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ORIGINAL ARTICLE

Treatment of patients with multiple myeloma over 65 yr: more tolerability or better response?

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Abstract

Objective: Two-thirds of newly diagnosed patients with multiple myeloma (MM) are over 65 yr and/or physically unfit. Such patients are not eligible for high-dose chemotherapy or stem cell transplantation. The treatment aims in these patients should be to prolong survival by obtaining the best possible response, while maintaining good tolerability. The aim of our study was to evaluate the response to treatment and treatment-related toxicities in patients treated with conventional and novel protocols. *Methods:* The records of 138 elderly (≥65 yr) patients with MM were retrospectively evaluated. *Results:* The median overall survival(OS) of the patients was 46 months. The median progression-free survival (PFS) was 18 months. The OS and PFS of the patients treated with the conventional protocols did not differ significantly from those treated with the novel protocols. The statistical analysis of the quality of the response to the treatment with the conventional and novel therapies showed that complete remission (CR), combined with a very good partial response (VGPR), was significantly higher in the latter. However, the toxicities were higher in the novel treatment group. *Conclusion:* The novel drug protocols significantly increased the quality of the responses of elderly patients with MM to therapy, but they did not increase the patients' tolerability.

Key words multiple myeloma; drug toxicity; elderly; quality of response

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Multiple myeloma (MM) is an incurable disease that affects plasma cells. MM comprises 1% of all cancers and 10% of hematologic malignancies. It usually affects older individuals. The median age at diagnosis is 70 yr, with two-thirds of patients with MM over 65 yr and/or physically unfit when the disease is first diagnosed. The survival of patients with MM has significantly improved in recent decades (1–3). However, the use of novel agents, such as bortezomib, thalidomide, and lenalidomide, together with high-dose therapy and autologous stem cell transplantation has mainly benefited young patients. A marginal benefit has been observed in patients older than 65 yr (4).

A combination of melphalan and prednisone (MP) has been the conventional treatment for elderly patients with MM for more than 40 yr (5). The advantages of MP treatment are it can be used orally on an outpatient basis, and it shows good tolerability. MP treatment yielded partial remission in 40–60% of patients and complete remission (CR) in <5% of patients (6). Novel drug protocols based on bortezomib, thalidomide, and lenalidomide have extended the options for patients with MM who are not candidates for transplants. In addition to the novel drug protocols for patients with MM, the aims of the therapy have changed. In the era of MP, the aim was to achieve a partial response (PR). In contrast, the principal goals today are to prolong disease-free and overall survival (OS). Prolonged treatment-free intervals and a good quality of life are additional important aims. CR has also become a new goal in elderly patients (7).

The older age/poor physical health of the majority of newly diagnosed patients with MM means they are not

eligible for high-dose chemotherapy and stem cell transplantation. The treatment aims in these patients should be to prolong survival by obtaining the best possible response, while maintaining a good quality of life. In a retrospective analysis of 1175 patients with newly diagnosed MM who were treated with MP and novel agents, 67% of those with CR had improved progression-free survival (PFS) at 3-yr follow-up, and 91% had improved OS (8). In the same study, PFS was 27% in those with a very good partial response (VGPR) or a PR, and the OS rates were 67–70% in those with a VGPR or a PR. Although the new drug protocols, including thalidomide, bortezomib, lenalidomide, and bendamustine, have significantly improved outcomes in elderly, unfit patients (9), these protocols are associated with more adverse events than conventional treatments. These include neuropathy, hematologic toxicity, and thromboembolic events, all of which can limit their use in elderly patients with MM (9).

We conducted a retrospective evaluation of patients who had received conventional treatments (including MP, vincristine plus doxorubicine plus dexamethasone [VAD], or dexamethasone) and new treatments, which included novel drugs (bortezomib, thalidomide, or lenalidomide). The aim of this study was to evaluate the response of these patients to the different treatments and treatment-related toxicities.

Patients and methods

The records of the Hematology Department of Kocaeli University, Baskent University in Istanbul and the local state hospital in Kocaeli on 138 elderly (≥65 yr) patients with MM followed up between February 2000 and October 2013 were retrospectively evaluated. Permission for the study was obtained from the hospital's ethics committee. The diagnosis of MM was based on Durie–Salmon (DS) criteria and those of the International Myeloma Working Group (10). The DS staging system and the international staging system (ISS) were used for staging the patients with MM (11, 12). The results of routine laboratory, radiologic, and pathologic analyses performed at the hospital were assessed. The patient's first attendance in the hematology department was accepted as the date of diagnosis, and their last attendance or the date of death was recorded as the last control time. Patients who failed to attend the hematology clinics were contacted by phone. If the patient did not answer, their relatives were asked whether the patient was still alive. The treatment decisions were based on current guidelines, considering the patient's performance status and comorbidity (13, 14). After completion of the treatment protocols, serum/urine immunoelectrophoresis was performed to determine the patient's response according to the criteria of the International Myeloma Working Group (10). As cytogenetic analyses were not available in our hospital, cytogenetic risk stratification of the patients could not be performed. Patients with solitary plasmacytomas and any malignancies other than MM were excluded from the study.

SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses. Visual (histogram and probability plots) and analytical methods (Shapiro–Wilk tests) were used to determine whether the variables were normally distributed. An independent samples *t*-test was used to compare parametric variables between the two groups. The Mann–Whitney *U*-test was used to compare non-parametric variables between the two groups. To detect the variables affecting survival and relative risks, Cox regression analysis was used. Do you mean: The Kaplan–Meier test was used for the survival analysis. A P value <0.05 was considered statistically significant. A chi-square test was used to assess the treatment-related toxicity of the two groups.

Results

One hundred and thirty-eight patients older than 65 yr who were admitted to the hematology department of our hospital and who were diagnosed with MM between 2000 and 2013 were enrolled in the study. The mean age of the patients was 72.42 ± 5.84 yr, and the group included 81 males and 57 females. The characteristics and laboratory values of the patients are shown in Table 1. As seen from the table, IgG kappa type MM (39.9%) was the most common type of MM. A total of 77.6% of the patients were admitted with ISS stage 2 and stage 3 disease, and most of the patients were classified as stage 2A and stage 3A according to the DS staging system (Table 1).

The rates of use of the conventional and novel drug protocols as the initial treatment are shown in Table 2. Bortezomib-dexamethasone (VD; 35.5%) and MP (34.1%) were the most commonly used treatment protocols.

The patients with MM were divided into two groups: patients who received the conventional therapy (MP, VAD, and dexamethasone) and those who received the novel protocol (bortezomib, thalidomide, and lenalidomide) as initial therapy. The characteristics of the groups are shown in Table 3. The groups did not differ significantly according to sex, age, laboratory parameters, or DS staging. However, the type of MM and the ISS stage of the patients differed significantly in the two groups ($P = 0.024$ and $P = 0.006$, respectively).

The median follow-up time of all the patients was 21 months (range: 1–109 months). The survival probability was 0.835 at 1 yr and 0.377 at 5 yr. The median survival was 46 months (95% CI: 33.2–58.8). The PFS probability was 0.706 at 1 yr and 0.194 at 5 yr. The median PFS was 18 months (95% CI: 12.2–23.2). The Kaplan–Meier survival curves are shown in Fig. 1. In the patients who received the conventional therapy initially, the survival probability was 0.763 and 0.410 at 1 yr and 5 yr, respectively. The PFS probability of these patients was 0.669 at 1 yr and 0.201 at

Table 1 Characteristics and laboratory values of the patients

Characteristics at diagnosis	No. of patients (*n* %)
Age (mean ± SD) (month)	72.42 ± 5.84
Gender	
Female	57 (41.3)
Male	81 (58.7)
Stage (ISS scoring system)	
I	16 (11.6)
II	56 (40.6)
III	51 (37)
Could not be evaluated	15 (10.9%)
Stage (Durie–Salmon scoring system)	
1A	14 (10.1)
2A	56 (40.6)
2B	13 (9.4%)
3A	43 (31.2%)
3B	12 (8.7%)
Type of MM	
IgA kappa	17 (12.3%)
IgA lambda	13 (9.4%)
IgG kappa	55 (39.9%)
IgG lambda	23 (16.7%)
Lambda light chain disease	17 (12.3%)
Non-secretory	2 (1.4%)
Hemoglobin, g/dL	10.05 ± 1.95
White blood cell,/μL	6070.34 ± 2702.5
Platelet, /mm^3	210.14 ± 88.78
Erythrocyte sedimentation rate, mm/h	78.34 ± 38.26
Creatinine mg/dL	1.76 ± 1.78
Calcium, mg/dL	9.44 ± 1.08
Albumin,g/dL	3.4 ± 0.69
Beta 2 microglobulin, mg/L	9.4 ± 13.1
LDH (U/L)	268.42 ± 149.75
CRP (mg/dL)	10.05 ± 21.88

LDH, lactate dehydrogenase; CRP, C-reactive protein.

5 yr. The median OS in these patients was 44 months (95% CI: 28.6–59.4), and the median PFS was 16 months (95% CI: 5.5–26.4). In the patients whose initial treatment included the new drugs, the survival probability was 0.879 and 0.319 at 1 yr and 5 yr, respectively. The PFS probability of these patients was 0.732 at 1 yr and 0.179 at 5 yr. The median OS of these patients was 47 months (95% CI: 30.5–63.5), and the median PFS was 20 months (95% CI: 15.5–24.4). The OS and PFS of the two groups were not significantly different ($P = 0.88$ and $P = 0.99$, respectively) (Fig. 2). Of the 138 patients, only 81 (58.7%) received second-line treatment. Seventy-two of these 81 (88.8%) patients were treated with the novel drug protocols. Fifty-four (39.9%) patients received the conventional treatment protocols, and 19 (34.5%) of these patients did not relapse or receive any chemotherapy. Thirty-six (65.5%) patients relapsed after the conventional therapy. Thirty (83.3%) of these 36 relapsing patients received the novel drug protocol as the second-line therapy, and the remaining 6 (16.6%) patients received the conventional protocol as the second-line therapy.

Table 2 Rate of use of the conventional and novel drug therapy protocols as the initial treatment

Treatment	*n* (%)
Conventional treatment protocol	
MP	47 (34.1%)
VAD	7 (5.1%)
D	1 (0.7%)
Novel drug treatment protocols	
VMP	15 (10.9%)
VD	49 (35.5%)
MPT	8 (5.8%)
VCD	7 (5.1%)
RD	1 (0.7%)
TD	3 (2.2%)

MP, melphalan 6–9 mg/m^2/d plus prednisolone 100 mg/d every 1–5 d for 28 d; VAD, vincristine 0.4 mg/m^2/d 1–4 d plus adriamycin 9 mg/m^2/d for 1–4 d plus dexamethasone 40 mg/d for 1–4, 9–12, and 17–20 d for 4 wk; D, dexamethasone 40 mg/d for 1–4, 9–12, and 17–20 d for 4 wk; VMP, bortezomib 1.3 mg/m^2/d every 1, 4, 8, and 11 d every 3 wk plus melphalan 6–9 mg/m^2/d plus prednisolone 100 mg/d for 1–5 d every 28 d; VD, bortezomib 1.3 mg/m^2/d for 1, 4, 8, and 11 d plus dexamethasone 40 mg/d for 1, 4, 8, 11 d for 3 wk; MPT, melphalan 6–9 mg/m^2/d plus prednisolone 100 mg/d for 1–5 d plus thalidomide 200 mg/d for 1–21 plus dexamethasone 40 mg/d for 1, 4, 8, and 11 d; RD, lenalidomide 25 mg/d for 1–21 d for 29 d plus dexamethasone 40 mg/d for 1–4, 9–12, 17–20 d for 4 wk; TD, thalidomide 200 mg/d plus dexamethasone 40 mg/d for 1–4, 9–12, 17–20 d for 4 wk. *N,* number of patients.

A Cox regression analysis of the factors that affected the survival of the patients showed that levels of serum calcium and beta 2 microglobulin had a significant impact on survival.

The statistical analysis of the quality of the response to the treatment with the conventional and novel therapies showed that the rate of CR, combined with a VGPR, was significantly higher in the latter. The rate of CR, combined with a VGPR, was 23.6% in the patients who received the conventional drugs, whereas it was 63.9% in those who received the novel drug protocol (thalidomide, lenalidomide, and bortezomib) (Fig. 3). Analysis of the side effects of the treatments revealed no statistically significant between-group differences in grade 3–4 anemia, grade 3–4 thrombocytopenia, thromboembolic events, zona zoster infection, constipation, elevation of liver function tests, or elevation of serum bilirubin and creatinine levels grade 3–4 neutropenia, neuropathy, and the frequency of infection was statistically different in the two groups (Table 4).

When the ratios of early mortality in the first year were analyzed, early mortality was significantly high among the patients who were treated with the novel drug protocols compared to those who were treated with the conventional therapies ($P = 0.046$). The most common cause of death with both types of therapy was infection. Other causes of death in all the patients were renal insufficiency, heart

Table 3 Characteristics of the patients who received the conventional and novel protocols as the initial therapy. *$P < 0.05$ was statistically significant

Parameters	Conventional therapy ($N = 55$)	Novel therapy ($N = 83$)	P
Sex (female/male)	25/30	32/51	0.422
Age (y)	74.2 ± 6.7	71.9 ± 5.1	0.051
White blood cell,/μL	6073.27 ± 2471.89	5988.80 ± 2755.74	0.554
Hemoglobin, g/dL	9.74 ± 2.02	9.96 ± 1.91	0.521
Platelet, /mm^3	211.95 ± 97.6	210 ± 94	0.906
Erythrocyte sedimentation rate, mm/h	77.64 ± 37.9	78.18 ± 39.58	0.936
CRP (mg/dL)	4.5 ± 9.3	11.79 ± 25.11	0.971
LDH (U/L)	251.7 ± 179.2	281.1 ± 157.7	0.152
Creatinine (mg/dL)	1.5 ± 1.2	1.8 ± 1.9	0.422
Calcium (mg/dL)	9.56 ± 1.14	9.4 ± 1	0.461
Albumin (g/dL)	3.5 ± 0.85	3.35 ± 0.6	0.288
Beta 2 microglobulin (mg/L)	7.27 ± 4	10.45 ± 15.59	0.779
Type of MM			
IgA kappa	5 (9.1%)	12 (14.5%)	0.024*
IgA lambda	3 (5.5%)	10 (12%)	
IgG kappa	23 (418%)	32 (38.6%)	
IgG lambda	14 (25.5%)	9 (10.8%)	
Kappa	4 (7.3%)	7 (8.4%)	
Lambda	6 (10.9%)	11 (13.3%)	
Non-secretory	0	2 (2.4%)	
ISS Stage			
1	5 (9.1%)	11 (13.3%)	0.006*
2	22 (40%)	34 (41%)	
3	15 (27.3%)	36 (43.4%)	
Could not be evaluated	13 (23.6%)	2 (2.4%)	
Durie–Salmon stage			
1A	5 (9.1%)	9 (10.8%)	0.932
1B	0	0	
2A	24 (43.6%)	32 (38.6%)	
2B	3 (5.5%)	10 (12%)	
3A	18 (32.7%)	25 (30.1%)	
3B	5 (9.1%)	7 (8.4%)	

failure, and myocardial infarction. There was no statistically significant between-group difference in causes of death ($P = 0.303$).

Discussion

We investigated general features, treatments, responses to the treatments, and side effects of patients with MM over 65 yr who were followed at three centers between February 2000 and September 2013. The most common type of MM was IgG lambda in this study. At the time of the diagnosis, the most common stages of the patients according to the ISS and DS staging system were stage 2–3 and 2A–3A, respectively. The patients who were treated with the conventional therapy and the novel drug protocol were divided two groups, and all the assessments were performed with these groups. The most common therapy in the conventional therapy group was MP. It was VD in the novel drug protocol group. The survival at 1 and 5 yr in the conventional and novel treatment groups was 83.5% and 37.7%, respectively, and the median survival was 46 months. There was no difference in the 1-yr and 5-yr survival probabilities between the two treatment groups. The serum calcium and beta 2 microglobulin levels affected survival. The quality of the response to the novel drug therapy was significantly better than the response to the conventional therapy ($P < 0.001$). The rate of CR, combined with a VGPR, was 23.6% (CR: 9.1%; VGPR: 14.5%) in the conventional therapy group and 63.9% (CR: 12%; VGPR: 51.8%) in the novel drug protocol group, but the CR and VGPR were not reflected in the OS ($P = 0.880$), which was similar in the two groups. When the side effects were evaluated in the two groups, grade 3–4 neutropenia was statistically significantly higher in the conventional therapy group, and the frequency of infection and neuropathy was statistically higher in the novel drug protocol group.

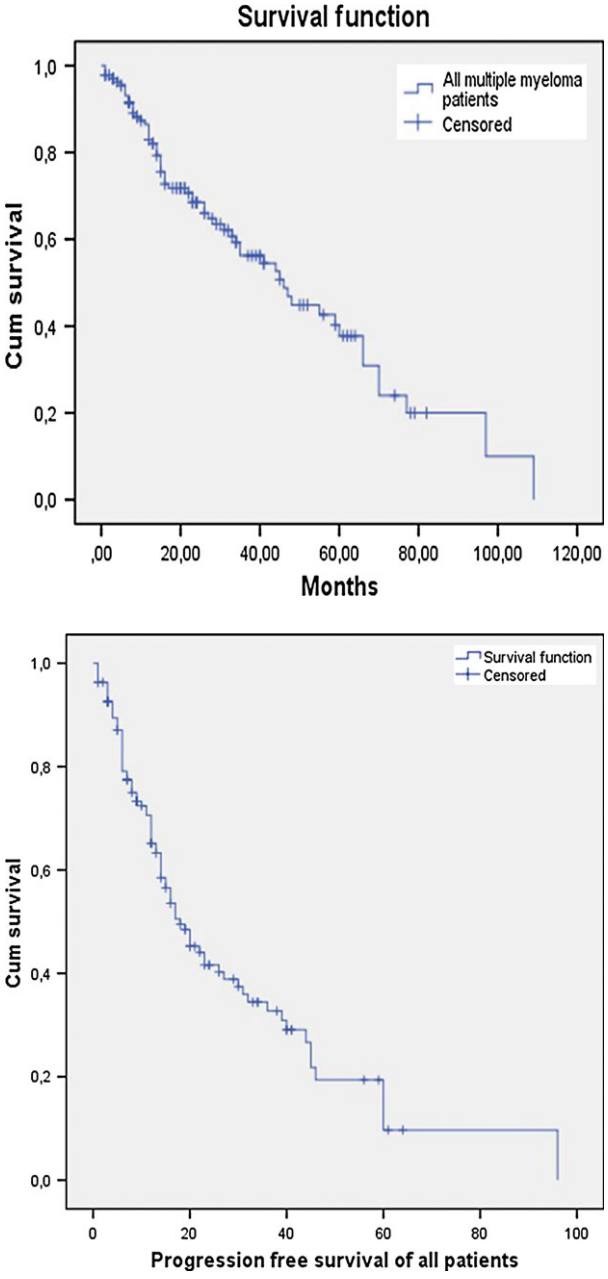


Figure 1 Kaplan–Meier overall survival (OS) and progression-free survival (PFS) curves of all the patients with multiple myeloma.

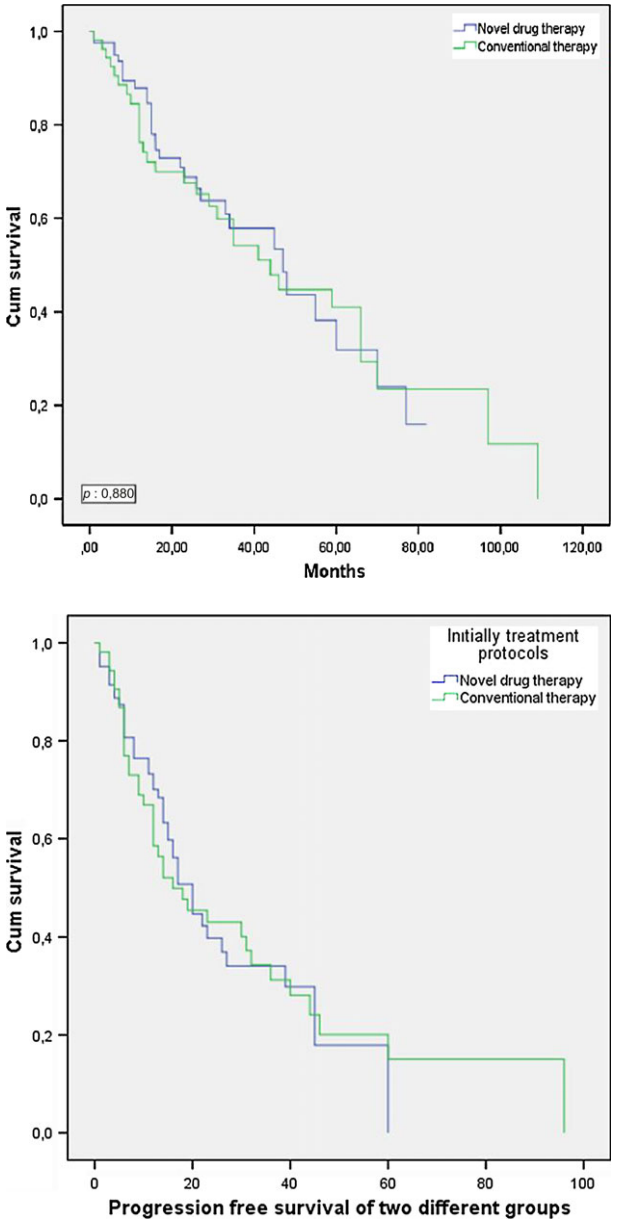
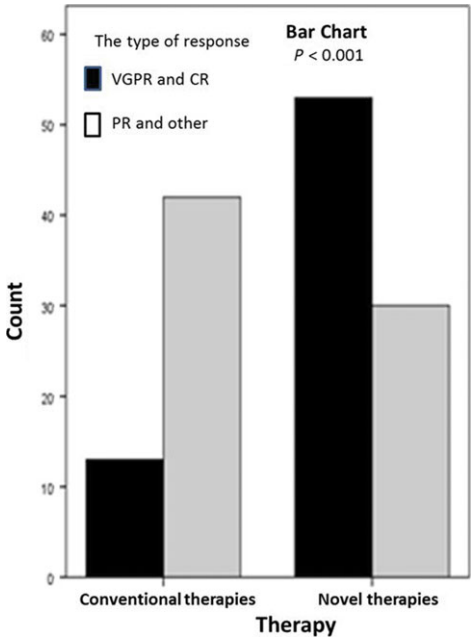


Figure 2 Initial treatment protocols cumulative survival and progression-free survival of the two groups.

MP has long been the traditional treatment of choice for patients over 65 yr with newly diagnosed MM who are not candidates for transplantation (15). Therapeutic options for MM have changed in the past several years. In several studies, treatment with non-traditional protocols, including immunomodulators, such as thalidomide, lenalidomide, and bortezomib, has increased the survival times of patients with MM, particularly younger ones (3, 16–19). Treatment options for older patients with MM aged more than 65 yr were severely limited in the past because they are not candidates for stem cell transplants. According to several clinical trials, such patients are candidates for novel drug treatments, with longer survival times (17, 20).

Palumbo *et al.* reported a VGPR and a CR ratio of 15% (3% CR and 12% VGPR) when the MP protocol was used as conventional therapy (21). In one study that included novel drugs, a CR ratio of 7–30% was reported, depending on the protocol used (9). In the present study, only the rate of CR (5%) was similar to that reported in the literature. The rate of CR, combined with VGPR, was higher than that reported in the literature (9) in this study of patients aged older than 65 yr with newly diagnosed MM. The quality of the response to the novel drug protocol was statistically significantly better than the response to the conventional



Quality of response	Conventional therapy (*N* = 55) (%)	Novel therapy (*N* = 83) (%)
CR plus VGPR	13 (23.6)	53 (63.9)
<PR	42 (76.4)	30 (36.1)

Figure 3 Assessment of the response to treatment with the conventional and novel therapies. CR: complete remission; VGPR: very good partial response; PR: partial response.

therapy. Some reviews reported that treatment with the new drug protocols in non-transplant candidate patients with MM improved the quality of the treatment response and prolonged their OS(8, 22, 23). In our retrospective study, there were no between-group differences in the parameters studied ($P = 0.880$). These results are in contrast to several randomized prospective studies and a retrospective study in the literature (8, 22, 23). The discord may be due to differences between the present study and the studies in the literature. These include the retrospective nature of our study, which avoids the selection bias inherent in all randomized studies. However, a retrospective analysis cannot exclude the possibility of imbalance in known and unknown prognostic factors between the treatment arms. The small number of patients and missing data might explain the low level of between-group differences in the present study. In addition, a large proportion (83.3%) of the patients in the conventional treatment arm who relapsed received the novel drugs. The low power due to the small numbers may contribute to the difference between previous studies and our study, but it may not be the main reason. The prevalence of side effects with the therapies was in accordance with that reported in the literature (22, 23).

In conclusion, this retrospective study showed that novel drug protocols, including bortezomib, thalidomide, and lenalidomide, in the treatment of patients with MM over 65 yr significantly increased the quality of their responses to therapy. The frequencies of infection and neuropathy were significantly higher in the novel drug treatment group compared to the conventional therapy group, and early death was also significantly more common in the novel drug treatment group. However, other hematologic and non-hematologic side effects were not different between the two groups. When OS was analyzed, there was no difference between the conventional and novel drug treatment groups. Therefore, when making decisions about the optimum therapy in patients over 65 yr who have comorbidity with MM, the questions 'Does it affect the quality of life? or Does it affect the quality of the response to the therapy?' may guide the selection of the treatment.

Table 4 Evaluation of the treatment-related side effects in the conventional and novel treatment groups

Side effects	Conventional therapies (*N* = 47)	Novel therapies (*N* = 83)	*P*
Grade 3–4 anemia	10 (21.27%)	8 (9.63%)	0.128
Grade 3–4 neutropenia	8 (17.02%)	9 (10.84%)	0.050*
Grade 3–4 thrombocytopenia	6 (12.76%)	3 (3.61%)	0.111
Elevation of LFT[1]	3 (6.38%)	2 (2.40%)	0.351
Elevation of serum bilirubin	3 (6.38%)	1 (1.20%)	0.134
Elevation of serum creatinine	1 (2.12%)	5 (6.02%)	0.417
Constipation	4 (8.51%)	18 (21.68%)	0.093
Zona zoster infection	2 (4.25%)	13 (15.66%)	0.095
Thromboembolic events	5 (10.63%)	2 (2.40%)	0.098
Neuropathy	6 (12.76%)	35 (42.16%)	0.001*
Infection	14 (29.78%)	41 (49.39%)	0.047*
Early mortality in the first year	25 (45.45%)	52 (62.65%)	0.046*

*$P < 0.05$ was statistically significant.
[1]LFT, liver function test.

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