Propensity-score matched analysis of the efficacy of maintenance/continuous therapy in newly diagnosed patients with multiple myeloma: a multicenter retrospective collaborative study of the Japanese Society of Myeloma

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Abstract

Background  Maintenance ± consolidation or continuous therapy is considered a standard of care for both transplant–eligible and –ineligible patients with multiple myeloma (MM). However, long-term benefits of such therapy have not yet been clarified in the context of clinical practice.

Purpose  To clarify the efficacy of maintenance/continuous approach, we retrospectively analyzed the cohort data of newly diagnosed MM patients by propensity-score matching based on age, gender, revised International Staging System (R-ISS) stage, and implementation of transplantation to reduce the bias due to confounding variables.

Findings  Among 720 patients, 161 were identified for each of the maintenance and no maintenance groups. Maintenance/continuous therapy employed immunomodulatory drugs (n = 83), proteasome inhibitors (n = 48), combination of both (n = 29), or dexamethasone alone (n = 1). Progression-free survival (PFS) was significantly prolonged in the maintenance group compared with the no maintenance group (median 37.7 and 21.9 months, p = 0.0002, respectively). Prolongation of PFS was observed in both transplanted and non-transplanted patients (p = 0.017 and p = 0.0008, respectively), with standard risk (p < 0.00001), R-ISS stage I (p = 0.037) and stage II (p = 0.00094), and those without obtaining complete response (p = 0.0018). There was no significant benefit in overall survival (OS), but it tended to be better in the maintenance group in non-transplanted patients. Regarding the treatment pattern, the substitution or addition of drugs different from the induction therapy and the combination with immunomodulatory drugs and proteasome inhibitors appeared to be more beneficial for PFS but not OS.

Conclusion  These results support the benefit of current maintenance/continuous approach in routine clinical practice in the management of MM.

Keywords  Multiple myeloma · Revised international staging system · Maintenance therapy · Continuous therapy · Autologous stem cell transplantation

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm characterized by the presence of monoclonal immunoglobulin (Ig) in serum and/or urine, clonal bone marrow plasmacytosis, and clinical symptoms related to hypercalcemia, renal insufficiency, anemia, and bone lesion (CRAB features), as well as other myeloma-defining events (International Myeloma Working Group 2003; Rajkumar et al. 2014). MM is a heterogeneous disease, and the survival outcome varies considerably depending on the presence of patient-related, disease-related, and treatment-related risk factors (Rajkumar 2020).

Recently, significant advances have been made in the treatment of MM. In particular, treatments incorporating novel agents and autologous stem cell transplantation (ASCT) have significantly improved survival of MM patients (Kumar et al. 2008, 2014; Ozaki et al. 2015). Besides, as a treatment option, maintenance with or without...
consolidation, or continuous therapy after induction therapy has been evaluated in both transplant–eligible and –ineligible MM patients in clinical trials and routine practice. Consolidation therapy is defined as a distinct course of limited number of cycles of combination therapy aimed at increasing the depth of response, and maintenance therapy is then applied for a prolonged period for at least 1–2 years or even until progression usually with a lower dose than that used during either induction or consolidation (Mohty et al. 2015). This treatment strategy has been developed to improve and sustain disease response, ultimately bringing a functional cure by long-term continuous treatment, and has now been recognized as a new paradigm in the management of MM (Dimopoulos et al. 2020a).

Randomized controlled studies of maintenance therapy after ASCT have demonstrated the efficacy and feasibility of immunomodulatory drugs (IMiDs) such as lenalidomide and thalidomide as well as proteasome inhibitors (PIs) comprising bortezomib and ixazomib (Attal et al. 2012; Dimopoulos et al. 2019; Goldschmidt et al. 2018; Jackson et al. 2019; McCarthy et al. 2012; Morgan et al. 2012; Palumbo et al. 2014b; Sonneveld et al. 2012). Most studies have confirmed the benefits of maintenance therapy in progression-free survival (PFS) but not in overall survival (OS), while meta-analyses did show the benefits also in OS (McCarthy et al. 2017; Morgan et al. 2012). The clinical benefits of lenalidomide or bortezomib as post-ASCT maintenance therapy have been investigated in routine clinical practice as well (Huang et al. 2018; Jagannath et al. 2018). In transplant–ineligible patients, randomized studies have shown the benefits of continuous therapy using lenalidomide, thalidomide, and/or bortezomib, or ixazomib in PFS (Dimopoulos et al. 2020b; Palumbo et al. 2014a, 2010, 2012). Meta-analysis of these studies involving non-transplanted patients has demonstrated the significant prolongation of PFS, PFS2, and OS (Dimopoulos et al. 2020a).

Randomized controlled studies of maintenance therapy after ASCT have been conducted with high-dose melphalan conditioning followed by peripheral blood stem cell transplantation according to the institutional protocol, and was performed only as initial treatment after induction therapy in eligible patients. Treatment response during the initial treatment was assessed according to the uniform response criteria reported by the IMWG (Durie et al. 2006). Change of treatment modality such as consolidation + maintenance or continuation of induction therapy in transplant–ineligible patients, and maintenance ± consolidation therapy after ASCT in transplant–eligible patients was also at the discretion of the attending physician. The

Patients and methods

Patients

The JSM retrospectively collected clinical data from 720 patients who were newly diagnosed and treated at 32 affiliated hospitals between January 2013 and December 2016 and had with at least stable disease response to initial treatment. Baseline demographics, clinical and laboratory data including fluorescence in situ hybridization (FISH) analysis, and details regarding induction, consolidation, maintenance, and continuous therapy, and the therapeutic response during the initial treatment were assessed. This study was conducted in accordance with the institutional guidelines with approval of the Ethics Committee/Institutional Review Board of Gunma University.

Diagnosis and stage

The diagnosis of MM was made according to the International Myeloma Working Group (IMWG) criteria (IMWG 2003) and the clinical stage of MM was determined based on the revised International Staging System (R-ISS) as previously published (Palumbo et al. 2015a). For risk stratification, t(4;14), t(14;16) and/or del(17p) were considered as high risk. Patients with asymptomatic (smoldering) MM and primary amyloidosis were excluded.

Treatment

Treatment decision for induction regimens and implementation of ASCT was made at the discretion of the physician-in-charge according to the treatment policy of each facility. ASCT was conducted with high-dose melphalan conditioning followed by peripheral blood stem cell transplantation according to the institutional protocol, and was performed only as initial treatment after induction therapy in eligible patients. Treatment response during the initial treatment was assessed according to the uniform response criteria reported by the IMWG (Durie et al. 2006).
unplanned substitution or addition of drugs should be considered a new line of therapy (Rajkumar et al. 2015); however, when these therapies continued as a part of the initial treatment different from salvage therapy at the discretion of the attending physician, we considered these as consolidation ± maintenance or continuous therapy. In this study, it was defined as maintenance therapy when the number of drugs was reduced after induction therapy, continuous therapy when the same drug as the induction therapy was used, and consolidation + maintenance therapy when additional drugs different from the induction therapy were used.

Propensity-score matched analysis

We implemented 1:1 matching for the maintenance group and no maintenance group to evaluate solely the efficacy of maintenance/continuous therapy in the study cohort. Patients were stratified according to clinical and laboratory parameters such as age, gender, R-ISS stage, and implementation of ASCT to reduce the bias due to patient-related and confounding factors between the groups. Two groups of patients were matched on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation by the nearest neighbor-matching method using the program in EZR version 1.42 (Saitama Medical Center, and Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

Statistical analysis

Fisher’s exact test was used to compare differences between categorical variables, whereas, the Mann–Whitney U test was used for continuous or nominal values. PFS and OS were calculated from the date of initial treatment. Kaplan–Meier method was used to create the PFS and OS curves, and differences between the curves were analyzed by the log-rank test. Cox model was used to estimate the hazard ratio with 95% confidence intervals (CI) in univariate and multivariate analysis on survival outcomes. Statistical analyses were performed using the program in EZR.

Results

Patient characteristics

Among 720 patients who achieved at least stable disease after induction therapy with or without subsequent ASCT, 161 patients of the maintenance group and another 161 patients of the no maintenance group were identified by propensity-score matching and studied. The follow-up periods from the time of diagnosis of these patients ranged from 0.2 to 78.4 months (median 31.7 months).

Baseline characteristics of each patient group at diagnosis are summarized in Table 1. The median age was 65-years old (33–89). There were 166 males and 156 females. Patient baseline features, including age, gender, performance status (PS), M protein isotype, and the percentages of patients with abnormal laboratory parameters such as hemoglobin, calcium, creatinine, albumin, β2-microglobulin, lactate dehydrogenase (LDH), high risk by FISH, and adverse karyotype were not significantly different between the patient groups. However, with regard to PS, PS 0 tended to be low and PS 3 high in the no maintenance group. The R-ISS stages I, II, and III were distributed in 65 patients (20.2%), 223 (69.2%), and 34 (10.6%), respectively, without significant difference between the groups.

Treatment

As for induction therapy, most patients were treated with bortezomib-based therapy including bortezomib + cyclophosphamide + dexamethasone (DEX) (n = 111, 34.4%), bortezomib + DEX (n = 85, 26.4%), bortezomib + melphalan + prednisolone (n = 53, 16.5%), and bortezomib + doxorubicin + DEX (n = 8, 2.5%), and also with a combination with lenalidomide such as bortezomib + lenalidomide + DEX (n = 29, 9.0%). In contrast, induction with lenalidomide-based therapy was less used and included lenalidomide + DEX (n = 16, 5.0%) and a combination with bortezomib (n = 29, 9.0%). Other regimens included melphalan + prednisolone, high-dose DEX, and vincristine + doxorubicin + DEX (Table 2). Between the maintenance and no maintenance groups, the percentages of induction regimen containing bortezomib + lenalidomide + DEX, other bortezomib-based regimens, and lenalidomide + DEX were 12.4% vs 5.6% (p = 0.05), 81.4% vs 78.3% (p = 0.58), and 2.5% vs 7.5% (p = 0.07), respectively.

As for the best response obtained during the initial treatment, 116 patients (36.0%) achieved complete response (CR) or better, and 206 patients (64.0%) achieved very good partial response (VGPR) or below. The response rate of CR or better was higher in the maintenance group (40.4% vs 31.7%), but there was no significant difference between the groups (p = 0.13). ASCT was performed in 87 patients in each group (54.0%).

Maintenance/continuous therapy

After initial treatment, the indication for maintenance ± consolidation or continuous therapy was decided by the attending physician. In transplanted patients, maintenance ± consolidation therapy was started approximately 3 months after ASCT. In non-transplanted patients,
| Characteristics                        | Maintenance (n = 161) | No maintenance (n = 161) | Total (n = 322) | p value |
|----------------------------------------|-----------------------|--------------------------|----------------|---------|
| Median age (range)                     | 65 (35–89) yr         | 65 (33–88) yr            | 65 (33–89) yr | 0.88    |
| Gender (M/F)                           | 84/77                 | 82/79                    | 166/156        | 0.91    |
| Performance status                     |                       |                          |                | 0.06    |
| 0                                      | 66 (46.5%)            | 46 (31.1%)               | 112 (38.6%)    |         |
| 1                                      | 44 (31.0%)            | 60 (40.4%)               | 104 (35.9%)    |         |
| 2                                      | 18 (12.7%)            | 18 (12.2%)               | 36 (12.4%)     |         |
| 3                                      | 9 (6.3%)              | 18 (12.2%)               | 27 (9.3%)      |         |
| 4                                      | 5 (3.5%)              | 6 (4.1%)                 | 11 (3.8%)      |         |
| M protein                              |                       |                          |                | 0.16    |
| IgG                                    | 97 (60.2%)            | 89 (55.3%)               | 186 (57.7%)    |         |
| IgA                                    | 22 (13.7%)            | 33 (20.5%)               | 55 (17.1%)     |         |
| IgD                                    | 1 (0.6%)              | 5 (3.1%)                 | 6 (1.9%)       |         |
| BJP                                    | 36 (22.4%)            | 32 (19.9%)               | 68 (21.1%)     |         |
| Others                                 | 5 (3.1%)              | 2 (1.2%)                 | 7 (2.2%)       |         |
| Hemoglobin                             |                       |                          |                | 1.0     |
| ≥ 10 g/dl                              | 86 (53.4%)            | 85 (52.8%)               | 171 (53.1%)    |         |
| < 10 g/dl                              | 75 (46.6%)            | 76 (47.2%)               | 151 (46.9%)    |         |
| Calcium                                |                       |                          |                | 1.0     |
| > 11 mg/dl                             | 12 (7.5%)             | 11 (6.8%)                | 23 (7.1%)      |         |
| ≤ 11 mg/dl                             | 149 (92.5%)           | 150 (93.2%)              | 299 (92.9%)    |         |
| Creatinine                             |                       |                          |                | 0.51    |
| > 2 mg/dl                              | 18 (11.2%)            | 23 (14.3%)               | 41 (12.7%)     |         |
| ≤ 2 mg/dl                              | 143 (88.8%)           | 138 (85.7%)              | 281 (87.3%)    |         |
| Albumin                                |                       |                          |                | 0.26    |
| ≥ 3.5 g/dl                             | 85 (52.8%)            | 96 (59.6%)               | 181 (56.2%)    |         |
| < 3.5 g/dl                             | 76 (47.2%)            | 65 (40.4%)               | 141 (47.8%)    |         |
| β2-microglobulin                       |                       |                          |                | 0.66    |
| < 3.5 mg/l                             | 72 (44.7%)            | 65 (40.4%)               | 137 (42.6%)    |         |
| 3.5–5.5 mg/l                           | 41 (25.5%)            | 48 (29.8%)               | 89 (27.6%)     |         |
| > 5.5 mg/l                             | 48 (29.8%)            | 48 (29.8%)               | 96 (29.8%)     |         |
| LDH                                    |                       |                          |                | 0.58    |
| Normal                                 | 126 (78.3%)           | 131 (81.4%)              | 257 (79.8%)    |         |
| Abnormal                               | 35 (21.7%)            | 30 (18.6%)               | 65 (20.2%)     |         |
| FISH                                   |                       |                          |                | 0.75    |
| Standard risk                          | 104 (77.6%)           | 88 (80.0%)               | 192 (78.7%)    |         |
| High risk                              | 30 (22.4%)            | 22 (20.0%)               | 52 (21.3%)     |         |
| Karyotype                              |                       |                          |                | 0.28    |
| Normal                                 | 113 (73.9%)           | 121 (79.6%)              | 234 (76.7%)    |         |
| Abnormal                               | 40 (26.1%)            | 31 (20.4%)               | 71 (23.3%)     |         |
| R-ISS stage                            |                       |                          |                | 0.91    |
| I                                      | 31 (19.3%)            | 34 (21.1%)               | 65 (20.2%)     |         |
| II                                     | 113 (70.2%)           | 110 (68.3%)              | 223 (69.2%)    |         |
| III                                    | 17 (10.6%)            | 17 (10.6%)               | 34 (10.6%)     |         |
| Response at front therapy              |                       |                          |                | 0.13    |
| ≥ CR                                   | 65 (40.4%)            | 51 (31.7%)               | 116 (36.0%)    |         |
| ≤ VGPR                                 | 96 (59.6%)            | 110 (68.3%)              | 206 (64.0%)    |         |
| ASCT                                   |                       |                          |                | 1.0     |
| Yes                                    | 87 (54.0%)            | 87 (54.0%)               | 174 (54.0%)    |         |
| No                                     | 74 (46.0%)            | 74 (46.0%)               | 148 (46.0%)    |         |

LDH lactate dehydrogenase, FISH fluorescence in situ hybridization, R-ISS revised International Staging System, CR complete response, VGPR very good partial response, ASCT autologous stem cell transplantation
maintenance ± consolidation or continuous therapy was started after initial treatment. The duration of initial treatment in the maintenance and no maintenance group was 12.2 ± 9.3 and 9.0 ± 7.2 months (mean ± standard deviation, p = 0.089), respectively.

Maintenance ± consolidation and continuous regimens were heterogeneous and included IMiDs-based [lenalidomide + DEX (n = 38), lenalidomide alone (n = 34), elotuzumab + lenalidomide + DEX (n = 6), and thalidomide alone (n = 5)]; PI-based [bortezomib + DEX (n = 18), bortezomib alone (n = 17), panobinostat + bortezomib + DEX (n = 1), ixazomib alone (n = 9), carfilzomib + DEX (n = 2), and bortezomib + melphalan + prednisolone (n = 1)]; combination of IMiDs and PI-based [bortezomib + lenalidomide + DEX (n = 10), bortezomib + thalidomide + DEX (n = 6), carfilzomib + lenalidomide + DEX (n = 6), ixazomib + lenalidomide + DEX (n = 6), and bortezomib + thalidomide (n = 1)]; and DEX alone (n = 1).

In transplanted patients, bortezomib or lenalidomide with or without DEX were classified as maintenance therapy (n = 61), and 3-drug regimens by adding drugs different from the induction such as elotuzumab + lenalidomide + DEX and carfilzomib + lenalidomide + DEX were as consolidation + maintenance therapy (n = 26). In non-transplanted patients, bortezomib therapy from bortezomib + DEX or bortezomib + cyclophosphamide + DEX induction, and lenalidomide therapy from lenalidomide + DEX induction were classified as continuous therapy (n = 38), and class switch of drugs such as lenalidomide therapy from bortezomib + melphalan + prednisolone induction were as consolidation + maintenance therapy (n = 36). The median duration from the start of maintenance/continuous therapy to the disease progression was 16.8 months for the maintenance or continuous group and 15.2 months for the consolidation + maintenance group, and 17.2 months for transplanted patients and 14.7 months for non-transplanted patients, respectively.

### Progression-free survival according to maintenance therapy

We first compared PFS between groups who received maintenance ± consolidation or continuous therapy (maintenance group) and those who did not (no maintenance group). PFS was significantly prolonged in the maintenance group compared with the no maintenance group (median 37.7 and 21.9 months, respectively, p = 0.0002, Fig. 1a). In terms of risk stratification by cytogenetic abnormalities by FISH, the median PFS was 39.7 and 21.1 months in standard-risk patients (p < 0.0001, Fig. 1b), and was 25.7 and 18.8 months in high-risk patients (p = 0.42, Fig. 1c), respectively. According to the R-ISS stage, significant difference in PFS was observed in patients with stage I (p = 0.037, Fig. 1d) and II (p = 0.00094, Fig. 1e) by maintenance, but not in patients with stage III disease (p = 0.37, Fig. 1f). As for the response status during the initial treatment before maintenance/continuous therapy, PFS was longer in patients who achieved CR or better than that in those who did not achieve CR, but significant difference in PFS by maintenance was observed only in ≤ VGPR patients (p = 0.0018, Fig. 1h) but not in ≥ CR patients (p = 0.27, Fig. 1g). As for ASCT, prolongation of PFS was observed in both transplanted (p = 0.017, Fig. 1i) and non-transplanted patients (p = 0.0008, Fig. 1j).

In the classification of treatment pattern, the median PFS of the consolidation + maintenance group and the maintenance or continuous group was 39.0 and 34.8 months, respectively, and both of which were significantly longer than that of the no maintenance group (p = 0.001, Fig. 1k). There was no significant difference in PFS between the consolidation + maintenance group and the maintenance or continuous group (p = 0.78). As for ASCT, a significant difference in these treatments was observed in both transplanted (p = 0.036, Supplementary Fig. 1a) and non-transplanted patients (p = 0.0033, Supplementary Fig. 1b); however, in transplanted patients, the consolidation + maintenance group showed a significant prolongation in PFS (p = 0.024), whereas, the maintenance or continuous group did not (p = 0.092) compared with the no maintenance group. Again, there was no significant difference between the consolidation + maintenance group and the maintenance group in transplanted patients (p = 0.27), and the consolidation + maintenance group and the continuous group in non-transplanted patients (p = 0.62).

According to different maintenance of the PI-based, IMiDs-based, and combination of PI + IMiDs-based regimens, the median PFS were 23.4, 37.7, and 48.3 months,
Fig. 1 Efficacy of maintenance therapy on PFS in each setting. PFS in total patients a; patients with standard risk b or high risk c by FISH; patients with R-ISS stage I d, stage II e, and stage III f; patients who achieved ≥ complete response g or ≤ very good partial response h after induction therapy; patients treated with upfront ASCT i or without ASCT j. PFS according to the treatment pattern k and maintenance regimen l. Maint maintenance/continuous therapy, Consoli consolidation, Conti continuous, PI proteasome inhibitors, IMiDs immunomodulatory drugs, M months, NR not reached.
respectively, and was longer in the combination with PI + IMiDs-based than PI or IMiDs alone groups in the whole maintenance cohort \((p = 0.021, \text{Fig. 1f})\). In terms of cytogenetic risk groups by FISH, the median PFS were 22.9 months, 39.0 months, and not reached in standard-risk patients \((p = 0.16, \text{Supplementary Fig. 1c})\), and 15.0, 18.4, and 48.3 months in high-risk patients \((p = 0.088, \text{Supplementary Fig. 1d})\) according to maintenance therapy with PI-based, IMiDs-based, or the combination of PI + IMiDs-based, respectively. In comparison of the PI- or IMiDs-based vs PI + IMiDs-based regimens, the median PFS was 39.0 months and not reached in standard-risk patients \((p = 0.094)\), and 18.4 and 48.3 months in high-risk patients \((p = 0.030)\), respectively. Thus, maintenance with combination of PI and IMID is likely to prolong PFS regardless of risk category by FISH. As for the effect of ASCT, the median PFS of transplanted patients were not reached, 38.7 months, and 48.3 months \((p = 0.69, \text{Supplementary Fig. 1e})\) and those of non-transplanted patients were 18.0 months, 35.4 months, and not reached \((p = 0.077, \text{Supplementary Fig. 1f})\) according to maintenance therapy with PI, IMiDs, or the combination of PI + IMiDs, respectively. In comparison of the PI- or IMiDs-based vs PI + IMiDs-based regimens, the median PFS was 39.7 and 48.3 months in transplanted patients \((p = 0.55)\) and 24.1 months and not reached in non-transplanted patients \((p = 0.063)\), respectively. Thus, maintenance therapy with combination of PI + IMiDs is likely to extend the PFS in non-transplanted patients although there was no statistically significant difference.

**Overall survival according to maintenance therapy**

The median OS was not reached in either group and there was no significant difference in OS by maintenance/continuous therapy \((p = 0.19, \text{Fig. 2a})\). In terms of cytogenetic risk by FISH, OS was not different between the maintenance vs no maintenance groups irrespective of risk status [standard risk \((p = 0.36, \text{Fig. 2b})\) and high risk \((p = 0.21, \text{Fig. 2c})\)]. Lack of OS difference between maintenance vs no maintenance was also noted in each of the R-ISS stages [stage I \((p = 0.14, \text{Fig. 2d})\); stage II \((p = 0.17, \text{Fig. 2e})\); and stage III \((p = 0.30, \text{Fig. 2f})\)]. As for the response status during the initial treatment before maintenance/continuous therapy, maintenance did not provide statistically significant benefit irrespective of response status \([ \geq CR \text{ patients} (p = 0.28, \text{Fig. 2g}) \text{ and } \leq VGPR \text{ patients} (p = 0.053, \text{Fig. 2h})\)] although there seemed to be an OS benefit from maintenance in \(\leq VGPR\) patients. As for ASCT, there was no significant difference in OS in transplanted \((p = 0.57, \text{Fig. 2i})\) and non-transplanted patients \((p = 0.13, \text{Fig. 2j})\), but OS appeared to be better with maintenance/continuous therapy in non-transplanted patients.

In the classification of treatment pattern, there was no significant difference in OS between the consolidation + maintenance group, the maintenance or continuous group, and the no maintenance group \((p = 0.27, \text{Fig. 2k})\). As for ASCT, no significant difference between these treatment groups was observed in transplanted \((p = 0.84, \text{Supplementary Fig. 2a})\) and non-transplanted patients \((p = 0.29, \text{Supplementary Fig. 2b})\).

According to the different maintenance regimens, OS was better in PI-based and combination of PI + IMiDs-based groups, but the difference in OS between three maintenance groups was not statistically significant \((p = 0.35, \text{Fig. 2l})\). We compared the differences in OS in terms of cytogenetic risk (Supplementary Fig. 2c and d) or implementation of ASCT (Supplementary Fig. 2e and f), but there was no significant difference between three maintenance groups.

**Univariate and multivariate analysis**

Next, the statistical significance of risk factors related to PFS and OS was evaluated by univariate and multivariate analysis. As shown in Table 3, \(\geq 65\text{-years old}, \text{R-ISS stage III, and non-CR response after initial therapy were significant poor prognostic factors for PFS, whereas, implementation of ASCT as well as maintenance/continuous therapy were significant favorable factors for PFS. In multivariate analysis, non-CR response after initial therapy, and implementation of ASCT as well as maintenance therapy were significant independent prognostic factors for OS (Table 4).}

**Discussion**

We retrospectively evaluated the efficacy of maintenance/continuous therapy by propensity-score matched analysis using the cohort data of the JSM studies. We have demonstrated that maintenance/continuous therapy significantly improved PFS but not OS in both transplant–eligible and –ineligible MM patients. Our results of PFS benefit by maintenance were consistent with those of previously reported as clinical trials (Attal et al. 2012; Dimopoulos et al. 2019, 2020b; Goldschmidt et al. 2018; Jackson et al. 2019; McCarthy et al. 2012; Morgan et al. 2012; Palumbo et al. 2010, 2012, 2014a, b; Sonneveld et al. 2012) and routine practice in transplant-eligible patients (Chakraborty et al. 2018;
Huang et al. 2018; Jagannath et al. 2018; Sivaraj et al. 2017), and further provide evidence of similar PFS benefit for transplant–ineligible patients as well in real world settings.

Regarding the OS, most of the clinical trials have failed to show the benefit of maintenance therapy on OS except for some limited studies (McCarthy et al. 2012; Morgan et al.
Fig. 2 Efficacy of maintenance therapy on OS in each setting. OS in total patients a; patients with standard risk b or high risk c by FISH; patients with R-ISS stage I d, stage II e, and stage III f; patients who achieved ≥ complete response g or ≤ very good partial response h after induction therapy; patients treated with upfront ASCT i or without ASCT j. OS according to the treatment pattern k and maintenance regimen l. Maintenance/continuous therapy, Consolidation. Continu maintenance/continuous therapy, IMiDs immunomodulatory drugs, M months, NR not reached

2012; Palumbo et al. 2014b), and thus, OS benefits of maintenance therapy have still been controversial (Dimopoulos et al. 2020a). In general, OS benefit is influenced by the efficacy of induction and salvage therapy, and accordingly, different results may have been due to differences in treatment regimens and durations, and in prognostic variables not properly assessed. Highly effective drugs with novel mechanisms such as daratumumab have emerged and are incorporated into clinical practice as salvage therapy (Dimopoulos et al. 2016; Palumbo et al. 2016), and more recently, as front-line therapy as well as continuous therapy, showing the excellent results in PFS and OS (Facon et al. 2019; Mateos et al. 2018, 2020). Thus, the present study should be interrupted as evidence before the era of daratumumab in both transplant–eligible and –ineligible patients in clinical practice.

In a subgroup analysis, the benefit of maintenance/continuous therapy was more significant in patients who did not achieve CR than those who had achieved CR or better after induction therapy. In addition, with regard to the cytogenetic abnormalities and R-ISS stage, the benefit of maintenance therapy in PFS was more notable in patients with cytogenetic standard risk or R-ISS stage I and II than those with cytogenetic high risk or R-ISS stage III. Thus, our results would indicate that there might be no additional effects of subsequent maintenance/continuous therapy in patients who had already achieved a deep response, and such therapy is most beneficial to patients with standard risk or R-ISS stage I and II. In fact, the benefit of maintenance therapy by lenalidomide or ixazomib was more apparent in PR patients than in CR patients of Myeloma XI and TOURMALINE-MM3 trials (Dimopoulos et al. 2019; Jackson et al. 2019). Moreover, OS benefit by lenalidomide maintenance post ASCT was less significant in patients with the ISS stage III by meta-analysis (McCarthy et al. 2017). Therefore, maintenance/continuous therapy appeared to exert benefit to patients with cytogenetic standard risk and R-ISS stages I and II, especially when deep response was not achieved by induction therapy.

With regard to the relationship between the depth of response and the treatment outcome, recent randomized clinical trials have shown almost the consistently superior PFS and OS in patients who achieved minimal residual disease (MRD) negativity, regardless of treatment regimens (four drugs or three drugs) (Mateos et al. 2020) and even with or without ASCT (Perrot et al. 2018). A large meta-analysis has confirmed the significance of MRD negativity as the most relevant surrogate marker not only for PFS but also for OS (Munshi et al. 2020). Taken together, these results suggest that the long-term outcome depends on the susceptibility of MM cells to any treatment. In this study, median PFS and OS were longer in ≥ CR patients than ≤ VGPR patients, but additional benefit of maintenance therapy was not observed in ≥ CR patients. Therefore, it would be necessary to develop more appropriate treatment strategy in patients with CR and MRD negativity to further control the disease status and eradicate the minimal residual disease if any.

In multivariate analysis, response of CR or better and implementation of upfront ASCT were independent favorable factors for both PFS (Table 3) and OS (Table 4), whereas maintenance therapy was an independent favorable factor for PFS alone and so was R-ISS stage for OS alone. These results indicate that maintenance therapy was useful in the short-term outcome such as prolongation of PFS but not for the long-term outcome such as OS that depends on the most crucial factors, including deep response as ≥ CR, implementation of ASCT, and R-ISS stage, leaving maintenance therapy less useful. More importantly, our results did not even show PFS benefits by maintenance therapy in patients with cytogenetic high risk or R-ISS stage III. Novel treatment strategies besides maintenance/continuous therapy are needed to further improve the outcome specifically in high-risk patients in clinical practice.

The righteousness of the concept of long-term/continuous treatment is now widely recognized; however, clinical issues regarding treatment factors such as optimal regimen and treatment duration, tumor factors including cytogenetic abnormality and drug sensitivity, and safety remain to be elucidated. With regard to therapeutic regimens, IMiDs and PIs have been studied extensively from the perspective of convenience and feasibility. First, Myeloma IX trial compared the effect of thalidomide maintenance and no maintenance in transplant–eligible and –ineligible MM patients (Morgan et al. 2012). Importantly, patients with favorable FISH showed improved PFS, whereas those with adverse FISH receiving thalidomide showed no significant PFS benefit but rather worse OS. These results raised the issue that thalidomide maintenance might select more aggressive clones at the time of relapse. Subsequently, lenalidomide-based maintenance showed the prolongation in PFS and OS in transplanted patients and was confirmed as the most effective regimen by a network meta-analysis (Gay et al. 2018), but there were problems such as less effectiveness in high-risk patients and the cumulative incidence rate of second primary malignancies (McCarthy et al. 2017). For risk-adapted approaches, several studies have reported that bortezomib maintenance was more beneficial than
lenalidomide in high-risk patients (Chakraborty et al. 2018; Sivaraj et al. 2017). Recent studies have shown the effectiveness of combination with IMiDs and PIs as maintenance/continuous therapy, for example, thalidomide + bortezomib, lenalidomide + bortezomib, or lenalidomide + carfilzomib (Durie et al. 2017, 2020; Gay et al. 2020; Palumbo et al. 2010, 2014a). More recently, a large cohort study of highly effective regimen such as bortezomib + lenalidomide + DEX induction and risk-adapted maintenance approach has shown the significant benefits of maintenance with PI + IMiDs in PFS and OS, especially in high-risk patients (Joseph et al. 2020). Our results have also suggested that the substitution or addition of drugs as consolidation + maintenance and the combination with PI + IMiDs were more beneficial than PI or IMiDs alone. Furthermore, ongoing trials have included daratumumab not only for induction therapy but also for maintenance, showing particularly encouraging results (Moreau et al. 2019; Voorhees et al. 2020). The efficacy and feasibility of these intensive approaches should be clarified in clinical practice.

The present study has several limitations because of its retrospective nature and the number of patients became limited due to the application of the propensity-score matched methods. The therapeutic regimens, timing, and duration of consolidation, maintenance, and continuous therapy varied because of the treatment optimization and policy of each facility. Therefore, survival outcomes were evaluated from the start of initial treatment, and the relationship between the duration and efficacy of maintenance itself could not be analyzed. The substitution or addition of drugs does not fit the definition of maintenance therapy (Mohty et al. 2015; Rajkumar et al. 2015); however, when these therapies continued as a part of the initial treatment different from salvage therapy, we considered these as continuous approach before progression and included in the analysis. When we classified as the consolidation + maintenance group and the maintenance or continuous group as well as categorized into three groups according to the treatment pattern, it became clear that the consolidation + maintenance group and the combination with PI and IMiDs appeared to be more beneficial for PFS. Although there was no significant difference in patient background between the maintenance group and the no maintenance group, the percentage of patients with PS 3 tended to be higher in the no maintenance group. Thus, we cannot exclude the possibility that the presence of more frail patients such as PS 3 may have been associated with poor prognosis of the no maintenance group. Also, induction therapy as front-line treatment was quite heterogeneous to be classified as bortezomib- and/or lenalidomide-based

| Variable | Univariate | Multivariate* |
|----------|------------|--------------|
|          | HR 95% CI  | p value      | HR 95% CI  | p value      |
| Age [≥ 65 years] | 1.542 1.128–2.109 | 0.0067 | 0.850 0.563–1.284 | 0.44 |
| Gender [male] | 1.028 0.756–1.399 | 0.86 | – | – |
| R-ISS [stage III] | 1.718 1.085–2.719 | 0.021 | 1.468 0.923–2.336 | 0.11 |
| Response [non-CR] | 2.376 1.650–3.421 | <0.0001 | 1.914 1.313–2.788 | 0.00073 |
| ASCT | 0.445 0.325–0.607 | <0.0001 | 0.428 0.282–0.648 | <0.0001 |
| Maintenance | 0.562 0.413–0.766 | 0.00026 | 0.529 0.386–0.725 | <0.0001 |

| Variable | Univariate | Multivariate* |
|----------|------------|--------------|
|          | HR 95% CI  | p value      | HR 95% CI  | p value      |
| Age [≥ 65 years] | 2.237 1.362–3.675 | 0.0015 | 1.223 0.647–2.313 | 0.53 |
| Gender [male] | 0.847 0.531–1.351 | 0.49 | – | – |
| R-ISS [stage III] | 2.774 1.541–4.994 | 0.00067 | 2.699 1.495–4.871 | 0.00098 |
| Response [non-CR] | 2.775 1.543–4.990 | 0.00065 | 2.120 1.160–3.876 | 0.015 |
| ASCT | 0.348 0.212–0.571 | <0.0001 | 0.475 0.250–0.903 | 0.023 |
| Maintenance | 0.731 0.458–1.165 | 0.19 | – | – |

R-ISS revised international staging system, Response response at front line therapy, ASCT autologous stem cell transplantation, Maintenance maintenance or continuous therapy

*Variables significance at p<0.1 in the univariate model were entered in the multivariate model
regimens, and the percentage of induction regimen containing bortezomib and lenalidomide was higher in the maintenance group than in no maintenance group. In this regard, the response rate of CR or better after initial therapy was higher in the maintenance group than in the no maintenance group, but there was no significant difference in the response rate of CR or better. In addition, no MRD data were available in this analysis and it is unclear whether maintenance therapy was effective in MRD-negative patients in clinical practice. Finally, we had not collected safety data of maintenance/continuous therapy. The balance between efficacy and feasibility should be evaluated to prevent over treatment during the maintenance/continuous therapy in the future.

In conclusion, our results have demonstrated that maintenance ± consolidation or continuous treatment were associated with a reduced risk of progression in both transplant–eligible and –ineligible patients, especially in patients with standard risk and/or suboptimal response to induction therapy. Although there were no statistically significant differences in OS by maintenance therapy, these approaches tended to improve OS in non-transplant patients and in those with suboptimal response. Regarding the maintenance regimens, the substitution or addition of drugs different from the induction therapy as consolidation + maintenance and the combination therapy of PI + IMiDs appeared to be more beneficial than PI or IMiDs alone. Therefore, the results of our study support the benefit of current maintenance/continuous approach in routine clinical practice in the management of MM.

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Author contributions All authors contributed to the study conception and design. SO, HM, and KS designed the research study. Data collection and analysis were performed by SO, HH, HK, TS, KS, TI, KS, TN, SI, YN, KS, and NN. The first draft of the manuscript was written by SO and KS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest HH received consultation fees from Janssen and Takeda; honoraria from Janssen, Takeda, Celegene, Bristol-Myers Squibb, Ono, and Sanofi; research funding from Celgene, Janssen, and Takeda; and sponsorship fund from Takeda, Kyowa Kirin, Chugai, and Daiichi-Sankyo. KS received honoraria from Celgene, Ono, Bristol-Myers Squibb, and Takeda; and research funding from Sanofi, AbbVie, Takeda, Bristol-Myers Squibb, Daiichi-Sankyo, Celegene, Alexion, Ono, Novartis, MSD, Astellas-Amgen, GSK, and Janssen. TI received honoraria from Sanofi, Takeda, Ono, Celegene, and Janssen. SI received honoraria from Sanofi, Daiichi-Sankyo, Takeda, Ono, Celegene, and Janssen; and research funding from AbbVie, Kyowa Kirin, Chugai, Sanofi, Bristol-Myers Squibb, Daiichi-Sankyo, Takeda, Ono, Celegene, and Janssen. YN received honoraria from Celegene, Chugai, Janssen, and Sanofi. KS received honoraria from Takeda, Janssen, Bristol-Myers Squibb, and Celegene. NN received honoraria from Janssen, Ono, Sanofi, and Bristol-Myers Squibb. HM received consultation fees from Sanofi; research funding from Bristol-Myers Squibb; and scholarship fund from Daiichi-Sankyo and Takeda. All other authors have no conflicts to disclose.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki and the institutional guidelines. Study protocol and amendments were reviewed by the Ethics Committee/Institutional Review Board of Gunma University and institutional review boards at each center.

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