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ORIGINAL ARTICLE

Impact of bortezomib-based versus lenalidomide maintenance therapy on outcomes of patients with high-risk multiple myeloma

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Abstract

Background: Lenalidomide maintenance after autologous stem cell transplant (ASCT) in multiple myeloma (MM) results in superior progression-free survival and overall survival. However, patients with high-risk multiple myeloma (HRMM) do not derive the same survival benefit from lenalidomide maintenance compared with standard-risk patients. The authors sought to determine the outcomes of bortezomib-based maintenance compared with lenalidomide maintenance in patients with HRMM undergoing ASCT.

Methods: In total, the authors identified 503 patients with HRMM who were undergoing ASCT within 12 months of diagnosis from January 2013 to December 2018 after receiving triplet novel-agent induction in the Center for International Blood and Marrow Transplant Research database. HRMM was defined as deletion 17p, t(14;16), t(4;14), t(14;20), or chromosome 1q gain.

Results: Three hundred fifty-seven patients (67%) received lenalidomide alone, and 146 (33%) received bortezomib-based maintenance (with bortezomib alone in 58%). Patients in the bortezomib-based maintenance group were more likely to harbor two or more high-risk abnormalities and International Staging System stage III disease (30% vs. 22%; $p = .01$) compared with the lenalidomide group (24% vs. 15%; $p < .01$). Patients who were receiving lenalidomide maintenance had superior progression-free survival at 2 years compared with those who were receiving either bortezomib monotherapy or combination therapy (75% vs. 63%; $p = .009$). Overall survival at 2 years was also superior in the lenalidomide group (93% vs. 84%; $p = .001$).

Conclusions: No superior outcomes were observed in patients with HRMM who received bortezomib monotherapy or (to a lesser extent) in those who received bortezomib in combination as maintenance compared with lenalidomide alone. Until prospective data from randomized clinical trials are available, post-transplant therapy should be tailored to each patient with consideration for treating patients in clinical trials that target novel therapeutic strategies for HRMM, and lenalidomide should remain a cornerstone of treatment.

KEYWORDS
bortezomib, lenalidomide, maintenance therapy, multiple myeloma, stem cell transplant

INTRODUCTION

Patients with high-risk multiple myeloma (HRMM), commonly defined as having deletion 17p/monosomy 17, t(14;16), t(4;14), t(14;20), or gain 1q by fluorescence in situ hybridization, have poor outcomes after autologous stem cell transplant (ASCT).[1,2] Lenalidomide maintenance after ASCT results in prolongation of both progression-free survival (PFS) and overall survival (OS), which has led to the widespread adoption and US Food and Drug Administration approval of lenalidomide maintenance as the standard of care for most patients with myeloma.[3,4] However, in a pooled analysis, patients with HRMM did not derive a survival benefit from maintenance lenalidomide.[5] In the HOVON trial (EudraCT no. 2004-000944-26), the inclusion of bortezomib as part of induction and maintenance was associated with improved survival outcomes in patients with HRMM.[6,7] Therefore, proteasome inhibitors, such as bortezomib or carfilzomib, are considered key drugs in induction regimens for patients with high-risk myeloma. There are limited data comparing lenalidomide alone versus other maintenance/consolidation regimens, specifically bortezomib-based regimens, in patients with HRMM in the era of novel agents.

The optimal maintenance strategy for HRMM patients is not defined, and treatment recommendations for post-ASCT maintenance for these patients can vary considerably across practices.[2,8] In a meta-analysis, Gay et al.[9] reported an improvement in OS with lenalidomide as maintenance post-transplant compared with thalidomide-based

regimens. A retrospective study from Emory University showed that combined bortezomib and lenalidomide maintenance was associated with an improvement in PFS in high-risk patients with myeloma.[10] In the FORTE trial (ClinicalTrials.gov identifier NCT02203643),[11,12] the use of carfilzomib, lenalidomide, dexamethasone induction followed by transplant and double maintenance with carfilzomib and lenalidomide was identified as superior to lenalidomide alone, including in subsets of high-risk patients. However, a different approach may be needed in transplant-ineligible patients. In the S1211 trial (ClinicalTrials.gov identifier NCT01668719),[13] the addition of elotuzumab to bortezomib, lenalidomide, and dexamethasone (RVD) without the intent for upfront transplantation did not improve PFS in patients with HRMM. In the E1A11[14] study(ClinicalTrials.gov identifier NCT01863550), patients were randomized to receive induction with carfilzomib, lenalidomide, dexamethasone versus RVD followed by maintenance with lenalidomide. In the patients with standard-risk cytogenetics, there was no significant difference in PFS in either group. In the current study, we used the Center for International Blood and Marrow Transplant Research (CIBMTR) database to investigate whether patients with HRMM who were receiving lenalidomide alone as maintenance after upfront ASCT have inferior outcomes compared with other approaches, specifically those receiving bortezomib-based consolidation/maintenance.

MATERIALS AND METHODS

Data sources

The CIBMTR is a research collaboration between The National Marrow Donor Program—Be the Match—and the Medical College of Wisconsin. It encompasses a voluntary working group of more than 500 transplantation centers worldwide. Participating centers are required to report all transplants consecutively; compliance is monitored by onsite audits, and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

Patient selection

The study population consisted of US adult patients who had HRMM and underwent upfront ASCT between 2013 and 2018 within 12 months of diagnosis after receiving triplet novel-agent induction reported to the CIBMTR from nonembargoed centers. Alive patients were required to have at least 3 months of follow-up data reported.

Definitions

High-risk cytogenetic features were defined as the presence of at least one of the following abnormalities: having deletion 17p/monosomy 17, t(14;16), t(4;14), t(14;20), or abnormality in 1q by fluorescence in situ hybridization. Abnormality 1q included both gain1q (three copies of 1q) and amplification 1q (four or more copies of 1q) as reported by centers. High-risk patients were further analyzed in two subgroups: (1) HRMM with traditional high-risk features with or without 1q abnormalities (17p/monosomy 17, t[14;16], t[4;14], t[14;20], with or without abnormal 1q), referred throughout this article as *group A*; and (2) abnormality 1q without any of the other high-risk markers, referred throughout as *group B*. Responses were defined according to the International Myeloma Working Group classification.[15] The primary outcome that was studied was PFS. Other outcomes of interest included relapse/progression and OS. PFS was defined as the time from ASCT to relapse, progression, or death from any cause. OS was defined as the time from ASCT to death from any cause.

Statistical analysis

Descriptive statistics were used to summarize our data. Categorical variables are presented as counts and percentages; continuous variables are described using the median, minimum, and maximum. The distribution of baseline characteristics was compared using the *t*-test, the Wilcoxon rank-sum test, the χ^2 test, or the Fisher exact test, as appropriate. For survival analysis, the Kaplan–Meier estimator was used to calculate the probability of OS and PFS, and the variance was estimated using the Greenwood formula. The probability of nonrelapse mortality was estimated using cumulative incidence estimates with relapse as a competing risk event. Comparison of survival curves and cumulative incidence curves was done using the log-rank test and the Gray test, respectively. A multivariate model was fitted using a Cox proportional hazards regression model to identify factors associated with outcomes. The main effect was maintenance by high-risk group among four groups: group A/lenalidomide, group B/lenalidomide, group A/bortezomib-based, and Group B/bortezomib-based. Variables that were adjusted included age at ASCT, sex, race, performance status, comorbidity index, International Staging System stage, creatinine function, melphalan dose, disease status at transplant, and time from diagnosis to ASCT. A stepwise model building approach was adopted, and variables that attained a p value <5% were retained in the final model. Factors that were considered in model building were patient-related, disease-related, transplant-related, and post-transplant–related covariates. We tested for interactions between the main effect (i.e., lenalidomide vs. bortezomib

plus other) and the variables in the final model. The assumption of proportional hazards was tested using time-dependent covariates.

RESULTS

Of 503 patients who met the study criteria, 357 (67%) received lenalidomide maintenance alone, and 146 (33%) received bortezomib-based maintenance (bortezomib alone: 85 patients, 58%; bortezomib plus lenalidomide: 58 patients, 40%; bortezomib plus other: three patients, 2%). Baseline characteristics are shown in Table 1. Patients receiving bortezomib-based maintenance had similar demographics compared with those receiving lenalidomide maintenance alone, including age, race, sex, and performance status. Patients in the bortezomib-based maintenance group were more likely to have group A abnormalities compared with those in the lenalidomide group (50% vs. 34%; $p < .01$). Patients in the bortezomib-based maintenance group were also more likely to possess two or more high-risk abnormalities compared with those in the lenalidomide group (24% vs. 15%; $p < .01$) as well as International Staging System stage III disease (30% vs. 22%; $p = .01$). There was no difference in renal function between the two groups either at diagnosis or before transplant. However, patients in the bortezomib-based arm were more likely to receive bortezomib, cyclophosphamide, and dexamethasone (VCD) induction (29% vs. 17%; $p < .01$) compared with RVD induction (67% vs. 82%; $p < .01$) before ASCT. Patients in the bortezomib-based maintenance group were also less likely to receive full-dose conditioning with melphalan 200 mg/m^2 (70% vs. 78%; $p = .05$).

Response rates

There was no difference in the pre-ASCT response rate, including the very good partial response (VGPR) or better rate in the bortezomib-based versus lenalidomide maintenance groups (59% vs. 60%; $p = .27$; Table 1). The response rate at 100 days post-ASCT was also similar between both groups, including the VGPR or better rate (69% vs. 73%) and the complete response rate (34% vs. 42%) in the bortezomib-based versus lenalidomide maintenance groups, respectively ($p = .66$; Table 2). The best response after ASCT was also similar in the bortezomib-based versus lenalidomide maintenance groups, including the VGPR or better rate (81% vs. 85%) and the complete response rate (53% vs. 55%), respectively ($p = .69$).

Outcomes

Table 3 shows the comparison of outcomes between patients receiving bortezomib-based and lenalidomide maintenance. The median follow-up for group A receiving lenalidomide was 30 months (range, 12–82 months), for group A receiving bortezomib-based maintenance it was 36 months (range, 11–84 months), for group B receiving lenalidomide it was 25 months (range, 7–78 months), and for group B receiving bortezomib-based maintenance it was 36 months (range, 12–73 months). Nonrelapse mortality at 2 years was similar in patients receiving bortezomib-based and lenalidomide maintenance (2% vs. 0%, respectively; $p = .16$). Patients in the lenalidomide group had superior PFS at 2 years compared with those in the bortezomib-based therapy group (75% vs. 63%; $p = .009$). OS at 2 years was also superior in the lenalidomide group (93% vs. 84%; $p = .001$). An additional comparison of patients in group A versus group B is also shown in Table 3. The 2-year PFS and OS in group A receiving lenalidomide versus bortezomib-based maintenance was 77% versus 61% ($p = .009$) and 94% versus 84% ($p = .006$), respectively. The 2-year PFS and OS in group B receiving lenalidomide versus bortezomib-based maintenance was 70% versus 65% ($p = .385$) and 92% versus 85% ($p = .109$), respectively. Figure 1 shows the PFS and OS for the four groups.

Multivariate analysis

Table 4 shows the results of the multivariate regression models. When evaluating PFS, with group B receiving lenalidomide maintenance as reference, no difference was seen with group A receiving lenalidomide maintenance (HR, 1:38; 95% CI, 0.89–2.15; $p = .15$). However, group A receiving bortezomib-based maintenance (HR, 1.77; 95% CI, 1.08–2.90; $p = .02$) and group B receiving bortezomib-based maintenance (HR, 1.93; 95% CI, 1.20–3.13; $p = .007$) had worse outcomes compared with the reference group. In group A, there was no statistically significant difference in PFS with bortezomib-based versus lenalidomide-alone maintenance (HR, 1.28; 95% CI, 0.76–2.16; $p = .36$); but, in group B (i.e., abnormality 1q alone), bortezomib-based maintenance was associated with inferior PFS compared with lenalidomide maintenance (HR, 1.93; 95% CI, 1.20–3.13; $p = .007$). Disease status of VGPR or better before ASCT was associated with superior PFS (overall $p = .01$).

Similar associations were observed for OS. With group B receiving lenalidomide maintenance as the reference group, group A receiving bortezomib-based maintenance (HR, 3.21; 95% CI, 1.34–7.70; $p = .009$) and group B receiving bortezomib-based maintenance (HR, 3.10; 95% CI, 1.29–7.45; $p = .011$) were associated with inferior OS. There was no difference in OS in group A with bortezomib-based versus lenalidomide-alone maintenance (HR, 2.08; 95% CI, 0.82–5.27; $p = .12$). In group A versus group B receiving bortezomib-based maintenance, no difference in OS was seen.

Subset analysis: Melphalan 200 mg/m^2

Because patients in the bortezomib-based group were less likely to have had received full-dose melphalan 200 mg/m^2 conditioning dose

TABLE 1 Characteristics of patients with high-risk multiple myeloma who underwent first autologous stem cell transplant from 2013 to 2018.

Characteristic	Bortezomib-based, *N* = 146, No. (%)	Lenalidomide alone, *N* = 357, No. (%)	*p*
No. of centers	52	77	
Median age at transplant [range], years	62 [38–75]	62 [34–79]	.79*
Sex			.03**
Men	65 (45)	197 (55)	
Women	81 (55)	160 (45)	
Race			.12**
White	91 (62)	213 (60)	
Black or African American	40 (27)	120 (34)	
Asian	7 (5)	12 (3)	
Native Hawaiian or Pacific Islander	1 (1)	0 (0)	
American Indian or Alaska Native	4 (3)	2 (1)	
Missing	3 (2)	10 (3)	
Karnofsky score			.43**
≥90	83 (57)	184 (52)	
<90	59 (40)	166 (46)	
Missing	4 (3)	7 (2)	
HCT-CI			.48**
0	35 (24)	83 (23)	
1	19 (13)	51 (14)	
2	24 (16)	78 (22)	
3	29 (20)	70 (20)	
4	17 (12)	41 (11)	
5	9 (6)	9 (3)	
≥6	12 (8)	21 (6)	
Missing	1 (1)	4 (1)	
High-risk marker			< .01**
t(4;14)	27 (18)	42 (12)	
t(14;16)	2 (1)	13 (4)	
t(14;20)	0 (0)	2 (1)	
del17p	9 (6)	14 (4)	
Abnormality at 1q	73 (50)	234 (66)	
≥2 high-risk	35 (24)	52 (15)	
High-risk marker group			< .01*
Group A: t(4:14)/t(14:16)/t(14:20)/del17p with/without 1q	73 (50)	123 (34)	
Group B: Abnormality at 1q alone	73 (50)	234 (66)	
ISS stage at diagnosis			.01**
Stage I	28 (19)	115 (32)	

(Continues)

TABLE 1 (Continued)

Characteristic	Bortezomib-based, *N* = 146, No. (%)	Lenalidomide alone, *N* = 357, No. (%)	*p*
Stage II	49 (34)	96 (27)	
Stage III	44 (30)	79 (22)	
Missing	25 (17)	67 (19)	
eGFR at diagnosis, median [min-max]	68 [5–170]	74 [4–215]	.24*
eGFR at HCT, median [min-max]	90 [6–241]	93 [7–192]	.38*
Lines of chemotherapy			.18**
1	121 (83)	312 (87)	
≥2	25 (17)	45 (13)	
Induction chemotherapy			< .01**
VTD	2 (1)	1 (0)	
VRD	98 (67)	292 (82)	
VCD	43 (29)	60 (17)	
KRD	3 (2)	4 (1)	
Melphalan dose in conditioning regimen, mg/m^2			.05**
MEL 140	44 (30)	78 (22)	
MEL 200	102 (70)	279 (78)	
Disease status before transplant			.27**
sCR/CR	21 (14)	61 (17)	
VGPR	65 (45)	153 (43)	
PR	54 (37)	129 (36)	
SD	4 (3)	12 (3)	
PD/relapse	2 (1)	0 (0)	
Missing	0 (0)	2 (1)	
Time from diagnosis to transplant, months			.15**
<6	82 (56)	175 (49)	
6–12	64 (44)	182 (51)	
Year of transplant			.04**
2013	13 (9)	32 (9)	
2014	15 (10)	24 (7)	
2015	21 (14)	46 (13)	
2016	26 (18)	33 (9)	
2017	21 (14)	73 (20)	
2018	50 (34)	149 (42)	
Median follow-up [range], months	36 [11–84]	25 [6–82]	

Abbreviations: CR, complete response; eGFR, estimated glomerular filtration rate; HCT-CI, hematopoietic cell transplant-specific comorbidity index; ISS, International Staging System; KRD, carfilzomib, lenalidomide, and dexamethasone; max, maximum; MEL, melphalan; min, minimum; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VCD, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

*Hypothesis testing: Kruskal–Wallis test.

**Hypothesis testing: Pearson χ^2 test.

TABLE 2 Posthematopoietic cell transplant responses in patients with high-risk multiple myeloma.

Characteristic	Bortezomib-based	Lenalidomide alone
No. of patients	146	357
Response at day 100 of ASCT		
sCR/CR	50 (34)	149 (42)
VGPR	51 (35)	111 (31)
PR	31 (21)	69 (19)
SD	9 (6)	21 (6)
PD/relapse	2 (1)	2 (1)
Missing	3 (2)	5 (1)
Best response to ASCT		
sCR/CR	77 (53)	196 (55)
VGPR	41 (28)	108 (30)
PR	20 (14)	41 (11)
SD	5 (3)	9 (3)
PD/relapse	1 (1)	2 (1)
Missing	2 (1)	1 (0)

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

compared with the lenalidomide group, we performed a subset analysis of patients who received melphalan 200 mg/m^2. In this group, 47 patients received bortezomib plus lenalidomide maintenance, 54 patients received bortezomib alone or bortezomib plus other maintenance, and 279 patients received lenalidomide alone as maintenance therapy. The results were very similar to the associations seen in the overall cohort, as shown in Table S1. PFS at 2 years was superior in the lenalidomide group compared with the bortezomib-based groups (76% for lenalidomide maintenance vs. 63% for bortezomib plus lenalidomide vs. 56% for bortezomib; $p = .005$), respectively. OS was also better in the lenalidomide group (94% for lenalidomide vs. 85% for bortezomib plus lenalidomide vs. 78% for bortezomib; $p < .001$). Results from the multivariate analysis were also similar to results from the overall cohort (Table S2).

DISCUSSION

Outcomes in multiple myeloma have improved dramatically over the last few years with the use of novel agents and combinations. The current treatment paradigm of multidrug induction therapy followed by ASCT and maintenance therapy has been shown to offer prolonged disease control. Lenalidomide-based maintenance has been the standard of care based on the results from multiple, large, prospective, randomized studies, including the Cancer and Leukemia Group B CALGB 100104 trial (ClinicalTrials.gov identifier NCT00114101),[16,17] the French Myeloma Intergroup trial IFM2005-02 (ClinicalTrials.gov identifier NCT00430365),[18] and the GIMEMA RV-MM-PI-209 trial (ClinicalTrials.gov identifier NCT00551928),[19] which demonstrated significant improvements in PFS and OS. However, this benefit has not been uniformly seen in patients with high-risk cytogenetics.[20] Therefore, there is no clear guidance for post-ASCT maintenance therapy among patients who have high-risk cytogenetics. In this study, we sought to compare maintenance strategies used in current practice in patients with HRMM after upfront ASCT, comparing lenalidomide alone versus bortezomib-based consolidation/maintenance. With the introduction of novel induction therapies, outcomes of patients who have melanoma with high-risk cytogenetics have improved, with approximately 60% of patients achieving a VGPR or better before transplant. Furthermore, that response is improved upon by ASCT with 69%–73% achieving a VGPR or better at the 100-day mark. Patients in the bortezomib-based arm were more likely to receive VCD induction (29% vs. 17%; $p < .01$) compared with RVD induction (67% vs. 82%; $p < .01$) before ASCT. A previous CIMBTR analysis[21] demonstrated no significant survival difference based on induction therapy in patients with multiple myeloma undergoing upfront ASCT after RVD or VCD induction. No difference in pre-ASCT and post-ASCT responses were noted by high-risk cytogenetics.

Bortezomib-based maintenance was evaluated in the HOVON-65 study[22,23] and was shown to be superior to thalidomide. In a subgroup analysis of patients with del(17p), long-term bortezomib use was associated with an improvement in OS, with 8-year OS rates of 52% versus 54%. There was no impact in other high-risk abnormalities, such as t(4;14) and gain 1q21. There are other smaller studies that support the role of post-transplant bortezomib-based triplet therapy for patients with high-risk cytogenetics.[24,25] Joseph et al.[26] reported improved outcomes with triplet maintenance using immunomodulatory drugs and proteasome inhibitors after ASCT in patients with HRMM, with a median PFS of 42.1 months versus 16.2 months in those without maintenance therapy. The recently published DETERMINATION trial (ClinicalTrials.gov identifier NCT01208662)[27] similarly established the benefit of early ASCT with a 21.3-month improvement in PFS. Those findings highlighted the need for sustained maintenance therapy in both arms. Rates of minimal residual disease (MRD) negativity were 40% in the RVD arm and 54% in the stem cell transplant arm, and 5-year PFS was improved in MRD-negative patients (59.2% in the RVD arm and 53.5% in the stem cell transplant group). This further supports the importance of MRD negativity regardless of therapy and its impact on outcomes. However, our analysis showed no benefit of bortezomib-based maintenance over lenalidomide maintenance in the group of patients who had deletion 17p, t(14;16), t(4;14), or t(14;20). Although we observed that bortezomib-based maintenance produced significantly worse outcome than lenalidomide alone, outcomes with bortezomib plus lenalidomide were improved compared with bortezomib monotherapy maintenance. Bortezomib

TABLE 3 Survival outcomes.

Outcome	No.	Prob (95% CI), %	No.	Prob (95% CI), %	p
	Lenalidomide alone, *N* = 357		Bortezomib-based, *N* = 146		
NRM	356		146		.160
1 year	296	0 (0–1)	105	1 (0–3)	
2 year	170	0 (0–1)	66	2 (0–4)	
Relapse	356		146		.019
1 year	296	10 (7–14)	105	22 (16–29)	
2 year	170	25 (20–30)	66	35 (27–44)	
PFS	356		146		.009
1 year	292	89 (86–92)	104	77 (70–84)	
2 year	167	75 (69–79)	65	63 (55–71)	
OS	357		146		.001
1 year	326	99 (98–100)	128	94 (90–98)	
2 year	216	93 (90–96)	90	84 (77–90)	

Outcome	No.	Group A	No.	Group B	No.	Group A	No.	Group B	p
	Lenalidomide alone, Prob (95% CI), %				Bortezomib-based, Prob (95% CI), %				
NRM	234		122		73		73		.080
1 year	196	0 (0–2)	100	0 (0–0)	53	1 (0–5)	53	0 (0–0)	
2 year	110	0 (0–2)	60	0 (0–0)	32	3 (0–9)	35	0 (0–0)	
Relapse	234		122		73		73		.048
1 year	196	8 (5–12)	100	15 (9–22)	53	19 (11–29)	53	25 (15–35)	
2 year	110	22 (17–29)	60	30 (22–40)	32	35 (24–48)	35	35 (24–47)	
PFS	234		122		73		73		.031
1 year	195	92 (88–95	97	85 (78–91)	52	79 (69–88)	52	75 (65–84)	
2 year	109	77 (71–83)	58	70 (61–78)	31	61 (49–73)	34	65 (53–76)	
OS	234		123		73		73		.014
1 year	211	99 (98–100)	115	99 (97–100)	63	96 (90–99)	65	93 (86–98)	
2 year	138	94 (91–97)	78	92 (85–96)	43	84 (73–92)	47	85 (75–92)	

Note: Group A, high-risk multiple myeloma with traditional high-risk features with or without 1q abnormalities (17p/monosomy 17, t[14;16], t[4;14], t[14;20]); group B, abnormality 1q without any of the other high-risk markers.

Abbreviations: CI, confidence interval; OS, overall survival; NRM, nonrelapse mortality; PFS, progression-free survival; Prob, probability.

monotherapy was associated with the most inferior outcomes. In our cohort, we observed that a higher percentage of patients with more than one high-risk cytogenetic feature were in the bortezomib-based maintenance group. This suggests a treatment bias toward bortezomib-based maintenance in this population, and our results highlight the dilemma that these patients still have early relapses regardless of the use of a maintenance strategy. It would be reasonable to consider a proteasome inhibitor-immunomodulatory drug combination with the aim of achieving deeper responses.

In the subgroup with abnormality 1q, we did not observe superior outcomes in patients who received bortezomib maintenance compared with lenalidomide alone, with 2-year PFS and OS with lenalidomide versus bortezomib-based maintenance rates of 70% versus 65%, respectively, and 92% versus 85%, respectively, suggesting that lenalidomide maintenance may be reasonable in this population. Abnormality in 1q has been identified as a prognostic marker of inferior outcomes in different studies.[28–30] In the Myeloma XI trial (ClinicalTrials.gov identifier NT01554852), which evaluated lenalidomide or thalidomide in combination with cyclophosphamide and dexamethasone followed by an autologous stem cell transplant for eligible patients and maintenance with lenalidomide versus observation, patients with abnormality 1q had worse OS, and the prognostic effect was more prominent among those who had amplification of 1q or co-occurrence of additional high-risk cytogenetic abnormalities.[31] The

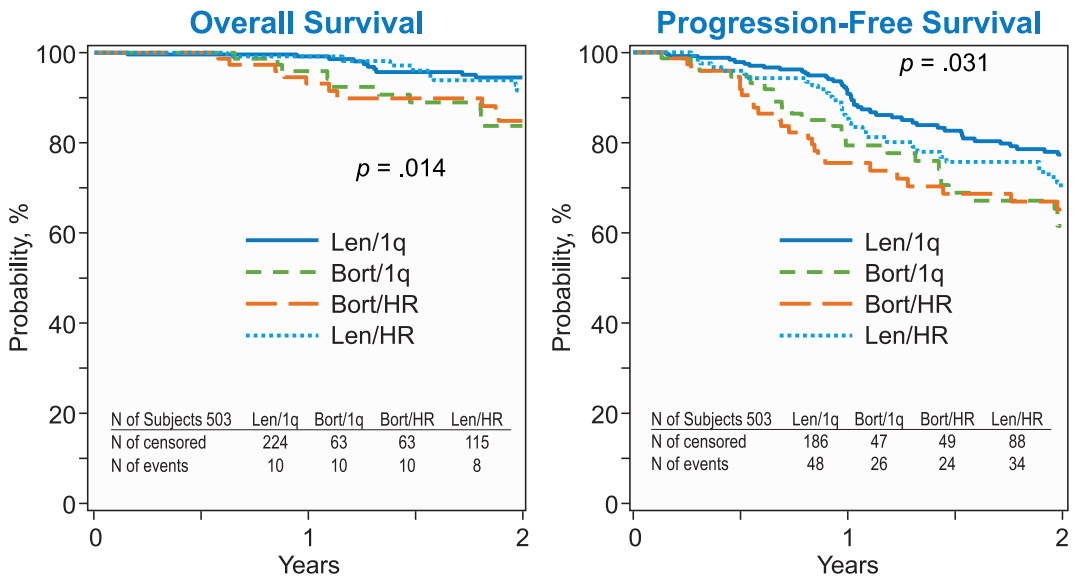

FIGURE 1 (*Left*) Overall survival and (*right*) progression-free survival in high-risk patients with multiple myeloma receiving bortezomib-based maintenance versus lenalidomide alone as maintenance therapy. Patients are divided into two groups, those with 1q abnormalities alone (1q) and those with any 17p, t(14;16), or t(4;14) abnormalities. Bort indicates bortezomib; HR, high risk; len, lenalidomide.

FORTE study[32,33] randomized transplant-eligible patients to receive four cycles of carfilzomib with cyclophosphamide and dexamethasone (KCd) followed by ASCT and four cycles of KCd consolidation, carfilzomib with lenalidomide/dexamethasone (KRd) for four cycles, followed by ASCT, and four cycles of KRd consolidation, or 12 cycles of KRd without transplantation. In that study, patients with gain 1q had worse survival in the KCd ASCT and KRd 12-cycle arms, but the risk was abrogated in the KRd ASCT arm. However, it was noted that patients with abnormality in 1q had dismal outcomes regardless of treatment arm, unless they were able to achieve negative MRD.[34]

The main limitation of our study is its retrospective nature. Because of the lack of prospective randomization, our analysis is subject to inherent selection bias. Although we focused on a homogenous cohort of patients, a bias in the choice of post-transplant maintenance therapy is certain. Furthermore, abnormality of 1q, as reported in the database, was a mixed population that included both gain 1q and amplification 1q, which we were not able to further delineate. Also, whereas we were able to separate patients in subgroups based on cytogenetic abnormalities and maintenance therapy, some of these subgroups, e.g., those receiving the combination of lenalidomide and bortezomib, were small in number and hence lacked statistical power for comparison. Finally, the absence of MRD data further limits our analysis because we were unable to study the impact of achieving MRD negativity in the setting of HRMM. The majority of patients in our study received single-agent maintenance, and our study cannot address whether dual bortezomib and lenalidomide maintenance may be an optimal strategy in high-risk patients.

Post-transplant maintenance therapy continues to be an evolving target in multiple myeloma. The optimal agent or combination for maintenance therapy in patients with HRMM is still an unmet need. In accordance with multiple studies, we observed that these patients continue to do poorly regardless of the type of maintenance therapy used. Our data serve as contemporaneous benchmarks of outcomes of patients who have HRMM after upfront ASCT. Given the observed poor outcomes of high-risk patients, additional maintenance strategies are needed in this patient subgroup. Outcomes are expected to improve with quadruplet-based regimens with the addition of anti-CD38 antibodies as part of the induction regimen.[35,36] These regimens have produced deeper responses with higher rates of MRD negativity. These studies provide a platform for assessing the impact of quadruplets and the impact of MRD negativity, particularly in patients with HRMM. Newer therapies, such as cereblon E3 ligase modulator agents,[37–39] bispecific T-cell–directed antibodies,[40,41] and chimeric antigen receptor T-cell therapy,[42,43] are additions to active antimyeloma therapies and serve as potential novel targets for post-transplant maintenance/consolidation in this population. Another clinically important question that remains to be answered is the optimal duration of treatment and the potential role of MRD evaluation in guiding treatment decisions.

In summary, we did not observe any difference in outcomes among patients with traditional high-risk abnormalities who received bortezomib-based versus lenalidomide maintenance, and most patients in the bortezomib group received singe-agent bortezomib maintenance. Lenalidomide was associated with superior outcomes in patients with 1q abnormalities alone. Until prospective data from randomized clinical trials are available, post-transplant therapy should be tailored to each patient with consideration for treating all of these patients in clinical trials targeting novel therapeutic strategies for HRMM, and lenalidomide-based treatment approaches should remain a backbone of treatment choice in this setting.[44]

TABLE 4 Multivariate analysis.

Variable	Level	No.	No. of events	Hazard ratio	95% hazard ratio confidence limits		*p*
Relapse							
Treatment group	Group B/Len	234	47	1.00	Reference		.0375
	Group A/Len	122	34	1.41	0.91	2.20	.1264
	Group B/Bort	73	24	1.83	1.12	3.00	.0167
	Group A/Bort	73	24	1.82	1.11	2.98	.0182
Disease status before transplant	sCR/CR	82	16	1.00	Reference		.0103
	VGPR	218	45	1.08	0.61	1.91	.794
	PR	182	63	1.97	1.14	3.42	.0154
	SD/PD/ relapse	18	4	1.07	0.36	3.20	.9078
	Missing	2	1	3.54	0.46	26.98	.2228
Contrast	Group A/Bort vs. group A/Len			1.28	0.76	2.17	.3595
	Group B/Bort vs. group A/Bort			1.01	0.57	1.77	.9802
Progression-free survival							
Treatment group	Group B/Len	234	48	1.00	Reference		.0256
	Group A/Len	122	34	1.38	0.89	2.15	.1499
	Group B/Bort	73	26	1.93	1.20	3.13	.007
	Group A/Bort	73	24	1.77	1.08	2.90	.023
Disease status before transplant	sCR/CR	82	16	1.00	Reference		.011
	VGPR	218	47	1.13	0.64	1.99	.6789
	PR	182	64	2.01	1.16	3.48	.0126
	SD/PD/ relapse	18	4	1.07	0.36	3.21	.903
	Missing	2	1	3.55	0.47	27.06	.2217
Contrast	Group A/Bort vs. group A/Len			1.28	0.76	2.16	.355
	Group B/Bort vs. group A/Bort			1.09	0.63	1.90	.756
Overall survival							
Treatment group	Group B/Len	234	10	1.00	Reference		0.0219
	Group A/Len	122	8	1.49	0.59	3.78	0.3996
	Group B/Bort	73	10	3.21	1.34	7.70	.0092
	Group A/Bort	73	10	3.10	1.29	7.45	.0114
Contrast	Group A/Bort vs. group A/Len			2.079	0.82	5.27	.123
	Group B/Bort vs. group A/Bort			1.03	0.43	2.49	.939

Note: Group A, high-risk multiple myeloma with traditional high-risk features with or without 1q abnormalities (17p/monosomy 17, t[14;16], t[4;14], t[14;20]); group B, abnormality 1q without any of the other high-risk markers.

Abbreviations: Bort, bortezomib; CR, complete response; Len, lenalidomide; PD, progressive disease; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

AUTHOR CONTRIBUTIONS

Naresh Bumma: Co-first author, primarily responsible for trial design, data collection, and contributed to writing the article. **Binod Dhakal:** Co-first author, primarily responsible for trial design, data collection, and contributed to writing the article. **Raphael Fraser:** Biostatistician, data analysis, and writing. **Noel Estrada-Merly:** Biostatistics, data analysis, and writing. **Kenneth Anderson**, **César O. Freytes**, **Gerhard C. Hildebrandt**, **Leona Holmberg**, **Maxwell M. Krem**, **Cindy Lee**, **Lazaros Lekakis**, **Hillard M. Lazarus**, **Hira Mian**, **Hemant S. Murthy**, **Sunita Nathan**, **Taiga Nishihori**, **Ricardo Parrondo**, **Sagar S. Patel**, **Melhem Solh**, **Christopher Strouse**, **David H. Vesole**, **Shaji Kumar**, **Muzaffar H. Qazilbash**, **Nina Shah:** Critical review of the article. **Anita D'Souza:** Co-senior author, primarily responsible for trial design, data collection, and contributed to writing the article. **Surbhi Sidana:** Co-senior author, primarily responsible for trial design, data collection, and contributed to writing the article. All authors reviewed and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Naresh Bumma reports personal fees from Amgen, Sanofi, Janssen, and Oncopeptides outside the submitted work. Binod Dhakal reports personal fees from Janssen, Amgen, Takeda, Sanofi, GlaxoSmithKline (GSK), Arcellx, AbbVie, and Natera; honoraria from GSK, Bristol Myers Squibb (BMS), and Karyopharm; and research funding from Janssen, BMS, Sanofi, GSK, Arcellx, Cartesian, Carsgen, and Fate outside the submitted work. Kenneth Anderson reports personal fees from Amgen, Janssen, Pfizer, Mana, Window, and Starton; and is scientific founder of C4Therapeutics, Oncopep, and Raqia Next RNA outside the submitted work. Leona Holmberg reports funding for studies from Seattle Genetics, Merck, Sanofi, BMS, Millennium-Takada, and Janssen; and royalties from UpToDate outside the submitted work. Maxwell M. Krem reports personal fees from Secura Bio (not related to stem cell transplant in multiple myeloma) outside the submitted work. Cindy Lee reports personal fees from Janssen, BMS, and Amgen outside the submitted work. Hira Mian reports an early career research award from Hamilton Health Sciences Foundation outside the submitted work. Hemant S. Murthy reports personal fees and research funding from CRISPR Therapeutics outside the submitted work. Taiga Nishihori reports institutional clinical trial support from Novartis and Karyopharm (drug supply only) outside the submitted work. Christopher Strouse reports personal fees from Janssen, GSK, and Curio Science outside the submitted work. Anita D'Souza reports institutional research funding from AbbVie, Caelum, Janssen, Prothena, Sanofi, Takeda, and TeneoBio; and personal fees from Janssen, Prothena, and BMS outside the submitted work. Surbhi Sidana reports research funding from Magenta Therapeutics, BMS, Allogene, and Janssen; and personal fees from Magenta Therapeutics, BMS, Janssen, Sanofi, and Oncopeptides outside the submitted work. The remaining authors made no disclosures.

DATA AVAILABILITY STATEMENT

The CIBMTR supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified data sets that comply with all relevant global regulations regarding privacy and confidentiality.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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