original report

Survival Outcomes of Younger Patients With Mantle Cell Lymphoma Treated in the Rituximab Era

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abstract

PURPOSE Mantle cell lymphoma (MCL) is a B-cell lymphoma characterized by cyclin D1 expression. Autologous hematopoietic cell transplantation (AHCT) consolidation after induction chemotherapy is often used for eligible patients; however, the benefit remains uncertain in the rituximab era. Herein we retrospectively assessed the impact of AHCT consolidation on survival in a large cohort of transplantation-eligible patients age 65 years or younger.

PATIENTS AND METHODS We retrospectively studied transplantation-eligible adults age 65 years or younger with newly diagnosed MCL treated between 2000 and 2015. The primary objective was to assess for improved progression-free survival (PFS) with AHCT consolidation and secondarily to assess for improved overall survival (OS). Cox multivariable regression analysis and propensity score–weighted (PSW) analysis were performed.

RESULTS Data were collected from 25 medical centers for 1,254 patients; 1,029 met inclusion criteria. Median follow-up for the cohort was 76 months. Median PFS and OS were 62 and 139 months, respectively. On unadjusted analysis, AHCT was associated with improved PFS (75 *v* 44 months with *v* without AHCT, respectively; $P < .01$) and OS (147 *v* 115 months with *v* without AHCT, respectively; $P < .05$). On multivariable regression analysis, AHCT was associated with improved PFS (hazard ratio [HR], 0.54; 95% CI, 0.44 to 0.66; $P < .01$) and a trend toward improved OS (HR, 0.77; 95% CI, 0.59 to 1.01; $P = .06$). After PSW analysis, AHCT remained associated with improved PFS (HR, 0.70; 95% CI, 0.59 to 0.84; $P < .05$) but not improved OS (HR, 0.87; 95% CI, 0.69 to 1.1; $P = .2$).

CONCLUSION In this large cohort of younger, transplantation-eligible patients with MCL, AHCT consolidation after induction was associated with significantly improved PFS but not OS after PSW analysis. Within the limitations of a retrospective analysis, our findings suggest that in younger, fit patients, AHCT consolidation may improve PFS.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Mantle cell lymphoma (MCL) is a subset of B-cell non-Hodgkin lymphoma characterized by the t(11,14) translocation that leads to overexpression of cyclin D1.[1-3] Clinical outcomes of MCL are heterogeneous[4-6]; high-risk patients have a median survival of only 37 months and 5-year overall survival (OS) of 20%.[4,7-9] Efforts to better prognosticate resulted in the MCL International Prognostic Index (MIPI)[10], $MIPI_B$, and combined MIPI with Ki-67 index.[11-13]

First-line treatment options are varied and depend on age, performance status (PS), and comorbidities.[14] No approach has shown superiority, although inclusion of cytarabine is associated with improved outcome.[15-17] The best outcomes for younger, fit patients were achieved using intensive induction chemoimmunotherapy followed by autologous hematopoietic cell transplantation (AHCT) consolidation[15,17]; this approach has become the current de facto standard. Examples include R-maxi-CHOP (rituximab plus high-dose cyclophosphamide, doxorubicin, vincristine, and prednisone) with high-dose cytarabine followed by AHCT[15] and R-CHOP alternating with R-DHAP (rituximab plus dexamethasone, cisplatin, and cytarabine) followed by AHCT.[17] The use of AHCT

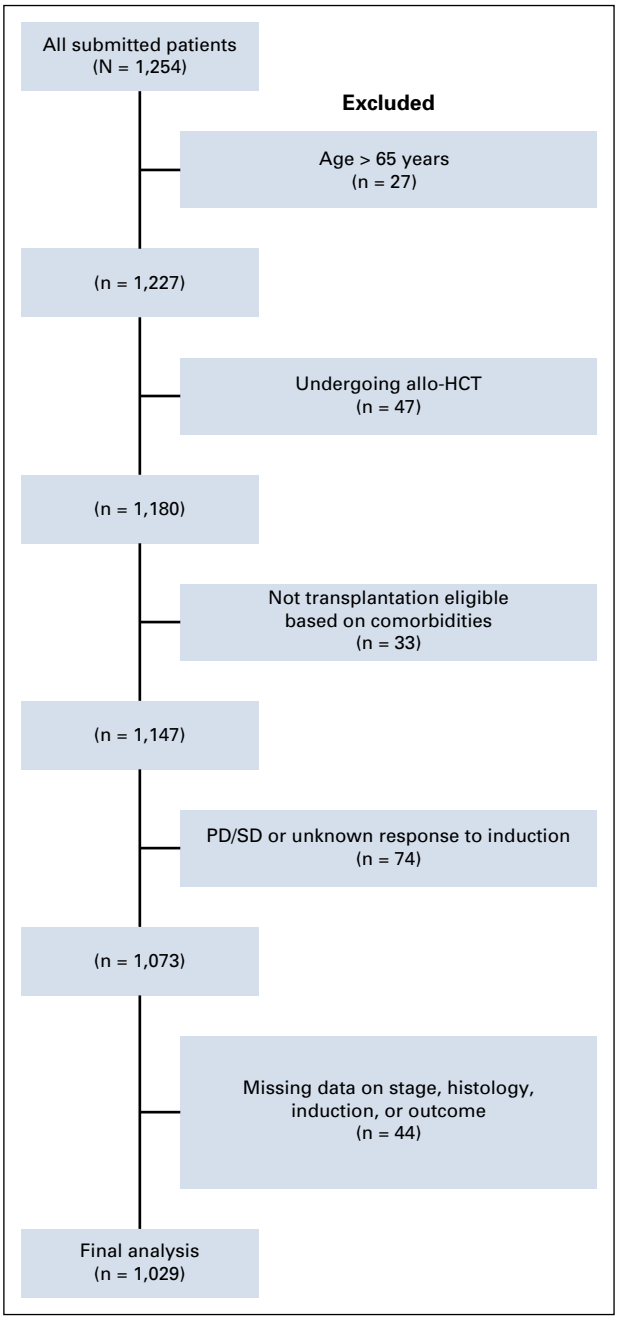

FIG 1. CONSORT diagram. allo-HCT, allogeneic hematopoietic cell transplantation; PD, progressive disease; SD, stable disease.

consolidation is supported by a randomized trial of younger patients with MCL that demonstrated improved progression-free survival (PFS) with AHCT consolidation (39 *v* 17 months) over maintenance with interferon alfa.[18] However, the lack of rituximab during induction, lack of cytarabine, and use of interferon maintenance make this approach less applicable to today's patients. Furthermore, intensive cytarabine-containing regimens (eg, R-hyperCVAD [rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) have shown prolonged disease-free survival without AHCT.[19,20] Last, targeted agents in first- or later-line therapy (eg, bortezomib, lenalidomide, and ibrutinib) may negate the need for aggressive induction.[21] Therefore, the true benefit of AHCT consolidation in younger, fit patients with MCL in the modern era is not clearly established. Herein we retrospectively assessed the impact of AHCT consolidation on survival in a large cohort of younger patients with MCL treated at multiple North American academic medical centers in the rituximab era.

PATIENTS AND METHODS

Patients

Patients were eligible if age ≤ 65 years, newly diagnosed with MCL, and deemed transplantation eligible at diagnosis by the institutional investigator by review of medical records. The diagnosis of MCL was made by a hematopathologist at each institution as per routine clinical practice. Patients must have received induction from 2000 to 2015 and achieved a partial response (PR) or complete response to induction; responses were defined by the local investigator using institutional standard imaging modalities at time of treatment (ie, computed tomography and/or positron emission tomography). Patients who received radiation therapy alone, achieved less than a PR, were deemed not transplantation eligible because of comorbidities or poor PS, or underwent consolidative allogeneic hematopoietic cell transplantation (allo-HCT) were excluded. AHCT consolidation was defined as transplantation within 6 months of induction. Centers performing transplantation in 0% or 100% of patients were excluded, as were patients with unknown histology, unknown induction regimen, or missing outcome data. The protocol was approved by the institutional review board of each participating center.

Data Collection

Data were collected for each patient on baseline characteristics and treatment, transplantation, and outcome (Appendix Table A1, online only). MIPI score was calculated for each patient with sufficient data as previously published.[10]

Statistical Analysis

The primary objective was to assess whether AHCT consolidation in first remission was associated with improved PFS, as calculated from day of diagnosis. The secondary objective was to assess for improved OS, also calculated from day of diagnosis. Patient, tumor, and treatment factors were compared between patients undergoing or not undergoing AHCT using χ^2, Fisher's exact, and Wilcoxon rank-sum tests, as appropriate.

Survival curves were calculated using the Kaplan-Meier method. Cox proportional hazards models were used to analyze the association of AHCT consolidation with survival after adjusting for confounders (sex, MIPI, cyclin D1 status,

TABLE 1. Baseline Patient Demographic and Clinical Characteristics

Variable	No. (%)			P
	All Patients	No AHCT	AHCT	
Patients	1,029 (100)	372 (36)	657 (64)	
Reason for no transplantation	NA		NA	NA
Clinician choice		249 (67)		
Patient preference		66 (18)		
Other		12 (3)		
Missing		45 (12)		
Sex				.62
Female	240 (23)	90 (24)	150 (23)	
Male	789 (77)	282 (76)	507 (77)	
Age, years				< .01
Median	57	58	56	
Range	22-65			
Median Ki-67 expression	475 (30)	209 (30)	266 (30)	< .01
MIPI				.05
Low	493 (48)	162 (46)	331 (50)	
Intermediate	194 (19)	67 (19)	127 (20)	
High	115 (11)	45 (12)	70 (11)	
Missing	227 (21)	98 (24)	129 (19)	
Bone marrow/blood involvement				< .01
No	193 (19)	79 (21)	114 (17)	
Yes	806 (79)	274 (74)	532 (81)	
Missing	30 (3)	19 (5)	11 (2)	
Blastoid/pleomorphic				.03
Yes	136 (13)	61 (16)	75 (11)	
No	893 (78)	311 (83)	582 (88)	
Cytogenetics				.05
Normal	674 (65)	231 (60)	443 (68)	
p53	28 (3)	11 (3)	17 (3)	
Complex	87 (8)	26 (7)	61 (9)	
Missing	240 (24)	104 (31)	136 (20)	
Cyclin D1				.73
Positive	915 (89)	327 (89)	588 (90)	
Negative	40 (4)	16 (4)	24 (3)	
Missing	74 (7)	29 (7)	45 (6)	
Induction				< .01
CHOP-like	443 (43)	158 (44)	285 (43)	
Intensive*	454 (44)	147 (39)	307 (47)	
Bendamustine based	119 (11)	56 (15)	63 (10)	
Other	13 (1)	11 (2)	2 (1)	
Anti-CD20 with induction				< .01
Yes	973 (95)	342 (92)	631 (96)	
No	56 (5)	30 (8)	26 (4)	

(continued on following page)

TABLE 1. Baseline Patient Demographic and Clinical Characteristics (continued)

Variable	No. (%)			P
	All Patients	No AHCT	AHCT	
Cytarabine with induction				< .01
No	556 (54)	229 (61)	327 (50)	
Yes	473 (46)	143 (38)	330 (50)	
Novel agent with induction				< .01
No	1,003 (97)	353 (95)	650 (99)	
Yes	26 (3)	19 (5)	7 (1)	
Response to induction				.54
CR	783 (76)	279 (75)	504 (77)	
PR	246 (24)	93 (25)	153 (23)	
Maintenance				< .01
No	644 (62)	216 (57)	428 (65)	
Rituximab	306 (30)	107 (30)	199 (30)	
Missing	79 (8)	49 (2)	30 (5)	

Abbreviations: AHCT, autologous hematopoietic cell transplantation; CHOP, cyclophosphamide, doxurobucin, vincristine, and prednisone; CR, complete response; MIPI, Mantle Cell Lymphoma International Prognostic Index; NA, not applicable; PR, partial response.

*Intensive includes hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), maxi-CHOP (high-dose CHOP), or DHAP (dexamethasone, cisplatin, and cytarabine) based.

bone marrow or peripheral blood involvement, extranodal disease, induction regimen, blastoid or pleomorphic morphology, response to induction, and receipt of maintenance therapy). Because of the time between diagnosis and consolidation with AHCT, we addressed potential immortal-time bias using two different methods.[22] For graphic presentation of survival curves, we excluded patients who died within 6 months of diagnosis in a landmark analysis. For all Cox model–based analyses, treatment was included in the model as a time-varying covariable, so time before transplantation was coded as "no AHCT," whereas time after transplantation was coded as "AHCT."[23] Covariates with 0% to 30% missing data were imputed via chained equations.[24] We used multiple imputation for variables with missing data, and standard deviations were calculated using Rubin's equation.[25] Ki-67 was excluded from the primary regression models because it was available in < 50% of patients. All regression models were stratified by treating institution, with separate baseline hazard functions fit to each stratum.

To assess the assumptions of the model, we conducted several sensitivity analyses (SAs). We fit models excluding stage, bone marrow/peripheral blood, and extranodal disease, because these covariates may be affected by institutional staging practices. We also ran models without imputing data, instead including categorical indicators for missing data.[25] We determined subgroup effects using regression models with subgroup × AHCT interactions; these models were conducted only in the patients with complete data on the particular variable of interest.

Propensity Score–Weighted Analysis

A propensity score–weighted (PSW) analysis was subsequently performed. Propensity scores (probability of AHCT) were estimated via logistic regression models on the basis of the imputed data sets, including the covariates listed in the main model and an indicator variable for missing data pattern.[26] We then applied variance-stabilized inverse probability of treatment weights to generate a pseudo sample in which covariates used to estimate the propensity score were balanced between treatment arms. Propensity score ranges were checked for sufficient overlap, and balance was assessed via standardized differences.[27] The weighted sample was then used to create Kaplan-Meier curves and fit time-varying Cox regression models, both of which accounted for confounders included in the propensity score via the weights. This method has been shown to successfully correct bias from measured confounders, but it does not address unmeasured confounding. We therefore conducted an SA to assess the degree of unmeasured confounding that would be required to change the conclusions of the analysis. We explored the potential impact of a particular unmeasured confounder on the estimated effect of AHCT under a range of possible scenarios.[28]

RESULTS

Patients and Disease Characteristics

Data for a total of 1,254 patients were collected from 25 North American academic centers. To identify patients, 32% (n = 8) of centers used a lymphoma database only,

4% (n = 1) used a transplantation registry only, 12% (n = 3) used a pathology database, 24% (n = 6) used both a lymphoma database and a transplantation registry, and 28% (n = 7) used another method. Median number of patients contributed per institution was 30, with a range of two to 285 patients. A majority of patients received AHCT consolidation, with a median rate of 67% (range, 26% to 92%); three centers had AHCT rates < 50%. Of 1,254 patients, we excluded: those age > 65 years (n = 27), those who underwent allo-HCT (n = 47), those achieving less than a PR to induction (n = 74), and those missing substantial data (n = 44; Fig 1).

A total of 1,029 patients were included in the final analysis. Patient and treatment characteristics are listed in Table 1. Sixty-four percent (n = 657) of patients received AHCT consolidation after induction. Of the 372 patients who did not undergo AHCT, the reason for no transplantation was physician choice in 67% (n = 249), patient preference in 18% (n = 66), other reason (eg, mobilization failure) in 3% (n = 12), and missing reason in 12% (n = 45). Median age at time of diagnosis was 57 years. The induction regimen was CHOP-like in 43% of patients (n = 443), intensive (hyperCVAD, maxi-CHOP, DHAP) in 44% (n = 454), bendamustine based in 11% (n = 119), and other (eg, clinical trial) in 1% (n = 13). Best response to induction was complete response for 76% of patients (n = 783). Overall, both groups were balanced with regard to prognostic features, tumor characteristics, and treatment modalities; small but statistically significant differences were detected in certain variables. The lymphomas of 89% (n = 915) of patients were cyclin D1 positive. Ki-67 expression in 43% and 57% of patient was < 30% and ≥ 30%, respectively (median value, 30%). Thirteen percent (n = 136) were diagnosed with blastoid or pleomorphic morphology. A majority of patients (95%; n = 973) received an anti-CD20 monoclonal antibody with induction; 30% (n = 306) received maintenance rituximab. Only 2.5% (n = 26) received a novel agent with induction.

Survival

After a median follow-up of 76 months (6.3 years; range, 1 to 205 months), median PFS for the entire cohort was 62 months (5.2 years; range, 1 month to 17.1 years), and

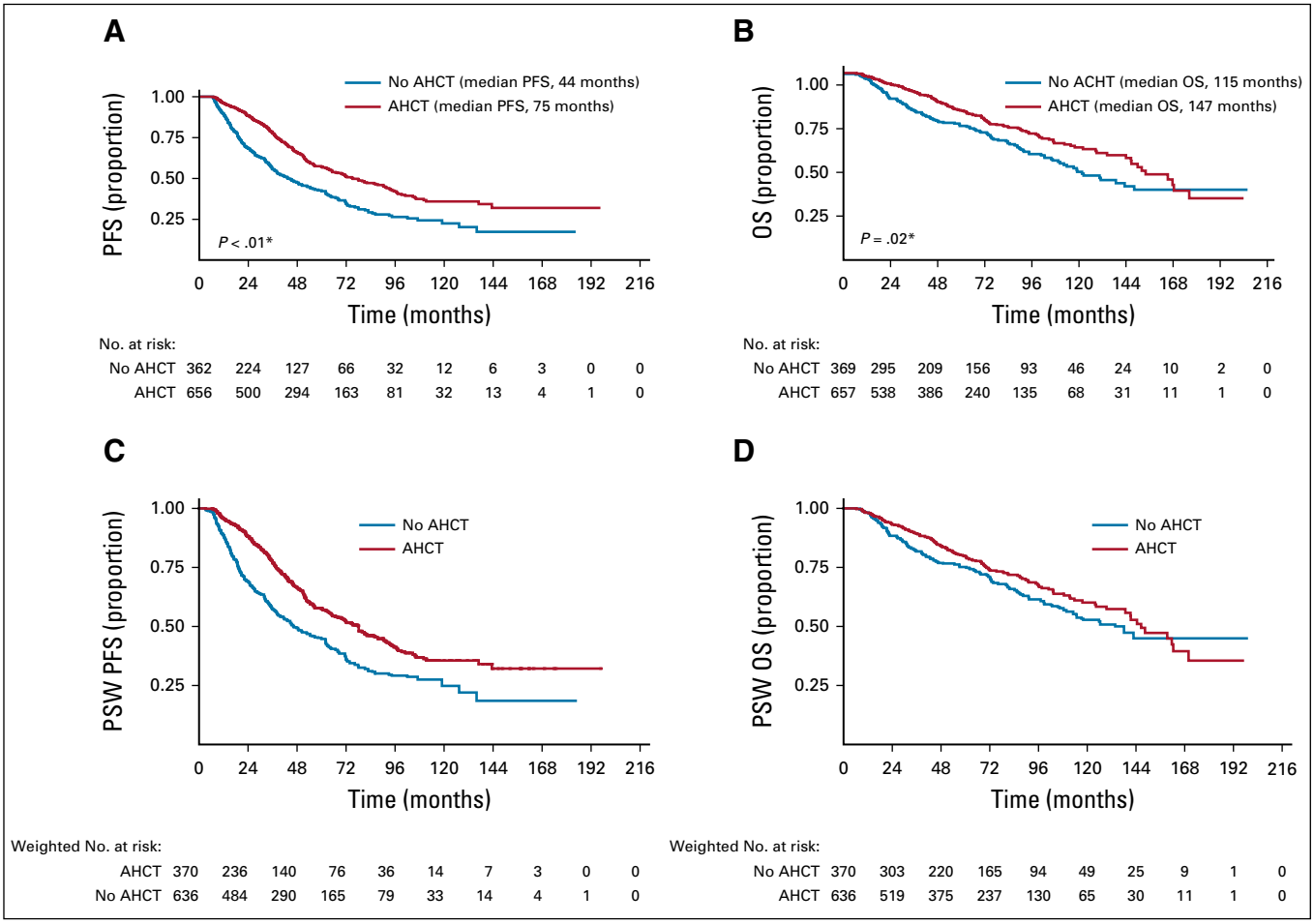

FIG 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) at 6 months and for (C) propensity score–weighted (PSW) PFS and (D) PSW OS at 6 months. AHCT, autologous hematopoietic cell transplantation. (*) Log-rank test.

median OS was 138 months (11.5 years; range, 1 month to 17.1 years; Appendix Fig A1, online only). Only three patients died < 6 months after induction. Unadjusted landmark analysis demonstrated a statistically significant improvement in PFS favoring use of consolidative AHCT after induction, with median PFS of 44 months without AHCT versus 75 months with AHCT (hazard ratio [HR], 0.64; 95% CI, 0.54 to 0.78; $P < .01$; Fig 2A). We also observed a significant improvement in OS with use of AHCT, from 115 to 147 months (HR, 0.79; 95% CI, 0.63 to 0.99; $P < .05$; Fig 2B).

On multivariable regression analysis (MVA) and with imputation for missing data, AHCT was associated with improved PFS (HR, 0.53; 95% CI, 0.43 to 0.66; $P < .01$) and a trend toward improved OS (HR, 0.77; 95% CI, 0.98 to 1.01; $P = .06$). Factors associated with improved PFS and OS are listed in Table 2. When analysis was restricted to the 91% of patient cases that were cyclin D1 positive, the HR for PFS and OS did not change significantly (Appendix Table A2, online only). On subgroup analyses, all subgroups demonstrated improved PFS with consolidative AHCT (Fig 3A). Improved OS was seen only in patients with high-risk MIPI scores, those who received CHOP-like induction, those with blastoid or pleomorphic morphology, and those who did not receive cytarabine with induction (Fig 3B). Kaplan-Meier curves demonstrated these findings (Appendix Fig A2, online only).

Of patients not undergoing AHCT, 224 had a progression event. Of these, 64 underwent AHCT or allo-HCT in the second-line setting. OS was significantly improved for patients receiving any type of transplant after relapse (Appendix Fig A3, online only).

TABLE 2. Factors Associated With Improved Survival on Multivariable Analysis (N = 1,029)

Survival	HR	95% CI	*P*
PFS			
MIPI low *v* high risk	0.55	0.42 to 0.72	< .01
Nonblastoid or nonpleomorphic morphology	0.54	0.42 to 0.71	< .01
Use of novel agent* with induction	0.24	0.10 to 0.62	.01
CR to induction	0.49	0.39 to 0.61	< .01
Maintenance rituximab	0.59	0.45 to 0.78	< .01
OS			
MIPI low *v* high risk	0.42	0.30 to 0.60	< .01
Nonblastoid or nonpleomorphic morphology	0.51	0.36 to 0.70	< .01
CR to induction	0.51	0.38 to 0.68	.01
Maintenance rituximab	0.59	0.42 to 0.82	< .01

Abbreviations: CR, complete response; HR, hazard ratio; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PFS, progression-free survival.

*Novel agent includes bortezomib, ibrutinib, or lenalidomide.

Survival After PSW Analysis

After PSW analysis (n = 1,003), median PFS improved from a median of 48.5 months without AHCT to 78.0 months with AHCT (HR, 0.70; 95% CI, 0.59 to 0.84, $P < .05$; Fig 2C). Improvement in OS was not observed, with a median OS of 138 months without AHCT and 147 months with AHCT (HR, 0.87; 95% CI, 0.69 to 1.10; $P = .24$; Table 3; Fig 2D).

Sensitivity for Unmeasured Confounding

In any observational study, a range of unmeasured confounders may bias the results. We hypothesized that PS after induction therapy would be the largest such confounder and chose to use it as an illustrative example. We expected PS would be worse in patients not undergoing AHCT and that PS > 0 would be associated with an HR of 2 to 3 for OS outcomes and 1.25 to 2 for PFS outcomes.[29-31] We assumed that rates of PS > 0 would be fairly low in this younger population (ie, 5% to 10% in the AHCT arm). We assessed the effect of varying HRs and differences in the rate of PS > 0 on the estimated OS and PFS effect of AHCT. Although the effect of AHCT on OS was nonsignificant after adjustment, we found that with modest imbalances in PS, the trend toward benefit with AHCT would disappear (ie, HR = 1 for AHCT on OS when HR for PS > 0 equaled 3 and the difference in rates between arms was 10%). The effect of AHCT on PFS was much more robust; to negate the improved PFS by AHCT, substantial effects of PS and imbalance between groups would be necessary (ie, when HR for PS > 0 equaled 2 and the difference in rates between arms was 25%; Appendix Table A3, online only).

Safety

In patients who underwent consolidative AHCT, 1.2% (n = 7) died within 100 days of transplantation. In the entire cohort and at a median follow-up of 76.8 months, 2% (n = 21) of patients developed secondary myelodysplastic syndrome or acute myeloid leukemia. The incidence of myelodysplastic syndrome or acute myeloid leukemia was not different in the AHCT and non-AHCT groups (2.5%; n = 16 *v* 1.3%; n = 5, respectively; $P = .36$).

DISCUSSION

In this large retrospective cohort of younger, transplantation-eligible patients with MCL who achieved a PR or better after induction chemotherapy, we demonstrated improved PFS for patients who underwent consolidative AHCT. After MVA, certain subgroups (patients with blastoid or pleomorphic morphology, those with high-risk MIPI scores, those treated with nonintensive CHOP-like induction, and those who did not receive cytarabine with induction) derived the largest improvement in OS. To reduce inherent biases of retrospective analyses, we elected to perform a PSW analysis and demonstrated persistence of the observed improvement in PFS. In contrast, although improved OS was observed on unadjusted analysis, this

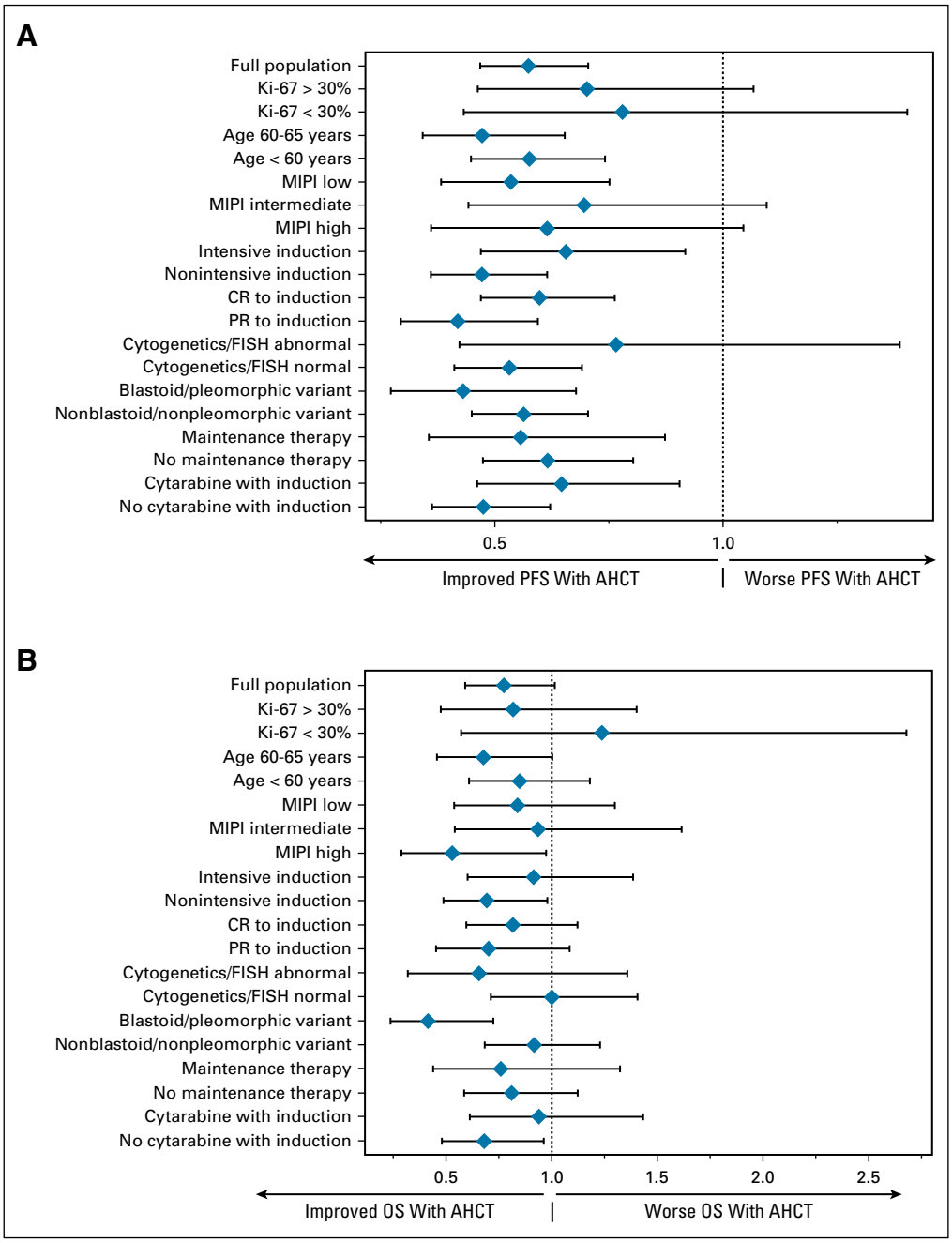

FIG 3. Forest plots for (A) progression-free survival (PFS) and (B) overall survival (OS) with autologous hematopoietic cell transplantation (AHCT). CR, complete response; FISH, fluorescence in situ hybridization; MIPI, Mantle Cell Lymphoma International Prognostic Index; PR, partial response.

improvement did not persist for the entire cohort after PSW analysis, raising the possibility that any observed benefits may have resulted from confounding.

MCL remains an incurable lymphoma with no clearly defined standard-of-care first-line treatment strategy. Prospective trials using intensive induction regimens such as the Nordic regimen followed by AHCT,[15] DHAP alternating with R-CHOP followed by AHCT,[17] and R-hyperCVAD with methotrexate and high-dose cytarabine without AHCT[19,20] have demonstrated improved survival compared with historical controls. Results from a smaller retrospective study[32] and a recently reported analysis of > 10,000 patients obtained using the National Cancer Database demonstrated an association between consolidative AHCT and improved OS.[33] With the caveats of retrospective analysis, our data also suggest an improvement in PFS with AHCT consolidation after induction in transplantation-eligible patients. The lack of improvement in OS after PSW analysis may be a result of effective salvage therapy (eg, novel agents and/or AHCT/allo-HCT) after relapse, which may abrogate any improvement of consolidative AHCT after induction.

TABLE 3. Survival After PSW Analysis (N = 1,029)

Survival	HR	95% CI	*P*
PFS (n = 1,003)	0.70	0.59 to 0.84	< .01
OS (n = 1,003)	0.87	0.69 to 1.10	.24

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSW, propensity score weighted.

In our subgroup analysis after MVA, most groups demonstrated improved PFS with AHCT, whereas improved OS with AHCT was limited to patients who received CHOP-like induction or induction without cytarabine, had blastoid or pleomorphic variant, or were MIPI-high. This suggests that patients who do not receive cytarabine with induction, receive CHOP-like induction, or have high-risk features (eg, MIPI-high or blastoid/pleomorphic MCL) may benefit most from AHCT consolidation. No differential treatment effect was observed for MIPI-low or -intermediate patients. MIPI score remained prognostic irrespective of receipt of AHCT consolidation. Furthermore, we did not observe a benefit of AHCT with respect to the Ki-67 index. These findings are consistent with the overarching prognostic impact of the combined MIPI score observed in both younger and older patients, as described by Hoster et al.[13]

Novel combinations using ibrutinib,[34] bortezomib,[35] and lenalidomide[36] have demonstrated favorable outcomes. In our data set, the number of patients who received novel agents with induction was small, limiting conclusions of this approach. The use of these agents at relapse may help explain the lack of improvement in OS after PSW analysis despite improved PFS.

The strengths of our study are the large number of patients (> 1,000) included in analysis; the high rate (89%) of cyclin D1–positive tumors, which balances lack of central pathology review; high rates of receipt of anti-CD20 antibodies with induction, confirming this population was treated with modern therapy; use of PSW analysis to limit selection bias; use of nontransplantation registries to identify patients at all but one center, limiting recall bias; and use of an SA to determine the effect of PS.

There are a number of limitations to our study, mostly inherent to its retrospective nature. Selection bias may have informed the decision for AHCT. We attempted to collect the reasons patients did not undergo AHCT, but there was potential for significant heterogeneity in the true reasons. For example, physicians may have recommended against AHCT for patients who experienced significant toxicity, those with comorbid conditions that were not strict contraindications, or those with aggressive disease over concern for lack of benefit. In addition, a substantial portion (18%) of patients elected to not undergo HCT, which may have reflected underlying differences in family support, socioeconomic status, or deterioration in PS after induction. Moreover, PS is subjective and can change during induction, and emotional states and quality-of-life measures of patients were not captured. Although we could not directly account for these factors, we did conduct an SA to assess the potential impact of unmeasured confounding on treatment outcomes; however, the underlying potential bias in retrospective data remains. Other limitations include that data were collected from tertiary centers only, which may have led to bias from referral patterns. Induction regimen varied both between and within centers, leading to heterogeneity in first-line treatment. There was a lack of standardized response assessment to induction, as well as no central review of the response assessment. There was no central pathology review, raising the possibility of incorrect diagnosis for some patients (although notably, results were not significantly different when analysis was restricted to patients positive for cyclin D1). Finally, certain data fields (eg, Ki-67) had a relatively large percentage of missing data.

In summary, in this cohort of > 1,000 young, transplantation-eligible patients treated in the rituximab era, the use of consolidative AHCT after induction was associated with improved PFS even after controlling for disease severity using PSW analysis. Although no improvement in OS was observed for the entire cohort after PSW analysis, certain high-risk patients and those who did not receive intensive induction or cytarabine with induction seemed to benefit. These findings must certainly be interpreted in light of the limitations inherent to the retrospective nature of our study. AHCT is not a random event, and although we adjusted for confounding, unmeasurable differences between patients may have influenced our findings. Prospective, randomized trials are urgently needed to determine the true benefit of consolidative AHCT. It is likely that some subgroups derive minimal benefit from AHCT consolidation, such as patients with certain genetic abnormalities (eg, *TP53* mutations) and those who achieve minimal residual disease negativity after induction, the latter of whom are being investigated in the ongoing EA4151 clinical trial (ClinicalTrials.gov identifier: NCT03267433). With this and other well-designed prospective trials as well as with well-validated predictive biomarkers, clinicians will be better able to provide a more refined, risk-adapted approach to first-line management of MCL.

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REFERENCES

1. Pérez-Galán P, Dreyling M, Wiestner A: Mantle cell lymphoma: Biology, pathogenesis, and the molecular basis of treatment in the genomic era. Blood 117: 26-38, 2011
2. Barista I, Romaguera J.E., Cabanillas F: Mantle-cell lymphoma. Lancet Oncol 2:141-148, 2001
3. Williams ME, Bernstein SH, Jares P, et al: Recent advances in mantle cell lymphoma: Report of the 2012 Mantle Cell Lymphoma Consortium Workshop. Leuk Lymphoma 54:1882-1890, 2013
4. Sander B, Quintanilla-Martinez L, Ott G, et al: Mantle cell lymphoma: A spectrum from indolent to aggressive disease. Virchows Arch 468:245-257, 2016
5. Jares P, Colomer D, Campo E: Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 122:3416-3423, 2012
6. Navarro A, Clot G, Royo C, et al: Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Res 72:5307-5316, 2012
7. Chandran R, Gardiner SK, Simon M, et al: Survival trends in mantle cell lymphoma in the United States over 16 years 1992-2007. Leuk Lymphoma 53: 1488-1493, 2012
8. Duggan MJ, Weisenburger DD, Ye YL, et al: Mantle zone lymphoma: A clinicopathologic study of 22 cases. Cancer 66:522-529, 1990
9. Vandenberghe E, De Wolf-Peeters C, Vaughan Hudson G, et al: The clinical outcome of 65 cases of mantle cell lymphoma initially treated with non-intensive therapy by the British National Lymphoma Investigation Group. Br J Haematol 99:842-847, 1997
10. Hoster E, Dreyling M, Klapper W, et al: A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 111:558-565, 2008
11. Hoster E, Klapper W, Hermine O, et al: Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. J Clin Oncol 32:1338-1346, 2014
12. Geisler C.H., Kolstad A, Laurell A, et al: The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 115:1530-1533, 2010
13. Hoster E, Rosenwald A, Berger F, et al: Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: Results from randomized trials of the European Mantle Cell Lymphoma Network. J Clin Oncol 34:1386-1394, 2016
14. Dreyling M, Campo E, Hermine O, et al: Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 28:iv62-iv71, 2017 (suppl 4):
15. Geisler C.H., Kolstad A, Laurell A, et al: Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 112:2687-2693, 2008
16. Campo E, Rule S: Mantle cell lymphoma: Evolving management strategies. Blood 125:48-55, 2015
17. Hermine O, Hoster E, Walewski J, et al: Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): A randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet 388:565-575, 2016
18. Dreyling M, Lenz G, Hoster E, et al: Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European MCL Network. Blood 105: 2677-2684, 2005
19. Bernstein SH, Epner E, Unger JM, et al: A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma: SWOG 0213. Ann Oncol 24:1587-1593, 2013
20. Romaguera JE, Fayad L, Rodriguez MA, et al: High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 23:7013-7023, 2005
21. Martin P, Ruan J, Leonard JP: The potential for chemotherapy-free strategies in mantle cell lymphoma. Blood 130:1881-1888, 2017
22. Giobbie-Hurder A, Gelber RD, Regan MM: Challenges of guarantee-time bias. J Clin Oncol 31:2963-2969, 2013
23. Klein J, Moeschberger ML: Survival Analysis: Techniques for Censored and Truncated Data (ed 2). New York, NY, Springer-Verlag, 2003
24. van Buuren S, Groothuis-Oudshoorn K: Multivariate imputation by chained equations in R. https://www.jstatsoft.org/article/view/v045i03

25. Little RJA, Rubin DB: Statistical Analysis With Missing Data (ed 2). Hoboken, NJ, John Wiley & Sons, 2014
26. Qu Y, Lipkovich I: Propensity score estimation with missing values using a multiple imputation missingness pattern (MIMP) approach. Stat Med 28:1402-1414, 2009
27. Austin PC, Stuart EA: Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 34:3661-3679, 2015
28. Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 54:948-963, 1998
29. Hedström G, Hagberg O, Jerkeman M, et al: The impact of age on survival of diffuse large B-cell lymphoma: A population-based study. Acta Oncol 54:916-923, 2015
30. Smith A, Crouch S, Howell D, et al: Impact of age and socioeconomic status on treatment and survival from aggressive lymphoma: A UK population-based study of diffuse large B-cell lymphoma. Cancer Epidemiol 39:1103-1112, 2015
31. Carey M.S., Bacon M, Tu D, et al: The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer. Gynecol Oncol 108:100-105, 2008
32. Touzeau C, Leux C, Bouabdallah R, et al: Autologous stem cell transplantation in mantle cell lymphoma: a report from the SFGM-TC. Ann Hematol 93:233-242, 2014
33. Sawalha Y, Radivoyevitch T, Tullio K, et al: The role of upfront autologous hematopoietic cell transplantation in the treatment of mantle cell lymphoma, a population based study using the National Cancer Data Base (NCDB). Presented at the 59th Annual Meeting of the American Society of Hematology, Atlanta GA, December 9-12, 2017
34. Maddocks K, Christian B, Jaglowski S, et al: A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. Blood 125:242-248, 2015
35. Robak T, Huang H, Jin J, et al: Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med 372:944-953, 2015
36. Ruan J, Martin P, Shah B, et al: Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med 373:1835-1844, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Survival Outcomes of Younger Patients With Mantle Cell Lymphoma Treated in the Rituximab Era

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APPENDIX

TABLE A1. Data Collection

Baseline Characteristic	Treatment Data	Transplantation Data	Outcome Data
Age	Induction regimen (defined as CHOP-like, intensive [eg, hyperCVAD, maxi-CHOP, DHAP], bendamustine based, cytarabine containing, or novel [lenalidomide, ibrutinib, or bortezomib containing])	Receipt of consolidative AHCT	Date of last follow-up
Sex	Receipt of an anti-CD20 antibody with induction	Time from initiation of treatment to transplantation	Occurrence and date of progression
Peripheral blood or bone marrow involvement	Response to induction (CR, PR, SD, or PD)	Reason for no transplantation if not received (investigator preference, patient preference, other reason, or unknown)	Cause of death (if dead)
No. of EN sites	Receipt of maintenance therapy (defined as any therapy administered after induction/ consolidation, with length of therapy not defined)		Development of treatment-related MDS or AML
ECOG PS			
Presence of B symptoms			
Lactate dehydrogenase at diagnosis (actual value as well as institutional upper limit of normal)			
Histologic subtype (ie, blastoid or pleomorphic histology)			
Cytogenetics			
Cyclin D1 status			
Ki-67 (if range, rounded to nearest 10%)			

Abbreviations: AHCT, autologous hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete response; DHAP, dexamethasone, cisplatin, and cytarabine; ECOG PS, Eastern Cooperative Oncology Group performance status; EN, extranodal; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; maxi-CHOP, high-dose cyclophosphamide, doxurobucin, vincristine, and prednisone; MDS, myelodysplastic syndrome; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE A2. Adjusted Model for Survival Limited to Cyclin D1–Positive Patients

Survival	HR	95% CI	*P*
OS (n = 915)	0.78	0.59 to 1.0	.06
PFS (n = 915)	0.54	0.43 to 0.68	< .01

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

TABLE A3. Sensitivity Analysis for PS

HR of PS*	Probability in AHCT Arm†	Probability in Non-AHCT Arm†	HR‡	LCL§	UCL§
OS					
No imbalance (original adjusted estimate)			0.868	0.688	1.10
2.0	0.10	0.20	0.947	0.750	1.20
2.5	0.10	0.20	0.982	0.777	1.24
3.0	0.10	0.20	1.013	0.802	1.28
2.0	0.05	0.3	1.075	0.851	1.36
2.5	0.05	0.3	1.171	0.928	1.48
3.0	0.05	0.3	1.263	1.000	1.59
PFS					
No imbalance (original adjusted estimate)		0.702	0.586	0.841	0.702
1.25	0.10	0.2	0.719	0.601	0.861
1.50	0.10	0.2	0.736	0.614	0.881
2.00	0.10	0.2	0.766	0.640	0.917
1.25	0.05	0.3	0.745	0.623	0.893
1.50	0.05	0.3	0.788	0.658	0.943
2.00	0.05	0.3	0.869	0.726	1.041

Abbreviations: AHCT, autologous hematopoietic cell transplantation; HR, hazard ratio; LCL, lower confidence limit; OS, overall survival; PFS, progression-free survival; PS, performance status; UCL, upper confidence limit.

*HR for PS $>$ 0.

†Probability of postinduction PS $>$ 0.

‡HR for AHCT adjusted for PS as an unmeasured confounder with the given properties.

§Of adjusted HR.

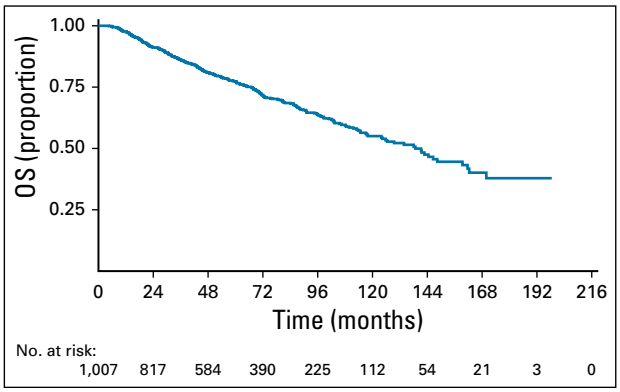

FIG A1. Overall survival (OS) of full cohort. Median survival, 76.8 months (6.4 years).

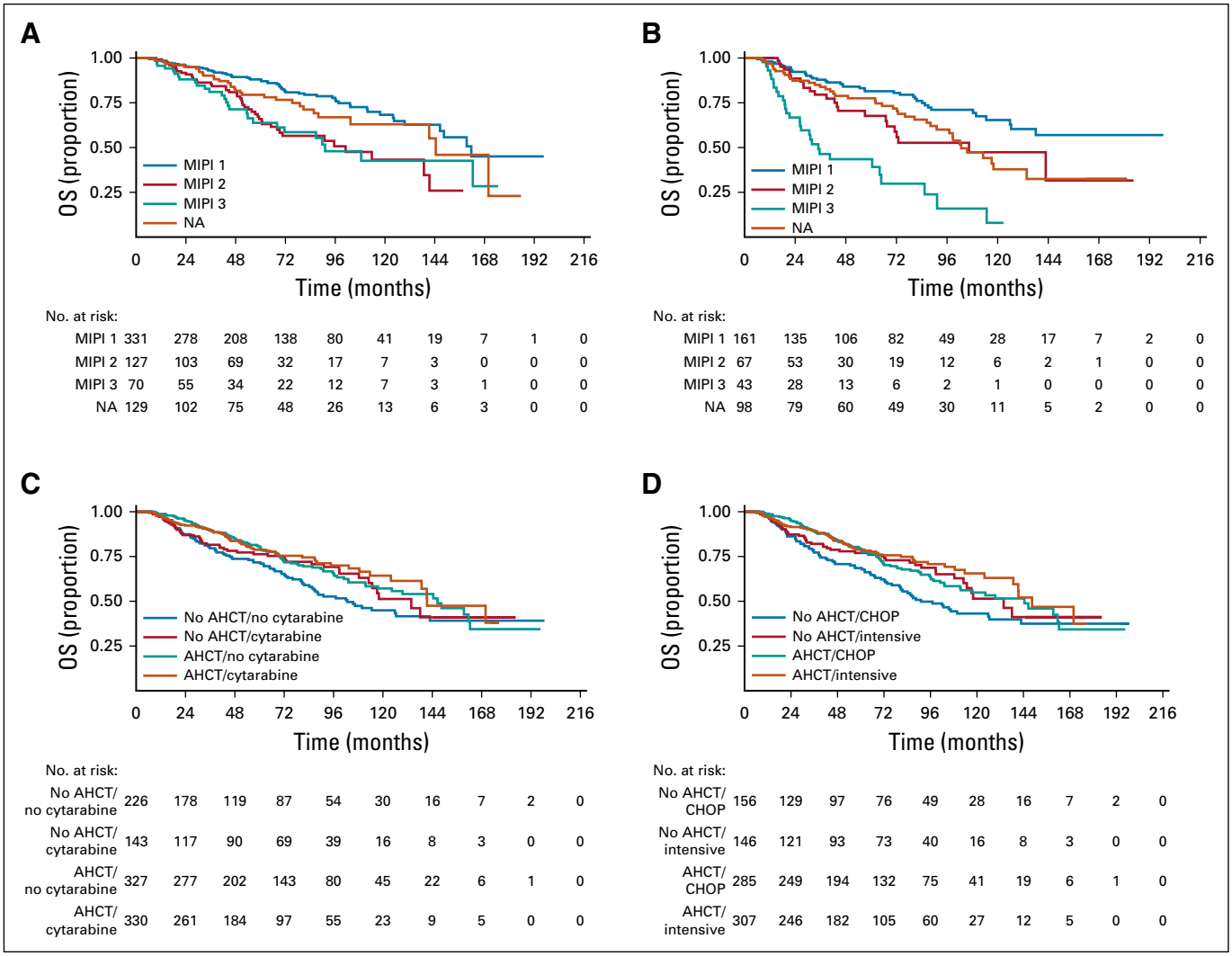

FIG A2. Overall survival (OS) for patients (A) undergoing or (B) not undergoing autologous hematopoietic cell transplantation (AHCT) by Mantle Cell Lymphoma International Prognostic Index (MIPI) score and for patients (C) by AHCT and receipt of cytarabine and (D) by AHCT and induction regimen. CHOP, cyclophosphamide, doxurobucin, vincristine, and prednisone; NA, not available.

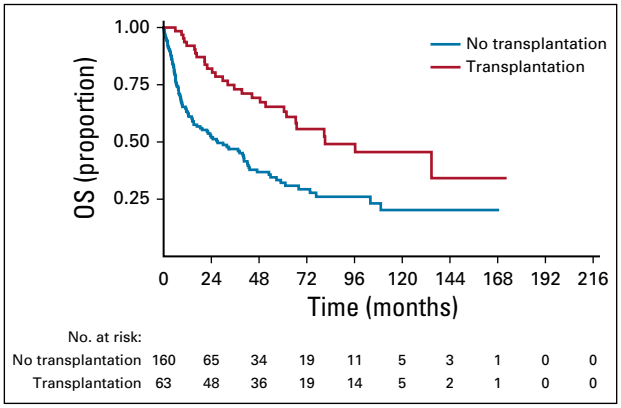

FIG A3. Overall survival (OS) after progression by second-line transplantation.