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Improved survival of multiple myeloma patients treated with autologous transplantation in the modern era of new medicine

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Abstract

New drugs for multiple myeloma (MM) have dramatically improved patients' overall survival (OS). Autologous stem cell transplantation (ASCT) remains the mainstay for transplant-eligible MM patients. To investigate whether the post-ASCT prognosis of MM patients has been improved by new drugs, we undertook a retrospective

Abbreviations: Allo-SCT, allogenic stem cell transplantation; ASCT, autologous stem cell transplantation; EMM, extramedullary multiple myeloma; CI, confidence interval; CR, complete response; IMiD, immunomodulatory drug; ISS, International Staging System; JSTCT, Japanese Society for Transplantation and Cellular Therapy; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; PS, performance status; SD, stable disease; TRUMP, Transplant Registry Unified Management Program; VGPR, very good partial response.

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observational analysis using the Transplant Registry Unified Management Program database in Japan. We analyzed 7323 patients (4135 men and 3188 women; median age, 59 years; range 16-77 years) who underwent upfront ASCT between January 2007 and December 2018. We categorized them by when they underwent ASCT according to the drugs' introduction in Japan: group 1 (2007-2010), group 2 (2011-2016), and group 3 (2017-2018). We compared the groups' post-ASCT OS. The 2-year OS rates (95% confidence interval [CI]) of groups 1, 2, and 3 were 85.8% (84.1%-87.4%), 89.1% (88.0%-90.1%), and 92.3% (90.0%-94.2%) ($P < .0001$) and the 5-year OS (95% CI) rates were 64.9% (62.4%-67.3%), 71.6% (69.7%-73.3%), and not applicable, respectively ($P < .0001$). A multivariate analysis showed that the post-ASCT OS was superior with these factors: age less than 65 years, performance status 0/1, low International Staging System (ISS) stage, receiving SCT for 180 days or less post-diagnosis, better treatment response pre-ASCT, later year of ASCT, and receiving SCT twice. A subgroup analysis showed poor prognoses for the patients with unfavorable karyotype and poor treatment response post-ASCT. The post-ASCT OS has thus improved over time (group 1 < 2 < 3) with the introduction of new drugs for MM. As the prognosis of high-risk-karyotype patients with ISS stage III remains poor, their treatment requires improvement.

KEYWORDS
autologous stem cell transplantation, multiple myeloma, overall survival, prognosis, new medicine

1 | INTRODUCTION

The development of new drugs for MM, especially PI and IMiDs, has dramatically improved the OS of patients with MM.[1] In addition to PI and IMiDs, mAbs such as elotuzumab, daratumumab, and isatuximab could further improve the prognosis of MM.[2] Even in the modern era, however, ASCT remains the mainstay for transplant-eligible MM patients.[3] The impact of novel drugs used to treat MM patients after they have undergone ASCT has not been fully clarified.

Our group reported that the prognosis of MM patients after ASCT improved with the introduction of PI.[4] However, only patients who underwent ASCT before 2011 were recruited in that study. Nishimura et al recently reported that long-term survival of MM patients after ASCT improved with the introduction of novel therapeutics after 2014.[5] They analyzed 4329 MM patients including those treated during the pre-novel medicine era, and they documented the improvement of prognosis with the introduction of thalidomide and bortezomib.[5]

To further clarify the impact of the drugs introduced after bortezomib on the prognosis of MM after ASCT and to investigate the prognostic factors in the modern era, we undertook a retrospective observational analysis using the TRUMP database of the JSTCT.

2 | MATERIALS AND METHODS

2.1 | Data source and patients

We analyzed the TRUMP database, which includes physician-reviewed data (with patient-informed consent) and yearly follow-ups.[6,7] This study was approved by the Data Management Committee of the JSTCT and the Kyoto University Hospital institutional review board (approval no. R1437). Bortezomib, thalidomide, lenalidomide, pomalidomide, elotuzumab, carfilzomib, ixazomib, daratumumab, and isatuximab were approved in Japan for the treatment of relapsed/refractory MM between December 2006 and August 2020. The approval dates of these drugs are provided in Table S1.

The database cases included 7323 patients (4135 men and 3188 women) with the median age of 59 (range, 16-77) years who underwent ASCT after treatment with high-dose melphalan (200 mg/m^2) for newly diagnosed symptomatic MM; we included the patients who underwent ASCT in Japan between January 2007 and December 2018. Given that we did not have the data regarding the details of the patients' treatment regimens before and after ASCT, we arbitrarily categorized the patients into three treatment cohorts

according to the year that ASCT was carried out: group 1, 2007-2010; group 2, 2011-2016; and group 3, 2017-2018.

In addition to conventional drugs, bortezomib, thalidomide, and lenalidomide were available for treatment in group 1. In group 2, pomalidomide, elotuzumab, and carfilzomib were available in addition to the drugs in group 1. In group 3, ixazomib and daratumumab were also available in addition to those in group 2. The patients who received an Allo-SCT after ASCT were censored at the day of Allo-SCT. All of the patients were diagnosed as having MM based on institutional assessment.

The patients' responses to treatment were assessed based on the criteria of the European Group for Blood and Marrow Transplantation[8] and the international uniform response criteria for MM.[9] The patients' responses before and after SCT were classified by institutional physicians into five categories: CR, VGPR, PR, SD, and PD.

We classified the patients into three categories by referring to the consensus of the International Myeloma Working Group with slight modification[10]: unfavorable cytogenetic abnormality, not-unfavorable cytogenetic abnormality, and unknown/insufficient data, based on the physicians' input data. "Unfavorable cytogenetic abnormality" included deletion 13q, deletion 17p, t(4;14), t(14;16), t(14;20), and 1q gain. Deletion 13q was identified by a karyotype analysis, and other unfavorable cytogenetic abnormalities were categorized by both a karyotype analysis and a FISH analysis. We categorized the patients with a cytogenetic abnormality other than an unfavorable cytogenetic abnormality into the "not-unfavorable cytogenetic abnormality" group. When mitosis figures could not be obtained or the karyotype data were not available, we categorized the case as "unknown," and if the karyotype data were insufficient for analysis, we categorized the case as "insufficient data."

2.2 | Statistical analyses

The distribution of categorical and continuous variables of groups 1, 2, and 3 were compared using Pearson's χ^2 test and the Kruskal-Wallis test, respectively. The OS was calculated from the time of the first ASCT until the date of death by any cause, the date of last contact, or censored at the day of Allo-SCT. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used for comparisons among groups. The Cox proportional hazard model was used to calculate the hazard ratios for each variable along with the 95% CI. A multivariate analysis was carried out for all variables that were significant ($P < .05$) in a univariate analysis. The cytogenetic abnormality analyses were excluded from the multivariate analysis and analyzed as subgroups due to insufficient data. All statistical analyses were carried out using the EZR (version 1.54) software package (Saitama Medical Center/Jichi Medical University) along with a graphical user interface for the R software package (version 4.0.3; The R Foundation for Statistical Computing).[11] P values less than .05 were considered significant in all analyses.

3 | RESULTS

3.1 | Overall survival of MM patients after ASCT in the era of new medicine

The characteristics of patients are summarized in Table 1. We divided the patients into three groups according to the years during which they underwent ASCT. There were no significant differences among the groups with regards to gender or MM type of heavy chain (Table 1). However, the following characteristics differed significantly among the groups: patient age at ASCT, PS at ASCT, ISS categorization at diagnosis, MM type of light chain, karyotype, number of collected $CD34^+$ cells per body weight, number of days from diagnosis at first ASCT, treatment response before and after first ASCT, number of ASCTs, and the follow-up period of survivors (Table 1). The median number of days from the diagnosis to ASCT was not significantly different among groups 1, 2, and 3 at 212, 232, and 213 days, respectively (Figure S1). Information about the patients' induction regimens and median cycles of induction therapies is summarized in Table S2.

When we analyzed the OS of the MM patients who had undergone ASCT during the years 2007-2018, we observed that OS significantly improved over time (Figure 1A, Table 2; $P < .0001$). The 2-year OS rates of groups 1, 2, and 3 were 85.8% (95% CI, 84.1-87.4), 89.1% (95% CI, 88.0-90.1), and 92.3% (95% CI, 90.0-94.2%), respectively. The median follow-up time of the survivors in groups 1, 2, and 3 were 2397, 1365, and 417 days, respectively. The median OS of groups 1, 2, and 3 were 2701 days, not reached, and not reached, respectively.

The other factors associated with superior OS in the univariate analysis were age 65 years or younger at the time of ASCT ($P < .0001$), female gender ($P < .0001$), a good PS (PS 0 or 1) ($P < .0001$), low ISS stage ($P < .0001$), and the treatment response before ASCT ($P < .0001$; Figures 1B–D, 2, and S2-S4, Table 2). The number of $CD34^+$ cell counts, the timing of ASCT 180 days or less after the diagnosis, and the number of ASCTs were not significant in the univariate analysis (Table 2). Because of insufficient data, we undertook a subgroup analysis for unfavorable cytogenetic abnormalities at the time of diagnosis and the treatment response after ASCT. This analysis revealed that both not having an unfavorable cytogenetic abnormality ($P < .0001$) and achieving a good response after ASCT ($P < .0001$) resulted in superior OS (Figures 3 and S5, Table 2).

We undertook a multivariate analysis regarding the patients' OS by analyzing all of the baseline factors except cytogenetic abnormality (unfavorable or not) and post-ASCT response, because of insufficient data. The factors that were independently associated with superior OS were age 64 years or less ($P = .0010$), a good PS (PS 0/1; $P = .0016$), low ISS stage ($P < .0001$), having undergone ASCT at 180 days or less after diagnosis ($P = .0226$), good treatment response before ASCT ($P < .0001$), the year of ASCT ($P = .0001$), and having undergone two ASCTs ($P = .0051$; Table 2).

TABLE 1 Characteristics of Japanese patients with multiple myeloma who underwent autologous stem cell transplant (ASCT)

		ASCT period (years)			
		2007-2010	2011-2016	2017-2018	*P* value
No. of cases		1816	3916	1591	
Age at ASCT, y; median (range)		58 (18-75)	60 (16-77)	61 (24-76)	<.0001
Age ≤65 y at ASCT		1656 (91.2)	3344 (85.4)	1201 (75.5)	<0.0001
Gender	Male	1051 (57.9)	2207 (56.4)	877 (55.1)	.2660
PS at ASCT	0 and 1	1514 (86.5)	3453 (89.9)	1437 (93.5)	<.0001
	2 or more	232 (13.3)	381 (9.9)	97 (6.3)	
	Unknown	4 (0.2)	6 (0.2)	3 (0.2)	
ISS stage at diagnosis	I	510 (33.0)	1159 (34.1)	485 (35.9)	<.0001
	II	547 (35.4)	1252 (36.9)	509 (37.7)	
	III	329 (21.3)	826 (24.3)	334 (24.7)	
	Unknown	161 (10.4)	160 (4.7)	23 (1.7)	
Myeloma type	IgG	918 (52.1)	2070 (53.9)	805 (52.4)	.0520
	IgA	341 (19.4)	744 (19.4)	299 (19.5)	
	BJP	351 (19.9)	742 (19.3)	336 (21.9)	
	IgD	57 (3.2)	104 (2.7)	40 (2.6)	
	IgM	1 (0.1)	16 (0.4)	5 (0.3)	
	IgE	1 (0.1)	4 (0.1)	1 (0.1)	
	Nonsecreting	54 (3.1)	82 (2.1)	32 (2.1)	
	Unknown	39 (2.2)	82 (2.1)	17 (1.1)	
Light chain	λ	683 (37.6)	1528 (39.0)	635 (39.9)	<.0001
	κ	951 (52.4)	2119 (54.1)	846 (53.2)	
	Unknown	182 (10.0)	269 (6.9)	110 (6.9)	
Cytogenetic abnormality	Not unfavorable	1426 (78.5)	3082 (78.7)	1188 (74.7)	<.0001
	Unfavorable	174 (9.6)	435 (11.1)	239 (15.0)	
	Unknown/insufficient data	216 (11.9)	399 (10.2)	164 (10.3)	
Collected CD34 cells per body weight ($\times 10^5$/kg)	<1.0	192 (14.6)	408 (19.0)	157 (18.0)	.0043
	≥1.0	1121 (85.4)	1743 (81.0)	717 (82.0)	
Time from diagnosis to first ASCT, d	≤180	617 (34.9)	1081 (28.1)	491 (31.9)	<.0001
	>180	1152 (65.1)	2768 (71.9)	1047 (68.1)	
Treatment response before first ASCT	CR	165 (10.5)	659 (18.8)	324 (23.3)	<.0001
	VGPR	496 (31.5)	1118 (32.0)	505 (36.3)	
	PR	718 (45.6)	1497 (42.8)	497 (35.7)	
	SD-PD	197 (12.5)	225 (6.4)	67 (4.8)	
	Unknown	240 (13.2)	417 (10.6)	198 (12.4)	
Treatment response after first ASCT	CR	88 (4.8)	1065 (27.2)	686 (43.1)	<.0001
	VGPR	45 (2.4)	629 (16.1)	385 (24.2)	
	PR	53 (2.9)	594 (15.2)	259 (16.3)	
	SD-PD	23 (1.3)	109 (2.8)	47 (3.0)	
	Unknown	1607 (88.5)	1519 (38.8)	214 (13.5)	
No. of ASCTs	1	1315 (72.8)	344 (88.4)	1493 (97.0)	<.0001
	2	491 (27.2)	449 (11.6)	46 (3.0)	
Follow-up period of survivor, d; median (range)		2397 (13-4569)	1365 (0-3147)	417 (0-980)	<.0001

Note: Data are shown as n (%) unless otherwise specified. The distribution of categorical and continuous variables of groups 1, 2, and 3 were compared using Pearson's χ^2 test and the Kruskal-Wallis test, respectively.

Abbreviations: CR, complete response; ISS, International Staging System; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VGPR, very good partial response.

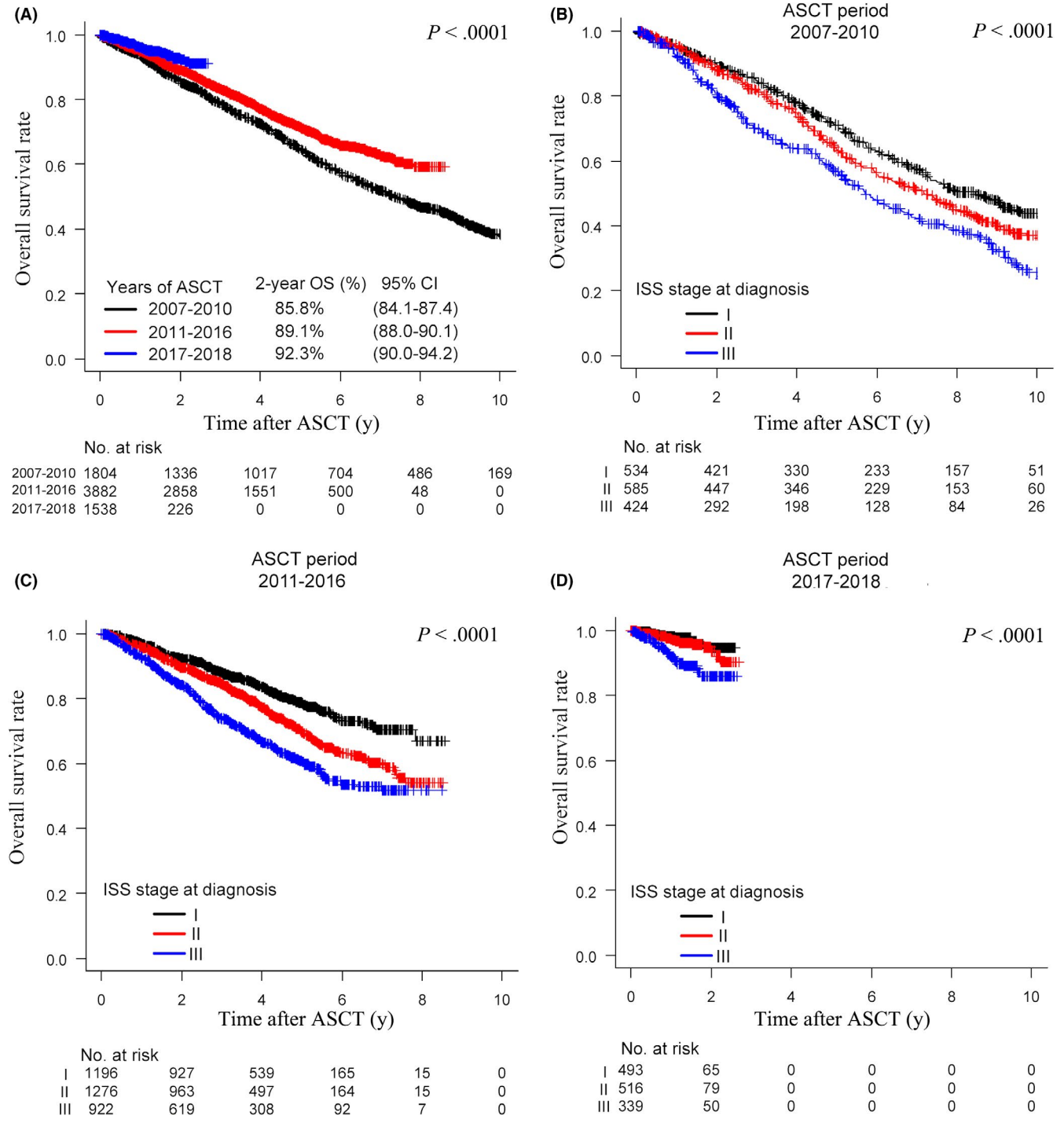

FIGURE 1 A, Overall survival (OS) from the time of autologous stem cell transplantation (ASCT) in Japanese patients with multiple myeloma (MM) who underwent ASCT in 2007-2010 (group 1; black), 2011-2016 (group 2; red), and 2017-2018 (group 3; blue). B–D, OS of MM patients after ASCT by the International Staging System (ISS) stage at diagnosis: stage I (black), stage II (red), and stage III (blue). The number of patients at risk in each group is shown in the lower panel of each figure

These results indicated that although traditional risk factors (such as older age, poor PS, high ISS stage, poor pre-ASCT response, and unfavorable cytogenetic abnormality) hold true in the modern era, the OS of patients in the era of new drugs for MM has significantly improved independently of the traditional risk factors.

3.2 | Impact of new drugs for treating MM across each risk factor

To further clarify the impact of new drugs for treating MM across various risk factors, we analyzed the differences in OS in relation to the years (period) of ASCT with respect to well-known

TABLE 2 Univariate and multivariate analysis for survival among patients with multiple myeloma who received autologous stem cell transplant (ASCT)

		Univariate analysis					Multivariate analysis		
Factor		2-year OS (%)	95% CI	5-year OS (%)	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age at ASCT, y	≤65	89.1	88.2-89.9	70.0	68.5-71.5	<.0001	1.0000		.0010
	>65	85.6	83.1-87.9	65.9	61.4-70.1		1.3430	1.126-1.602	
Gender	Male	87.4	86.2-88.5	67.1	65.1-69.0	<.0001			.1944
	Female	90.2	89.0-91.3	72.6	70.4-74.7				
PS at ASCT	0 or 1	89.9	89.0-90.7	70.5	69.0-72.0	<.0001	1.0000		.0016
	2 or more	77.6	74.1-80.7	60.1	55.6-64.4		1.3900	1.157-1.670	
	Unknown	73.8	38.5-90.8	49.2	16.4-75.8		0.4970	0.069-3.572	
ISS stage at diagnosis	I	92.0	90.7-93.2	76.3	73.8-78.7	<.0001	1.0000		<.0001
	II	89.8	88.3-91.1	67.8	65.1-70.4		1.2040	1.033-1.403	
	III	83.1	80.9-85.2	58.3	54.8-61.7		1.9400	1.662-2.264	
	Unknown	86.6	82.1-90.0	67.8	61.2-73.5		1.6370	1.145-2.340	
CD34 counts per body weights ($\times 10^5$/kg)	<1.0	86.6	83.7-89.0	65.7	60.8-70.1	.183			.2077
	≥1.0	89.5	88.3-90.6	69.1	67.1-71.1				
Time from diagnosis to ASCT, d	≤180	89.3	87.7-90.6	70.6	67.9-73.1	.442	1.0000		.0226
	>180	88.4	87.3-89.3	69.1	67.3-70.8		1.1740	1.023-1.348	
Pre-ASCT response	CR	94.1	92.3-95.4	78.1	74.4-81.4	<.0001	1.0000		<.0001
	VGPR	90.4	88.9-91.7	71.8	69.1-74.3		1.5030	1.202-1.881	
	PR	88.0	86.6-89.3	66.9	64.5-69.2		1.7970	1.448-2.230	
	SD-PD	70.6	66.0-74.8	43.9	38.3-49.3		3.3200	2.576-4.279	
Year of ASCT	2007-2010	85.8	84.1-87.4	64.9	62.4-67.3	<.0001	1.0000		.0001
	2011-2016	89.1	88.0-90.1	71.6	69.7-73.3		0.8070	0.705-0.923	
	2017-2018	92.3	90.0-94.2	NA	NA		0.5020	0.341-0.738	
No. of ASCT	1	87.8	86.9-88.7	68.9	67.2-70.5	.1760	1.0000		.0051
	2	93.2	91.4-94.7	73.0	69.6-76.0		0.8108	0.700-0.939	
Cytogenetic abnormality	Not unfavorable	90.2	89.3-91.0	71.5	69.9-73.0	<.0010			
	Unfavorable	79.6	76.3-82.5	56.2	51.2-60.8				
	Unknown/insufficient data	85.9	82.7-88.6	67.7	63.0-72.0				
Post-ASCT response	CR	94.7	93.4-95.8	79.5	76.3-82.4	<.0010			
	VGPR	90.8	88.5-92.6	73.3	68.7-77.3				
	PR	88.5	86.0-90.6	70.4	65.8-74.5				
	SD-PD	74.4	66.6-80.7	58.5	48.3-67.5				

Note: Overall survival (OS) was calculated from the time of ASCT. Univariate and multivariate analyses against OS were undertaken for the following factors. For the univariate analysis, age (>65 y at ASCT), gender, performance status (PS) at ASCT, International Staging System (ISS) stage at diagnosis, CD34 counts per body weight, days from diagnosis to ASCT, pre-ASCT response, year of ASCT, number of ASCTs, cytogenic abnormality and post-ASCT responses were chosen, and the percentage of 2-year and 5-year OS with the 95% confidence interval (CI) and *P* value are shown. For the multivariate analysis, the following factors were chosen: age (>65 y at ASCT), gender, PS at ASCT, ISS stage at diagnosis, CD34 counts per body weight, days from diagnosis to ASCT, pre-ASCT response, year of ASCT, and number of ASCTs were chosen. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *P* value are shown.

Abbreviations: CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

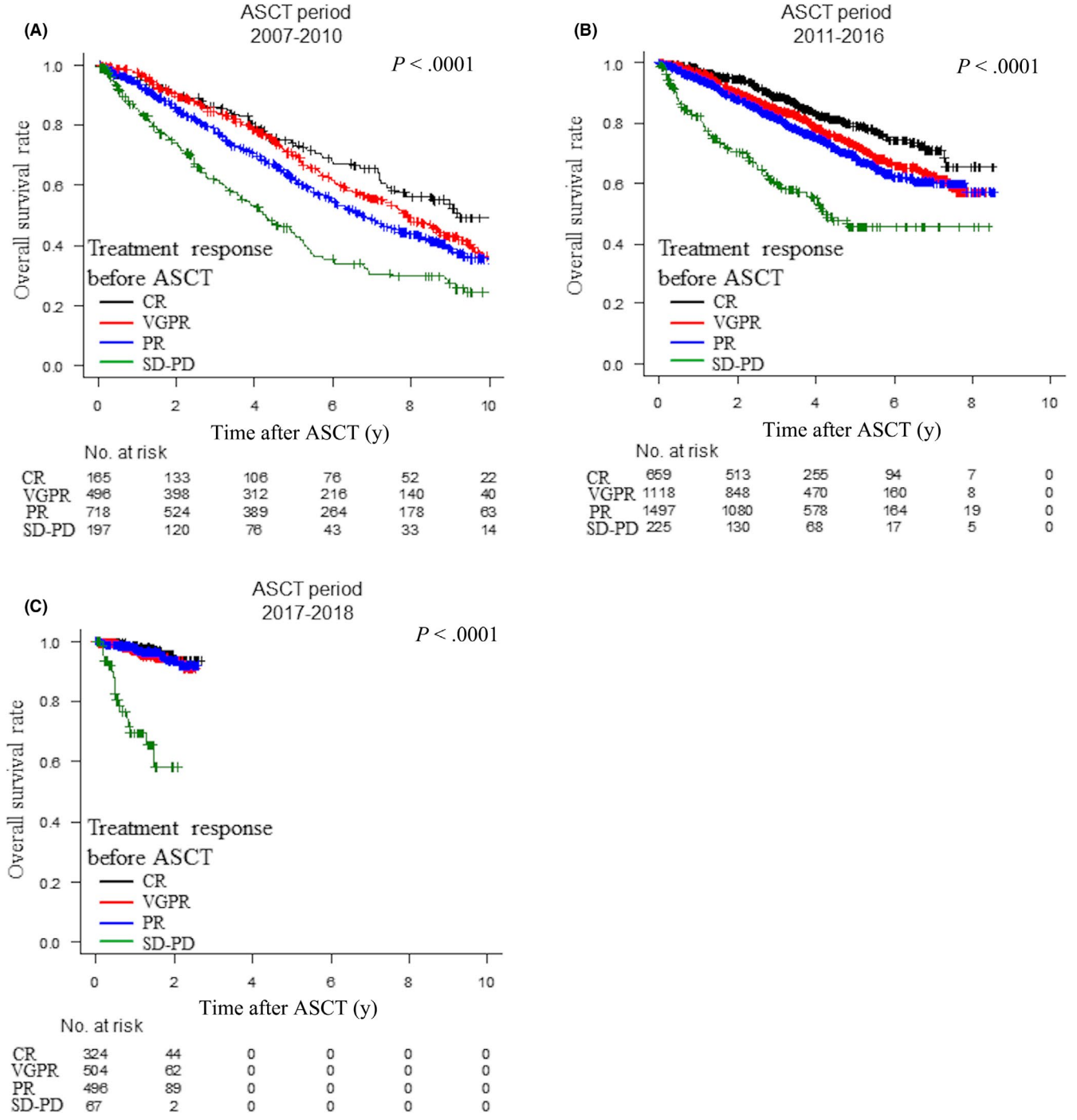

FIGURE 2 Overall survival of Japanese patients with multiple myeloma after autologous stem cell transplantation (ASCT) according to treatment response before ASCT: complete response (CR; black), very good partial response (VGPR; red), partial response (PR; blue), and stable disease-progressive disease (SD-PD; green). (A) Group 1, ASCT in 2007-2010. (B) Group 2, ASCT in 2011-2016. (C) Group 3, ASCT in 2017-2018

prognostic factors (Figure 4). When we compared OS between groups 1 and 2, we observed that patients in group 2 with the following factors showed better OS: any age ($P < .0001$ for age ≤65 years and $P = .0004$ for age >65 years), either gender ($P = .0001$ for males and $P < .0001$ for females), any PS ($P = .0009$ for PS = 0 or 1 and $P < .0001$ for PS > 1), ISS stages I ($P < .0001$) and II ($P = .0135$) at diagnosis, partial response before ASCT ($P = .0006$), and not having an unfavorable cytogenetic abnormality at diagnosis ($P < .0001$). When we compared OS between groups 2 and 3, the following factors showed superior OS in group 3: age 65 years or less ($P = .0044$), female gender ($P = .0259$), PS 0 or 1 ($P = .0494$), partial response before ASCT ($P = .0066$), and not having an unfavorable cytogenetic abnormality at diagnosis ($P = .0011$).

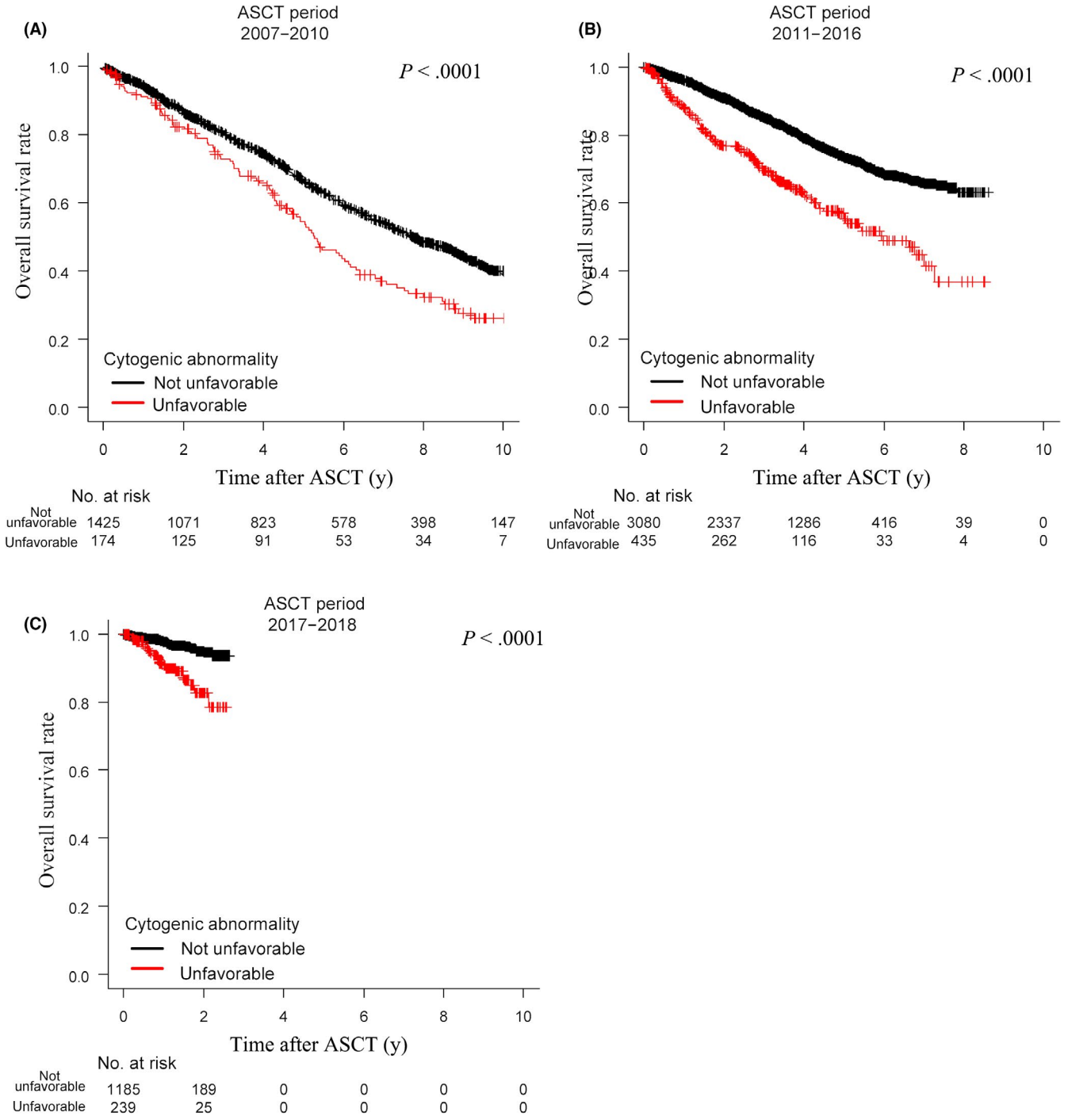

FIGURE 3 Overall survival of Japanese patients with multiple myeloma after autologous stem cell transplantation (ASCT) according to the type of cytogenic abnormality, ie, not-unfavorable cytogenic abnormality (black) and unfavorable cytogenic abnormality (red) in (A) group 1, ASCT in 2007-2010, (B) group 2, ASCT in 2011-2013, and (C) group 3, ASCT in 2017-2018

It may thus be concluded that: (a) the OS of MM patients improved significantly among both low-risk and high-risk patients in group 2 compared to group 1, and (b) the OS of MM patients improved significantly among the low-risk patients in group 3 (low-risk = with characteristics such as younger age, good PS, and not having an unfavorable cytogenetic abnormality).

3.3 | Correlation between pre- and post-ASCT responses and OS

We next analyzed the relationship between OS in the modern era and treatment response before ASCT. Our analyses revealed that in groups 1, 2, and 3, the rates of CR (10.5%, 18.8%, and 23.3%,

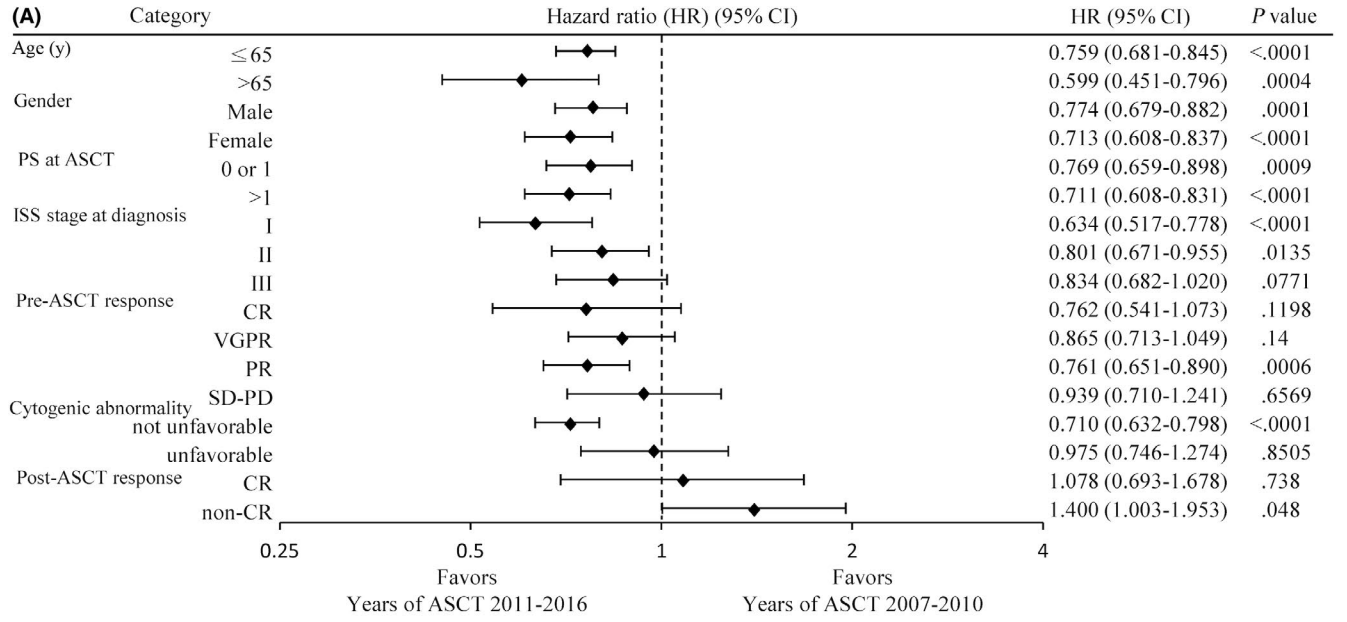

FIGURE 4 Impact of autologous stem cell transplantation (ASCT) on the overall survival of Japanese patients with multiple myeloma treated with new drugs. The effects of ASCT on each group are shown as forest plots. Diamonds on the lines indicate the hazard ratios (HR) for comparisons of (A) group 2 (ASCT in 2011-2013) with group 1 (ASCT in 2007-2010) and (B) group 3 (ASCT in 2017-2018) with group 2. Horizontal lines indicate corresponding 95% confidence interval (CI). CR, complete response; ISS, International Staging System; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VGPR, very good partial response

respectively) and VGPR (31.6%, 31.9%, and 36.2%, respectively) increased over time (Figure 5A). In contrast, in groups 1, 2, and 3, the rates of PR (45.5%, 42.8%, and 35.7%, respectively) and SD to PD (12.5%, 6.4%, and 4.8%, respectively) decreased over time (Figure 5A). We also observed that the CR (42.1%, 44.4%, and 49.8%, respectively) and VGPR (21.5%, 26.2%, and 28.0%, respectively) rates after first ASCT increased over time (Figure 5B), and the rates of PR (25.4%, 24.8%, and 18.8%, respectively) and SD to PD (11.0%, 4.5%, and 3.4%, respectively) decreased over time (Figure 5B).

As depicted in Figure 2, the patients who had achieved a better response before ASCT were able to achieve better OS after ASCT. The patients who achieved a better response after their first ASCT showed superior OS over time ($P = .179$, $P < .0001$, and $P < .0001$ in groups 1-3, respectively; Figure S5). We thus concluded that the improvement

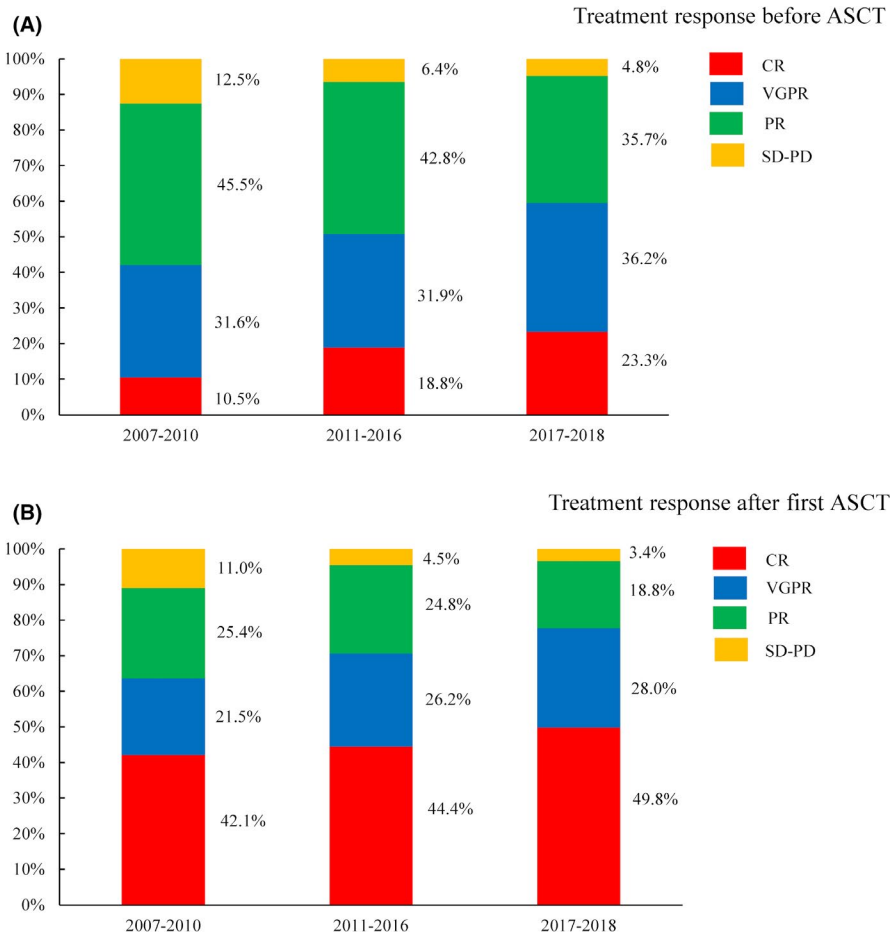

FIGURE 5 Percentages of treatment response (A) before and (B) after autologous stem cell transplantation (ASCT) in Japanese patients with multiple myeloma according to the year of ASCT: group 1, 2007-2010; group 2, 2011-2016; and group 3, 2017-2018. Treatment responses before and after ASCT were divided into four categories: complete response (CR; red), very good partial response (VGPR; blue), partial response (PR; green), and stable disease-progressive disease (SD-PD; yellow)

of both the pre- and post-ASCT responses enhanced the post-ASCT OS among MM patients in the modern era of new medicines.

4 | DISCUSSION

The results of our present analyses of 7323 Japanese patients with MM clearly showed the improvement of OS over time (group 1 [2007-2010] < group 2 [2011-2016] < group 3 [2017-2018]) with the introduction of new drugs for treating MM patients after ASCT. Our earlier study showed that the prognosis of MM patients after ASCT improved with the introduction of PI.[4] The present study further analyzed the impact of other new drugs brought into clinical settings after 2011.

The prognosis of MM was dramatically improved in the present group 2 compared to that of group 1. The prognosis of group 3 was improved compared to that of group 2, but the most marked improvement was limited to the traditionally low-risk patients (eg, those with younger age, a good PS, and not having an unfavorable karyotype). The standard error shown in Figure 4B is longer compared to that in Figure 4A; the difference between these two graphs might be due in part to the smaller number of patients analyzed in group 3. As we noted above, the observation period might be short for detecting the differences in OS, particularly in group 3.

When we focused on the treatment response before ASCT, we observed that the rates of CR and VGPR before ASCT increased over time. We speculate that the improvement in the patients' pre- and post-ASCT responses in the modern era of new MM drugs contributed to the improvement in the patients' OS.

The results of our analyses also confirmed the favorable prognostic factors in the modern era, ie, age less than 65 years, a good PS, a low ISS stage, early ASCT, a good treatment response before ASCT, receiving ASCT during the modern era, and double ASCT. We observed that these traditional prognostic factors (such as PS and ISS) are holding true even in the era of new MM drugs, but these traditional markers against the prognosis are becoming less important. However, the type of cytogenetic abnormality was revealed as an important prognostic factor (Figure 3).

Based on the improvement of both PFS and OS in the EMN02 study, ASCT became the mainstay for transplant-eligible MM patients.[12] The improvement of PFS was also demonstrated in the IFM 2009 study, but an improvement in OS was not detected in that study.[13] This result might indicate that the significance of early ASCT could change in the era of new drugs for treating MM.

Our findings could not verify some of the prognostic markers that were identified in previous studies.[14-16] First, in ASCT-eligible MM patients, it has been recommended that ASCT be undertaken at an early time point, particularly within 6 months after diagnosis.[14,15] The present study revealed the beneficial effects of early

ASCT on the patients' OS in the multivariate analysis, but not in the univariate analysis. We speculate that there is a subgroup of patients who could obtain benefit from double ASCT. However, it would be more important to achieve a better treatment response before ASCT regardless of other risk factors. The correlation between a deeper response during ASCT and favorable prognosis has been shown in other studies.[13,17,18]

Second, it was reported that the stem cell dose correlated with better OS before PI, IMiDs, and mAbs were available.[16] However, in our present investigation, the number of $CD34^+$ cells did not correlate with OS. The importance of early ASCT and the stem cell dose might be changing in the modern era of new medicine.

Another study reported the improvement of prognosis in high-risk MM patients by the introduction of bortezomib.[19] Our present findings are partly compatible with this result when we compare the prognoses of the ISS stage I and II patients in group 3. However, the prognosis of MM in patients with an unfavorable cytogenetic abnormality or ISS stage III remained worse in our study. The improvement of the prognosis of advanced-stage MM patients with high-risk cytogenetic abnormalities remains an important task.

Double ASCT did not improve the OS of MM patients as a whole in previous studies, and the question of whether high-risk patients might benefit from double ASCT has not been answered.[20,21] We observed a benefit of double ASCT on the patients' OS in the multivariate analysis but not in the univariate analysis (Table 2, Figures S6 and S7). Double ASCT might be beneficial for a subgroup of patients (particularly those in group 1), but we could not precisely determine the subgroup. Monoclonal Abs and carfilzomib could overcome the disadvantage of high-risk patients. It has been widely accepted that once an MM patient has relapsed, a second relapse would be unavoidable, and the interval before the second relapse would be shorter than that of the first relapse. The results of our analyses indicated that the treatment response before ASCT was correlated with OS in both the high-risk and non-high-risk patients. To overcome the poor prognosis of high-risk cases, we think that it is especially important to obtain as deep a response as possible by using the new drugs at an earlier time point of treatment. We plan to confirm this new treatment strategy in a future prospective study.

There are some limitations in this study. First, given that we did not have enough data regarding the details of the patients' treatment regimens, we arbitrarily categorized the patients into three treatment cohorts. The observation period in group 3 could be short, and the data from group 3 are considered to be exploratory. Second, we could not directly analyze the impact of each new drug on the patients' OS, because we did not have detailed information about the treatment regimens of groups 1, 2, and 3 in the TRUMP database. Third, we could not calculate the patients' PFS due to limited data regarding the relapse of MM in this study. Finally, we were able to analyze the cases of only some of the patients based on the risk of cytogenetic abnormality or post-ASCT response, because the information about cytogenetic abnormality and post-ASCT responses was limited. Additionally, we could not analyze the influence of new drugs against EMM, which is associated with poor prognosis due to relapse and refractoriness to treatment,[22] because the category of EMM has not been included in the TRUMP database. These limitations need to be analyzed in future studies.

In conclusion, the results of this study showed that the OS of patients with MM after ASCT has improved over time along with the introduction of new drugs for the treatment of MM. The prognosis of high-risk MM patients with a cytogenetic abnormality and ISS stage III requires further improvement.

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DISCLOSURE

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SUPPORTING INFORMATION

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