Biol Blood Marrow Transplant 19 (2013) 625–631

Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Unresponsive Mantle Cell Lymphoma: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research

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Article history:
Received 5 November 2012
Accepted 15 January 2013

Key Words:
Non-Hodgkin lymphoma
Myeloablative conditioning
Reduced intensity conditioning
Chemorefractory disease
Graft-versus-host disease

A B S T R A C T

Patients with chemorefractory mantle cell lymphoma (MCL) have a poor prognosis. We used the Center for International Blood and Marrow Transplant Research database to study the outcome of 202 patients with refractory MCL who underwent allogeneic hematopoietic cell transplantation (allo-HCT) using either myeloablative (MA) or reduced-intensity/nonmyeloablative conditioning (RIC/NST), during 1998-2010. We analyzed nonrelapse mortality (NRM), progression/relapse, progression-free survival (PFS), and overall survival (OS). Seventy-four patients (median age, 54 years) received MA, and 128 patients (median age, 59 years) received RIC/NST. Median follow-up after allo-HCT was 35 months in the MA group and 43 months in the RIC/NST group. At 3 years post-transplantation, no significant between-group differences were seen in terms of NRM (47% in MA versus 43% in RIC/NST; $P = .68$), relapse/progression (33% versus 32%; $P = .89$), PFS (20% versus 25%; $P = .53$), or OS (25% versus 30%; $P = .45$). Multivariate analysis also revealed no significant between-group differences in NRM, relapse, PFS, or OS; however, receipt of a bone marrow or T cell–depleted allograft was associated with an increased risk of NRM and inferior PFS and OS. Our data suggest that despite a refractory disease state, approximately 25% of patients with MCL can attain durable remission after allo-HCT, and conditioning regimen intensity does not influence outcome of allo-HCT.

INTRODUCTION

Mantle cell lymphoma (MCL) accounts for approximately 6% of non-Hodgkin lymphomas (NHL) and typically presents as advanced-stage disease that frequently involves bone marrow, peripheral blood, and extranodal sites [1]. MCL generally follows an aggressive clinical course, with frequent relapses after conventional chemotherapy regimens. Over the last decade, strategies including multiagent immunochemotherapy either alone [2] or as induction therapy, followed by consolidation with high-dose therapy and autologous hematopoietic cell transplantation (auto-HCT) [3-5] or rituximab maintenance [6,7], have produced higher response rates and improved disease-free survival. Although these modalities have undoubtedly improved the prognosis of patients with MCL [8], the disease course remains characterized by frequent relapses. After first relapse, the prognosis of MCL is poor, with a median survival of approximately 1-2 years [9]. This is especially true for patients with relapsed MCL with chemotherapy-refractory disease.

The results of auto-HCT in patients with chemorefractory MCL have been uniformly disappointing [10-12]. Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially

Financial disclosure: See Acknowledgments on page 630.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.01.009

curative modality for a variety of hematologic malignancies, including indolent and aggressive lymphomas [13-17]. Advantages of allo-HCT include a tumor-free graft, as well as a potential allogeneic effect exerted by donor T cells, known as the graft-versus-lymphoma effect.

Despite the greater risk of transplantation-related morbidity and mortality with allo-HCT, selected patients with relapsed MCL, especially those with chemosensitive disease, can achieve long-term remission after allo-HCT [18-20]. Patients with MCL who are refractory to salvage chemotherapy have a very poor prognosis, however, and only limited data are available on outcomes after allo-HCT in this extremely high-risk group. However, because the graft-versus-lymphoma effect can occur even in the absence of chemosensitivity, in theory allo-HCT may still offer benefits even in chemoresistant patients. Moreover, the influence of conditioning regimen intensity—that is, myeloablative (MA) conditioning versus reduced-intensity conditioning (RIC) or nonmyeloablative conditioning (NST) regimens—in this uniquely chemorefractory cohort of patients is not known. Here we report outcomes of allo-HCT in patients with refractory MCL relative to the intensity of pretransplantation conditioning regimens using the observational database of the Center for International Blood and Marrow Transplant Research (CIBMTR). This report represents the largest study of patients with chemotherapy-unresponsive MCL undergoing allo-HCT to date.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program (NMDP) established in 2004. Both the IBMTR and the NMDP had been collecting data for more than 1 decade before the establishment of the CIBMTR. The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive auto-HCTs and allo-HCTs to a Statistical Center at the Medical College of Wisconsin, Milwaukee, Wisconsin and the NMDP Coordinating Center in Minneapolis, Minnesota.

Participating transplantation centers are required to report all HCTs consecutively, with compliance monitored by onsite audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' reviews of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with HIPAA regulations as a public health authority and in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by continuous review of the Institutional Review Boards of the NMDP and the Medical College of Wisconsin since 1985.

The CIBMTR collects data at 2 levels: transplant essential data (TED) and comprehensive report form (CRF) data. TED data include disease type, age, sex, pretransplantation disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow– and/or blood-derived progenitor cells), conditioning regimen, post-transplantation disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR teams contribute TED data. More detailed disease and pretransplantation and post-transplantation clinical information are collected from a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF level data are collected pretransplantation, at 100 days post-transplantation, at 6 months post-transplantation, and annually thereafter up to death.

Patients

The study population included all patients with chemotherapy-unresponsive MCL who underwent allo-HCT reported to the CIBMTR between 1998 and 2010. Patients with evidence of chemosensitive disease (ie, those in complete remission or partial remission [PR]) at the time of allo-HCT were excluded. Pediatric patients (n = 5) and recipients of planned tandem auto/allo-HCT (n = 50), syngeneic HCT (n = 7), and umbilical cord blood transplantation (n = 29) were not included in the analysis. The patient- and disease-related variables that are not reported for registration-only patients are indicated in Table 1.

Definitions

Conditioning regimens were categorized based on intensity as either MA or RIC/NST using established consensus criteria [21]. Previously established criteria for categorizing the degree of HLA matching were used for unrelated donor transplants [22]. Well-matched patients had either no identified HLA mismatching and informative data at 4 loci or allele matching at HLA-A, -B, and -DRB1 (6/6). Partially matched pairs had a defined, single-locus mismatch and/or missing HLA data. Mismatched cases had 2 or more allele or antigen mismatches.

Study Endpoints

Primary outcomes were nonrelapse mortality (NRM), progression/relapse, progression-free survival (PFS), and overall survival (OS). NRM was defined as death from any cause during the first 28 days after transplantation or death without evidence of lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete remission; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. For relapse, NRM, and PFS, patients alive without evidence of disease relapse or progression were censored at last follow-up. OS was defined as the interval from the date of transplantation to the date of death or last follow-up.

Other outcomes analyzed included acute and chronic graft-versus-host disease (GVHD) and cause of death. Acute GVHD was defined and graded based on the pattern and severity of organ involvement using established criteria [23]. Chronic GVHD was defined as the development of any evidence of chronic GVHD based on clinical criteria [24]. Neutrophil engraftment was defined as the first of 3 successive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L after a post-transplantation nadir. Platelet engraftment was considered to have occurred on the first of 3 consecutive days with a platelet count $\geq 20 \times 10^9$/L, in the absence of platelet transfusion for 7 consecutive days. For engraftment and GVHD, death without the event was considered a competing risk.

Statistical Analysis

Probabilities of PFS and OS were calculated using the Kaplan-Meier estimator, with variance estimated using the Greenwood formula. Probabilities of NRM, lymphoma progression/relapse, acute and chronic GVHD, and engraftment were calculated using cumulative incidence curves to accommodate for competing risks [25]. Patient-, disease-, and transplantation-related factors were compared between the RIC/NST and MA groups using the χ^2 test for categorical variables and the Wilcoxon 2-sample test for continuous variables. Associations among patient-, disease-, and transplantation-related variables and outcomes of interest were evaluated using multivariate Cox proportional hazards regression. A stepwise selection multivariate model was built to identify covariates that influenced outcomes. Covariates with a P value $<.05$ were considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were stratified in the Cox regression model. Results are expressed as relative risk (RR) or the relative rate of occurrence of the event.

The following variables were reported for both registration-level and research-level patients and were considered in multivariate analyses: age at allo-HCT, sex, Karnofsky Performance Score (KPS) at allo-HCT, previous auto-HCT, time interval between diagnosis and allo-HCT, disease status at allo-HCT, conditioning regimen intensity (RIC/NST versus MA), donor type, donor–recipient sex match, graft source, year of allo-HCT, and type of GVHD prophylaxis.

RESULTS

Patient-, Disease-, and Transplantation-Related Variables

Between 1998 and 2010, a total of 202 patients underwent allo-HCT for refractory MCL, 74 with MA allo-HCT and 128 with RIC/NST allo-HCT. Median follow-up of survivors was 35 months in the MA group and 43 months in the RIC/NST group. The follow-up completion rate at 3 years was 80% in both groups, reflecting good follow-up to that time point [26]. Table 1 presents patient-, disease-, and transplantation-related characteristics of the 2 groups. The RIC/NST group was older than the MA group (median age, 59 years versus 54 years; $P < .001$). Approximately half of the patients in both groups had a pretransplantation KPS <90. Median time from

Table 1
Characteristics of Patients with Refractory MCL who Underwent Allo-HCT Reported to the CIBMTR between 1998 and 2010

Variable	MA	RIC/NST	*P* Value
Patient-related			
Number of patients	74	128	
Number of centers	28	63	
Age, years, median (range)	54 (27-69)	59 (42-75)	<.001
Male sex, n (%)	63 (85)	99 (77)	.181
KPS <90%, n (%)	36 (49)	61 (48)	.264
Disease related			
Disease stage at diagnosis, n (%)*			.836
I-II	2 (11)	5 (8)	
III-IV	14 (78)	52 (84)	
Missing	2 (11)	5 (8)	
Extranodal involvement before allo-HCT, n (%)*			.616
No	2 (11)	11 (18)	
Yes	14 (78)	51 (82)	
Missing	2 (11)	0	
Central nervous system involvement before allo-HCT, n (%)*			.467
No	16 (89)	60 (97)	
Yes	0	2 (3)	
Missing	2 (11)	0	
Bulky disease, n (%)*			.414
<5 cm	3 (17)	12 (19)	
≥5 cm	3 (17)	19 (31)	
Missing	12 (66)	31 (50)	
Disease status before allo-HCT, n (%)			.453
Primary induction failure–resistant	37 (50)	57 (45)	
Relapse-resistant	37 (50)	71 (55)	
Transplantation related			
Interval from diagnosis to HCT, months, median (range)	15 (4-184)	29 (5-135)	.001
Interval from auto-HCT to allo-HCT, months, median (range)	32 (7-69)	22 (8-77)	.501
Number of previous chemotherapy lines, median (range)	3 (2-5)	4 (1-5)	.024
Rituximab before HCT, n (%)*			.013
Yes	11 (52)	52 (80)	
No	10 (48)	13 (20)	
Conditioning regimen, n (%)*			NA
Cyclophosphamide/TBI	25 (53)	0	
Busulfan/cyclophosphamide	13 (28)	0	
TBI low-dose <500 cGY single/TBI <800 cGY fraction	0	5 (7)	
Fludarabine/melphalan	0	23 (31)	
Fludarabine/busulfan	0	10 (13)	
TBI 200 cGY	0	11 (15)	
Fludarabine + TBI 200 cGY	0	15 (20)	
Fludarabine + cyclophosphamide	0	10 (13)	
TBI ≥500 cGY single/TBI ≥800 cGY fraction	2 (4)	0	
Busulfan >9 mg/kg	6 (13)	0	
Busulfan + melphalan	1 (2)	0	
Cyclophosphamide, carmustine, + etoposide/similar	0	1 (1)	
Donor–recipient sex match, n (%)			.351
Male-male	30 (41)	61 (48)	
Male-female	5 (7)	18 (14)	
Female-male	25 (34)	36 (28)	
Female-female	4 (5)	11 (9)	
Missing	10 (14)	2 (2)	
Graft source, n (%)			.719
Bone marrow	13 (18)	20 (16)	
Peripheral blood	61 (82)	108 (84)	
Type of donor, n (%)*			<.001
HLA-identical sibling	47 (64)	37 (29)	
Other relative	3 (4)	4 (3)	
URD, well-matched	12 (16)	57 (45)	
URD, partially matched	5 (7)	12 (9)	
URD, mismatched	1 (1)	4 (3)	
URD, HLA match unknown	6 (8)	14 (11)	
Year of allo-HCT, n (%)			.103
1998-2001	25 (34)	26 (20)	
2002-2005	22 (30)	44 (34)	
2006-2010	27 (36)	58 (45)	
GVHD prophylaxis, n (%)			.123
Ex vivo T cell depletion	5 (7)	1 (1)	
Tacrolimus with and without others	32 (43)	67 (52)	
Cyclosporine with and without others	29 (39)	51 (40)	
CD34 selection	2 (3)	2 (2)	
Other, not specified	6 (8)	7 (5)	
Follow-up of survivors, months, median (range)	35 (3-124)	43 (4-96)	

TBI indicates total body irradiation; URD, unrelated donor.
* Research-level patients only.

Table 2
Univariate Analysis

Outcome Event	MA		RIC/NST		*P* Value*
	n	Probability (95% CI)	n	Probability (95% CI)	
Time to ANC >0.5 × 10^9/L	58		117		
28 days		90 (78-95)		92 (85-96)	.579
100 days		90 (78-95)		94 (88-97)	.343
Platelet recovery ≥20 × 10^9	39		91		
28 days		72 (54-84)		80 (70-87)	.337
100 days		82 (66-91)		87 (78-92)	.510
Acute GVHD (grade II-IV)	50		98		
100 days		36 (23-50)		37 (28-46)	.930
Chronic GVHD	49		105		
1 year		35 (22-48)		43 (33-52)	.347
3 years		37 (24-51)		49 (39-58)	.160
NRM	71		120		
100 days		33 (23-45)		26 (18-34)	.281
1 year		43 (31-54)		38 (29-48)	.561
3 years		47 (35-59)		43 (34-53)	.679
Relapse/progression	71		120		
1 year		26 (17-38)		24 (16-32)	.664
3 years		33 (22-45)		32 (23-41)	.890
PFS	71		120		
1 year		31 (20-42)		38 (29-48)	.316
3 years		20 (11-32)		25 (17-34)	.531
OS	74		128		
1 year		33 (22-44)		46 (37-54)	.066
3 years		25 (16-36)		30 (22-39)	.455

ANC indicates absolute neutrophil count.

* Probabilities of neutrophil and platelet recovery, platelet recovery, acute GVHD, chronic GVHD, treatment-related mortality and progression/relapse were calculated using cumulative incidence estimates. PFS and OS were calculated using Kaplan-Meier product limit estimates.

diagnosis to transplantation was significantly longer in the RIC/NST group (29 months versus 15 months; $P < .001$).

No significant difference at baseline was observed between the 2 groups in terms of disease stage at diagnosis, bone marrow or extranodal involvement, disease bulk, central nervous system involvement, disease status at transplantation (primary refractory disease versus refractory at relapse) and graft type (bone marrow versus peripheral blood). Significantly more patients in the RIC/NST group had a history of previous auto-HCT (33% versus 13%; $P = .004$), had received rituximab therapy before transplantation (41% versus 15%; $P = .01$), and had undergone unrelated donor allo-HCT (68% versus 32%; $P < .001$). Patients in the RIC/NST group were also more heavily pretreated (median lines of previous chemotherapy, 4 versus 3; $P = .02$). The most frequently used MA conditioning regimens were

Table 3
Causes of Death

Cause of Death	MA, n (%)	RIC/NST, n (%)
Total number	56	93
Graft rejection	2 (4)	1 (1)
Infection	8 (14)	11 (12)
Pulmonary syndrome	0	2 (2)
Acute respiratory distress syndrome	0	1 (1)
GVHD	3 (5)	12 (13)
Primary disease	22 (39)	39 (42)
Organ failure	7 (13)	8 (9)
2nd malignancy	0	2 (2)
Hemorrhage	3 (5)	2 (2)
Accidental death	0	1 (1)
Vascular	0	1 (1)
Toxicity	2 (4)	3 (3)
Other cause, not specified*	9 (16)	10 (11)

* Six cases reported as "other HSCT related cause."

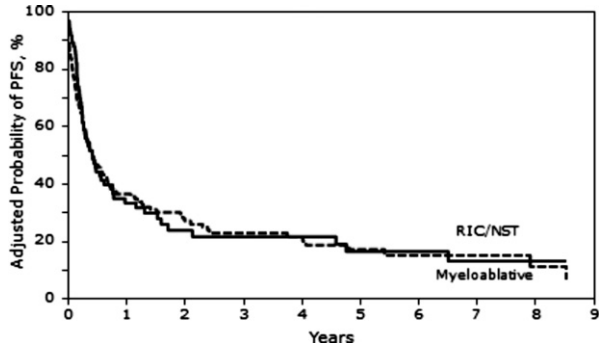

Figure 1. Kaplan-Meier estimates of adjusted PFS after allo-HCT for mantle cell lymphoma.

cyclophosphamide/total body irradiation and busulfan/cyclophosphamide, whereas fludarabine-based conditioning was the most popular RIC-NST regimen. The majority of the patients in both groups received calcineurin inhibitor-based GVHD prophylaxis.

Outcomes

Outcomes after allo-HCT are summarized in Tables 2 and 3.

Engraftment and GVHD

The cumulative incidence of neutrophil engraftment at day +28 was 90% (95% confidence interval [CI], 78%-95%) in the MA group and 92% (95% CI, 85%-96%) in the RIC/NST group ($P = .58$) (Table 2). The cumulative incidence of platelet recovery at day +28 was 72% (95% CI, 54%-84%) in the MA group and 80% (95% CI, 70%-87%) in the RIC/NST group ($P = .34$). The cumulative incidence of grade II-IV acute GVHD at day +100 was 36% (95% CI, 23%-50%) in the MA group and 37% (95% CI, 28%-46%) in the RIC/NST group ($P = .93$) (Table 2). The cumulative incidence of chronic GVHD at 1 year post-transplantation was 35% (95% CI, 22%-48%) in the MA group and 43% (95% CI, 33%-52%) in the RIC/NST group ($P = .35$) (Table 2). In the MA group, chronic GVHD was limited in 3 patients and extensive in 13 patients in the MA group and limited in 12 patients and extensive in 36 patients in the RIC/NST group. The extent of chronic GVHD (limited versus extensive) was not known in 3 patients.

NRM

Day +100 NRM rates were 33% (95% CI, 23%-45%) for the MA group and 26% (95% CI, 18%-34%) for the RIC/NST group ($P = .28$) (Table 2). The bumulative incidence estimate of NRM at 3 years was 47% (95% CI, 35%-59%) for the MA group and 43% (95% CI, 34%-53%) for the RIC/NST group ($P = .68$). On multivariate analysis, receipt of a bone marrow allograft compared with a peripheral blood graft (RR, 1.89; 95% CI, 1.10-3.24; $P = .02$) and GVHD prophylaxis with ex vivo T cell depletion or $CD34^+$ selection compared with tacrolimus-based GVHD prophylaxis (RR, 6.11; 95% CI, 2.60-14.36; $P < .001$) were associated with an increased risk of NRM. Conditioning regimen intensity was not associated with NRM (MA versus RIC/NST; RR, 1.04; 95% CI, 0.66-1.63; $P = .87$).

Relapse/Progression

The 1- and 3-year probabilities of relapse/progression were similar in the MA and the RIC/NST groups; at 3 years, it

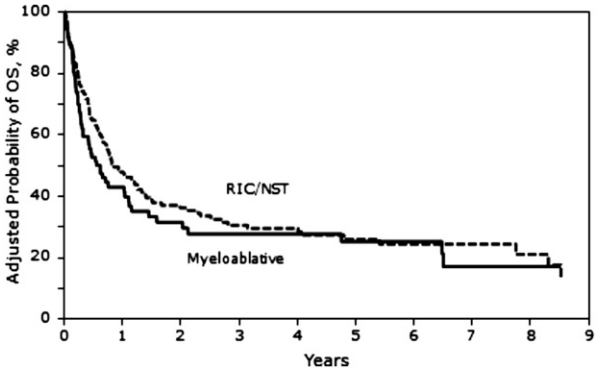

Figure 2. Kaplan-Meier estimates of adjusted OS after allo-HCT for mantle cell lymphoma.

was 33% (95% CI, 22%-45%) in the MA group and 32% (95% CI, 23%-41%) in the RIC/NST group ($P = .89$) (Table 2). No correlation was observed between the risk of relapse/progression and development of grade II-IV acute GVHD (RR, 0.73; 95% CI, 0.35-1.51; $P = .39$), grade III-IV acute GVHD (RR, 1.11; 95% CI, 0.52-2.36; $P = .78$), or chronic GVHD (RR, 0.77; 95% CI, 0.35-1.58; $P = .45$). None of the variables tested were significantly associated with a risk of relapse/progression on multivariate analysis. Moreover, conditioning regimen intensity was not associated with the risk of relapse/progression on multivariate analysis (MA versus RIC/NST; RR, 1.16; 95% CI, 0.68-1.99; $P = .59$).

PFS

PFS estimates were not significantly different in the MA and RIC/NST groups at 1 year (31% [95% CI, 20%-42%] versus 38% [95% CI, 29%-48%]; $P = .32$) or at 3 years (20% [95% CI, 11%-32%] versus 25% [95% CI, 17%-34%]; $P = .53$) (Table 2). On multivariate analysis, receipt of a bone marrow allograft compared with a peripheral blood graft (RR, 1.72; 95% CI, 1.11-2.67; $P = .02$) was associated with inferior PFS. Similarly inferior PFS was associated with ex vivo T cell–depleted or $CD34^+$ cell–selected allo-HCT (RR, 4.89; 95% CI, 2.36-10.12; $P < .001$). Conditioning regimen intensity was not associated with PFS on multivariate analysis (MA versus RIC/NST, RR, 1.09; 95% CI, 0.77-1.56; $P = .60$) (Figure 1).

OS

OS estimates were not significantly different in the MA and RIC/NST groups at 1 year (33% [95% CI, 22%-44%] versus 46% [95% CI, 37%-54%]; $P = .07$) or at 3 years (25% [95% CI, 16%-36%] versus 30% [95% CI, 22%-39%]; $P = .45$) (Table 2). On multivariate analysis, receipt of a bone marrow allograft compared with a peripheral blood graft (RR, 1.84; 95% CI, 1.21-2.78; $P = .004$) was associated with inferior OS. GVHD prophylaxis with ex vivo T cell depletion/$CD34^+$ selection (RR, 3.42; 95% CI, 1.64-7.12; $P = .001$) or with a cyclosporine-based regimen (RR, 1.42; 95% CI, 1.00-2.02; $P = .04$) also were associated with inferior OS. Conditioning regimen intensity was not associated with OS (MA versus RIC/NST, RR, 1.22; 95% CI, 0.86-1.72; $P = .25$) (Figure 2).

Causes of Death

Disease relapse and/or progression accounted for 39% (n = 22) of the mortality in the MA group and 42% (n = 39) in the RIC/NST group. Causes of death are summarized in Table 3.

DISCUSSION

The aims of the present study were to define outcomes of patients with chemotherapy-unresponsive MCL after allo-HCT relative to the intensity of conditioning regimens and other variables, including graft source and previous auto-HCT. Our analysis of this large cohort of refractory MCL patients undergoing allo-HCT in multiple centers has yielded several important observations. First, despite refractory disease at baseline, approximately 25% of the patients with MCL were alive and in remission at 3 years after allo-HCT. Second, in this uniquely chemotherapy-refractory group, the intensity of the pretransplantation conditioning regimen used apparently had no significant affect on rates of NRM, relapse/progression, PFS, and OS. Third, bone marrow as a graft source and ex vivo T cell depletion seem to be associated with inferior survival outcomes, likely owing due to associated significantly higher rates of NRM. Fourth, high NRM and relapse rates after allo-HCT in this high-risk group will continue to be the main barrier to wider application of this modality.

Published data on the role of allo-HCT in patients with chemotherapy-refractory MCL are limited (Table 4). The Fred Hutchinson Cancer Center reported 2-year OS and PFS rates of 65% and 60%, respectively, in a cohort of 33 patients with MCL undergoing NST allo-HCT with fludarabine and low-dose total body irradiation [19]. Although that report included 13 patients with refractory disease, these patients' outcomes were not described separately. The M.D. Anderson Cancer Center reported encouraging outcomes (6-year PFS and OS of 46% and 53%, respectively) in 35 patients with relapsed MCL after NST allo-HCT [27]. In that report, disease remission at allo-HCT was not significantly associated with survival outcomes; however, the series included only 6 refractory patients. The British Society for Bone Marrow Transplantation registry reported outcomes of RIC allo-HCT for patients with MCL, including 12 refractory patients [28]. The 3-year OS and PFS rates for this very small subgroup of refractory patients were only 38% and 0%, respectively. Along similar lines, a recent French study reported 2-year OS of 31% and 2-year PFS o 11% in a series of 15 refractory patients [29]. Our present study, the largest reported to date, indicates that approximately 25% of patients with chemotherapy-unresponsive MCL can attain a prolonged remission after allo-HCT. It is important to interpret these results in the context of the dismal long-term prognosis of patients with refractory MCL treated with conventional chemotherapies, as well as the fact that only 30%-40% of our patients had a KPS $\geq$90 before allo-HCT.

In patients with refractory lymphoid malignancies at the time of allo-HCT, the relative importance of conditioning regimen intensity is unknown. It is likely that, owing to their inherent chemoresistance, patients with refractory NHL may derive no net benefit from higher-intensity conditioning regimens. In the present study, the more-intense MA conditioning regimens were not associated with a reduced risk of relapse/progression or with improved OS and PFS. However, our study included 2 different groups of patients with significant differences before undergoing allo-HCT. This study is not a substitute for a randomized comparison of high-intensity and low-intensity conditioning regimens. We cannot discount inherent selection bias, that is, a tendency of transplantation physicians to preferentially offer MA allo-HCT to patients with higher-risk, primary refractory, or blastoid MCL. Whether the MA group was enriched with patients with progressive disease at the time of

Table 4
Studies Reporting Outcomes of Allo-HCT in at least 30 Patients with MCL

Study	No. of Patients	No. with Refractory Disease	Conditioning	Relapse Rate, % (Year)	NRM, % (Year)	PFS, % (Year)	OS, % (Year)	PFS of RD Patients, % (Year)	OS of RD Patients, % (Year)
Maris et al. [19]	33	13	NST	9* (2)	24* (2)	60* (2)	65* (2)	NR	NR
Tam et al. [27]	35	6	NST	NR	9* (1)	46* (6)	53* (6)	NR	NR
Cook et al. [28]	70	12	RIC	65* (5)	21* (5)	37* (5)	14* (5)	0 (3)	38 (3)
Le Gouill et al. [29]	70	15	RIC	NR	32* (2)	50* (2)	53* (2)	11 (2)	31 (2)
CIBMTR (current)	202	202	RIC/NST and MA	33-32 (3)	43-47 (3)	NA	NA	20-25 (3)	25-30 (3)

NA indicates not applicable; NR, not reported.
* Includes chemosensitive patients.

transplantation is unknown, because this information is not collected by the registry.

The time interval between diagnosis and allo-HCT was shorter in the MA group compared with the RIC/NST group, possibly indicating a more aggressive disease biology in the former group. Of note, however, the patients in RIC/NST group were more heavily pretreated and older, and a significantly higher proportion had previous rituximab exposure, had undergone previous auto-HCT, or had received an unrelated donor allograft. The latter 2 factors likely contributed to the longer time interval between diagnosis and eventual allo-HCT in the RIC/NST group. With these limitations in mind, our data suggest that in patients with MCL who are refractory to conventional therapies, escalating the intensity of conditioning regimens is unlikely to improve patient outcomes.

It is important to point out that our report included both registration- and research-level patients reported to the CIBMTR. The primary objective of this study was to describe transplantation outcomes in patients with chemorefractory MCL relative to the intensity of conditioning regimens. Noteworthy variables missing in registration-level patients include disease stage at diagnosis, history of radiation exposure, bulky disease status, B symptoms, serum lactate dehydrogenase level, bone marrow involvement, and extranodal involvement at any time point before allo-HCT. Although some of these variables have prognostic value for MCL, the significance of their presence at any time point before transplantation (as opposed to their presence at the time of transplantation) in an exclusive cohort of patients with chemotherapy-refractory MCL is not known. Because key data regarding remission status at transplantation, type of conditioning regimen, donor/graft source, patient age, KPS, history of previous auto-HCT and all post-transplantation outcomes of interest (eg, engraftment, GVHD, NRM, OS, PFS) were available on both registration- and research-level patients, we decided to include both patient populations.

The 3-year relapse/progression rate of 30% and NRM rate of 45% in our study cohort are high. In previous reports of predominantly chemosensitive MCL undergoing RIC/NST allo-HCT, the rates of disease relapse at 5 years have ranged from 30% to 65% [27,28], whereas reported 2-year NRM are approximately 20%-35% [19,29]. One-third of our RIC/NST allo-NCT recipients had undergone previous auto-HCT, a possible reason for the high NRM in our cohort. Our multivariate analysis did not identify this factor as associated with a higher NRM. Moreover, other investigators have not consistently found that previous auto-HCT significantly influences NRM after allo-HCT [16,17]. Nonetheless, the urgent need to mitigate NRM and relapse rates through the development of novel conditioning regimens designed to provide improved disease control while maintaining acceptable NRM rates is clear. Along these lines, in a cohort composed predominately of patients with refractory B cell NHL, Gopal et al. [30] reported a 30-month 54% survival with a NRM rate of 16% with radioimmunotherapy-based NST findings, similar to those of Bethge et al. [31].

In the present study, on multivariate analysis, bone marrow as graft source and ex vivo T cell depletion/CD34$^+$ cell selection were consistently associated with higher NRM and inferior PFS and OS. Considering that these 2 variables were not associated with an elevated risk of disease relapse/progression, we speculate that the inferior OS and PFS in these patients are likely related to higher rates of NRM. A possible explanation for the higher NRM with bone marrow allografts and ex vivo T cell depletion is delayed immune reconstitution and the resulting increased susceptibility to infectious complications in these patients. Nonetheless, caution must be exercised when interpreting these results, owing to the small number of patients in the subgroup that underwent ex vivo T cell depletion/CD34$^+$ cell selection. The use of peripheral blood as a graft source has been reported to improve PFS in patients with MCL undergoing allo-HCT [27].

In conclusion, our analysis of this large set of registry data demonstrates that approximately 25% of patients with refractory MCL can attain durable remission after allo-HCT, and that the intensity of the conditioning regimen does not influence outcomes. In the absence of a clinical trial, consideration of a T cell –replete, allogeneic peripheral blood transplant is a viable option for otherwise healthy patients with refractory MCL.

ACKNOWLEDGMENTS

We thank Ulrike Bacher, César O. Freytes, Miguel-Angel Perales, and Sonali Smith for their helpful comments and insights as members of the study committee.

Financial disclosure: The Center for International Blood and Marrow Transplant Research is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; contract HHSH234200637015C with the Health Resources and Services Administration; grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from Allos, Amgen, Angioblast, anonymous donation to the Medical College of Wisconsin, Ariad, Be the Match Foundation, Blue Cross and Blue Shield Association, Buchanan Family Foundation, CaridianBCT, Celgene, CellGenix, Children's Leukemia Research Association, Fresenius-Biotech North America, Gamida Cell Teva Joint Venture, Genentech, Genzyme, GlaxoSmithKline, HistoGenetics,

Kiadis Pharma, Leukemia and Lymphoma Society, Medical College of Wisconsin; Merck & Co, Takeda Oncology, Milliman, Miltenyi Biotec, National Marrow Donor Program, Optum Healthcare Solutions, Osiris Therapeutics, Otsuka America Pharmaceutical, RemedyMD, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals, Soligenix, StemCyte, Stemsoft Software, Swedish Orphan Biovitrum, Tarix Pharmaceuticals, Teva Neuroscience, THERAKOS, and Wellpoint. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the US Government. The authors have no conflicts of interest to report.

Authorship Statement: Mehdi Hamadani, Wael Saber, and Hillard M. Lazarus designed the study, interpreted data, and had primary responsibility for manuscript preparation, including writing the manuscript and approving the final manuscript. Kwang Woo Ahn and Jeanette Carreras performed the statistical analyses. Mitchell S. Cairo, Timothy S. Fenske, Robert Peter Gale, John Gibson, Gregory A. Hale, Parameswaran N. Hari, Jack W. Hsu, David J. Inwards, Rammurti T. Kamble, Anderas Klein, Dipnarine Maharaj, David I. Marks, David A. Rizzieri, Bipin N. Savani, Harry C. Schouten, Edmund K. Waller, and Baldeep Wirk participated in data interpretation, manuscript preparation, and approval of the final manuscript.

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