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Abstract

Novel agents such as thalidomide, lenalidomide and bortezomib have dramatically changed the treatment paradigm of multiple myeloma (MM). However, it is not clear whether these agents improve the prognosis of elderly patients who have undergone autologous stem cell transplantation (auto-SCT). We retrospectively analyzed the outcome of 318 newly diagnosed patients aged 65-70 years who were treated between January 1, 2004, and December 31, 2009. As initial therapy, 192 patients were treated with conventional chemotherapy, 88 with novel agent-containing regimens, 21 with conventional chemotherapy plus auto-SCT and the remaining 17 with novel agents plus auto-SCT. The median progression-free survival was 19.1, 24.5, 26.8 and 35.2 months, respectively, and the 5-year overall survival (OS) was 40, 62, 63 and 87%, respectively. Initial therapy with novel agents ($p < 0.001$) or auto-SCT ($p < 0.02$) significantly improved OS compared with the group without these treatment modalities. Salvage therapy with novel agents also significantly improved survival after relapse compared with conventional chemotherapy alone ($p < 0.04$). In a multivariate analysis, the use of novel agents was an independent prognostic factor significantly associated with extended OS ($p < 0.003$). These results indicate that novel agents and auto-SCT had a major impact on OS in eligible patients in this subgroup of MM.

Key Words

- Autologous stem cell transplantation

- Bortezomib
- Immunomodulatory drugs
- Multiple myeloma

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm characterized by the production of monoclonal immunoglobulin (Ig) and various clinical features such as hypercalcemia, renal failure, anemia and osteolytic bone lesions, as well as immunodeficiency [1]. MM remains incurable; however, the response rate, progression-free survival (PFS) and overall survival (OS) have significantly improved due to the introduction of initial treatment incorporating novel agents such as thalidomide, lenalidomide and bortezomib, and autologous stem cell transplantation (auto-SCT) [2,3,4]. Based on the results from randomized phase III studies, the National Comprehensive Cancer Network guidelines recommended the use of thalidomide, lenalidomide and bortezomib in the treatment of both transplant-eligible and noneligible patients [5,6]. Thus, novel agents have become the standard of care for symptomatic MM as primary therapy and salvage therapy.

Auto-SCT is the standard front-line consolidation therapy, especially for younger patients less than 65 years of age. In elderly patients more than 65 years old, the efficacy and feasibility of an intermediate dose of melphalan (100-140 mg/m^2) as a conditioning regimen have been reported previously [7,8,9]. However, it is not clear whether the combined use of novel agents with auto-SCT translates into better outcome in elderly patients.

To clarify this issue, we retrospectively analyzed the clinical features and treatment outcome of unselected MM patients aged 65-70 years in the facilities of the Japanese Society of Myeloma and the European Myeloma Network.

Methods

Patients

Between January 1, 2004, and December 31, 2009, a total of 318 newly diagnosed MM patients aged 65-70 years were treated in 39 facilities of the Japanese Society of Myeloma and the European Myeloma Network. The diagnosis and clinical staging of MM were based on the Durie-Salmon staging system and the International Staging System (ISS) [10,11]. Baseline demographics, clinical and laboratory data at diagnosis and information concerning treatment and response were collected retrospectively during January 2012 and May 2012. This survey covered unselected patients treated at the participating facilities, including several patients who had been enrolled in clinical trials, but most patients had been treated in routine practice. This retrospective study was approved by the Ethics Committee/Institutional Review Board of Tokushima Prefectural Central Hospital.

Treatment

The primary objective was to assess the outcome of patients treated with different initial therapy. Treatment for each patient was determined by the corresponding physician. The short-term use of

dexamethasone for emergent disease control was not considered conventional chemotherapy. Novel agents included thalidomide, lenalidomide and bortezomib in combination with dexamethasone and/or chemotherapeutic agents. Auto-SCT was performed as up-front therapy after induction therapy by using a high or intermediate dose of melphalan followed by peripheral blood SCT according to the institutional protocol. The transplantation-related mortality was defined as death due to any cause other than disease progression or relapse within 100 days after transplantation. Clinical response was evaluated according to the international uniform response criteria for MM [12].

Statistical Analysis

PFS and OS curves were calculated using the Kaplan-Meier estimate, and differences between the curves were evaluated with the log-rank test. The Cox proportional hazards model was used to determine independent predictors associated with extended OS. Variables included baseline patient factors, prognostic factors and treatment-related factors.

Results

Patients

A total of 318 patients were studied. There were 167 males and 151 females. The median age was 67 years (range 65-70). The type of monoclonal Ig was IgG in 169 patients, IgA in 80, light chain in 56, IgD in 7 and others in 6. Performance status of 0, 1 and ≥2 were found in 88, 96 and 93 patients, respectively. Twenty-two patients were classified as Durie-Salmon stage I, 73 as stage II, 216 as stage III and 7 as unknown. With regard to the ISS, 86 patients were stage I, 107 stage II and 102 stage III. Unfortunately, data on cytogenetic abnormalities were not available for most patients.

As initial therapy, 192 patients were treated with conventional chemotherapy, as follows: melphalan + prednisone in 83, vincristine + adriamycin + dexamethasone in 56, high-dose dexamethasone in 25 and other regimens in 28, including ranimustine + vindesine + melphalan + prednisone, vincristine + melphalan + dexamethasone ± ranimustine, and methyl prednisone + vincristine + melphalan + prednisone. Another 88 patients were treated with novel agent-containing regimens composed of bortezomib + dexamethasone ± adriamycin in 33 patients, melphalan + prednisone + bortezomib in 29, melphalan + prednisone + lenalidomide in 17, and thalidomide + dexamethasone or melphalan + prednisone + thalidomide in 9. An additional 21 patients were treated with conventional chemotherapy (either vincristine + adriamycin + dexamethasone, melphalan + prednisone or high-dose dexamethasone) plus auto-SCT (13 single SCT and 8 tandem SCT), and the remaining 17 patients were treated with a novel agent-based regimen (bortezomib and dexamethasone) plus auto-SCT (14 single SCT and 3 tandem SCT). As the conditioning regimen before auto-SCT, 140 mg/m^2 melphalan was used in 2 patients in the novel agent group and 200 mg/m^2 melphalan was used in the remaining 36 patients. Baseline characteristics according to the initial therapy are summarized in table 1.

Table 1. Patient characteristics according to initial therapy

	Conventional chemotherapy		Novel agent		Chemotherapy + auto-SCT		Novel agent + auto-SCT	
Patients	192		88		21		17	
Males/females	102/90		47/41		9/12		9/8	
Mean age ± SD, years	67±1		67±1		66±1		67±1	
Type of M protein: IgG/IgA/IgD/BJP/other	104/47/5/31/5		45/24/2/16/1		10/4/0/7/0		10/5/0/2/0	
Performance status: 0/1/≥2[a]	46/65/76		29/16/9		6/10/3		7/5/5	
Durie-Salmon stage: I/II/III[b]	14/39/139		6/23/52		0/9/12		2/2/13	
ISS: I/II/III[c]	45/62/72		23/29/27		8/10/2		10/6/1	
Therapy	MP	83	BD/BAD	33	VAD + sHDM	9	BD + sHDM[e]	14
	VAD	56	MPB	29	VAD + tHDM	7	BD + tHDM	3
	HDD	25	MPL	17	MP + sHDM	2		
	other[d]	28	TD/MPT	9	MP + tHDM	1		
					HDD + sHDM	2		
Best response								
CR	4 (2%)		10 (11%)		5 (24%)		4 (24%)	
VGPR	15 (8%)		21 (24%)		10 (48%)		7 (41%)	
PR	85 (44%)		33 (38%)		5 (24%)		5 (29%)	
SD	73 (38%)		22 (25%)		1 (5%)		1 (6%)	
PD	15 (8%)		2 (2%)		0 (0%)		0 (0%)	

Values represent numbers of patients, except where indicated otherwise. MP = Melphalan + prednisolone; VAD = vincristine + adriamycin + dexamethasone; HDD = high-dose dexamethasone; BD = bortezomib + dexamethasone; BAD = bortezomib + adriamycin + dexamethasone; MPB = melphalan + prednisolone + bortezomib; MPL = melphalan + prednisolone + lenalidomide; TD = thalidomide + dexamethasone; MPT = melphalan + prednisolone + thalidomide; sHDM = single high-dose melphalan; tHDM = tandem high-dose melphalan; SD = stable disease; PD = progressive disease.

[a] Data not available for 41 patients.

[b] Data not available for 7 patients.

[c] Data not available for 23 patients.

[d] Other regimens were: ranimustine + vindesine + melphalan + prednisolone; vincristine + melphalan + dexamethasone ± ranimustine; methyl prednisolone + vincristine + melphalan + prednisolone.

[e] Two patients received 140 mg/m^2 melphalan and the other patients received 200 mg/m^2 melphalan.

Outcome according to Clinical Stage

We first assessed PFS and OS according to clinical stage. The median PFS for Durie-Salmon stage I, II and III was 40.5, 25.6 and 20.9 months, respectively, and a significant difference was found between stages I and III ($p < 0.02$; fig. 1a). The median OS was 55.2 months for stage III but was not reached in either stage I or II.

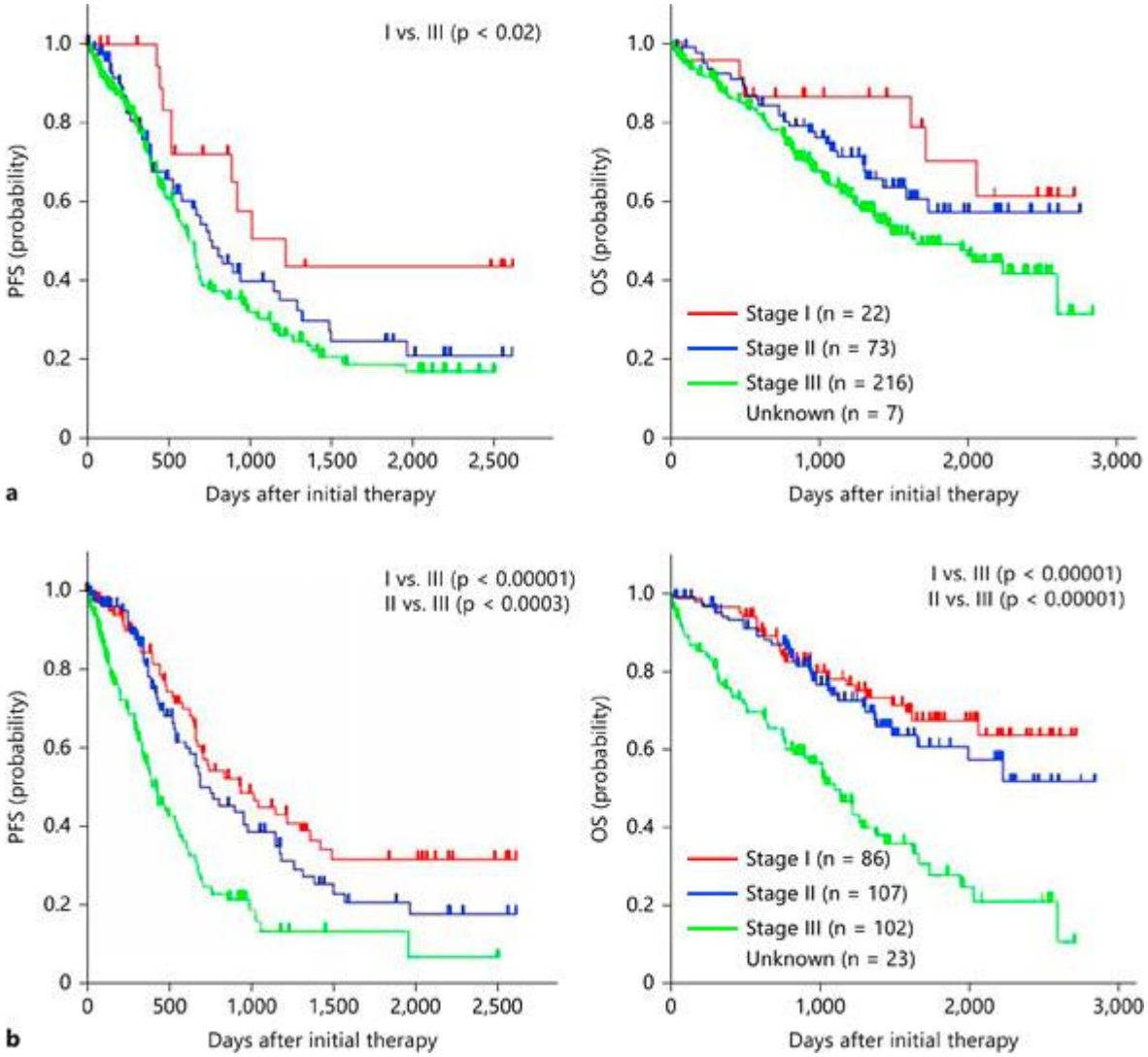

Fig. 1. Outcome according to clinical stage. a PFS and OS according to Durie-Salmon stage. b PFS and OS according to the ISS.

As for ISS stage I, II and III, the median PFS was 31.1, 25.0 and 14.2 months, respectively, and significant differences were found between stages I and III ($p < 0.00001$), and stages II and III ($p < 0.0003$; fig. 1b). The median OS was 36.8 months for stage III but was not reached in stages I and II. OS was significantly shorter for ISS stage III compared with that for stage I or II ($p < 0.00001$).

Outcome according to Initial Therapy

We next compared PFS and OS according to initial therapy. The median PFS of the 4 different treatment groups, i.e. conventional chemotherapy, novel agents, conventional chemotherapy plus auto-SCT and novel agents plus auto-SCT, was 19.1, 24.5, 26.8 and 35.2 months, respectively (fig. 2a). PFS was significantly improved in patients treated with a novel agent-containing regimen ($p < 0.01$) and in those treated with novel agents plus SCT ($p < 0.04$) compared with that of the patients treated with the conventional chemotherapy alone. The median OS of the conventional chemotherapy group was 46.0 months, while it was not reached in the other groups. When we

compared the outcome of the conventional chemotherapy group, there was a significant improvement in OS in the following treatment groups: novel agent-containing regimen ($p < 0.001$), chemotherapy plus SCT ($p < 0.02$) and novel agents plus SCT ($p < 0.02$). In terms of auto-SCT or novel agents as the front-line treatment, the median OS was significantly improved in the auto-SCT group compared with the non-SCT group (not reached vs. 57.9 months, $p < 0.02$) and more so in the novel agents group compared with the non-novel agents group (not reached vs. 49.3 months, $p < 0.001$; fig. 2b). No transplantation-related mortality was observed.

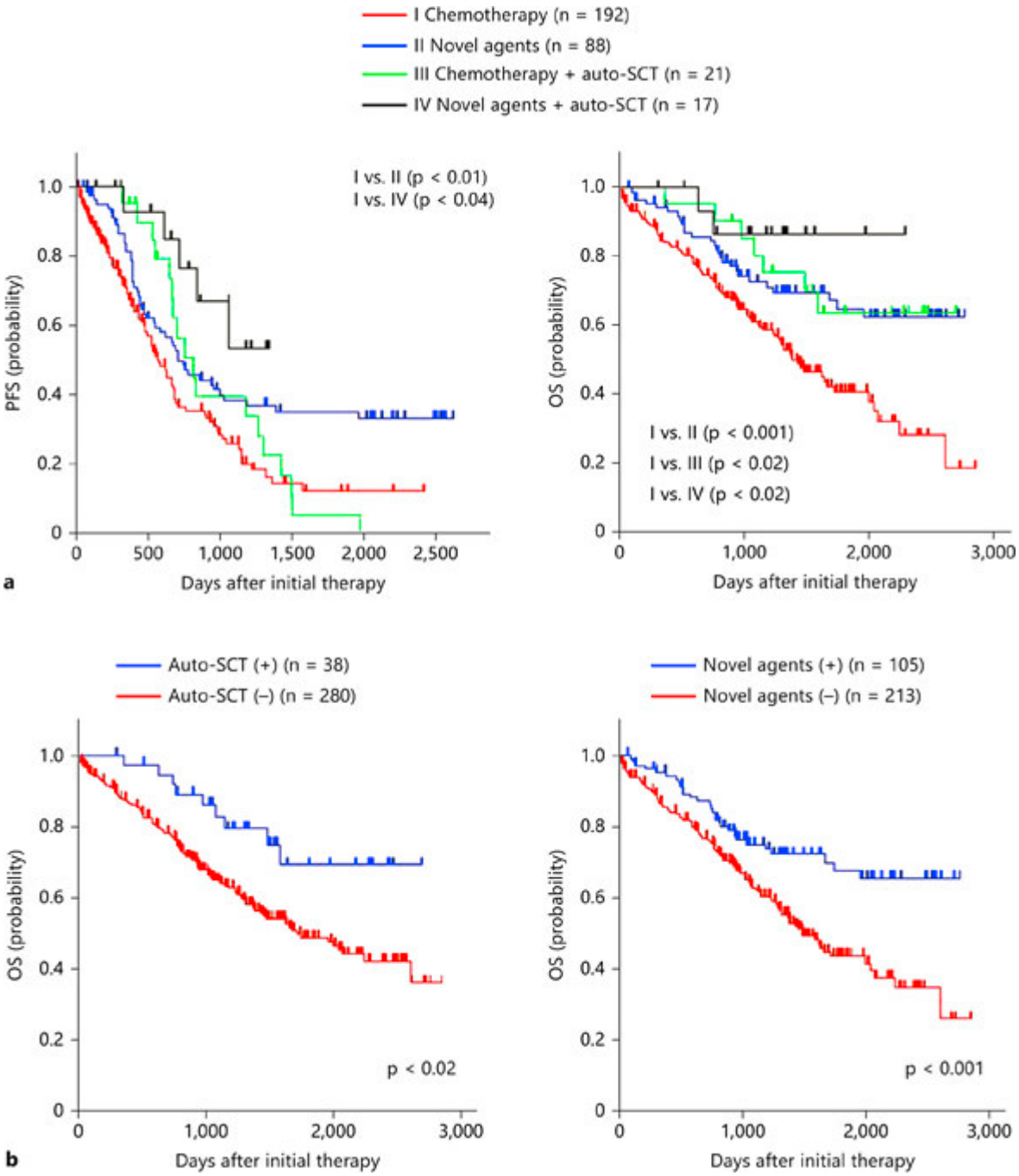

Fig. 2. Outcome according to initial therapy. a PFS and OS according to initial therapy, i.e. either conventional chemotherapy, novel agents, conventional chemotherapy plus auto-SCT or novel agents plus auto-SCT. b OS of patients treated with first-line auto-SCT or novel agents.

Efficacy of Novel Agents on OS

Because the induction therapy with novel agents had a significant impact on OS, we further evaluated the impact of novel agents as salvage therapy. When we analyzed OS in terms of the use of novel agents, the median OS was significantly improved in the group of patients treated with novel agents either as first-line or salvage therapy (second- and third-line) compared with those treated with conventional chemotherapy alone [86.7 months (n = 232) vs. 38.0 months (n = 86), $p < 0.0001$; fig. 3a]. Among 168 relapsed patients who received either conventional chemotherapy, novel agents or auto-SCT as initial therapy, 148 patients were treated with novel agent-containing regimens and the remaining 20 patients with conventional chemotherapy alone as salvage therapy. The median survival from the time of relapse was significantly extended in the novel agent group (45.5 months) compared with the chemotherapy group (15.0 months, $p < 0.04$; fig. 3b). No patient was treated with auto-SCT as salvage therapy.

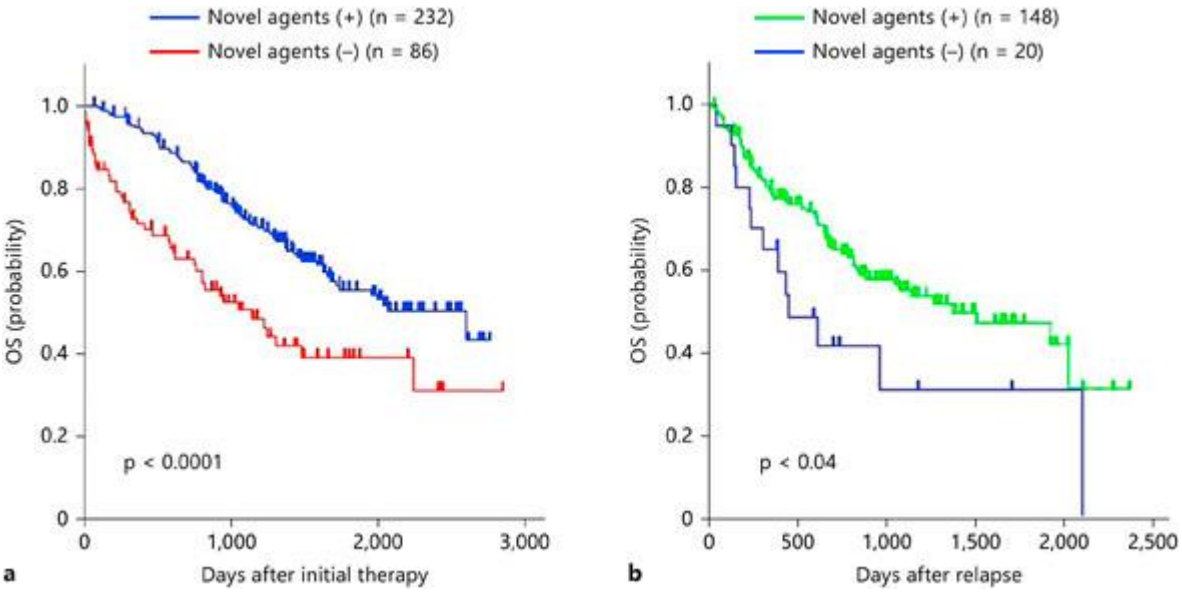

Fig. 3. Efficacy of novel agents on OS. a OS of patients treated with at least one novel agent-containing regimen during the clinical course. b Survival after relapse for relapsed patients treated with either conventional chemotherapy or novel agents as salvage therapy.

Outcome according to Response

The best response to treatment in the 318 patients was a complete response (CR) in 26 patients (8.2%), very good partial response (VGPR) in 56 (17.6%), partial response (PR) in 127 (39.9%), stable disease in 92 (28.9%) and disease progression in 17 (5.3%). Achievement of CR or VGPR was mostly observed in patients treated with auto-SCT (table 1). A significant difference in OS was found between the CR and PR groups ($p < 0.003$) and between the VGPR and PR groups ($p < 0.05$; fig. 4).

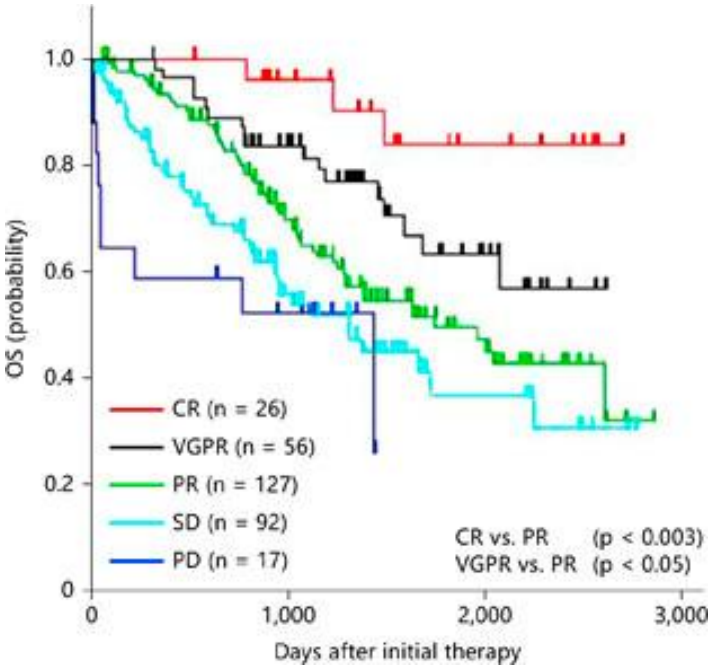

Fig. 4. Outcome according to response. OS according to best response, i.e. CR, VGPR, PR, stable disease (SD) or progressive disease (PD).

Multivariate Analysis

Finally, we performed a multivariate analysis to identify predictors independently associated with OS by using the Cox proportional hazards model. Variables included in the analysis were baseline patient factors (age, gender and type of M protein), prognostic factors (albumin, β_2-microglobulin and ISS stage) and treatment-related factors (the use of novel agents and auto-SCT). In this analysis, serum albumin ($p < 0.00005$) and β_2-microglobulin ($p < 0.02$) were important prognostic factors for OS (table 2). As for the type of M protein, the BJP type ($p < 0.01$) was found to be a significant prognostic factor associated with poor OS. Among treatment-related factors, the use of novel agents ($p < 0.003$) was an independent favorable predictor significantly associated with extended OS.

Table 2. Multivariate analysis for OS

Variable	β	SE (β)	Z	p value
Age	0.10093	0.07053	1.43112	0.1524
Gender	−0.0239	0.19621	0.12176	0.9031
Type of M protein	−0.7012	0.26077	2.68887	0.0072
Albumin	−0.7308	0.15411	4.74216	<0.00005
β_2-Microglobulin	0.02670	0.01110	2.40455	0.0162
ISS stage	0.17161	0.15183	1.13021	0.2584
Novel agent	−0.6770	0.22269	3.04012	0.0024
Auto-SCT	−0.5614	0.38184	1.47022	0.1415

Novel agents included thalidomide, lenalidomide and bortezomib.

Discussion

In this study, we performed a retrospective analysis of the prognosis of newly diagnosed MM patients aged 65-70 years. We evaluated an unselected group of patients who had been treated between January 1, 2004, and December 31, 2009. During this period, novel agents such as thalidomide, lenalidomide and bortezomib were available in clinical trials and routine practice. Therefore, this survey allowed us to compare the difference in outcome in terms of the use of novel agents.

Our data have shown that front-line therapy with novel agents or auto-SCT significantly prolonged OS when compared with conventional chemotherapy alone and that the use of novel agents followed by auto-SCT consolidation further improved OS. The additional use of novel agents as salvage therapy also prolonged the survival period after relapse. These findings suggest that treatment with novel agents and auto-SCT were effective approaches in this subgroup of MM patients.

In the current study, treatment for each patient was determined by the corresponding physician, and the baseline patient characteristics were different between each treatment group according to initial therapy. Therefore, the results cannot be compared equally across the groups. At that time, novel agents, especially bortezomib, were not used in vulnerable patients with performance status ≥ 3 because of the possibility of severe adverse events such as interstitial pneumonitis [13]. Thus, there was a bias in the patient background; that is, the conventional chemotherapy group included more fragile patients compared with the novel agent-containing regimen group or the auto-SCT group. Nevertheless, the median PFS in the conventional chemotherapy group was 19.1 months, which is similar to the previous data observed in clinical trials of melphalan + prednisone or other conventional chemotherapy (approximately 18 months) [14]. This suggests that the treatment outcome in the conventional chemotherapy group was not inferior to that in the historical standard chemotherapy group. Taken together, our results rather indicate a possible survival benefit of novel agents and auto-SCT in particular eligible patients.

We also found that the median OS in the conventional chemotherapy group (46.0 months) was longer than that in previous clinical trials (29 months) [14]. This is most likely due to the improvement of salvage therapy with novel agents. In fact, the survival after relapse was significantly improved by novel agent-containing regimens compared with conventional chemotherapy alone regardless of the use of novel agents as initial therapy. These findings also support the efficacy of novel agents as salvage therapy in MM.

Auto-SCT has been mostly applied to younger patients aged 65 or younger. Nevertheless, in this survey, 38 of 318 patients (12%) aged 65-70 years had been successfully managed with auto-SCT without transplantation-related mortality. Our results suggest that auto-SCT is a safe and effective approach for eligible patients with a good health condition, and this transplant eligibility in the elderly population is another prognostic factor for extended OS. Thus, auto-SCT is still an important strategy for so-called transplant-ineligible patients, as was reported previously [7,9].

Recent treatment strategies with novel agents have significantly improved response rates in both younger and elderly patients with MM [15,16,17,18]. The achievement of CR and VGPR has been shown to be associated with prolonged PFS and OS in both transplant-eligible and -ineligible patients [3,4]. In this study, CR and VGPR were mostly observed in the groups of patients treated with novel agents and/or auto-SCT, and these patients exhibited significantly longer OS compared with those achieving PR or inferior responses. Thus, the achievement of CR or VGPR was another favorable factor associated with extended OS, regardless of initial therapy.

By multivariate analysis, we confirmed that serum albumin and β_2-microglobulin were independent prognostic factors for OS. Among the types of M protein, the BJP type was related to a poor prognosis. The reason is probably because most patients with BJP type had the complication of renal damage. As for the treatment, the use of novel agents was an independent favorable prognostic factor associated with extended OS. Treatment with auto-SCT was not a significant prognostic factor, probably due to the small number of patients treated with auto-SCT.

In conclusion, our results indicate that treatment with novel agents and auto-SCT had a major impact on OS in eligible patients aged 65-70 years. We should evaluate the possible clinical indications of using novel agents plus auto-SCT even in this subgroup of elderly patients with MM.

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