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Changing trends in prognostic factors for patients with multiple myeloma after autologous stem cell transplantation during the immunomodulator drug/proteasome inhibitor era

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Key words

Autologous stem cell transplantation, immunomodulator drugs, International Staging System, multiple myeloma, proteasome inhibitors

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We evaluated the clinical significance of prognostic factors including the International Staging System (ISS) and modified European Group for Blood and Marrow Transplantation response criteria in 1650 Japanese patients with multiple myeloma (MM) who underwent upfront single autologous stem cell transplantation (ASCT). We categorized patients into two treatment cohorts: pre-novel agent era (1995–2006) and novel agent era (2008–2011). The combined percentage of pre-ASCT complete response and very good partial response cases (463 of 988, 47%) significantly increased during the novel agent era compared with the pre-novel agent era (164 of 527, 31%; $P < 0.0001$). The 2-year overall survival (OS) rate of 87% during the novel agent era was a significant improvement relative to that of 82% during the pre-novel agent era ($P = 0.019$). Although significant differences in OS were found among ISS stages during the pre-novel agent era, no significant difference was observed between ISS I and II ($P = 0.107$) during the novel agent era. The factors independently associated with a superior OS were female gender ($P = 0.002$), a good performance status ($P = 0.024$), lower ISS ($P < 0.001$), pre-ASCT response at least partial response ($P < 0.001$) and ASCT during the novel agent era ($P = 0.017$). These results indicate that the response rate and OS were significantly improved, and the ISS could not clearly stratify the prognoses of Japanese patients with MM who underwent upfront single ASCT during the novel agent era.

The prognosis of patients with multiple myeloma (MM) has improved since the introduction of novel treatment agents such as bortezomib, thalidomide and lenalidomide. Bortezomib is classified as a proteasome inhibitor and thalidomide/lenalidomide as immunomodulator drugs. During the pre-novel agent era, an international collaborative project developed the International Staging System (ISS) based on serum albumin and β2-microglobulin levels.[1] This system has been widely used in both young and elderly patients with MM treated with either conventional chemotherapy or autologous stem cell transplantation (ASCT) after high-dose melphalan conditioning during the novel agent era. However, the validity of the ISS for prognostic predictions has not been verified in Asian patients with MM. We analyzed the prognostic factors of a large cohort of newly diagnosed Japanese patients with MM who underwent upfront single ASCT after high-dose melphalan (200 mg/m^2; Mel 200) treatment during both the pre-novel and novel agent eras.

Materials and Methods

Data source and patients. For this retrospective observational study, data were collected and analyzed using the Transplant Registry Unified Management Program (TRUMP) of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Patient consent is not required for JSHCT TRUMP registration because the registry data comprise anonymized clinical information. This study was approved by the data management committees of JSHCT and the institutional review boards of the Kanazawa University Graduate School of Medical Science, Japan.

Because bortezomib, thalidomide and lenalidomide were released for treatment of relapse/refractory MM in Japan in December 2006, February 2009 and July 2010, respectively,

we categorized the patients into two treatment cohorts: pre-novel (1995–2006) and novel agent eras (2008–2011). The study participants included 1650 Japanese patients (936 men and 714 women) with a median age of 58 years (range: 18–73 years) who underwent upfront single ASCT after Mel 200 treatment for newly diagnosed symptomatic MM; all patients underwent an ASCT in Japan between October 1995 and December 2011. Because bortezomib was released for the treatment of relapse/refractory MM on 1 December 2006 and approved for the treatment of previously untreated MM on 16 September 2011, most patients who underwent an ASCT in 2007–2011 were first treated with conventional chemotherapies, such as VAD (infusional vincristine, doxorubicin and pulsed dexamethasone) or high-dose dexamethasone, but when patients did not achieve a sufficient response, they were then treated with novel agents before ASCT. Patients who underwent an ASCT in 2007 were excluded, because bortezomib was released in December 2006 and a relatively large number of these patients were assumed to have received induction chemotherapy without the use of novel agents. The overall survival (OS) curve of patients who underwent an ASCT in 2007 was located between that in 1995–2006 and that in 2008–2011 (data not shown). All patients were diagnosed with MM based on institutional assessment. When ASCT was performed between January 2004 and December 2011, patient responses to therapy were assessed based on the criteria of the European Group for Blood and Marrow Transplantation,[2] which was modified to include very good partial response (VGPR) and stable disease (SD), and categorized as either a complete response (CR), VGPR, partial response (PR), SD or

Table 1. Patient characteristics

	ASCT during pre-novel agent era (until 31 December 2006) (n = 654)		ASCT during novel agent era (after 1 January 2008) (n = 996)	P-value
	October 1995–December 2003 (n = 117)	January 2004–December 2006 (n = 537)	January 2008–December 2011	
Median age, years (range) at ASCT	54 (23–68)	57 (22–70)	59 (18–73)	<0.001
Age ≤65 at ASCT, n (%)	113 (96.6)	517 (96.3)	937 (94.1)	0.0497
Male, n (%)	62 (53.0)	297 (55.3)	577 (58.0)	0.223
Performance status at ASCT, n (%)				
0 or 1	100 (85.5)	475 (88.5)	906 (91.0)	0.789
>1	7 (6.0)	51 (9.5)	87 (8.7)	
Unknown	10 (8.5)	11 (2.0)	3 (0.3)	
ISS stage at diagnosis, n (%)				
I	21 (17.9)	148 (27.6)	342 (34.3)	0.992
II	21 (17.9)	167 (31.1)	376 (37.8)	
III	19 (16.2)	90 (16.8)	216 (21.7)	
Unknown	56 (47.9)	132 (24.6)	62 (6.2)	
Myeloma type, n (%)				
Light-chain only	23 (19.7)	81 (15.1)	182 (18.3)	0.194
IgA	21 (17.9)	109 (20.3)	198 (19.9)	
IgG	65 (55.6)	316 (58.8)	553 (55.5)	
IgD	5 (4.3)	16 (3.0)	28 (2.8)	
IgM	0	1 (0.2)	2 (0.2)	
Non-secreting	0	9 (1.7)	31 (3.1)	
Unknown	3 (2.6)	5 (0.9)	2 (0.2)	
Planned post-ASCT therapy, n (%)				
Thalidomide	0	1 (0.2)	28 (2.8)	<0.001
Bortezomib	0	0	24 (2.4)	<0.001
Lenalidomide	0	0	31 (3.1)	<0.001
Pre-ASCT response, n (%)		CR 45 (8.4)	CR 123 (12.3)	
nCR	18 (15.4)	VGPR 119 (22.2)	VGPR 340 (34.1)	
PR	64 (54.7)	PR 285 (53.1)	PR 434 (43.6)	
SD	11 (9.4)	SD 62 (11.5)	SD 76 (7.6)	
PD	4 (3.4)	PD 16 (3.0)	PD 15 (1.5)	
NA	20 (17.1)	NA 10 (1.9)	NA 8 (0.8)	
CR + VGPR	NA	164 (31.1)	463 (46.9)	<0.001
Non-CR + Non-VGPR	NA	363 (68.9)	525 (53.1)	
Post-ASCT response, n (%)	NA	CR 45 (15.9)	182 (26.4)	<0.001
		Non-CR 238 (84.1)	508 (73.6)	
		NA 254	306	

P-value, comparison between pre-novel and novel agent eras. Because the response of patients (n = 4) who underwent ASCT between October 1995 and December 1996 was based on institutional assessment, we excluded them from the pre-ASCT response assessment. ASCT, autologous stem cell transplantation; CR, complete response; ISS, International Staging System; NA, not assessed; nCR, near complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response or better.

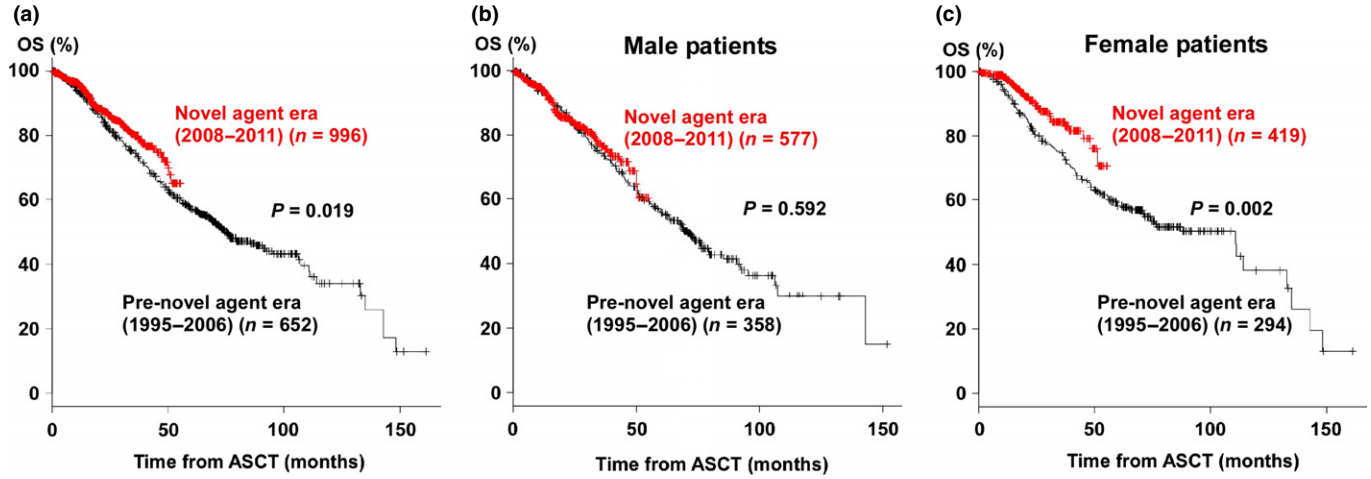

Fig. 1. Overall survival (OS) from the time of autologous stem cell transplantation (ASCT) of patients who underwent ASCT during the pre-novel and novel agent eras (a); males (b) and females (c).

Table 2. Comparison of factors associated with survival

	2-years survival (%) (95% CI)	*P*-value
Age ≤65 at ASCT	84.5 (82.3–86.4)	0.603
Age >65 at ASCT	83.2 (70.5–90.8)	
Male	83.9 (81.0–86.3)	0.014
Female	85.2 (81.9–87.9)	
Performance status at ASCT		
0 or 1	85.7 (83.6–87.7)	<0.001
>1	74.0 (65.0–81.1)	
ISS stage at diagnosis		
I	90.1 (86.6–92.7)	<0.001
II	83.2 (79.3–86.5)	
III	79.4 (73.9–83.9)	
Pre-ASCT response		
CR	85.3 (77.3–90.6)	<0.001
VGPR	88.1 (84.2–91.1)	
PR	85.3 (82.1–88.0)	
SD	78.6 (69.6–85.1)	
PD	51.6 (31.4–68.6)	
Post-ASCT response		
CR	90.6 (84.8–94.3)	0.001
Non-CR	85.4 (82.3–88.1)	
ASCT during pre-novel agent era	82.0 (78.7–84.8)	0.019
ASCT during novel agent era	86.8 (84.1–89.2)	

Pre-ASCT and post-ASCT responses were analyzed using the data of pre-novel (January 2004–December 2006) and novel agent eras (January 2008–December 2011). The overall survival was calculated from the time of ASCT. ASCT, autologous stem cell transplantation; CR, complete response; ISS, International Staging System; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response or better.

progressive disease (PD). Because we could not exclude the possibility that immunofixation electrophoresis tests were not performed in some VGPR cases, VGPR or better is indicated in this study. VGPR was defined by a ≥90% reduction in M-component levels in the serum by electrophoresis (EP) in addition to PR criteria, and SD was defined as minor response (MR) plus no change (NC). In contrast, when ASCT was performed between January 1997 and December 2003, the responses to therapy were assessed as follows: near CR required the absence of detectable M-component levels in the serum and urine by EP and plasmacytomas, which was maintained for a minimum of 4 weeks without the emergence of new lesions, together with ≤5% plasma cells in the bone marrow on the recovery of peripheral white blood cell counts, platelet counts, and Hb to ≥2.5 × 10^9/L, ≥100 × 10^9/L and ≥10 g/dL, respectively. If chemotherapy and/or interferon treatment had adverse effects on blood recovery, the aforementioned peripheral blood recovery was not required. PR was defined by a ≥50% reduction in M-component levels in the serum and urine by EP and a ≥50% reduction in the size of plasmacytomas (=long diameter × short diameter), if two dimensions were measurable, or a ≥30% reduction, if only one dimension was measurable, which was maintained for a minimum of 4 weeks without the emergence of new lesions. MR was defined as follows: (i) a 25–50% reduction in M-component levels in the serum and urine by EP, or a ≥50% reduction in M-component levels in the serum and urine by EP for <4-week duration; (ii) a 25–50% decrease in plasmacytoma size (=long diameter × short diameter), if two dimensions were measurable, or a ≥50% decrease in plasmacytoma size for <4-week duration (a 15–30% decrease, if only one dimension was measurable, or ≥30% decrease in plasmacytomas size for <4-week duration); and (iii) no emergence of new lesions for a minimum of 4 weeks. PD was defined as an increase in M-component levels and/or plasmacytomas or the emergence of new lesions. The remaining patients without new lesions for a minimum of 4 weeks were considered as NC, and SD was defined as MR plus NC. Because the response of patients (n = 4) who underwent ASCT between October 1995 and December 1996 was based on an institutional assessment, we excluded them from the pre-ASCT response assessment.

Statistical analysis. Continuous variables were analyzed using the Student t test, and categorical variables were analyzed using Fisher's exact test. The OS was calculated from the time of diagnosis or ASCT until the date of death, by any cause, or the date of last contact. Patients who could not be followed up were censored at the date of last contact. Survival curves were plotted according to the Kaplan–Meier method, and the log-rank test was used for comparisons among the groups. The Cox proportional hazard model was used to calculate the hazard ratios (HR) for each variable along with the 95% confidence interval (CI). A multivariate analysis was conducted by

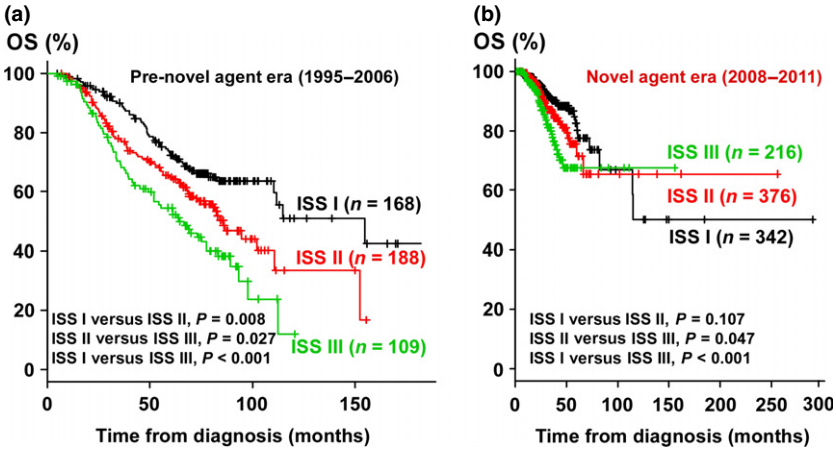

Fig. 2. The International Staging System (ISS) scores for patients who underwent autologous stem cell transplantation (ASCT) during the pre-novel (a) and novel agent eras (b). The overall survival (OS) was calculated from the time of diagnosis.

entering all variables that were associated with survival at a significance level of $P < 0.05$ into a Cox proportional hazard model. All statistical analyses were performed using the EZR software package (Saitama Medical Center/Jichi Medical University, Saitama, Japan)[3] along with a graphical user interface for the R software package (version 2.13.0; The R Foundation for Statistical Computing). A multivariate analysis was performed using the EZR software package (Saitama Medical Center/Jichi Medical University)[3] and SAS version 9.2 software (SAS Institute, Cary, NC, USA). *P*-values of <0.05 were considered significant in all analyses.

Results

The characteristics of patients before and after the approval of novel agents are shown in Table 1. There were no significant differences between the groups with regard to gender, performance status (PS) at ASCT, ISS categorization at diagnosis and myeloma type, except for age at ASCT, and planned post-ASCT therapy.

During the pre-novel agent era, 654 patients in Japan (359 men and 295 women) with a median age of 56 years (range: 22–70 years) underwent upfront single ASCT after Mel 200 treatment between October 1995 and December 2006. The median follow-up duration was 4.2 years with a 2-year OS rate of 82.0% (95% CI, 78.7–84.8), a 4-year OS rate of 64.7% (95% CI, 60.6–68.4) and the median survival was 6.3 years. During the novel agent era, 996 patients in Japan (577 men and 419 women) with a median age of 59 years (range: 18–73 years) underwent single ASCT after Mel 200 treatment between January 2008 and December 2011. The median follow-up duration was 1.6 years with a 2-year OS rate of

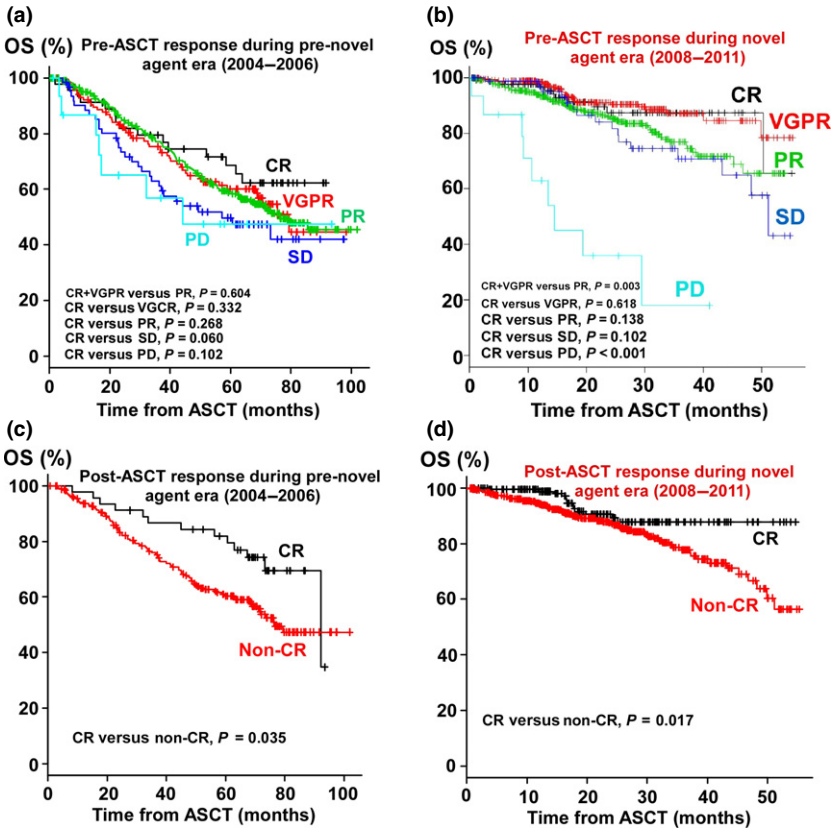

Fig. 3. Pre-autologous stem cell transplantation (ASCT) responses of patients who underwent ASCT during the pre-novel agent ([a] complete response [CR], 45 cases; very good partial response [VGPR], 119 cases; partial response [PR], 285 cases; stable disease [SD], 62 cases; progressive disease [PD], 16 cases) and novel agent eras ([b] CR, 123 cases; VGPR, 340 cases; PR, 434 cases; SD, 76 cases; PD, 15 cases). Post-ASCT responses of patients who underwent ASCT during the pre-novel agent ([c] CR, 45 cases; non-CR, 238 cases) and novel agent eras ([d] CR 182 cases; non-CR, 508 cases). Overall survival (OS) was calculated from the time of ASCT. These responses were analyzed using the data of pre-novel (January 2004–December 2006) and novel agent eras (January 2008–December 2011) based on the same response criteria.

86.9% (95% CI, 84.1–89.2). The OS during the novel agent era was significantly improved in comparison to the OS during the pre-novel agent era ($P = 0.019$; Fig. 1a). The factors associated with a superior OS were female gender ($P = 0.014$), a good PS ($P < 0.001$) and a low ISS score ($P < 0.001$; Table 2). Although the OS of female patients with MM significantly improved during the novel agent era ($P = 0.002$), the OS of male patients with MM did not ($P = 0.592$; Figs 1b,c,5). The median survival rates from the time of diagnosis for the ISS I ($n = 168$), II ($n = 188$) and III ($n = 109$) groups during the pre-novel agent era were 12.9, 7.2 and 5.4 years, respectively (Fig. 2a). The OS was significantly different when the ISS I group was compared with the ISS II ($P = 0.008$) and III ($P < 0.001$) groups and between the ISS II and III groups ($P = 0.027$). The 2-year OS rates from the time of diagnosis for the ISS I ($n = 342$), II ($n = 376$) and III ($n = 216$) groups during the novel agent era were 96%, 93% and 90%, respectively (Fig. 2b). In the ISS I group, the OS was significantly prolonged compared with the ISS III group ($P < 0.001$), but no significant differences were found between the ISS I and II groups ($P = 0.107$; Fig. 2b). The period from diagnosis to ASCT in the pre-novel agent era was 64–6079 days (median 213 days) and that in the novel agent era was 18–7201 days (median 218 days), and the difference between these groups was not significant ($P = 0.82$ by unpaired *t*-test; $P = 0.60$ by Mann–Whitney *U*-test). The pre-ASCT responses during the pre-novel agent era (January 2004–December 2006) were as follows: CR, 45 cases (8%); VGPR, 119 cases (22%); PR, 285 cases (53%); SD, 62 cases (12%); PD, 16 cases (3%); and no data, 10 cases (2%; Table 1). The 2-year OS rates for the CR, VGPR, PR, SD and PD groups were 82%, 82%, 85%, 73% and 65%, respectively. The median survival durations for the CR, VGPR, PR, SD and PD groups were not reached, 6.6, 6.4, 4.8, and 3.7 years, respectively (Fig. 3a). There were no significant differences in the OS between the CR group and the other response groups. The pre-ASCT responses during the novel agent era were as follows: CR, 123 cases (12%); VGPR, 340 cases (34%); PR, 434 cases (44%); SD, 76 cases (8%); PD, 15 cases (2%); and no data, eight cases (1%; Table 1). The 2-year OS rates for the CR, VGPR, PR, SD, and PD groups were 87%, 91%, 86%, 84% and 36%, respectively. There were no significant differences in the OS between the CR group and the other response groups, except between CR and PD ($P < 0.001$; Fig. 3b). The percentage of pre-ASCT CR + VGPR cases (463 of 988, 47%) during the novel agent era significantly increased in comparison with that during the pre-novel agent era (164 of 527, 31%; $P < 0.001$; Table 1), and there was a significant difference in the OS between the pre-ASCT CR + VGPR and PR groups during the novel agent era ($P = 0.003$; Fig. 3b). The post-ASCT CR rate during the novel agent era (182 of 690, 26%) also significantly increased compared with the pre-novel agent era rate (45 of 283, 16%; $P < 0.001$; Table 1). There were significant differences in the OS between the post-ASCT CR and non-CR groups during both the pre-novel and novel agent eras (Fig. 3c,d).

In a multivariate analysis, we analyzed the baseline factors that were significant in a univariate analysis; the post-ASCT response was excluded based on data unavailability for a large number of cases. The factors that were independently associated with superior OS were female gender ($P = 0.002$), PS of 0 or 1 ($P = 0.024$), ISS I versus II ($P = 0.046$) and III ($P < 0.001$), a pre-ASCT response better than or equal to PR ($P < 0.001$), and ASCT during the novel agent era ($P = 0.017$; Table 3). We classified patients into five categories on the basis of the number of prognostic factors (male gender, PS of 2, 3 or 4, ISS II or III, a pre-ASCT response less than PR, and ASCT during the pre-novel agent era). The numbers of patients with 0, 1, 2, 3, 4 and 5 prognostic factors were 251, 593, 394, 126, 17 and 1, respectively. We conducted Kaplan–Meier analysis according to the number of prognostic factors and revealed a clear OS stratification (Fig. 4). Only one patient displayed all five prognostic factors, and his OS was not shown. The patients who were included in this analysis underwent an ASCT during pre-novel (October 1995–December 2006) and novel agent (January 2008–December 2011) eras.

To further clarify the effects of novel agents across the various risk groups, we analyzed the differences in the OS of the groups before and during the novel agent era with respect to well-known prognostic factors (Fig. 5). In a comparison of the pre-novel and novel agent eras, the following factors were associated with a better OS: age ≤65 years ($P = 0.024$) at

Table 3. Univariate and multivariate analysis for survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age >65 *vs* ≤65 at ASCT	1.130 (0.713–1.791)	0.603	NA	
Male *vs* female	1.275 (1.049–1.550)	0.015	1.456 (1.155–1.837)	0.002
PS >1 *vs* 0 or 1 at ASCT	1.321 (1.142–1.528)	<0.001	1.477 (1.053–2.071)	0.024
ISS stage at diagnosis				
I	1.000	–	1.000	–
II	1.413 (1.079–1.852)	0.012	1.322 (1.005–1.739)	0.046
III	1.408 (1.220–1.624)	<0.001	1.840 (1.376–2.461)	<0.001
Pre-ASCT response				
CR/nCR/VGPR/PR *vs* SD/PD	1.206 (1.110–1.311)	<0.001	1.680 (1.240–2.277)	<0.001
Post-ASCT response				
Non-CR *vs* CR	1.939 (1.284–2.930)	0.002	NA	
ASCT during pre-novel agent era *vs* during novel agent era	1.310 (1.044–1.643)	0.020	1.366 (1.060–1.761)	0.017

The overall survival was calculated from the time of ASCT. The patients who were included in this analysis underwent an ASCT during pre-novel (October 1995–December 2006) and novel agent (January 2008–December 2011) eras. ASCT, autologous stem cell transplantation; CR, complete response; ISS, International Staging System; NA, not applicable; nCR, near complete response; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VGPR, very good partial response or better.

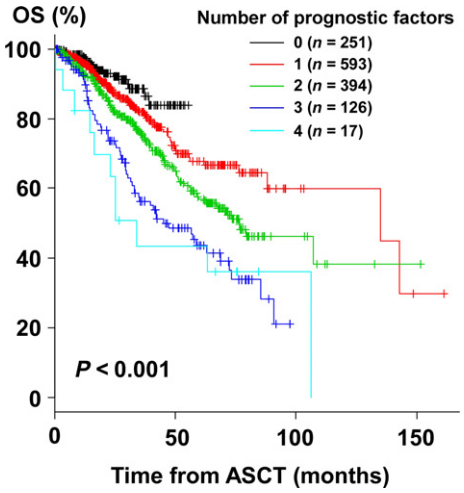

Fig. 4. Overall survival (OS) from the time of autologous stem cell transplantation (ASCT) according to the number of prognostic factors; male gender, performance status (PS) of 2, 3 or 4, the International Staging System (ISS) II or III, a pre-autologous stem cell transplantation (ASCT) response less than the partial response (PR), and ASCT during the pre-novel agent era. Only one patient displayed all five prognostic factors and his OS was not shown. The patients who were included in this analysis underwent an ASCT during pre-novel (October 1995–December 2006) and novel agent (January 2008–December 2011) eras.

ASCT, female gender ($P = 0.002$), PS of 0 or 1 ($P = 0.044$) at ASCT and ISS II ($P = 0.046$) at diagnosis.

Discussion

Novel agents have markedly changed therapies for MM. Thalidomide, lenalidomide and bortezomib were approved in the USA in 2006, 2006 and 2003, respectively, and were approved in many European Union member nations in 2008, 2007 and 2004, respectively. According to clinical studies performed in Europe and the USA in which novel agents had been introduced earlier than in Asian countries, significant improvements in responses and survival were observed in patients with MM who had been treated with novel agents.[4–6] However, few reports have described the outcomes of patients with MM who have been treated with novel agents in Asian countries. Our first aim was to provide the initial analysis of prognostic factors in a large cohort of newly diagnosed Japanese patients with MM who underwent single upfront ASCT during the novel agent era. OS significantly improved during the novel agent era and significant improvements in the 2-year OS were confirmed in patients with MM who were younger (≤65 years at ASCT; 82% *vs* 87%; $P = 0.024$), female (80% *vs* 90%; $P = 0.002$) and with a good PS (0 or 1 at ASCT; 83% *vs* 88%; $P = 0.044$; Fig. 5). These findings are consistent with those of previous reports.[6] Kastritis *et al.* demonstrate that the median OS in patients who began treatment after the introduction of novel agents increased by 12 months (48 *vs* 36 months; $P < 0.001$). This improvement was more pronounced in younger (≤70 years; 39 *vs* 74 months; $P < 0.001$) and female (36 *vs* 59 months; $P = 0.001$) patients but was less evident in older (>70 years; 26 *vs* 33 months; $P = 0.27$) and male patients (37.5 *vs* 40.5 months; $P = 0.062$).[6] Kumar *et al.*[4] report that in a larger cohort of 2981 newly diagnosed patients with myeloma, those who had been diagnosed in the previous decade experienced a 50% improvement in the OS (44.8 *vs* 29.9 months; $P < 0.001$). Furthermore, Costa *et al.*[7] also demonstrate by multivariate analysis using Center for International Blood and Marrow Transplant Research (CIBMTR) data that ASCT in the 2000–2004 cohort ($n = 6408$; HR = 0.77) or in the 2005–2010 cohort ($n = 11\,644$; HR = 0.68) were associated with lower risk of death compared with the 1995–1999 ($n = 2226$) cohort. Although we do not know the reason for a superior OS in female MM patients, Kristinsson *et al.*[8] and Kumar *et al.*[4] also show enhanced survival in female patients with MM using a total of 14 381 and 2981 patients, respectively. Landgren *et al.*[9] report that estrogen medication has been found to reduce the risk of developing MM among females, potentially due to the blocking effects on interleukin-6-mediated MM cell growth.[10]

Our second aim was to validate the ISS in Japanese patients with MM during the pre-novel and novel agent eras. Although our results demonstrate that the ISS could be used to stratify the OS of patients who underwent ASCT during the pre-novel agent era, we could not clearly stratify the prognosis of Japanese patients with MM in the ISS I and II groups who underwent upfront single ASCT during the novel agent era. In the pre-novel agent era, Nagura *et al.*[11] report that the ISS could stratify Japanese patients with MM who were treated with chemotherapy and ASCT. Kim *et al.*[12] also report that the ISS could predict the prognosis of Korean patients with MM who underwent ASCT as a first-line therapy during the pre-novel agent era. Furthermore, Kastritis *et al.*[6] report that the ISS was applicable in patients during the novel agent era. In contrast, Hari *et al.*[13] demonstrate using the CIBMTR data that the ISS III stage ($n = 449$) was associated with a higher risk

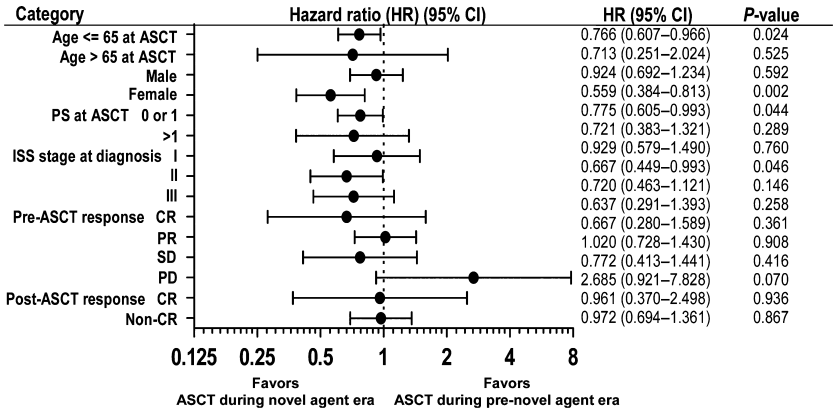

Fig. 5. Impact of autologous stem cell transplantation (ASCT) during the novel agent era on the overall survival (OS) from the time of ASCT in each stratified category. Effects of ASCT during the novel agent era are shown as forest plots. Circles on lines indicate hazard ratios compared with "ASCT during the pre-novel agent era," and horizontal lines represent the corresponding 95% confidence interval (CI). Pre-ASCT responses were analyzed using the data of pre-novel (January 2004–December 2006) and novel agent eras (January 2008–December 2011) based on the same response criteria. ISS, International Staging System; PS, performance status.

of mortality compared with the ISS II stage ($n = 230$; $P = 0.007$) but not the ISS II stage compared with the ISS I stage ($n = 50$; relative risk = 1.10, $P = 0.482$) in patients who received upfront ASCT for MM in the pre-novel agent era. Tan *et al.*[14] recently compared the OS of 221 patients with MM in Singapore who had been diagnosed from 2006 to 2009 (era 2), when an upfront bortezomib combination was approved for high-risk MM, with the OS of 262 patients who had been diagnosed from 2000 to 2005 (era 1), when bortezomib could only be administered upon relapse. The median OS was 4.2 years and was not reached in eras 1 and 2 ($P = 0.03$). The ISS retained its prognostic significance in era 1 ($P < 0.001$) but not in era 2 ($P = 0.07$), a finding that was consistent with our results. Iriuchishima *et al.*[15] also report the lack of a significant difference between the ISS stages among Japanese patients with MM in the novel agent era. The patients in the previous reports who received initial treatment other than single ASCT following high-dose melphalan (200 mg/m^2; Mel 200), such as tandem ASCT, melphalan <200 mg/m^2 or conventional chemotherapy, were included; therefore, it is of particular concern that this analysis was based on highly selected patients who underwent single ASCT following Mel 200. In the near future, novel prognosis models that include chromosomal and genetic data will be used to accurately predict the OS of patients with MM in place of the ISS.

Given the lack of available pre-ASCT induction regimen information in our database, we could not extract the data for patients with MM who actually received novel agents during the novel agent era for our analysis. The Kansai Myeloma Forum, a Japanese MM study group, reported that 95 cases received high-dose melphalan therapy with stem cell support from 2006 to 2013 and 83 of the 95 (87%) cases received at least one of the novel agents during their clinical courses.[16] According to that report, in clinical practice, from 2006, approximately 90% of all transplant-eligible Japanese patients with MM received therapy with the novel agents. Therefore, it is reasonable to assume that many of the patients who underwent ASCT between 2008 and 2011 were treated with novel agents. Bortezomib, thalidomide and lenalidomide were administered for refractory/relapse MM cases between December 2006 and September 2011; therefore, improvement in the OS of Japanese patients with MM during the novel agent era is probably due to the salvage therapy for insufficient response to pre-ASCT induction or relapse cases.

The findings in this article should be confirmed in prospective studies.

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Disclosure Statement

The authors declare no conflicts of interest except that Drs Hiroyuki Takamatsu and Kazutaka Sunami have received honoraria fees from Celgene Corporation.

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