five consecutive patients with diagnoses of low-grade lymphoma (n = 17), CLL/small lymphocytic lymphoma (SLL) (n = 9), or MCL (n = 9), according to the Working Formulation or REAL (Revised European American Lymphoma) classifications [38,39], underwent allogeneic BMT from HLA-identical siblings between January 1992 and September 1, 1999 at the Johns Hopkins Oncology Center. Patients with follicular large cell lymphoma or transformation to a high-grade lymphoma prior to transplantation were excluded. All pathology specimens were reviewed by the Pathology Department at Johns Hopkins University. All patients met the following protocol eligibility criteria: (1) age, ≥ 60 years; (2) Karnofsky Performance Score, $\geq 70\%$; (3) left ventricular ejection fraction, $\geq 45\%$; (4) both forced expiratory volume in 1 second and diffusing capacity for carbon monoxide, $\geq 50\%$ (75% in patients who received thoracic irradiation); (5) total bilirubin, ≤ 2.0 mg/dL; (6) creatinine, < 2.0 mg/dL; and (7) human immunodeficiency virus, negative. All patients provided written informed consent and were treated with protocols approved by the institutional review board.

Disease response was evaluated according to standard criteria for non-Hodgkin's lymphoma [40] and CLL [41]. Sensitive disease was defined as achieving at least a partial remission with the last chemotherapeutic intervention prior to allogeneic BMT.

Conditioning Regimens

Thirty-one patients received cyclophosphamide, 50 mg/kg per day, intravenously (IV) for 4 days followed by total body irradiation (TBI), 1200 cGy, given as 300 cGy/d \times 4 days at a rate of 9 to 10 cGy/min, with the lungs shielded beginning on the third day of treatment [42]. Four patients who had received radiation prior to transplantation received busulfan 1 mg/kg per dose orally (PO) every 6 hours for 16 doses over 4 days, with dosing adjusted on the second and subsequent days based on pharmacokinetic studies and the area under the curve of busulfan. The 4 patients then received cyclophosphamide, 50 mg/kg per day, IV for 4 days [43].

Donors

The donor marrow sources were HLA-matched siblings in all cases. All grafts were manipulated by T-cell depletion using counter flow centrifugal elutriation along with CD34⁺ augmentation via positive selection [44,45]. This procedure resulted in a reduction of T cells in the graft to an average of 5.5×10^5 CD3⁺ T cells/kg.

Supportive Care

All patients were treated in HEPA filtered rooms with reverse isolation and received GVHD prophylaxis consisting of cyclosporin A, 5 mg/kg per day IV, with rapid conversion to oral dosing and a target maintenance dose of 7.5 mg/kg per day PO for a period of 6 months. Each patient received infection prophylaxis consisting of fluconazole, vancomycin, and an oral fluoroquinolone. Patients positive for herpes simplex virus received acyclovir or a derivative as prophylaxis. Pneumocystis prophylaxis was trimethoprim/sulfamethoxazole or aerosolized pentamidine for a minimum of 6 months following transplantation and longer if immunosuppressive agents were continued for management of GVHD. Blood products were irradiated.

Posttransplantation Evaluation and Response Criteria

All patients were followed daily until full engraftment occurred and all acute issues were resolved. Patients then underwent scheduled evaluations, including complete tumor measurements, at approximately day 100, 6 months, and once a year thereafter. GVHD was graded according to standard criteria [46,47].

Statistical Methods

The primary treatment outcomes evaluated were event-free survival (EFS) and TRM. EFS was defined as survival without any evidence of lymphoma posttransplantation. For EFS evaluation, patients were censored at the time of relapse or death from any cause; patients alive in continuous remission were censored at the last follow-up evaluation. TRM was defined as any death occurring within the first 100 days after transplantation or any death determined to have occurred as a direct result of the transplantation procedure. Other outcomes evaluated included rates of both acute GVHD and chronic GVHD.

Event-time distributions were estimated using the method of Kaplan and Meier [48] and compared using the log-rank statistic [49] or the proportional hazards regression model [50]. Factors tested for prognostic value included age, diagnosis, sex, patient/donor-sex mismatch, preparative regimen, resistance of disease, cytomegalovirus (CMV) positivity, and fludarabine use. In univariate analysis, the number of previous treatments was entered as a continuous effect and the relative hazard reflects the risk of death per unit change in the value of the factor. Other variables were entered as binary effects and the estimated hazard ratios (HRs) for these factors reflect either their presence or absence. Diagnosis is a categorical variable for more than 2 groups, and the HRs are expressed relative to the CLL group having been arbitrarily chosen as the reference category.

All *P* values reported are 2-sided. Computations were performed using the Statistical Analysis System [51] or EGRET software [52].

RESULTS

Patient Characteristics

Patient characteristics for the entire cohort are listed in Table 1. The median age of the cohort was 46 years. The majority of patients had advanced-stage disease and only 31% were in complete remission at the time of transplantation. Of

Table 1. Patient Characteristics*

Characteristic	No. of Patients	Percentage of Total	Median (Range)
Total patients	35	100%	
Male patients	23	66%	
Age at transplantation, y			46 (26-61)
Patient age			
≥40 years	28	80%	
<40 years	7	20%	
Recipient CMV-positive serology	19	54%	
Histology			
Small lymphocytic/CLL	9	26%	
Follicular small-cleaved	6	17%	
Follicular mixed	10	27%	
Mantle cell	9	26%	
MALT	1	3%	
Disease stage at diagnosis (non-CLL)			
I	1	3%	
II	3	10%	
III	8	27%	
IV	16	53%	
Disease stage at diagnosis for CLL using modified Rai staging			
Low	2	29%	
Intermediate	4	57%	
High	1	14%	
Patients in CR at transplantation	11	31%	
Response to chemotherapy			
Sensitive	28	80%	
Resistant	7	20%	
Prior treatment regimens, n			2 (1-6)
Time interval from diagnosis to BMT, mo			21 (5-144)
Year of transplantation			
1994-1996	9	26%	
1997-1999	26	74%	
Donor-recipient sex match			
M-M	6	17%	
M-F	4	11%	
F-M	16	46%	
F-F	8	23%	
Unknown	1	3%	
Conditioning regimen			
Cy/TBI	31	89%	
Bu/Cy	4	11%	
Fludarabine treatment prior to BMT	12	34%	

*MALT indicates mucosa-associated lymphoid tumors; CR, complete remission; Cy, cyclophosphamide; Bu, busulfan.

the patients, 80% were considered sensitive to the treatment regimen given immediately prior to transplantation. The median number of treatments received prior to transplantation was 2 (range, 1-6).

Outcomes

The median time to an absolute neutrophil count of $>500 \times 10^9/L$ for 2 consecutive days was 18 days; the median time to a transfusion-independent platelet count of $>20 \times 10^9/L$ was 16 days.

Sixteen (46%) patients died of transplantation-related causes (Table 2). Transplantation-related deaths were divided into early and late. An early death was defined as any death occurring within 100 days after transplantation. A late death was defined as any death occurring more than 100 days after transplantation. Conditioning-regimen toxic-

ity, late infections, multiorgan failure, and pulmonary toxicity were the most common causes of TRM.

The rate of acute GVHD grade >2 was 6%. The rate of acute GVHD grade 1 and grade 2 was 37%. Chronic GVHD was seen in only 2 patients (6%). Only 1 patient died of GVHD.

At a median follow-up of 25 months, the EFS rate was 50% (95% CI, 33%-66%) (Figure 1). An increasing number of previous treatments, resistant disease, and diagnosis of MCL, follicular mixed lymphoma (FML), or follicular small-cleaved lymphoma (FSC) were significant factors associated with lower EFS rates in univariate analyses (Table 3). Patients with resistant disease had a hazard ratio of 4.44 (95% CI, 1.49-13.2), $P = .007$, compared to those not having resistant disease. Compared to patients with CLL, patients with MCL, FML, and FSC had significantly

Table 2. Causes of Death*

	No. of Patients	Percentage of Total
Transplantation related	16	46%
Early death†	10	
Pulmonary	3	
Multiorgan failure	3	
VOD	1	
CNS hemorrhage	1	
Lymphoma	1	
Infection	1	
Late death‡	6	
Late infections	3	
HUS	1	
Multiorgan failure	1	
GVHD	1	
Progressive disease	1	3%
Pulmonary	1	3%
Subsequent malignancy‡	1	3%

*VOD indicates veno-occlusive disease; CNS, central nervous system; HUS, hemolytic uremic syndrome.

†Early death is defined as death within the first 100 days posttransplantation; late death, after 100 days posttransplantation.

‡This patient died of an unrelated pancreatic carcinoma 5 years after transplantation, without evidence of recurrence of original lymphoproliferative disease.

lower EFS rates: HR = 13.1 (95% CI, 1.59-108.8), $P = .02$; HR = 9.84 (95% CI, 1.16-83.2), $P = .04$; and HR = 7.89 (95% CI, 0.92-68.0), $P = .06$, respectively. An increasing number of previous treatments was also associated with a lower EFS rate (HR = 1.49 [95% CI, 1.07-2.07]), $P = .02$. Patients given fludarabine had a slightly improved EFS rates (HR = 0.56 [95% CI, 0.20-1.56]), but this finding was not significant ($P = .27$). Age, CMV positivity, sex, and patient/donor-sex mismatch were not prognostic for EFS.

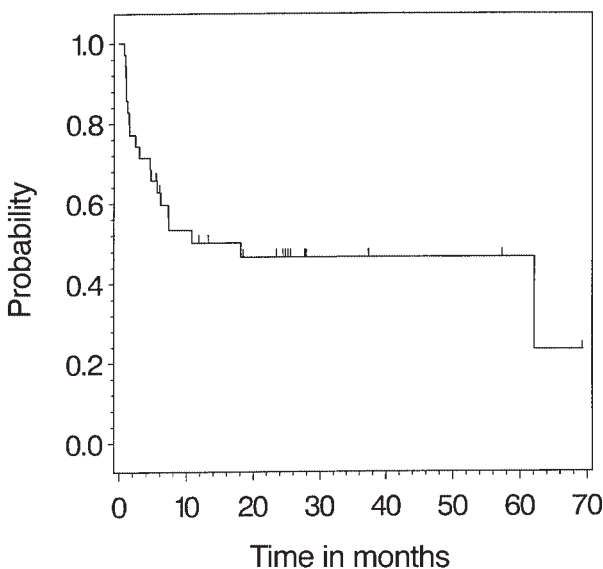


Figure 1. Event-free survival. The Kaplan-Meier EFS rate at a median follow-up of 25 months for the entire cohort of 35 patients was 50% (95% CI, 33%-66%).

Table 3. Factors Tested for Effect on Survival of Patients With Low-Grade Lymphoma and CLL: Univariate and Multivariate Analyses

	Hazard Ratio	95% CI	P
Univariate analysis			
Fludarabine use	0.56	0.20-1.56	.27
Recipient CMV positivity	0.79	0.32-1.95	.61
Age	1.07	0.99-1.12	.07
Recipient/donor sex mismatch	1.20	0.48-3.01	.69
Male sex	1.91	0.63-5.85	.26
Increasing no. of prior treatments	1.49	1.07-2.07	.02
Resistant disease	4.44	1.49-13.2	.007
Diagnosis			
FSC	7.89	0.92-68.0	.06
FML	9.84	1.16-83.2	.04
MCL	13.13	1.59-108.8	.02
Multivariate analysis			
Diagnosis			
MCL	14.29	1.19-120.5	.01
FML/FSC	5.31	0.67-42.18	.11
>1 Previous treatment	3.76	1.00-14.18	.05
Resistant disease	2.95	0.91-9.50	.07

Adjusting for previous treatments and resistant disease, patients with MCL had an HR of 14 (95% CI, 1.2-120.5) compared to the CLL patients ($P = .01$). FML and FSC likewise had an adverse effect on EFS (HR = 5.3 [95% CI, 0.7-42.2]), but this result was not significant ($P = .11$). Previous treatments were grouped to compare patients with only 1 previous treatment to those having >1 previous treatment. Adjusting for diagnosis and resistant disease, those with >1 previous treatment had 3.8 times the risk of lower EFS rates (95% CI, 1.00-14.18) than the group with only 1 prior treatment ($P = .05$). Resistant disease also increased the risk of a lower rate of EFS; HR = 3.0 (95% CI, 0.91-9.50), $P = .07$, after adjustment for diagnosis and previous treatments.

After adjusting for histologic diagnosis and using the 2 most significant parameters predictive of a worse outcome, resistant disease and >1 treatment prior to transplantation, distinct differences in the TRM and overall survival emerged. The TRM for patients with resistant disease and ≥ 2 prior treatments was 86%. The TRM for patients with sensitive disease and ≥ 2 prior treatments was 57%. On the other hand, the TRM for patients with sensitive disease and <2 prior treatments was 14% (Table 4). Similarly, the Kaplan-Meier EFS curves for these 3 groups are shown in Figure 2. At a median follow-up time of 25 months, the EFS rate was 79% (95% CI, 47%-93%) for the sensitive and <2-prior-treatments group, 32% (95% CI, 10%-57%) for the sensitive and ≥ 2 -prior-treatments group, and 0% (95% CI, 0%-0%) for the resistant and ≥ 2 -prior-treatments group. The patient characteristics of the 3 groups are shown in Table 5. Finally, the EFS was 23.3% (95% CI, 7.5%-44%) and the TRM was 62% for the group of patients with ≥ 2 prior treatments, regardless of disease sensitivity.

DISCUSSION

The TRM of 46% and the EFS of 50% reported in the present series is in line with previously published reports

Table 4.
Transplantation-Related Mortality (TRM) by Disease Sensitivity

Total TRM	46%
TRM in patients with resistant disease and ≥ 2 prior treatments	86%
TRM in patients with sensitive disease and ≥ 2 prior treatments	57%
TRM in patients with sensitive disease and < 2 prior treatments	14%

from various investigators on allogeneic BMT in low-grade lymphomas [21-37]. The largest of these studies was the International Bone Marrow Transplant Registry series, which reported an EFS of 49%, TRM of 40%, acute GVHD of 27%, and chronic GVHD of 66% [31]. Furthermore, small series suggest that MCL patients appear to have a poor outcome following allogeneic BMT [53-54]. Likewise, in the series reported here, carrying the diagnosis of MCL was the strongest negative predictor for outcome.

Interestingly, however, the data presented here suggest that it may be possible to stratify prospective allogeneic transplant recipients into distinct risk groups regardless of their individual histologies. Figure 2 clearly identifies 3 distinct groups of patients with divergent rates of both TRM and overall survival depending on the presence of 0, 1, or 2 risk factors. Risk factors predicting an adverse outcome identified by multivariate analysis were resistant disease and ≥ 1 treatment course prior to transplantation. The group with both risk factors had a high TRM of 86% and none of these patients was alive at 6 months. The group expressing 1 factor (> 1 prior treatment; there were no patients with resistant disease and ≤ 1 prior treatment) had an intermediate TRM rate of 57% and an EFS of 32% at a median follow-up of 25 months. The group expressing neither of these risk factors had a TRM of only 14% and EFS of 79% at a median follow-up of 25 months. Similarly, the high TRM of 62% and EFS

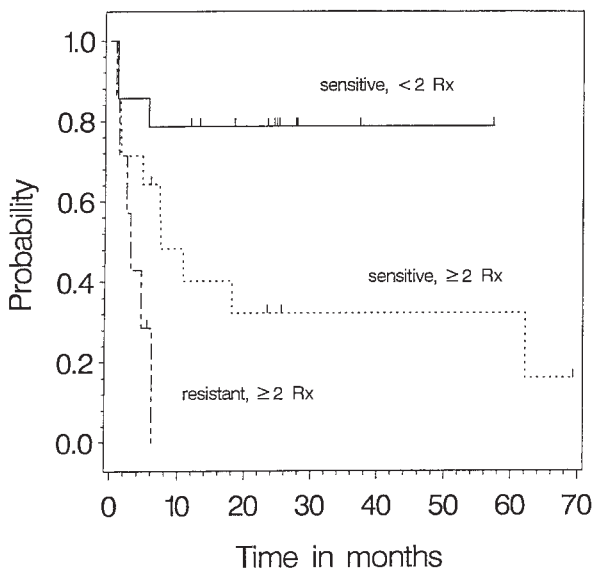


Figure 2. Event-free survival. The Kaplan-Meier EFS rates for 3 distinct subgroups, based on the presence of no risk factors, 1 risk factor, or 2 risk factors (both resistant disease and > 1 prior treatment). At a median follow-up of 25 months, the EFS rates were 79%, 32%, and 0%, respectively. Rx indicates treatments.

Table 5.
Patient Characteristics for Select Subgroups

	All Patients	Sensitive, < 2 Rx	Sensitive, ≥ 2 Rx	Resistant, ≥ 2 Rx
No. of patients	35	14	14	7
Male patients	66%	43%	79%	86%
Median age, y	46	43	46	53
Histology				
SLL/CLL	9 (26%)	5 (36%)	3 (21%)	1 (14%)
Follicular	16 (46%)	3 (21%)	9 (64%)	4 (57%)
MCL	9 (26%)	5 (36%)	2 (14%)	2 (28%)
MALT	1 (3%)	1 (7%)	0 (0%)	0 (0%)
Median interval to BMT, mo	21	10	31	27
Acute GVHD (grade ≥ 2)	31%	7%	43%	43%
Chronic GVHD	6%	0%	14%	0%
No. of patients relapsed	1	0	1	0

rate of 23% in the group with ≥ 2 prior treatments further illustrate the prognostic implication of prior treatments alone for outcome. The characteristics of the patients in each subset are depicted in Table 5. The patients in the 2-risk-factor group were slightly older than the patients in the other 2 groups, but there was no significant difference in age between the 0- and 1-risk-factor groups, although they still showed significantly different outcomes. The subgroup numbers were too small to determine statistical significance, but it should be noted that age alone was not a significant risk factor predicting poor outcome in univariate analysis of the entire group. The 0-risk-factor group had a slightly higher number of CLL patients, but had an even greater number of MCL patients, which likely balances the prognostic implications of the different histologies in the various groups.

The rates of acute and chronic GVHD seen in this cohort compare favorably to that reported in the literature of mixed and/or non-T-cell-depleted populations [23,27,28,31,33,35]. The difference was especially striking in the extremely low rates of grades 3 and 4 acute GVHD and chronic GVHD observed. Another important observation is that the rates of acute GVHD in the different subsets stratified by risk factors were quite different and may partly account for the different rates of TRM observed. The group without any adverse risk factors had an incidence of 7% acute GVHD and 0% chronic GVHD. The group with 1 adverse risk factor had incidences of 43% acute GVHD and 14% chronic GVHD. Finally, the group with 2 risk factors had incidences of 43% acute GVHD and 0% chronic GVHD. The low rate of chronic GVHD observed in the latter group is not unexpected given the lack of survivors beyond the 6-month interval. This data points to the relative importance of controlling GVHD and subsequent TRM. The low rates observed are likely due to the use of T-cell depletion by elutriation as has been reported by this group for other disease subsets [44,45].

A concern with any T-cell-depletion protocol is the potential adverse impact on the GVL effect. T-cell depletion by elutriation as used in this cohort of patients causes significant but incomplete T-cell depletion. Furthermore, relapse rates with T cell-depleted BMT in lymphoma and other hematologic disorders similar to those observed in nonmanipulated grafts have been reported [36,44]. The

pattern of minimal relapse in this cohort of patients at 25 months post-BMT suggests a potential GVL effect, although longer follow-up will be paramount given the potential for late relapses in these patients.

The data reported in this retrospective study challenges the common practice of reserving allogeneic BMT as a modality of last resort. Instead, the low rates of GVHD and subsequent low TRM seen in patients with sensitive disease and <2 prior treatments suggest that if there is a role for allogeneic BMT in the treatment of patients with low-grade or mantle cell lymphomas, it is early in the course when patients have sensitive disease and have not been heavily treated. Long-term follow-up will determine whether this decrease in transplantation-related mortality will ultimately translate into an increase in survival for this patient population. The high TRM in the patients with >1 prior treatments and/or resistant disease should prompt further investigation in this patient population with alternate transplantation techniques, such as the use of nonmyeloablative allogeneic or purged autologous BMT or enrollment in clinical trials.

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