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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/m²; 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, 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 (%)  |                                                            |                                                             |         |
| nCR                       | 18 (15.4)                                                   | 45 (8.4)                                                     | 123 (12.3) |         |
| PR                        | 64 (54.7)                                                   | 119 (22.2)                                                   | 340 (34.1) |         |
| SD                        | 285 (53.1)                                                  | 28 (2.8)                                                     | 434 (43.6) |         |
| PD                        | 16 (3.0)                                                    | 10 (1.9)                                                     | 8 (0.8)   |         |
| NA                        | 164 (32.1)                                                  | 463 (46.9)                                                   |         | <0.001 |
| CR + VGPR                 | NA                                                          | 525 (53.1)                                                   |         | <0.001 |
| Non-CR + Non-VGPR         | 363 (68.9)                                                  | 508 (73.6)                                                   |         | <0.001 |
| Post-ASCT response, n (%) |                                                            |                                                             |         |
| CR                        | 45 (15.9)                                                   | 182 (26.4)                                                   |         | <0.001 |
| Non-CR                    | 238 (84.1)                                                  | 508 (73.6)                                                   |         | <0.001 |
| 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.

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responses to therapy were assessed as follows: near CR (MR) plus no change (NC). In contrast, when ASCT was performed to PR criteria, and SD was defined as minor response 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). Because the response of patients of new lesions, together with ≤5% plasma cells in the bone marrow on the recovery of peripheral white 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. 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

**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) | 0.014 |
| Male                        | 83.9 (81.0–86.3) |      |
| 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|
| VGR                         | 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; VGR, 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 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.

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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; VGR, 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).
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) 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) 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...
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, 6.5, 6.4 and 3.7 years, respectively (Fig. 3a). 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...

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**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 vs during novel | 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.
original article
recent prognostic factors in multiple myeloma

ASCT andISS II (on behalf of Japanese Cancer Association. 2014 The Authors. Cancer Science published by Wiley Publishing Asia Pty Ltd © in responses and survival were observed in patients with MM who underwent ASCT in Europe and the USA in which novel agents had been intro-
duced in 1995–1999, 2000–2004, and 2005–2010, 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. 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. 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). Kumar et al. 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. 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 cohort (n = 2226). Although we do not know the reason for a superior OS in females compared with males, this suggests 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.

Our second aim was to validate the ISS in Japanese patients with MM. 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. report that the ISS could stratify Japanese patients with MM who were treated with chemotherapy and ASCT. Kim et al. 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. report that the ISS was applicable in patients during the novel agent era. In contrast, Hari et al. demonstrate using the CIBMTR data that the ISS III stage (n = 449) was associated with a higher risk

**Discussion**

Novel agents have markedly changed therapies for MM. Thalidomide, lenalidomide and bortezomib were approved in the USA in 2006, 2003, 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. 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. 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). Kumar et al. 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. 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 cohort (n = 2226). Although we do not know the reason for a superior OS in females compared with males, this suggests 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.

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. report that the ISS could stratify Japanese patients with MM who were treated with chemotherapy and ASCT. Kim et al. 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. report that the ISS was applicable in patients during the novel agent era. In contrast, Hari et al. demonstrate using the CIBMTR data that the ISS III stage (n = 449) was associated with a higher risk

**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 0 for all 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.

**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.

**Table 1.** Prognostic factors and their impact on overall survival (OS) in patients with myeloma.

| Category                          | Hazard ratio (HR) (95% CI) | P-value |
|-----------------------------------|---------------------------|---------|
| Age <= 65 at ASCT                 | 0.768 (0.601–0.966)       | 0.024   |
| Age > 65 at ASCT                  | 0.713 (0.521–0.984)       | 0.025   |
| Male                              | 0.924 (0.692–1.234)       | 0.592   |
| Female                            | 0.591 (0.384–0.893)       | 0.002   |
| PS at ASCT ≥ 3                    | 0.735 (0.560–0.998)       | 0.044   |
| ISS stage at diagnosis            |                           |         |
| I                                | 0.721 (0.383–1.321)       | 0.289   |
| II                               | 0.927 (0.547–1.450)       | 0.756   |
| III                              | 0.677 (0.449–0.993)       | 0.058   |
| Pre-ASCT response CR             | 0.720 (0.453–1.212)       | 0.146   |
| PR                               | 0.852 (0.519–1.293)       | 0.258   |
| SD                               | 1.020 (0.728–1.430)       | 0.908   |
| PD                               | 0.772 (0.413–1.441)       | 0.416   |
| Post-ASCT response CR            | 0.961 (0.370–2.498)       | 0.938   |
| Non-CR                           | 0.972 (0.694–1.361)       | 0.867   |
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 \((n = 50; \text{relative risk } = 1.10, P = 0.482)\) in patients who received upfront ASCT for MM in the pre-novel agent era. \(^{14}\) 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 \((200 \text{ mg/m}^2; \text{Mel } 200)\), such as tandem ASCT, melphalan \(<200 \text{ mg/m}^2\) 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 based on highly selected patients who underwent single ASCT induction or relapse cases. The findings in this article should be confirmed in prospective studies.

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Disclosure Statement

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