BMC Cancer

RESEARCH

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Real-world outcomes of maintenance therapy post-autologous stem cell transplantation in newly diagnosed multiple myeloma

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Abstract

Background In the Republic of Korea, only lenalidomide, bortezomib, ixazomib, and thalidomide monotherapy are available as maintenance therapy post-autologous stem cell transplantation (ASCT).

Methods To determine whether maintenance therapy confers a survival benefit in the real world, we compared treatment outcomes according to the use and type of maintenance therapy in patients who underwent ASCT following frontline therapy with the triplet regimen of bortezomib, thalidomide, and dexamethasone for newly diagnosed multiple myeloma in 15 nationwide centers.

Results A total of 512 patients were analyzed (no-maintenance group, $n=359$, and maintenance group, $n=153$ patients). Among those receiving maintenance therapy, 104 (68%) received thalidomide, 33 (21%) lenalidomide, and 16 (10%) bortezomib or ixazomib. The median progression-free survival (PFS) from the time of ASCT was 26.4 and 44.1 months in the no-maintenance and maintenance groups, respectively. In the multivariate analysis, the use of maintenance therapy was significantly associated with better PFS. After adjustment for the type and duration of maintenance therapy, the use of bortezomib or ixazomib was associated with better PFS than other drugs. Longer duration of therapy was associated with improved PFS. No statistically significant difference was observed in overall survival and secondary malignancy rates by use or type of maintenance.

Conclusion Despite practical limitations, maintenance therapy after ASCT demonstrated a gain in PFS in the real world, and there was no clear increase in the risk of secondary malignancy. Therefore, it may be prudent to consider implementing maintenance therapy in a feasible manner.

Keywords Multiple myeloma, Autologous stem cell transplantation, Maintenance, Thalidomide, Lenalidomide, Bortezomib, Ixazomib

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Introduction

Current guidelines recommend maintenance therapy after autologous stem cell transplantation (ASCT) for patients with newly diagnosed multiple myeloma (NDMM) eligible for high-dose therapy [1–3]. Lenalidomide monotherapy is generally recommended, and bortezomib monotherapy or combination therapy with lenalidomide and bortezomib, carfilzomib, or daratumumab could be used in cases of high-risk disease. Ixazomib monotherapy might be considered as an option.

Lenalidomide monotherapy is the most extensively studied maintenance therapy. Four large randomized controlled trials (CALGB 100104, GIMEMA, IFM 2005–02158, and the UK MRC Myeloma XI) have shown a survival benefit with lenalidomide [4–7]. Despite concerns regarding hematologic toxicity and the risk of secondary malignancy, the survival benefit of lenalidomide should be considered for use in eligible patients as it might outweigh the risks. However, as most trials were conducted in the 2010s, the proportion of patients receiving triplet induction regimens as frontline therapy is relatively small (approximately 30% of the total patient population). Trials of other maintenance therapies are similar [8–13]. When a triplet regimen containing proteasome inhibitors and immunomodulatory drugs is used as the standard frontline therapy, it is uncertain whether the results of the above-mentioned studies can be directly extrapolated in the real world.

The limitations of using maintenance therapy in the real world should also be considered. In the Republic of Korea, for example, lenalidomide, bortezomib, ixazomib, and thalidomide monotherapy have been approved as maintenance therapies. Of these drugs, only lenalidomide has been covered by insurance since January 2023. In other words, prior to January 2023, the use of maintenance therapy was a challenge due to issues pertaining to cost. In these situations, thalidomide maintenance therapy, which is cost-effective, has been used in the real world despite the uncertain benefits in terms of survival gain and the presence of toxicities such as peripheral neuropathy [14–16]. In addition, in the real world, even when maintenance therapies other than thalidomide are used, many cases involve early discontinuation, which differs from the approach of previous trials where the drugs were used until progression.

Given the above limitations, information is required to determine whether maintenance therapy confers a survival benefit in the real world. In addition, each maintenance therapy requires an evaluation of toxicities, including secondary malignancies. In this study, we compared the treatment outcomes based on the use and type of maintenance therapy in patients with NDMM from 15 nationwide centers in the Republic of Korea who underwent ASCT following frontline therapy with the triplet regimen of bortezomib, thalidomide, and dexamethasone (VTD) regimen.

Materials and methods

Patients

Data were obtained from patients with NDMM treated with ASCT following VTD frontline therapy until October 2020 at 15 medical centers in the Republic of Korea. All patients were followed up until August 2023, and the data were retrospectively collected. Patients undergoing tandem ASCT were excluded. Information on baseline characteristics, treatment outcomes, adverse events, and other details was obtained by reviewing the patients' medical records.

Patients diagnosed with multiple myeloma between April 2011 and October 2020 were enrolled in this study. During this period, the approved VTD regimen in Korea was as follows: Bortezomib was administered subcutaneously at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11; dexamethasone was administered at a dose of 40 mg on days 1–4 and day 9–12; and thalidomide was administered orally, starting at 50 mg/day and increasing to 200 mg/day. Each cycle was repeated every 28 d for up to 6 cycles [17]. There was no insurance coverage for maintenance therapy during this period and the patients were responsible for all costs. Under these conditions, thalidomide was approved for oral administration at a dose of 50–200 mg daily for up to 1 year, whereas bortezomib was approved for subcutaneous or intravenous administration at a dose of 1.3 mg/m^2 once every 2 weeks for up to 2 years. Lenalidomide, ixazomib, and other maintenance therapies outside of the above doses and schedules were administered based on individual institutional approval. The type, dose, and duration of maintenance therapy were determined solely by local investigators, regardless of clinical characteristics or patient preference.

The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of each medical center, and all data were completely anonymized. As this study was conducted using anonymous patient data, the requirement for informed consent was waived following the regulations of each medical center's IRB.

Clinical endpoints

The primary endpoint was progression-free survival (PFS) from the time of ASCT according to the use or non-use of maintenance therapy in patients treated with ASCT following frontline therapy with a VTD regimen. The secondary endpoints were PFS from the time of ASCT according to type; overall survival (OS) by use and type; and the duration, reasons for discontinuation,

adverse events during, and secondary malignancy by use and type of maintenance therapy.

For the univariate and multivariate analyses, the following data were collected: use and type of maintenance therapy, age, sex, Eastern Cooperative Oncology Group (ECOG) performance score [18], type of myeloma, International Staging System (ISS) [19], presence of high-risk chromosomal abnormalities, extramedullary disease, disease status according to the International Myeloma Working Group response criteria [20], conditioning regimen of ASCT, time from diagnosis to ASCT, and duration of maintenance therapy. High-risk cytogenetic abnormalities included del(17p)/monosomy 17/*TP53* mutations, del(1p32), t(4;14), t(14;16), t(14;20), *MYC* translocation, and 1g21 gain/1q21 amplification, accompanied by other abnormalities.

Statistical analysis

Baseline characteristics were compared using the Mann–Whitney U test or Chi-squared test, as appropriate. PFS was defined as the duration from day 0 of ASCT to the date of relapse, death, or censoring. OS was defined as the duration from day 0 of ASCT to death from any cause or censoring. PFS and OS were calculated using Kaplan–Meier survival analysis and compared using the log-rank test. Multivariate analyses for PFS and OS were performed using the Cox proportional hazards method. The IBM Statistical Package for Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 512 patients were analyzed (no-maintenance group, $n=359$ patients; and maintenance group, $n=153$ patients; Table 1). The overall median age was 57 years (range: 28.0–67.0 years), with a lower median age in the maintenance group compared to that in the no-maintenance group ($p=0.024$), which was (56 years [range: 32.0–67.0 years] vs. 58 years [range: 28.0–65.0 years]). The post-ASCT response assessment did not show a significant difference in the proportion of patients achieving partial or better responses between the two groups. However, the proportion of patients achieving a complete response was higher in the no-maintenance group than that in the maintenance group (73.3% versus 66.7%, $p=0.050$). The time from diagnosis to ASCT was shorter in the maintenance group compared to that in the no-maintenance group (6.2 months versus 5.2 months, $p=0.005$). The proportion of patients receiving melphalan 140 or 200 mg/m^2 as an ASCT conditioning regimen was lower in the maintenance group than that in the no-maintenance group (76.6% versus 61.4%, $p=0.001$). No differences were observed in other baseline characteristics, including sex, ECOG performance score, type of myeloma, ISS stage, presence of high-risk chromosomal abnormalities and extramedullary disease, and pre-ASCT response assessment.

Characteristics of the patients receiving maintenance therapy

The characteristics of the 153 patients who received maintenance therapy are shown in Table 2. The median duration of maintenance therapy was 10.9 months for thalidomide (range: 0.5–44.3 months), 21.7 months for lenalidomide (range: 2.0–56.1 months), and 28.6 months for bortezomib or ixazomib (range: 3.3–44.6 months). The percentage of patients who received maintenance therapy in combination with steroids was 17.3% for thalidomide, 3.0% for lenalidomide, and 18.8% for bortezomib or ixazomib, respectively. The common dosage for thalidomide, lenalidomide, and bortezomib was 50 mg (66.4%), 10 mg (66.7%), and 1.6 mg/m^2 (81.3%), respectively.

Reasons for discontinuation of thalidomide maintenance were as follows: completion of treatment (48.1%), disease progression (23.1%), and adverse events (21.2%). In the case of lenalidomide, the corresponding percentages were 30.3%, 15.2%, and 12.1%, respectively. In the case of bortezomib or ixazomib, the reason for discontinuation was the completion of treatment (31.3%) and the occurrence of adverse events (12.5%). The adverse events, verified by medical records in patients undergoing thalidomide maintenance therapy, were neuropathy (6 patients), general weakness (6 patients), cytopenia (3 patients), skin rash (2 patients), eosinophilic myositis (1 patient), and seizure (1 patient). General weakness (1 patient), rash (1 patient), and neutropenia/thrombocytopenia (1 patient) occurred with lenalidomide treatment, and general weakness (1 patient) and hepatitis (1 patient) occurred with bortezomib or ixazomib treatment, respectively.

Of the 153 patients who received maintenance therapy, we were able to assess their response within 1 month before and after ASCT in all cases. Additionally, the response of 140 patients (thalidomide: 100/104 patients, lenalidomide: 29/33 patients, and bortezomib or ixazomib: 11/16 patients) were assessed within 1 month before or after discontinuation of maintenance therapy. The percentage of responses at each time point based on the number of patients for whom a response assessment was possible is shown in Fig. 1. In cases where thalidomide was used as maintenance therapy, there was a trend towards a decrease in the proportion of complete responses at the time of discontinuation of maintenance

Table 1 Baseline characteristics at initial diagnosis

Baseline characteristics	Total patients ($n=512$)	Patients not receiving maintenance treatment ($n=359$)	Patients receiving maintenance treatment ($n=153$)	*p* value
Median age, years (range)	57 (28–67)	58 (28–65)	56 (32–67)	**0.024**
Sex, n (%)				0.324
Male	309 (60.4)	222 (61.8)	87 (56.9)	
Female	203 (39.6)	137 (38.2)	66 (43.1)	
ECOG performance status score, n (%)				0.227
0–1	410 (80.1)	282 (78.6)	128 (83.7)	
2–4	102 (19.9)	77 (21.4)	25 (16.3)	
Type of myeloma, n (%)				0.369
IgG	278 (54.3)	188 (52.4)	90 (58.8)	
IgA	94 (18.4)	66 (18.4)	28 (18.3)	
IgM or IgD	8 (1.6)	7 (1.9)	1 (0.7)	
Light chain disease	122 (23.8)	89 (24.8)	33 (21.6)	
Non-secretary	10 (2.0)	9 (2.5)	1 (0.7)	
International Stage System, n (%)[a]				0.734
I	176 (35.2)	128 (36.3)	48 (32.7)	
II	167 (33.4)	117 (33.1)	50 (34.0)	
III	157 (31.4)	108 (30.6)	49 (33.3)	
High-risk cytogenetic abnormalities, n (%)	236 (46.1)	174 (48.5)	62 (40.5)	0.101
Extramedullary disease, n (%)	65 (12.7)	42 (11.7)	23 (15.0)	0.312
Response before ASCT, n (%)[b]				0.147
Complete response	280 (54.8)	208 (58.1)	72 (47.1)	
Very good partial response	143 (28.0)	92 (25.7)	51 (33.3)	
Partial response	82 (16.0)	53 (14.8)	29 (19.0)	
Minimal response	1 (0.2)	1 (0.3)	0 (0.0)	
Stable disease	3 (0.6)	3 (0.8)	0 (0.0)	
Progressive disease	2 (0.4)	1 (0.3)	1 (0.7)	
Response after ASCT, n (%)				0.050
Complete response	365 (72.7)	263 (73.3)	102 (66.7)	
Very good partial response	76 (15.1)	46 (12.8)	30 (19.6)	
Partial response	49 (9.8)	30 (8.4)	19 (12.4)	
Minimal response	1 (0.2)	0 (0.0)	1 (0.7)	
Stable disease	2 (0.4)	2 (0.6)	0 (0.0)	
Progressive disease	9 (1.8)	8 (2.2)	1 (0.7)	
Time from diagnosis to ASCT, months (range)	6.2 (2.1–96.1)	6.2 (2.1–96.1)	5.2 (3.1–18.6)	**0.005**
Type of conditioning regimen, n (%)				**0.003**
Melphalan 140 or 200 mg/m2	369 (72.1)	275 (76.6)	94 (61.4)	
Bulsulfan and melphalan	74 (14.5)	44 (12.3)	30 (19.6)	
Busulfan and cyclophosphamide ± etoposide	37 (7.2)	24 (6.7)	13 (8.5)	
Others	32 (6.3)	16 (4.5)	16 (10.5)	
Time from ASCT to start maintenance, months (range)	—	—	4.9 (0.7–24.5)	—
Type of maintenance, n (%)				—
Thalidomide	—	—	104 (68.0)	
Lenalidomide	—	—	33 (21.6)	
Bortezomib or ixazomib	—	—	16 (10.5)	

Abbreviation: ECOG Eastern Cooperative Oncology Group, *ASCT* Autologous stem cell transplantation, *Ig* Immunoglobulin

[a] Missing data for 12 participants: six participants in the no maintenance group and the others in the maintenance group

[b] Missing data for one participant in the no maintenance group

Table 2 Characteristics of patients receiving maintenance treatment

Characteristics	Thalidomide ($n=104$)	Lenalidomide ($n=33$)	Bortezomib or ixazomib ($n=16$)
Median treatment duration, months (range)	10.9 (0.5–44.3)	21.7 (2.0–56.1)	28.6 (3.3–44.6)
Administered with steroid, n (%)	18 (17.3)	1 (3.0)	3 (18.8)
Dose, n (%)[a]	50 mg: 69 (66.4) 100 mg: 32 (30.8)	5 mg: 1 (3.0) 10 mg: 22 (66.7)	1.3 mg/m^2: 2 (12.5) 1.6 mg/m^2: 13 (81.3)
Cause of discontinuation, n (%)[b]			
Complete of treatment	50 (48.1)	10 (30.3)	5 (31.3)
Disease progression	24 (23.1)	5 (15.2)	0 (0.0)
Adverse events	22 (21.2)	4 (12.1)	2 (12.5)

[a,b] The information is limited to patients whose relevant medical records could be accessed

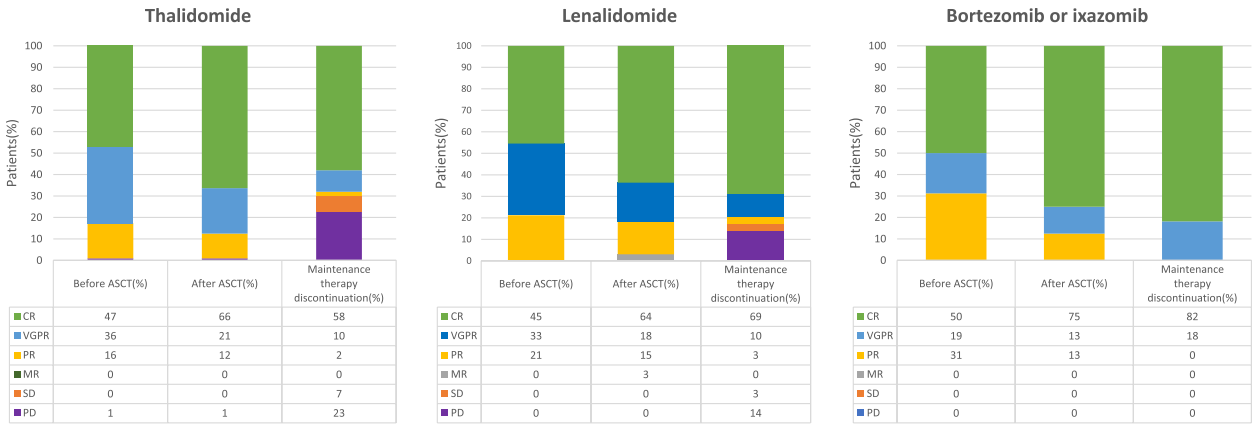

Fig. 1 Longitudinal response kinetics in patients receiving maintenance therapy. *Abbreviations:ASCT* Autologous stem cell transplantation, *CR* Complete response, *VGPR* Very good partial response, *PR* Partial response, *MR* Minimal response, *SD* Stable disease, *PD* Progressive disease

therapy. Contrastingly, lenalidomide, bortezomib, or ixazomib tended to increase the proportion of complete responses at the time of maintenance therapy discontinuation.

Survival data and analysis of factors affecting PFS and OS

From ASCT day 0 to the last follow-up, the median follow-up duration for the entire patient population was 42.1 months (range: 1.3–77.9 months), 41.8 months (range: 1.3–77.9 months) in the no-maintenance group, and 43.6 months (range: 7.4–77.7 months) in the maintenance group, respectively. The median PFS from the time of ASCT was 26.4 months (95% confidence interval [CI]: 21.3–31.4 months) in the no-maintenance group and 44.1 months (95% CI: 25.0–54.9 months) in the maintenance group ($p=0.008$). Multivariate analysis showed that maintenance therapy was significantly associated with better PFS (hazard ratio [HR]: 0.728, 95% confidence interval [CI]: 0.549–0.964, $P=0.027$; Table 3 and Fig. 2). An ASCT conditioning regimen consisting of busulfan and melphalan was associated with improved PFS (HR, 0.543; 95% CI, 0.362–0.816; $p=0.003$). Male sex (HR: 1.355, 95% CI: 1.052–1.746, $p=0.019$), ISS stage III (HR: 1.656, 95% CI: 1.211–2.265, $p=0.002$), presence of high-risk cytogenetic abnormalities (HR, 1.586; 95% CI, 1.240–2.029; $p<0.001$), and less than a complete response after ASCT were correlated with worse PFS.

A similar analysis of PFS was performed only for the maintenance group, adjusting for the type of maintenance therapy and duration of maintenance therapy (Supplementary Table 1 and Fig. 3). The median PFS from the time of ASCT was 27.3 months (95% CI: 21.5–33.1 months) in the patients treated with thalidomide maintenance. However, this was not reached in patients treated with lenalidomide, bortezomib, or ixazomib ($p<0.001$). In multivariate analysis, the use of bortezomib or ixazomib was associated with better PFS than the use of thalidomide (HR, 0.090; 95% CI, 0.012–0.681; $p=0.020$) and lenalidomide (HR, 0.116; 95% CI, 0.013–1.033; $p=0.053$). A longer maintenance therapy

Table 3 Univariate and multivariate analyses of variables associated with progression-free survival in the total number of patients enrolled in the study

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Maintenance versus no use	0.701 (0.539–0.913)	**0.008**	0.728 (0.549–0.964)	**0.027**
Age	0.998 (0.982–1.015)	0.819	–	–
Male versus female	1.280 (1.008–1.626)	**0.042**	1.355 (1.052–1.746)	**0.019**
ECOG performance status score 0–1 versus ≥ 2	1.318 (1.000–1.736)	**0.050**	–	–
Type of myeloma			–	–
IgG	1			
IgA	1.239 (0.926–1.659)	0.149		
IgM or IgD	0.488 (0.155–1.530)	0.218		
Light chain disease	0.841 (0.627–1.128)	0.247		
Non-secretary	0.801 (0.327–1.950)	0.624		
International Stage System				
I	1		1	
II	1.469 (1.091–1.976)	**0.011**	1.298 (0.953–1.767)	0.098
III	2.204(1.511–2.710)	**< 0.001**	1.656 (1.211–2.265)	**0.002**
High-risk cytogenetics abnormalities versus absence	1.530 (1.216–1.924)	**< 0.001**	1.586 (1.240–2.029)	**< 0.001**
Extramedullary disease versus absence	1.0227 (0.728–1.450)	0.879	–	–
Response after ASCT				
Complete response	1		1	
Very good partial response	1.606 (1.177–2.192)	**0.003**	1.674 (1.213–2.310)	**0.002**
Partial response	2.149 (1.505–3.068)	**< 0.001**	2.839 (1.944–4.147)	**< 0.001**
Minimal response	15.842(2.168–115.779)	**0.006**	–	–
Stable disease	2.150 (0.533–8.674)	0.282	1.620 (0.391–6.707)	0.056
Progressive disease	5.574 (2.835–10.960)	**< 0.001**	3.745 (1.876–7.475)	**< 0.001**
Time from diagnosis to ASCT	0.966 (0.922–1.011)	0.132	–	–
Type of conditioning regimen				
Melphalan 140 or 200 mg/m^2	1		1	
Bulsulfan and melphalan	0.574 (0.394–0.836)	**0.004**	0.543 (0.362–0.816)	**0.003**
Busulfan and cyclophosphamide ± etoposide	0.836 (0.544–1.285)	0.415	0.632 (0.395–1.009)	0.055
Others	0.746 (0.461–1.206)	0.231	0.615 (0.373–1.016)	0.058

Bold text indicates statistical significance

Abbreviation: HR Hazard ratio, *CI* Confidence interval, *ECOG* Eastern Cooperative Oncology Group, *ASCT* Autologous stem cell transplantation, *Ig* Immunoglobin

duration was associated with improved PFS (HR, 0.918; 95% CI, 0.887–0.951; $p < 0.001$). The median OS was not reached in either the no-maintenance or maintenance groups, and there was no statistically significant difference in the OS according to the use or type of maintenance.

Secondary malignancy

During the follow-up period, four patients were identified as having secondary malignancies, consisting of one case each of lung, sigmoid colon, prostate, and skin cancers. Three cases were identified in the no-maintenance group, and one was observed in the thalidomide maintenance group. No significant difference was observed in the incidence of secondary malignancies between the no-maintenance and maintenance groups.

Discussion

In this study, the use of maintenance therapy in patients with NDMM undergoing ASCT after frontline therapy with a VTD regimen demonstrated a PFS benefit in a real-world setting where the choice and duration of maintenance therapy are limited. In addition, there was no significant increase in the risk of secondary malignancy.

To date, there has been a paucity of research on the effectiveness of maintenance therapy that is based on real-world data. The study conducted under conditions

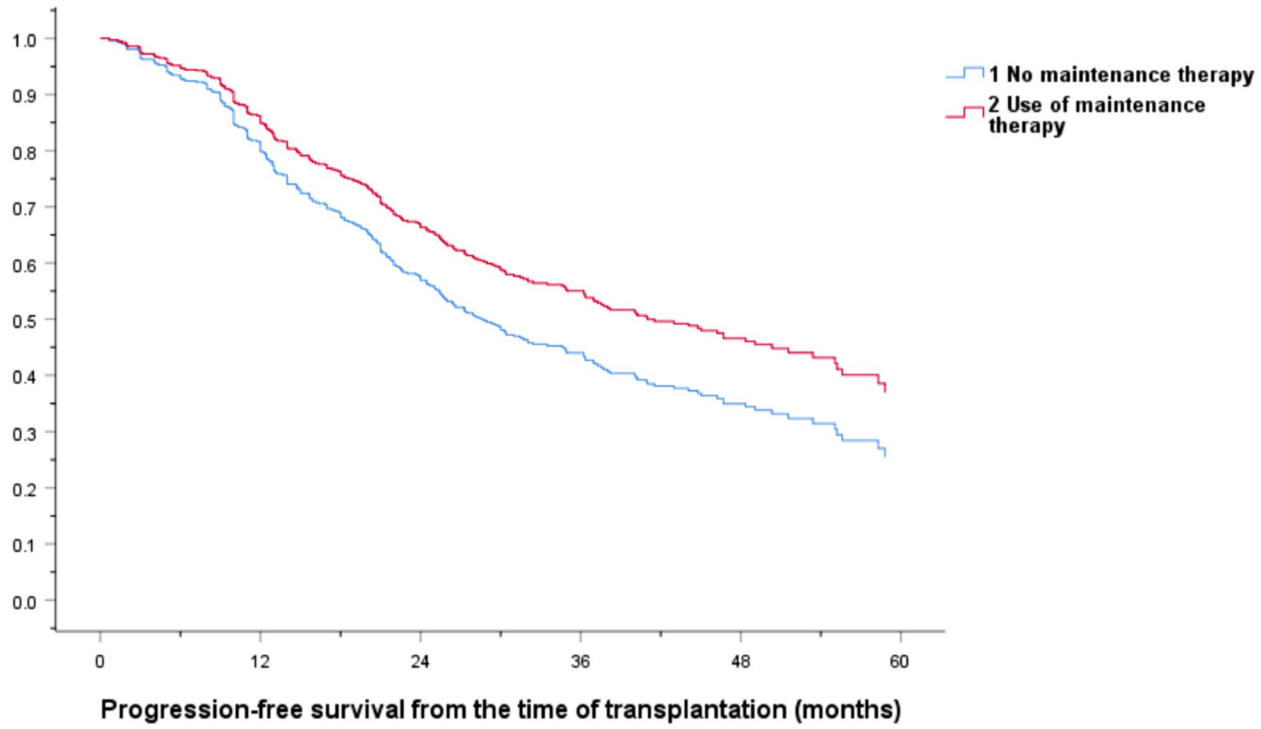

Fig. 2 Progression-free survival from autologous stem cell transplant according to maintenance therapy use in study patients

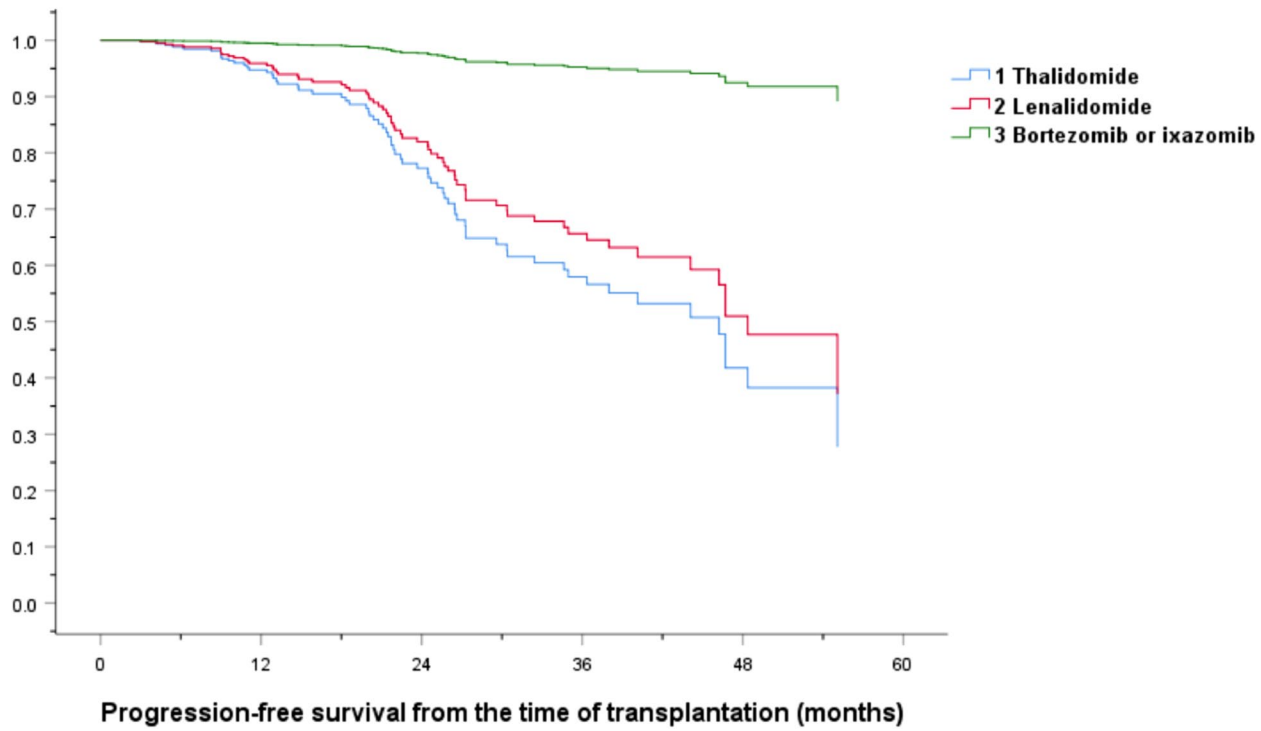

Fig. 3 Progression-free survival from autologous stem cell transplant according to maintenance therapy type in study patients

closest to real-world clinical scenarios was reported by Gaballa et al., and it reported that the 3-year PFS was approximately 70% in patients receiving lenalidomide maintenance after frontline therapy with a bortezomib, lenalidomide, and dexamethasone (VRD) regimen and ASCT [21]. Another study by Ammann et al. reported a 3-year PFS of approximately 65% in the lenalidomide maintenance group and approximately 25% in the no-maintenance group in patients who underwent frontline therapy with the VRD regimen (60% of all patients), followed by ASCT [22]. In this study, after frontline therapy with the VTD regimen and ASCT, the 3-year PFS was 68.8% in the lenalidomide maintenance group and 42.6% in the no-maintenance group. Compared to previous studies, PFS in the lenalidomide maintenance group showed a similar distribution. In contrast, the no-maintenance group had a slightly higher PFS.

Even little research on maintenance therapy shows the best performance in real-world settings. Although direct comparative information is lacking, the 3-year PFS in the bortezomib maintenance group was approximately 60% in the study by Ammann et al., which was not significantly different from lenalidomide maintenance [22]. On the contrary, in this study, the 3-year PFS for the bortezomib or ixazomib maintenance group was 93.8%. Even after adjustment for baseline characteristics and maintenance therapy duration, the bortezomib or ixazomib maintenance demonstrated superior PFS compared with that in other maintenance therapies (versus thalidomide: HR, 0.090, 95% CI, 0.012–0.681, $p=0.020$; and versus lenalidomide: HR, 0.116, 95% CI, 0.013–1.033, $p=0.053$, Supplementary Table 1). This may be due to the use of bortezomib at a higher dose (1.6 mg/m^2) in this study compared to the conventional dose used in maintenance. Alternatively, in cases where bortezomib or ixazomib was used as maintenance therapy, the increased proportion of complete response and very good partial response observed at the time of discontinuation of maintenance therapy suggests that bortezomib or ixazomib may have been more effective in deepening the response compared to other maintenance therapies. However, no statistically significant difference was observed in the multivariate analysis when compared with lenalidomide maintenance. Furthermore, due to the limited number of patients in this group, further studies with larger numbers of patients are required to confirm that bortezomib or ixazomib maintenance has superior effectiveness compared to other maintenance therapies.

Another consideration is whether it is appropriate to use thalidomide maintenance when other maintenance therapies are not available. Recent guidelines do not recommend thalidomide maintenance [1–3]. This is due to the uncertainty of the OS benefit despite the PFS benefit. In addition, thalidomide is poorly tolerated due to side effects such as peripheral neuropathy [14–16]. However, the uncertainty regarding OS gain applies to all other maintenance therapies except lenalidomide maintenance [23, 24]. In a study conducted in the Asian population, there were no reported discontinuations due to adverse events when thalidomide was used at a daily dose of 50–100 mg for maintenance therapy [25]. In this study, the median PFS from the time of ASCT was 26.4 months (95% CI: 21.3–31.4 months) in the no-maintenance group and 27.3 months (95% CI: 21.5–33.1 months) in the patients treated with thalidomide maintenance. When the thalidomide maintenance group was compared with the no-maintenance group, the PFS curves crossed (Supplementary Fig. 1). In addition, the median duration of thalidomide maintenance was approximately 12 months (Table 2), probably due to the earlier approval of thalidomide maintenance in the Republic of Korea, when the duration was limited to 12 months after ASCT. Therefore, given the difficulty in applying the Cox proportional hazards method, we chose to perform a logistic regression analysis for 2-, 3-, 4-, and 5-year PFS categorized into no-maintenance, thalidomide maintenance <12 months, and thalidomide maintenance ≥ 12 months. In the multivariate analysis, thalidomide maintenance for ≥ 12 months showed a favorable 3-year PFS; however, no statistical significance was observed for other cases (Supplementary Table 2). Based on this study's results, thalidomide maintenance cannot be recommended as a priority over other maintenance therapies. However, in practice, thalidomide maintenance may be considered as an option when other maintenance therapies are not feasible, considering the risks and benefits.

The study has several limitations. First, this study analyzed data retrospectively and included a relatively small number of patients who received maintenance therapy, especially those treated with lenalidomide, bortezomib, or ixazomib maintenance. Second, in situations where maintenance therapy was not covered by insurance, the timing and duration of maintenance therapy varied widely depending on physician decisions and the types of maintenance therapies available in the real-world. Therefore, only outcomes based on exposure and the type of maintenance therapy could be analyzed in this study. There were limitations to the dataset itself to observe changes in outcomes based on the timing of maintenance therapy initiation, disease status at that time, changes in response assessment after maintenance therapy, or duration of maintenance therapy. Third, the median follow-up for the entire patient population was 42.1 months (range: 1.3–77.9 months), which may not be sufficient to confirm the incidence of secondary malignancy. Therefore, caution should

be exercised when interpreting the incidence of secondary malignancy based on the use or type of maintenance therapy. Nevertheless, the significance of this study is substantial in confirming the PFS benefit of maintenance therapy, particularly in the real-world setting after frontline therapy with the VTD regimen and ASCT, especially in the Asian population, where relevant research is limited. In addition, the study is noteworthy for providing information on the prescription patterns of maintenance therapy, the associated adverse events, and incidence of secondary malignancy in a real-world context.

In conclusion, despite practical limitations, maintenance therapy after ASCT demonstrated a gain in PFS in the real world, and there was no clear increase in the risk of secondary malignancy in this study. Based on this, it may be prudent to consider implementing maintenance therapy in a feasible manner. Further research is required to determine the most effective method of maintenance therapy in the clinical and practical circumstances of individual patients.

Abbreviations

ASCT	Autologous stem cell transplantation
CR	Complete response
VGPR	Very good partial response
PR	Partial response
MR	Minimal response
SD	Stable disease
PD	Progressive disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13518-0.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements

We are grateful for the cooperation of the Korean Multiple Myeloma Working Party in conducting the study.

Authors' contributions

Study design: Ka-Won Kang finalized this based on the feedback from the KMMWP members. Patient enrollment and data collection: Ka-Won Kang, Dae Sik Kim, Se Ryeon Lee, Mi Hwa Heo, Hyeon-Seok Eom, Jongheon Jung, Ji Hyun Lee, Sung-Hyun Kim, Youngil Koh, Chang-Ki Min, Seung Shin Lee, Sung-Nam Lim, Ho-Young Yhim, Myung-won Lee, Je-Jung Lee, Sung-Hoon Jung, Soo-Mee Bang, Kihyun Kim. Data Analysis: Ka-Won Kang. Original draft writing: Ka-Won Kang. Revision of the paper: All the authors.

Funding

This research was supported by the Korea Health Technology R&D Project grant through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant numbers: HE23C0024 and RS-2022-KH129263).

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of each medical center; all data were completely anonymized. As this study was conducted using anonymous patient data, the requirement for informed consent was waived following the regulations of each medical center's IRB (Korea University Anam Hospital: 2021AN0410; Korea University Guro Hospital: 2025GR0016; Korea University Ansan Hospital: 2024AS0320; Dongsan Medical Center: DSMC 2021–09-052; National Cancer Center: NCC2022-0087; Dong-A University Hospital: DAUHIRB-21–243; Seoul National University Hospital: H-2112–020-1280; Seoul St. Mary's Hospital: KC22RIDI0327; Wonkwang University Hospital: WKUH IRB 2022–01-010; Haeundae Paik Hospital: 2024–12-019; Jeonbuk National University Hospital: CUH 2021–09-064; Chungnam National University Hospital: CNUH IRB 2021–09-058; Chonnam National University Hwasun Hospital: CNUHH-2023–016; Seoul National University Bundang Hospital: B-2302–812-103; Samsung Medical Center: SMC 2021–09-073).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 16 March 2024 Accepted: 14 January 2025
Published online: 05 February 2025

References

1. Callander NS, Baljevic M, Adekola K, Anderson LD, Campagnaro E, Castillo JJ, et al. NCCN Guidelines® Insights: Multiple myeloma, version 3.2022. J Natl Compr Canc Netw. 2022;20:8–19.
2. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). Ann Oncol. 2021;32:309–22.

3. Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. Br J Haematol. 2021;193:245–68.
4. Holstein SA, Jung SH, Richardson PG, Hofmeister CC, Hurd DD, Hassoun H, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol. 2017;4:e431–42.
5. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371:895–905.
6. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1782–91.
7. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20:57–73.
8. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30:2946–55.
9. Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood. 2013;121:4647–54.
10. Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. J Clin Oncol. 2015;33:3921–9.
11. Goldschmidt H, Lokhorst HM, Mai EK, van der Holt B, Blau IW, Zweegman S, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia. 2018;32:383–90.
12. Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019;393:253–64.
13. Goldschmidt H, Dimopoulos MA, Rajkumar SV, Weisel KC, Moreau P, Chng WJ, et al. Deepening responses associated with improved progression-free survival with ixazomib versus placebo as posttransplant maintenance in multiple myeloma. Leukemia. 2020;34:3019–27.
14. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289–94.
15. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354:1021–30.
16. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119:7–15.
17. Rosiñol L, Oriol A, Teruel AI, Hernández D, López-Jiménez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120:1589–96.
18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
19. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412–20.
20. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: A review. JAMA. 2022;327:464–77.
21. Gaballa MR, Ma J, Tanner MR, Al-Juhaishi T, Bashir Q, Srour SA, et al. Real-world long-term outcomes in multiple myeloma with VRD induction, Mel200-conditioned auto-HCT, and lenalidomide maintenance. Leuk Lymphoma. 2022;63:710–21.
22. Ammann EM, Lam A, Tang W, Kampfenkel T, Sharma M, Lee C, et al. Real-world use of maintenance therapy and associated outcomes following autologous stem cell transplant in US patients with newly diagnosed multiple myeloma. Blood. 2020;136:25–6.
23. Gay F, Jackson G, Rosiñol L, Holstein SA, Moreau P, Spada S, et al. Maintenance treatment and survival in patients with myeloma: A systematic review and network meta-analysis. JAMA Oncol. 2018;4:1389–97.
24. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: A meta-analysis. J Clin Oncol. 2017;35:3279–89.
25. Murakami H, Kasamatsu T, Murakami J, Kiguchi T, Kanematsu T, Ogawa D, et al. Thalidomide maintenance therapy in Japanese myeloma patients: a multicenter, phase II clinical trial (COMET study). Int J Hematol. 2019;109:409–17.

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