Autologous or Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Sensitive Mantle-Cell Lymphoma: Analysis of Transplantation Timing and Modality

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ABSTRACT

Purpose

To examine the outcomes of patients with chemotherapy-sensitive mantle-cell lymphoma (MCL) following a first hematopoietic stem-cell transplantation (HCT), comparing outcomes with autologous (auto) versus reduced-intensity conditioning allogeneic (RIC allo) HCT and with transplantation applied at different times in the disease course.

Patients and Methods

In all, 519 patients who received transplantations between 1996 and 2007 and were reported to the Center for International Blood and Marrow Transplant Research were analyzed. The early transplantation cohort was defined as those patients in first partial or complete remission with no more than two lines of chemotherapy. The late transplantation cohort was defined as all the remaining patients.

Results

Auto-HCT and RIC allo-HCT resulted in similar overall survival from transplantation for both the early (at 5 years: 61% auto-HCT v 62% RIC allo-HCT; $P = .951$) and late cohorts (at 5 years: 44% auto-HCT v 31% RIC allo-HCT; $P = .202$). In both early and late transplantation cohorts, progression/relapse was lower and nonrelapse mortality was higher in the allo-HCT group. Overall survival and progression-free survival were highest in patients who underwent auto-HCT in first complete response. Multivariate analysis of survival from diagnosis identified a survival benefit favoring early HCT for both auto-HCT and RIC allo-HCT.

Conclusion

For patients with chemotherapy-sensitive MCL, the optimal timing for HCT is early in the disease course. Outcomes are particularly favorable for patients undergoing auto-HCT in first complete remission. For those unable to achieve complete remission after two lines of chemotherapy or those with relapsed disease, either auto-HCT or RIC allo-HCT may be effective, although the chance for long-term remission and survival is lower.

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INTRODUCTION

Mantle-cell lymphoma (MCL) accounts for approximately 6% of non-Hodgkin lymphoma cases. In recent years, progress in the treatment of MCL has improved median survival to 5 to 7 years.¹⁻⁶ More intensive induction chemotherapy, introduction of new agents, and more extensive use of hematopoietic stem-cell transplantation (HCT) may account for this trend.^{1-3,6-17}

Despite these improvements, there is a lack of consensus regarding the optimal timing and modality of HCT in MCL. Some studies have found that autologous HCT (auto-HCT) appears more effective when performed in first complete remission (CR1).^{1,9,16} As a result, many transplantation centers do not consider auto-HCT for patients with MCL beyond first response. The role of allogeneic HCT (allo-HCT) also remains controversial. We addressed this uncertainty by using the Center for International Blood

and Marrow Transplant Research (CIBMTR) database to retrospectively compare outcomes in patients with chemotherapy-sensitive MCL undergoing auto-HCT or reduced-intensity conditioning (RIC) allo-HCT as a first HCT.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a statistical center at the Medical College of Wisconsin. Centers report HCTs consecutively, with compliance monitored by on-site audits. Patients are followed longitudinally with yearly follow-up. Observational studies by the CIBMTR are performed in compliance with federal regulations with ongoing review by the institutional review board of the Medical College of Wisconsin.

Patients

All recipients of an auto-HCT or RIC allo-HCT between 1996 and 2007 as a first HCT for MCL reported to the CIBMTR were included. RIC allo-HCT included both nonmyeloablative and RIC allo-HCT. Disease status before transplantation was categorized into the following four groups: (1) CR1; (2) primary induction failure-sensitive (PIF-sensitive), defined as a partial remission (PR) with no history of a prior CR; (3) relapsed-sensitive, defined as relapse after a CR and subsequent sensitivity to the latest chemotherapy before transplantation; and (4) second or subsequent complete remission (CR2+).

The outcomes of the 519 patients with chemotherapy-sensitive MCL receiving a first HCT were analyzed. Patients were compared in two cohorts:

early versus late. The early transplantation cohort ($n = 299$) was defined as patients in their first PR or CR with no more than two prior lines of chemotherapy. The late transplantation cohort ($n = 220$) was composed of the remaining patients (Table 1).

Recipients of myeloablative conditioning or in vitro T-cell depleted ($n = 32$), syngeneic ($n = 2$), cord blood ($n = 5$), or mismatched related donor grafts ($n = 12$) were excluded. In the early RIC allo-HCT group ($n = 50$), there were 24 unrelated donor transplantations. Of these, there were 19 HLA matched, four partially matched, and one mismatched. In the late RIC allo-HCT group ($n = 88$), there were 52 unrelated donor transplantations. Of these, there were 40 HLA matched, 10 partially matched, and two mismatched. To allow for meaningful comparisons between cohorts, patients with chemotherapy-resistant disease ($n = 84$) were excluded since these patients preferentially underwent RIC allo-HCT.

Study End Points

Primary outcomes were overall survival (OS), relapse/progression, progression-free survival (PFS), and nonrelapse mortality (NRM). Relapse/progression represented new or larger areas of lymphoma ($\geq 25\%$ increase in largest diameter) compared with the best post-transplantation lymphoma state. It could follow a period of stable disease post-transplantation, or a PR or CR. Relapse/progression was summarized by the cumulative incidence estimate with NRM as the competing risk. Chemotherapy-sensitive was defined as achieving either a CR or PR to the pretransplantation chemotherapy regimen. NRM was defined as death as a result of any cause during the first 28 days post-transplantation or death without relapse/progression; relapse/progression was considered a competing risk. For NRM and relapse/progression, patients alive without evidence of relapse/progression were censored at last

Table 1. Patient and Disease Characteristics

Variable	Early HCT				Late HCT				P*
	Autologous		RIC Allogeneic		Autologous		RIC Allogeneic		
	No.	%	No.	%	No.	%	No.	%	
No. of patients	249		50		132		88		
Age at transplantation, years									.001
Median	59		54		61		58		
Range	34-75		23-71		33-78		26-75		
Male	192	77	39	78	101	77	70	80	.958
Karnofsky performance status < 90%	69	28	10	20	38	29	20	23	.056
Disease stage at diagnosis									.272
I-II	29	12	6	12	27	20	12	14	
III-IV	213	86	43	86	99	75	72	82	
Unknown	7	3	1	2	6	5	4	5	
“B” symptoms at diagnosis	87	35	19	38	38	29	20	23	.092
LDH increased at diagnosis	43	17	13	26	17	13	17	19	.196
Bone marrow involvement at diagnosis	141	57	36	72	55	42	54	61	.004
No. of prior lines of chemotherapy									N/A
1	134	54	29	58	6	5	2	2	
2	115	46	21	42	26	20	22	25	
3	0		0		63	48	33	38	
4	0		0		33	25	17	19	
5	0		0		4	3	11	13	
Disease status prior to transplantation									N/A
PIF sensitive	73	29	15	30	23	17	19	22	
CR1	176	71	35	70	29	22	5	6	
REL sensitive	0		0		42	32	34	39	
CR2+	0		0		38	29	30	34	
Rituximab prior to transplantation	106	43	31	62	48	36	65	74	< .001

Abbreviations: CR1, first complete remission; CR2+, second or subsequent complete remission; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase; N/A, not applicable; PIF, primary induction failure; REL, relapsed; RIC, reduced-intensity conditioning.

**P* values reflect comparison across the four groups.

follow-up. OS was evaluated from time of diagnosis or time of transplantation to the date of death or last follow-up and was summarized by a survival curve.

Statistical Analysis

Patient-, disease-, and transplantation-related factors were compared between auto-HCT and RIC allo-HCT groups by using the χ^2 test for categorical variables and the Wilcoxon two-sample test for continuous variables.

Two sets of statistical analysis were performed. First, univariate analyses were used to evaluate NRM, relapse/progression, PFS, and OS (from time of transplantation). Probabilities of PFS and OS were calculated by using the Kaplan-Meier estimator. Probabilities of NRM and relapse/progression were calculated by using cumulative incidence curves to accommodate competing risks.¹⁸ Five-year probabilities with 95% CIs and *P* values of pointwise tests were reported.

Second, to evaluate the optimal timing for HCT in the natural history of MCL, we analyzed survival from diagnosis for patients receiving HCT. Several potential sources of bias were adjusted. To address differences in time to treatment and additional potential bias caused by an imbalance of patient-, disease-, and transplantation-related factors between study cohorts, a left-truncated Cox multivariate proportional hazards model was used. Variables considered in multivariate analyses are listed in Appendix Table A1 (online

only). A stepwise selection multivariate model was built to identify covariates that influenced outcomes. Covariates with a *P* value less than .05 were considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor. Covariates violating the proportional hazards assumption were stratified in the Cox regression model. Results are expressed as relative risk (RR) of death. Analyses were performed by using SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient-, Disease-, and Transplantation-Related Variables

Table 1 and Table 2 depict patient-, disease-, and transplantation-related characteristics based on transplantation timing and modality. Compared with RIC allo-HCT recipients, auto-HCT recipients were slightly older and had lower rates of bone marrow involvement with MCL. The early transplantation cohorts had a median time from diagnosis to transplantation of 7 and 9 months for auto-HCT and RIC

Table 2. Transplantation Characteristics

Variable	Early HCT				Late HCT				P
	Autologous		RIC Allogeneic		Autologous		RIC Allogeneic		
	No.	%	No.	%	No.	%	No.	%	
Interval from diagnosis to transplantation, months									< .001
Median	7		9		19		30		
Range	3-71		4-38		4-144		4-160		
Donor type									N/A
Autologous	249		0		132		0		
HLA-identical sibling	0		26		0		36		41
Unrelated	0		24		0		52		59
Conditioning regimens for autologous transplantation									
TBI-based	55		22		26		20		N/A
BEAM or similar	149		60		81		61		
CBV or similar	25		10		12		9		
Busulfan + melphalan or busulfan + cyclophosphamide	11		4		13		10		
Others	9		4		0				
Conditioning regimens for RIC allogeneic transplantation									N/A
TBI < 5 Gy			1				3		3
Fludarabine + melphalan			13				16		18
Fludarabine + busulfan			5				9		10
TBI 2 Gy			13				13		15
Fludarabine + cyclophosphamide			8				35		40
CBV or similar			5				2		2
Missing			5				10		11
Graft type									
Bone marrow	3		1		2		2		17
Peripheral blood	246		99		130		98		71
Year of HCT									< .001
1996-1998	68		27		56		42		0
1999-2001	49		20		37		28		13
2002-2004	65		26		22		17		33
2005-2007	67		27		17		13		42
Rituximab post-transplantation	18		7		6		5		3
Follow-up of survivors, months									.462
Median	41		48		47		37		
Range	3-158		3-132		3-160		3-102		

Abbreviations: BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, and etoposide; HCT, hematopoietic cell transplantation; N/A, not applicable; RIC, reduced-intensity conditioning; TBI, total body irradiation.

allo-HCT, respectively. In contrast, the late transplantation cohorts had a median time from diagnosis to transplantation of 19 and 30 months for auto-HCT and RIC allo-HCT, respectively. Within the early and late cohorts, however, the auto-HCT and RIC allo-HCT groups were similar in terms of number of prior lines of chemotherapy and disease status before transplantation (Table 1). Median follow-up of the four cohorts ranged from 37 to 48 months. RIC allo-HCT patients had a higher rate of rituximab treatment before transplantation ($P < .001$), reflecting that more of these patients underwent transplantation in recent years. In total, 11 patients whose first transplantation was an auto-HCT, subsequently underwent an allo-HCT. Outcomes of those second transplantations are not included in the analyses for this study.

OS

OS at 5 years after HCT was similar for early auto-HCT versus early RIC allo-HCT (61% [95% CI, 53% to 68%] ν 62% [95% CI, 46% to 74%]; $P = .951$ for pointwise comparison at 5 years; $P = .122$ for log-rank test considering the complete Kaplan-Meier curves; Fig 1A). In late transplantation patients, post-transplantation survival was also similar for the auto-HCT and RIC allo-HCT groups (44% [95% CI, 34% to 53%] ν 31% [95% CI, 16% to 47%]; $P = .202$ for pointwise comparison at 5 years; $P = .230$ for log-rank test). As expected, among auto-HCT patients, 5-year survival after HCT was superior for early transplantation patients (61% ν 44%; $P = .004$). Similarly, among the RIC allo-HCT patients, 5-year survival post-transplantation was superior for early transplantation patients (62% ν 31%; $P = .005$).

We analyzed OS in the early auto-HCT patients in more detail (Fig 1B). For patients in CR1 with one line of therapy pretransplantation, CR1 with 2 lines of therapy pretransplantation, and those with PIF-sensitive disease, the 5-year OS was 75%, 70%, and 38%, respectively. For those in CR with one line of therapy versus two lines of therapy, survival was not statistically different; however, the patients with PIF-sensitive disease had a significantly worse survival when compared with those in CR1 ($P < .001$ for pointwise comparison at 5 years; $P = .001$ for log-rank test).

Relapse/Progression

The 5-year incidence of relapse/progression for the early transplantation cohort was 32% (95% CI, 25% to 39%) for auto-HCT versus 15% (95% CI, 7% to 27%) for RIC allo-HCT ($P = .009$). For the late transplantation cohort, the 5-year rate of relapse/progression was 51% (95% CI, 41% to 59%) for auto-HCT and 38% (95% CI, 26% to 50%) for RIC allo-HCT ($P = .105$; Fig 1C). Within the group of auto-HCT patients, relapse/progression at 5 years was significantly lower for early versus late transplantation patients (32% ν 51%; $P < .001$). Within the group of RIC allo-HCT patients, relapse/progression was also significantly lower for early versus late transplantation patients at 5 years (15% ν 38%; $P = .005$).

Among the early auto-HCT patients, those with CR1 with one line of therapy, CR1 with two lines of therapy, and PIF-sensitive disease had 5-year rates of relapse/progression of 21%, 35%, and 39% ($P = .047$ for comparison of CR1 (one line) ν others; Fig 1D).

PFS

The 5-year PFS for the early transplantation cohort was 52% (95% CI, 45% to 59%) for auto-HCT and 55% (95% CI, 39% to 68%) for RIC allo-HCT ($P = .746$ for pointwise comparison at 5 years;

$P = .157$ for log-rank test). This correlates with a cumulative incidence of treatment failure (relapse/progression plus NRM) at 5 years after HCT of 48% and 45%, respectively, with each modality. In the late transplantation cohort, the 5-year PFS was 29% (95% CI, 21% to 38%) for auto-HCT and 24% (95% CI, 12% to 39%) for RIC allo-HCT ($P = .556$ for pointwise comparison at 5 years; $P = .213$ for log-rank test; Fig 1E). Among the auto-HCT patients, PFS at 5 years was 52% for early and 29% for late transplantation patients ($P < .001$). Among the RIC allo-HCT patients, PFS at 5 years was 55% for early and 24% for late transplantation ($P = .003$).

For early auto-HCT patients in the CR1 with one line of therapy, CR1 with two lines of therapy, and PIF-sensitive groups, 5-year PFS was 70%, 56%, and 30%, respectively (for comparison of CR1 to PIF-sensitive, $P < .001$ for pointwise comparison at 5 years; $P < .001$ for log-rank test; Fig 1F).

NRM and Causes of Death

NRM for the four cohorts is depicted in Figure 2. Within the early cohort, the incidence of NRM was higher for RIC allo-HCT versus auto-HCT patients (at 1 year: 25% [95% CI, 14% to 38%] ν 3% [95% CI, 2% to 6%]; $P < .001$). Within the late cohort, there was a trend toward increased NRM with RIC allo-HCT versus auto-HCT (at 1 year: 17% [95% CI, 10% to 26%] ν 9% [95% CI, 4% to 14%]; $P = .068$). Within the group of auto-HCT patients, there was a trend toward slightly lower NRM if transplantation occurred early versus late in the disease course (3% ν 9% at 1 year; $P = .066$). Within the group of RIC allo-HCT patients, a statistically similar rate of NRM was seen in the early versus late transplantation patients (25% ν 17% at 1 year; $P = .278$).

In the entire cohort of 519 patients, 229 deaths occurred. Within the auto-HCT cohort, 67% of the 163 deaths were the result of lymphoma. Within the RIC allo-HCT cohort, 26% of deaths were the result of lymphoma (Appendix Table A2, online only). Of the 20 deaths that occurred in early RIC allo-HCT patients, four were due to idiopathic pneumonia syndrome. All four of these patients had exposure to rituximab prior to transplantation.

Multivariate Analysis

Multivariate analysis was performed from the time of diagnosis (as opposed to the time of HCT) to analyze the impact of the timing and modality of transplantation and other factors on OS (see Appendix Table A1 for a list of the variables tested in the model). Higher age (≥ 60 years), no rituximab exposure pretransplantation, increased lactate dehydrogenase at diagnosis, and HCT beyond CR1 were all associated with inferior survival (Table 3). Pretransplantation exposure to methotrexate or cytarabine was not associated with improved survival. Within the auto-HCT group, there was improved survival with early auto-HCT (RR of death, 0.70; $P = .037$) versus late auto-HCT. Within the RIC allo-HCT group, early RIC allo-HCT was associated with higher short-term mortality (within 24 months of HCT; the RR of death was 2.34; $P = .017$). However, for survival beyond the first 2 years since diagnosis, early RIC allo-HCT was superior (RR of death, 0.31; $P = .017$). Within either the early or late transplantation cohorts, it was not possible to demonstrate a survival benefit in favor of one transplantation modality over the other. Overall survival from time of diagnosis is shown graphically for the four cohorts in Appendix Figure A1 (online only).

Fig 1. Probabilities of survival and incidence of relapse. Probability of overall survival for (A) all four hematopoietic cell transplantation (HCT) cohorts, and (B) the early autologous HCT cohort, by disease status. Cumulative incidence of relapse/progression for (C) all four HCT cohorts, and (D) the early autologous HCT cohort, by disease status. Probability of progression-free survival in (E) all four HCT cohorts, and (F) the early autologous HCT cohort, by disease status. allo, allogeneic hematopoietic cell transplantation; auto, autologous hematopoietic cell transplantation; CR1, first complete remission; PIF sens, primary induction failure-sensitive.

Fig 2. Cumulative incidence of nonrelapse mortality. Allo, allogeneic hematopoietic cell transplantation; auto, autologous hematopoietic cell transplantation.

DISCUSSION

Despite a lack of consensus on the best use of HCT in patients with MCL, HCT is still commonly used for therapy. However, there are still many questions regarding the optimal timing or modality of HCT in MCL. We therefore studied a large cohort of patients with chemotherapy-sensitive MCL who received a first HCT between 1996 and 2007. To the best of our knowledge, this constitutes the largest published retrospective study evaluating HCT timing and modality in MCL. The main outcomes for all four cohorts are summarized in Appendix Table A3 (online only).

As expected, patients transplanted later in the disease course had shorter OS when measured from the time of transplantation. In addition, in our study, among patients who received a transplantation either early or late, no survival benefit was detected for one transplantation modality over the other. However, because of the increased

NRM with allo-HCT, our analysis supports the choice of auto-HCT for patients in CR1. For patients receiving auto-HCT in CR1 after one prior line of chemotherapy, the outcomes were excellent, with 75% OS and 70% PFS at 5 years. Lower rates of lymphoma relapse/progression were seen with early RIC allo-HCT versus early auto-HCT, although there was an important caveat of increased NRM with the former. There was also a trend toward lower relapse/progression in late RIC allo-HCT versus late auto-HCT. As observed by others, there was a plateau in relapse/progression and PFS after 1 to 2 years with RIC allo-HCT and a more continuous pattern of relapse/progression in auto-HCT patients.^{2,9,10,13} This may represent a graft-versus-lymphoma effect. However, this potential benefit of RIC allo-HCT in terms of long-term disease control was negated by higher NRM rates after allo-HCT, resulting in a similar PFS compared with auto-HCT.

To more effectively detect an impact of a particular transplantation modality or transplantation timing on OS, we performed a left-truncated multivariate analysis of OS from the time of diagnosis. We chose this approach because we believe that the OS from the time of diagnosis (rather than PFS or survival from transplantation) is a more meaningful end point. This analysis indicated that early HCT is associated with a survival benefit. Specifically, a modest survival benefit was associated with early auto-HCT relative to late auto-HCT. Similarly, a survival benefit was also evident with early RIC allo-HCT (relative to late RIC allo-HCT) when considering patients who survived at least 2 years postdiagnosis. However, early RIC allo-HCT was associated with a significantly higher risk of death related to NRM within the first 2 years.

There are several findings from our study that may inform clinical practice. First, HCT early in the disease course is associated with improved OS relative to HCT applied later in the disease course. Second, we confirm the excellent outcome of patients in CR1 who undergo auto-HCT. Third, even later in the disease course, auto-HCT can offer meaningful clinical benefit. Finally, in this large series, RIC allo-HCT does in fact appear to be potentially curative for some patients with MCL. However, because of the relatively high rates of

Table 3. Multivariate Analysis for Mortality

Variable	No.	RR	95% CI	P
Main effect				
Early HCT: allogeneic v autologous	50 v 249			< .001*
Risk of death within 2 years from diagnosis	21 v 53	4.69	2.55 to 8.62	< .001†
Risk of death beyond 2 years from diagnosis	29 v 196	0.63	0.25 to 1.57	.320
Late HCT: allogeneic v autologous	88 v 132	1.39	0.94 to 2.06	.097
Autologous: early MCL v late MCL	249 v 132	0.70	0.49 to 0.98	.037
Allogeneic: early MCL v late MCL	50 v 88			< .001†
Risk of death within 2 years from diagnosis	21 v 10	2.34	1.17 to 4.70	.017
Risk of death beyond 2 years from diagnosis	29 v 78	0.31	0.12 to 0.81	.017
Other significant covariates				
Age at transplantation: ≥ 60 v < 60 years	235 v 284	1.88	1.43 to 2.46	< .001
Rituximab prior to transplantation: yes v no	250 v 269	0.72	0.54 to 0.96	.024
LDH increased at diagnosis: yes v no	90 v 429	1.54	1.12 to 2.11	.008
Disease status prior to transplantation				
PIF-sensitive/REL-sensitive/CR2+ v CR1	274 v 245	1.94	1.40 to 2.70	< .001

Abbreviations: CR1, first complete remission; CR2+, second or subsequent complete remission; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase; MCL, mantle-cell lymphoma; PIF, primary induction failure; REL, relapsed; RR, relative risk.

*Overall test, 4 degrees of freedom.

†Overall test, 2 degrees of freedom.

Fig 3. Recommended algorithm for first hematopoietic cell transplantation (HCT) in patients with mantle-cell lymphoma. (*) Choice based on donor availability, anticipated NRM incorporating HCT-CI, and relapse risk. (†) Hamadani et al.¹⁹ Allo, allogeneic hematopoietic cell transplantation; auto, autologous hematopoietic cell transplantation; CR, complete remission; RIC, reduced-intensity conditioning; Rx, therapy.

NRM in the first 1 to 2 years after RIC allo-HCT, it was not possible to demonstrate a survival benefit for RIC allo-HCT (relative to auto-HCT) in either the early or late transplantation patients. On the basis of these data, a reasonable argument can be made for early RIC allo-HCT only for patients anticipated to have a low rate of NRM (based on comorbidity scoring) along with a high risk of relapse after auto-HCT (such as those not in CR). For other patients, we believe auto-HCT is a superior option, with the best outcomes seen with early auto-HCT. Figure 3 depicts our suggested treatment algorithm.¹⁹ Of note, this algorithm is largely concordant with that put forth by the recent National Comprehensive Cancer Network (NCCN) guidelines,²⁰ with one exception. Although the results for auto-HCT are clearly best in patients in CR1, our data indicate that for patients in first PR or even those with relapsed disease, auto-HCT may be a reasonable option.

Our study has several limitations. In addition to patient selection bias inherent in retrospective studies, there could be unmeasured differences in important characteristics such as histopathologic variants (eg, blastoid), proliferation rate, or Mantle Cell Lymphoma International Prognostic Index (MIPI) score among the patient groups. Some treatments preferentially benefit lower-risk patients as assessed by the MIPI score.^{21,22} Since the variables incorporated in the MIPI were not uniformly collected during the period under study, it was impossible to determine the impact of MIPI on outcomes. Our late transplantation cohort of patients with MCL is somewhat heterogeneous, with some patients in CR1 (after three or more lines of therapy), and others having had multiple relapses. Lastly, our study does not address the efficacy of performing a RIC allo-HCT in patients who relapse or progress after an auto-HCT.

In this study, relatively favorable outcomes occurred with auto-HCT in both early and late transplantation patients. Recent studies showing favorable outcomes of various nontransplantation first-line regimens have led some to conclude that early auto-HCT may not

truly improve outcomes in patients with MCL.²³⁻²⁵ Because all patients in our study underwent transplantation, we are unable to directly address this question. However, we are able to conclude that survival of patients with MCL is enhanced by the use of early auto-HCT compared with late auto-HCT. In addition, even the late auto-HCT patients (all of whom had either relapsed or received three or more induction regimens before auto-HCT) had a 5-year relapse/progression rate of only 51% and a median survival of approximately 4 years post-transplantation. Considering that patients with relapsed/refractory MCL treated on clinical trials historically have a PFS between 3 and 8 months and a median OS between 10 and 24 months,^{8,14,26-29} we also conclude that many relapsed patients with chemotherapy-sensitive MCL may be best served with HCT. Looking forward, there are several drugs with significant activity in MCL currently in development such as mammalian target of rapamycin (mTOR) inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, and phosphatidylinositol-3 phosphate kinase (PI3K) inhibitors. These agents will likely change the landscape of treatment options for MCL, which in turn may alter how HCT is used for MCL in the future.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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GLOSSARY TERMS

mTOR: The mammalian target of rapamycin belongs to a protein complex (along with raptor and GβL) that is used by cells to sense nutrients in the environment. mTOR is a serine/threonine kinase that is activated by Akt and regulates protein synthesis on the basis of nutrient availability. It was discovered when rapamycin, a drug used in transplantation, was shown to block cell growth presumably by blocking the action of mTOR.

Multivariate proportional hazards model: Proportional hazards or COX regression modeling is a general method in medical statistics to analyze the influence of several (patient specific) covariates on time-to-event end points. No assumption is made concerning the form of the underlying time-to-event curve. The only assumption made is that the effect of the covariates on the hazard rate in the study population is multiplicative and does not change over time.

PI3K: Phosphatidylinositol-3 phosphate kinase (PI3K) adds a phosphate group to PI3, which is a downstream signaling molecule involved in survival/proliferative pathways mediated by growth factors such as the EGF and the PDGFs.

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Appendix

Table A1. Variables Tested in Three Cox Proportional Hazards Regression Models

Main effect for early and late subgroups: autologous HCT v RIC allogeneic HCT
Main effect for autologous only and RIC/allogeneic only subgroups: early v late
Patient-related variables
Age at transplantation: < 60 v ≥ 60 years
Sex: male v female
Karnofsky performance status at transplantation: ≥ 90% v < 90% v missing
Disease-related variables
“B” symptoms at diagnosis: yes v no v missing
Bone marrow involvement at diagnosis: yes v no
Rituximab prior to transplantation: yes v no
LDH increased at diagnosis: yes v no
Cytarabine/methotrexate: cytarabine + methotrexate v cytarabine (no methotrexate) v methotrexate (no cytarabine) v none
Disease status prior to transplantation: CR1 v CR2+ v PIF sensitive v REL sensitive
For patients in the late MCL group: < 1 v > 1 year from diagnosis to transplantation
Treatment-related variables
Year of transplantation: 1996-2001 v 2002-2007
Total-body irradiation conditioning regimen v chemotherapy alone conditioning regimen

Abbreviations: CR1, first complete remission; CR2+, two or more complete remissions; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase; MCL, mantle-cell lymphoma; PIF, primary induction failure; REL, relapse; RIC, reduced-intensity conditioning.

Table A2. Causes of Death

Cause of Death	Early HCT				Late HCT			
	Autologous		RIC Allogeneic		Autologous		RIC Allogeneic	
	No.	%	No.	%	No.	%	No.	%
No. of deaths	86		20		77		46	
Graft rejection/failure	0		0		0		0	
Infection	4	5	3	15	1	1	8	17
Idiopathic pneumonia	0		4	20	0		1	2
Acute respiratory distress syndrome	0		0		1	1	0	
Graft-versus-host disease*	1	1	5	25	1	1	7	15
Primary disease	54	63	3	15	56	73	14	30
Organ failure	5	6	1	5	5	6	5	11
Second malignancy†	6	7	1	5	2	3	0	
Hemorrhage	1	1	1	5	0		1	2
Accidental death	0		0		0		1	2
Vascular disease	0		0		0		1	2
Toxicity	0		2	10	0		2	4
Missing/other cause	15	18	0		11	14	6	13

Abbreviations: HCT, hematopoietic cell transplantation; RIC, reduced-intensity conditioning.

*In patients with graft-versus-host disease listed as the cause of death, an allogeneic transplantation occurred after the autologous transplantation.

†In patients with second malignancy listed as the cause of death, the malignancies were lung cancer (n = 1), colorectal cancer (n = 1), lymphoma (n = 1), and unspecified (n = 6).

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Table A3. Summary of Main Outcomes for All Four Cohorts

Cohort	OS at 5 Years (%)	95% CI	<i>P</i>	Relapse/Progression at 5 Years (%)	95% CI	<i>P</i>	PFS at 5 Years (%)	95% CI	<i>P</i>	NRM at 1 Year (%)	95% CI	<i>P</i>
Early HCT												
Auto-HCT	61	53 to 68	.004	32	25 to 39	.009, < .001	52	45 to 59	< .001	3	2 to 6	< .001
RIC allo-HCT	62	46 to 74		15	7 to 27	.009, .005	55	39 to 68	.003	25	14 to 38	< .001
Late HCT												
Auto-HCT	44	34 to 53	.004	51	41 to 59	< .001	29	21 to 38	< .001	9	4 to 14	
RIC allo-HCT	31	16 to 47		38	26 to 50	.005	24	12 to 39	.003	17	10 to 26	

NOTE. All *P* values are for comparisons in which outcomes were significantly different (eg, overall survival was superior for early auto-HCT compared with late auto-HCT, with a *P* value of .004).

Abbreviations: allo, allogeneic; auto, autologous; HCT, hematopoietic cell transplantation; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival.

Fig A1. Overall survival from time of diagnosis. Allo, allogeneic hematopoietic cell transplantation; auto, autologous hematopoietic cell transplantation.