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Retrospective Evaluation of Immunomodulatory Agents' Response and Side Effects In Relapsed and Refractory Multiple Myeloma Patients

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ABSTRACT

Objective: In this study, we aimed to determine the most appropriate approaches to shape our daily practice by revealing treatment responses, side effects and side effect management of relapsed and refractory multiple myeloma patients who were treated with immunomodulatory drugs(IMIDs).

Method: This study was carried out among the patients with multiple myeloma who underwent IMIDs between June 2001 and September 2018. General characteristics, overall survival, response rates, side effects profiles, prophylaxis used to prevent side effects of IMIDs are evaluated.

Results: The median age of 85 patients included in the study was 62 (38 − 83). Fifty (58.8%) of the patients were male. The mean follow-up period of the patients was 64 months Overall survival of the patients was 87 months (5.70; 75.83 - 98.18). Of the 85 patients included in the study, 11 received thalidomide, 78 received lenalidomide, and 15 received pomalidomide. While none of the patients receiving thalidomide was discontinued due to side effects, the dose was reduced in 1 (9.1%) patient. In 25 (32.1%) of the patients receiving lenalidomide, the drug was discontinued, while the dose was reduced in 21 (26.9%) patients. In 1 of the patients using pomalidomide, the drug was discontinued, and no dose reduction was made in any of the patients.

Conclusion: IMIDs are drugs that are frequently used in RRMM and have a pronounced response. In order to use the drugs effectively, prophylactic approaches to prevent the side effects before they are developed should be determined according to patient characteristics.

Key Words: Relapsed and refractory multiple myeloma, immunomodulatory drugs (IMIDs), lenalidomide, thalidomide, pomalidomide, effect, side effect

I. INTRODUCTION

Multiple myeloma is a neoplastic plasma cell disease with an unknown cause that is characterized by the presence of monoclonal proteins in the serum and/or urine and end-organ damage linked to these monoclonal proteins. It is caused by malignant plasma cells that are undergoing clonal proliferation in the bone marrow. Monoclonal immunoglobulins, also known as M protein or immunoglobulin light chains, are secreted by neoplastic malignant plasma cells. Immunoglobulins are not produced normally (1). It constitutes 10% of all hematological cancers (2, 3). The median age of the patients is 68 for men and 70 for women, and the incidence increases with age.

The median life expectancy offered by traditional treatments is 3–4 years, however autologous stem cell transplantation has raised this time to 5-7 years. Studies carried out over the years have significantly improved 5-year survival rates, which were reported to have increased from 20% to 51.8% in the study of Bilmark et al. (4). With new therapeutic drugs, the 10-year survival rate is about 30% (5).

IMIDs are thalidomide, lenalidomide and pomalidomide. Peripheral neuropathy in the use of thalidomide is seen as a side effect that limits the use of the drug and should be followed up. Neurological follow-up is an important point in patients using thalidomide. It is necessary to be vigilant in terms of infectious diseases that may develop in patients receiving treatment with lenalidomide and pomalidomide. At this point, antibiotic prophylaxis can be used if necessary. Another condition that requires dose adjustment is kidney failure. Drug dosage should be determined according to creatinine clearance. Venous thromboembolism that may develop during lenalidomide treatment should be kept in mind and thromboembolism prophylaxis should be applied. Again, patients should be followed up in terms of cytopenia that may develop while using these agents, and dose adjustments should be made. Dose reduction or G-CSF support can be considered in neutropenia that may develop during the use of lenalidomide. Due to side effects, patients may have difficulty completing the doses they need to take during follow-up. At the same time, side effect management should be done well in terms of treatment compliance. VTE prophylaxis, prophylactic antibiotics, and regular neurological evaluation play a critical role in the management of side effects.

In this study, we aimed to reveal how the side effects are managed in daily practice by revealing the treatment responses of the patients receiving IMID group treatment in our center, the side effects they encounter, the prophylactic treatments preferred in our center for these side effects, and the side effect management.

II. MATERIAL and METHOD

The current study was conducted in a single tertiary medical center and was designed as a retrospective comparative cohort study. This study was complied with the ethical guidelines of the 1975 Helsinki Declaration that was then modified in 2008. The study protocol was approved by Dokuz Eylül University Scientific Research Assessment and Ethics Committee (Approval No: Ethical Board – E1-18-1069).

The study comprised patients who used at least one of the immunomodulatory drugs (IMID) thalidomide, lenalidomide, and/or pomalidomide in one phase of their treatment and were monitored in the hematology clinic of Dokuz Eylul University between June 2001 and September 2018. Laboratory results, the patients' ages at the time of diagnosis, the treatments they initially received, their responses to those treatments, whether or not autologous stem cell transplantation was performed, the order in which IMID group drugs were taken, the response attained with those drugs, the side effects that developed while taking the treatment, and prophylactic approaches were all examined at.

The revised international staging system (R-ISS) was used in the staging of patients with multiple myeloma. Accordingly, patients with serum β2 microglobulin level <3.5mg/dL and serum albumin level ≥3.5gr/dL, without high-risk cytogenetic anomalies detected by FISH, and with normal serum LDH values were considered stage I. Patients with serum β2 microglobulin level ≥5.5mg/dL and presence of del 17p and/or presence of t(4;14) and/or presence of t(14;16) or high serum LDH levels, which are high-risk chromosomal abnormalities

detected by FISH, are considered stage III. Stage II was evaluated as patients who did not comply with stage I and stage III (6).

In addition, the Durie-Salmon stages of the patients were determined and recorded. Accordingly, stage 1 patients have myeloma cell concentration <0.6 x 10^{12} cell/m², in addition to Hb >10 g/dL, Normal serum calcium level or ≤12 mg/dL, ≤1 bone lesion, Low M protein component, IgG <5g /dL, IgA <3g/dL were recorded as patients with urine Bence-Jones protein <4g/24 hours. Stage 2 patients were evaluated as patients with a myeloma cell concentration of $0.6 - 1.2$ x 10^{12} cell/m² and not meeting stage 1 and 3 criteria.Stage 3 patients have myeloma cell concentration >1.2 x 10^{12} cell/m² accompanied by Hb <8.5 g/dL, serum calcium >12 mg/dL, >3 bone lesions, High M protein component, IgG >7g/dL, IgA It was determined as patients with >5g/dL, Urine Bence-Jones protein >12g/24 hours. A and B groups were determined according to the serum creatinine value. Those with serum creatinine <2 mg/dL were determined as A and those with serum creatinine ≥2 mg/dL were determined as B group (7).

Response evaluation was based on the International Myeloma Working Group (IMWG) response criteria. Accordingly, serum and urine immunofixation was negative, the plasma cell percentage of the bone marrow was $<5\%$, the absence of soft tissue plasmacytomas, and the inability to detect the original paraprotein in serum and urine for at least 6 weeks by immunofixation method were evaluated as complete response (CR). Serum and urine M protein could not be detected in electrophoresis, but could be detected in immunofixation, or a decrease of $\geq90\%$ in serum M protein, a urine M protein of <100 mg/24 hours, and no increase in the number and size of lytic lesions were evaluated as very good partial response (VGPR). 50% decrease in serum M protein and 90% decrease in 24-hour urine M protein or decrease below 200 mg/24 hours, no increase in the number and size of lytic lesions, $\geq50\%$ decrease in the difference of affected/unaffected free light chain levels if serum or urine M protein cannot be measured or, if these could not be measured, a decrease of $\geq50\%$ in bone marrow plasma cells was considered as partial response (PR) (8).

In contrast, the development of new plasmacytomas or the appearance of lytic bone lesions, significant growth in the size of existing plasmacytomas or bone lesions; $\geq50\%$ increase in the sum of the serially measured radii of the measurable lesion and at least 1 cm increase, hypercalcemia (serum calcium >11.5 mg/dL), decrease in hemoglobin ≥2 g/dL, increase in serum creatinine ≥2 mg/dL were considered as relapse.

III.   Statistical Analysis

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was the statistical program that we used for analyses. Variables indicated by count were summarized with percentage distribution. The variables indicated by the measurement were analyzed by summarizing with their median, minimum, and maximum values. The overall survival of the patients was analyzed by Kaplan Meier method. Statistical significance level was accepted as $p<0.05$.

IV.   RESULTS

The median age of 85 patients included in the study was 62 (38 – 83). Fifty (58.8%) of the patients were male and 35 (41.2%) were female. The mean follow-up period of the patients was 64 months, and the median follow-up period was 57 (5-177) months. During this period, 47 (55.3%) of the patients followed were still alive, while 38 (44.7%) died. As a result of Kaplan Meier analysis, the mean overall survival of the patients was found to be 87 months (standard deviation: 5.70; 75.83 - 98.18), while the median survival was found to be 77 months (standard deviation: 7.95; 61.40 - 92.60). The demographic characteristics of the patients, multiple myeloma M-protein types and staging, first-line treatments and response rates, and autologous stem cell transplantation status are given in Table 1.

The patients were evaluated in terms of the imaging methods applied. According to this, it was determined that 74 (87.1%) of 85 patients had bone survey. Involvement was detected in 46 of these patients (54.1% of all patients). The number of patients who underwent MRI or CT was 50 (58.8%), and 42 of them (49.4% of all

patients) was involved. Imaging was performed with FDG-PET in 29 (34.1%) of the patients. There was involvement in 25 of these patients (29.4% of all patients). In 9 (32.1%) of 28 patients whose involvement was not detected by bone survey, involvement was detected by MR, CT or PET.

Of the 85 patients included in the study, 11 received thalidomide, 78 received lenalidomide, and 15 received pomalidomide. In Table 2, IMIDs' adverse effect profiles, therapeutic characteristics, and results are compared.

V. Thalidomide

Eleven of the 85 patients included in the study received thalidomide treatment in part of their treatment, and the median age of these patients was 59 years (47-79). 5 of the patients were male and 6 were female. The median follow-up period of the patients was 56 months (5 – 139). As the initial dose, 50 mg of thalidomide was used in 1 patient (9.1%), 100 mg in 7 patients (63.6%), and 200 mg in 3 patients (27.3%). 45.5% of the patients (5 patients) were able to use the treatment for only 1 month. The median duration of use was found to be 24 months (1 – 120) in patients who could use it for a long time. It was observed that none of the patients discontinued the treatment due to side effects. On the other hand, dose reduction was performed in 1 patient (9.1%) due to grade 3 neuropathy.

VI. Lenalidomide

Of the 85 patients included in the study, 78 received lenalidomide treatment in part of their treatment. The median age of these patients was 62 (38 – 83). Of the patients, 46 (59.0%) were male and 32 (41.0%) were female. The median follow-up period of the patients was 65 months (10 – 177). Of the patients, 44 (56.4%) were still alive, and 34 (43.6%) had died. The initial dose of lenalidomide was 25 mg in 32 patients (41.0%), 15 mg in 24 patients (30.8%), 10 mg in 16 patients (20.5%), and 5 mg in 6 patients (7.7%). The median duration of use of lenalidomide treatment of the patients was 12 months (1 – 46). It was observed that 69 of the patients (88.5%) achieved at least PR response with treatment. In 56 of the patients (71.7%), the response was obtained 2 months or earlier.

Of the patients receiving lenalidomide medication, 49 (62.8%) received antimicrobial prophylaxis. The median prophylaxis time was 9 months (1–26), while the mean prophylaxis time was 9.3 months for the patients. All lenalidomide patients received VTE prophylaxis with at least ASA.

When the hematological side effect profile was evaluated, various degrees of neutropenia were found in 54 patients (69.2%) and 18 patients (23.1%) received G-CSF prophylaxis due to deep neutropenia. When non-hematological side effects were examined, it was observed that no thromboembolic event was experienced in 70 (89.8%) of 78 patients who received lenalidomide treatment. On the other hand, deep vein thrombosis (DVT) was seen in 4 patients (5.1%) and DVT + pulmonary thromboembolism (PTE) in 4 patients (5.1%). When the infections that developed during drug use were examined, it was observed that 53 patients (67.9%) did not develop an infection that required interruption of the drug or dose reduction. On the other hand, the most common infection was pneumonia with 21 patients (27.0%). During the follow-up, treatment was interrupted for various reasons in 25 patients (32.1%). The most common reason for discontinuing treatment was pneumonia in 15 patients (19.2%). This was followed by DVT, PTE and hepatotoxicity with two (2.6%) patients. Apart from this, treatment was interrupted in one patient (1.3%) due to deep neutropenia, urinary system infection (pyelonephritis), sepsis and syncope.

The mean duration of treatment interruption was 11 days, and the median 7 days (7-30). In 15 patients (19.2%), the treatment was interrupted for 7 days, while in 3 patients (3.9%), it was observed that it was necessary to interrupt the treatment for 21 days or more. The reasons for interrupting the treatment in these patients were prolonged neutropenia in 2 patients and pulmonary embolism in 1 patient. When evaluated in general, it was observed that the treatment was interrupted in 17 patients (21.8%) due to infectious reasons, and in 4 patients (5.2%) due to venous thromboembolism.It was observed that 10 of 17 patients whose treatment was interrupted due to infectious reasons did not receive any antibiotic prophylaxis until infection. Accordingly, the rate of

infection that was serious enough to require interruption of treatment in patients receiving antibiotic prophylaxis was 14.2%, while this rate was determined as 58.8% in patients who did not receive prophylaxis.

Dose reduction was observed in 21 (26.9%) of 78 patients who received lenalidomide treatment. The most common reasons for dose reduction were infectious reasons in 8 patients (10.3%), cytopenia in 5 patients (6.4%), and venous thromboembolism in 2 patients (2.6%). It was observed that 4 of 8 patients who had dose reduction due to infectious reasons did not receive prophylaxis until dose reduction. According to this, the rate of infection that would require dose reduction was 8.1% in patients who received prophylaxis, while this rate was 50.0% in patients who did not receive prophylaxis.

VII.   Pomalidomide

Fifteen of the 85 patients included in the study received pomalidomide treatment in part of their treatment, and the median age of these patients was 55 (38 - 70). Seven of the patients were male and 8 were female. The median follow-up period of the patients was 59 months (20 – 138). As the initial dose, 4 mg of pomalidomide was used in 14 (93.3%) of 15 patients, and 2 mg (4 mg every other day) in one. It was observed that 11 of the patients (73.3%) achieved at least PR response with treatment. Four of the patients (26.7%) were unresponsive to treatment.

It was observed that 11 (73.3%) of the patients receiving pomalidomide treatment were given antibiotic prophylaxis. All patients treated with pomalidomide were given VTE prophylaxis with at least ASA. It was observed that 10 of the patients (66.7%) received prophylaxis only with ASA and 5 patients (33.3%) received prophylaxis with ASA + low molecular weight heparin (LMWH).

When the hematological side effect profile was evaluated, various degrees of neutropenia were detected in 11 patients (73.3%), and 5 patients (33.3%) received G-CSF prophylaxis due to profound neutropenia. When non-hematological side effects were examined, it was observed that none of the 15 patients who received pomalidomide treatment experienced any thromboembolic events. When the infections that developed during drug use were examined, it was seen that 11 (73.3%) of the patients did not develop an infection that required interruption of the drug or dose reduction. On the other hand, the most common infection was pneumonia with 3 patients (20.0%). In 2 (13.3%) of these 3 patients, sepsis developed due to pneumonia and the patients died from sepsis. Serious urinary tract infection developed in 1 patient (6.7%), and this patient died due to urosepsis. Patients who died due to infection were also patients who were unresponsive to treatment. Three of them were receiving antibiotic prophylaxis. Apart from these, no serious side effects developed in any of the patients.

Treatment was interrupted for 14 days due to pneumonia in only one of the patients receiving pomalidomide treatment. Apart from this, it was observed that treatment was not interrupted in any of the patients. No dose reduction was made in any patient.

VIII.   DISCUSSION

A neoplastic disease with an unknown cause, multiple myeloma is characterized by the presence of monoclonal proteins in the serum and urine and end-organ damage brought on by these monoclonal proteins. It occurs due to plasma cells going through clonal proliferation in the bone marrow. When the literature is examined at, the F:M ratio is around 3:2 and the median age of multiple myeloma is 69 years (2, 3). The 5-year survival rate with current treatments has been reported to be 51.8% (4), with a median life expectancy of 5-7 years. IgG secretion was shown to occur most frequently in multiple myeloma types (52%), followed by IgA (20%) and light chain (16%) (9). Epidemiological statistics, survival data, and the distribution of multiple myeloma subtypes were consistent with previous research in our study.

Skeletal system-related complications are encountered in 80-85% of patients with multiple myeloma. Approximately 50% of these have vertebral problems and 30% of them have non-vertebral bone involvement (10). When the imaging methods applied in the patients included in our study were examined, it was found that

uptake was found in 54.1% of the patients with bone survey, 49.4% with MRI or CT, and 29.4% with FDG-PET. In 9 (32.1%) of 28 patients whose involvement was not detected by bone survey, involvement was detected by MR, CT or PET. With these data, it is seen that MR, CT or PET examination is superior to bone survey for bone involvement, which guides in early disease staging and treatment selection.

In our study, it was observed that 88.5% of the patients who received lenalidomide treatment achieved at least PR response with treatment. CR was obtained in 14.1% of the patients. In 71.7% of the patients, the response was obtained 2 months or earlier. In the study conducted by Dimopoulos et al., the rate of at least PR response was found to be 60.2% in relapsed and refractory multiple myeloma patients, and CR was obtained in 15.1% of them, and the median response time was found to be 2.1 months (11). In another study, the response rate was found to be 64.6% and the rate of CR to be 19.0% (12). At this point, the CR rates in our patients were followed in line with the literature, and the least PR response rates were found above the literature data. The biggest reason for this may be that our patients have not experienced these drugs before, as IMID group drugs cannot be used in the first-line treatment in our country, that is, they are in a naive state of IMID. However, it should be kept in mind that overall survival and progression-free survival rates are higher with the use of IMID group drugs as first-line induction therapy.

Thrombocytopenia is the most common side effect of lenalidomide (62%). This is followed by neutropenia with a rate of 59% (13). In another study, grade 3 neutropenia was found to be 35% and thrombocytopenia was found to be 13% (14). In our study, various degrees of neutropenia were detected in 69.2% of the patients, and G-CSF prophylaxis was given in 23.1% of the patients because of deep neutropenia. It was observed that 33.3% of the patients developed thrombocytopenia and 10.3% of them developed anemia. On the other hand, dose reduction was made in only 5.1% of the patients due to deep neutropenia, and the treatment was interrupted or terminated in 5.1% of the patients. Although it is close to the literature data, the frequency of neutropenia was found to be higher, and thrombocytopenia was found to be lower. The reason for the higher rates of neutropenia was thought to be that while IMID group treatments were used in the ASCT preparation regimen in the first place in studies, the use of IMID group drugs at a higher rate in our country and the associated lower bone marrow reserve. However, grade 3 and higher neutropenia was observed at a lower rate. At this point, it has been observed that the treatment at the optimum dose and for the desired time can be maintained with appropriate interventions for the cytopenia developed in multiple myeloma patients followed up in our clinic. Utilizing G-CSF when needed and maintaining treatment by applying general measures to clinically stable patients were considered as another reason for the success in response rates.

In the MM-009 and MM-010 studies, the incidence of VTE was found to be 8.8-14.7% with the combination of lenalidomide - dexamethasone (15). No thromboembolic event was observed in 70 (89.8%) of the 78 patients included in our study who received lenalidomide treatment. On the other hand, 5.1% DVT and 5.1% DVT + PTE developed. These rates are consistent with the literature. In 5.2% of the patients included in our study, the dose was reduced due to VTE, the treatment was interrupted in 2.6%, and the treatment was terminated in 2.6%. When the patients who developed pulmonary thromboembolism were examined, it was determined that these patients were generally elderly, had multiple comorbidities, had high disease activities, and were followed for more than 80 months. All these patients experienced VTE under ASA, and LMWH treatment was added afterwards. Conditions that increase the risk of thromboembolism with IMID group drugs are summarized in Table 7, and even MM disease is considered a risk factor. It seems more appropriate to perform VTE prophylaxis with ASA + LMWH in high-risk patients.

When the literature is examined, although mostly mild infections develop, serious infections can also be seen in 10-20% of patients. For this reason, it is recommended to give antibiotic prophylaxis especially in patients using lenalidomide in combination with high-dose dexamethasone (16). In a meta-analysis compiled by Ying et al., the incidence of severe infection was found to be between 6.94% and 21.47% (17). In our study, when the infections that developed during the use of lenalidomide were examined, in 21.8% of the patients, the drug was interrupted due to infection, the dose was reduced in 10.2%, and the treatment was terminated in 6.4% of the

patients. The most common infection was pneumonia in 19.2% of the cases. It was observed that 10 of 17 patients whose treatment was interrupted for infectious reasons did not receive any antibiotic prophylaxis until infection. Accordingly, as a result of the analysis, the rate of infection that is serious enough to require interruption of treatment in patients receiving antibiotic prophylaxis was 14.2%, while this rate was determined as 58.8% in patients who did not receive prophylaxis. When the patients who had dose reduction due to infectious reasons were examined, it was observed that 4 of 8 patients did not receive prophylaxis until dose reduction. Accordingly, the rate of infection in patients who received prophylaxis was 8.1%, which required dose reduction, while this rate was 50.0% in patients who did not receive prophylaxis. These rates are statistically significant ($p < 0.05$). When the infection rates were examined, it was found to be compatible with the literature.

Although it was predicted that the treatments containing lenalidomide might have infectious side effects when they were first used, they had not been experienced enough yet. When infections began to appear in patients using lenalidomide, the need for antibiotic prophylaxis arose. However, since there was no specific protocol, various antibiotic prophylaxis was tried. However, with recent experience, TMP-SMZ and clarithromycin prophylaxis have come to the fore. Serious infection rates decreased with the use of prophylaxis. It was observed that 62.8% of the patients included in our study were given antibiotic prophylaxis with various agents, and the mean prophylaxis duration of the patients was 9.3 months, and the median prophylaxis duration was 9 months (1 - 26). In our study, it was observed that the incidence of infectious side effects requiring treatment termination, dose reduction or interruption of treatment decreased with prophylaxis. When the literature was examined, the recommended prophylaxis duration was generally determined as 3 months, but it was observed that no prophylaxis agent was recommended in the foreground (14). For this reason, it seems appropriate that the prophylactic agent should be chosen by the clinician according to the dominant pathogens in the community and clinic.

Since the number of patients included in our study who received pomalidomide and thalidomide was significantly less than lenalidomide, the statistical significance of the data obtained in these patients was found to be lower, but valuable data were obtained. In the literature, the average response rate with thalidomide was 55% (18, 19); it was found to be 63% with pomalidomide (20). In various studies conducted with pomalidomide, response rates were found to vary between 33% and 70% (21). In our study, it was found to be 54.5% with thalidomide and 66.7% with pomalidomide.

It was observed that there was no dose reduction due to side effects in patients receiving thalidomide treatment, and only 1 (9.1%) patient was terminated due to neuropathy. When the literature was examined, the rate of thalidomide-induced neuropathy was found to be 25.4% in all grades, and it was seen as the most common side effect leading to dose reduction and treatment termination (22).

In a study conducted by Kumar et al. with 345 patients, the most common side effects with pomalidomide were found to be neutropenia with 31%, and anemia was found in 16%, thrombocytopenia in 12%, pneumonia in 8%, and VTE in 3% (23). In our study, all patients receiving pomalidomide treatment were given at least ASA prophylaxis, while high-risk patients (33.3%) were given ASA + LMWH prophylaxis. None of the patients developed VTE. In contrast, 33.3% of patients developed neutropenia and received G-CSF. Pneumonia developed in 20% of the patients, and one of them died due to sepsis due to pneumonia. Apart from this, one patient died due to neutropenic fever and one patient died due to urosepsis. In addition, when the patients who died due to infectious side effects were examined, it was seen that all these patients were unresponsive to treatment.

IX.   CONCLUSION

Immunomodulatory agents are very effective in the treatment of multiple myeloma, and it is important that the treatments are administered in sufficient doses and for a period so that patient compliance is best. For this, it is necessary to manage the side effects related to the treatments well and to use appropriate prophylaxis when

necessary. After the effective use of prophylaxis in our center, side effects are well tolerated and interruption of treatment due to side effects is minimized. In this way, treatment responses were improved. To obtain the best response in treatment, it has been emphasized by the data in clinical practice that attention should be paid to the close follow-up of patients using immunomodulatory therapy, the use of timely and effective infection prophylaxis, and the regulation of thromboembolism prophylaxis by considering the risk profiles of the patients.

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Table 1. Demographics and descriptives of study group

	Total n=85
Age, years, median (min-max)	62 (38-83)
Gender, male, n (%)	50 (58.8%)
Follow-up, months,	
Mean	64
Median (min-max)	57 (5-177)
Survival status, n (%)	
Dead	38 (44.7%)
Alive	47 (55.3%)
Overall survival, months	
Mean (standard deviation)	87 (5.70; 75.83 – 98.18)
Median (standard deviation)	77 (7.95;61.40 – 92.60)
Multiple Myeloma M-Protein, n (%)	
IgG Kappa	39 (45.9%)
IgG Lambda	17 (20.0%)
IgA Kappa	11 (12.9%)
IgA Lambda	6 (7.1%)
Lambda light chain	5 (5.9%)
Kappa light chain	4 (4.7%)

Non-secretory	3 (3.5%)
R-ISS stage, n (%)	
I	22 (25.9%)
II	32 (37.6%)
III	31 (36.5%)
Durie Salmon stage, n (%)	
1A	10 (11.8%)
1B	0
2A	25 (29.4%)
2B	3 (3.5%)
3A	28 (32.9%)
3B	19 (22.4%)
First line treatment, n (%)	
VAD	23 (27.1%)
AD	19 (22.4%)
VCD	15 (17.6%)
MPV	13 (15.0%)
VD	10 (11.8%)
CD	5 (5.9%)
Response to first line treatment, n (%)	
No response	11 (12.9%)
PR	74 (87.1%)
Autologous stem cell transplantation, n (%)	49 (57.6%)
IMIDs	
Thalidomide	11 (12.9%)
Lenalidomide	78 (91.8%)
Pomalidomide	15 (17.6%)
R-ISS: revised international staging system; VAD: vincristine + doxorubicin + dexamethasone; AD: doxorubicin + dexamethasone; VCD: bortezomib + cyclophosphamide + dexamethasone; MPV: melphalan + prednisolone + bortezomib; VD: bortezomib + dexamethasone; CD: cyclophosphamide + dexamethasone; IMIDs: immunomodulatory drugs	

Table 2. IMIDs' adverse effect profiles, therapeutic characteristics, and results

	Thalidomide n=11	Lenalidomide n=78	Pomalidomide n=15
Age, years, median (min-max)	59 (47-79)	62 (38-83)	55 (38-70)
Gender, male, n (%)	5 (45.5%)	46 (59.0%)	7 (46.7%)
Follow-up, months, median (min-max)	56 (5-139)	65 (10-177)	59 (20-138)
Survival Status, n (%)			
Dead	3 (27.3%)	34 (43.6%)	6 (40.0%)
Alive	8 (72.7%)	44 (56.4%)	9 (60.0%)
Line of treatment, n (%)			
2nd line	3 (27.3%)	10 (12.8%)	0
3rd line	4 (36.4%)	64 (82.1%)	0
4th line	3 (27.3%)	3 (3.8%)	6 (40.0%)
5th line	1 (9.1%)	1 (1.3%)	7 (46.7%)
6th line	0	0	2 (13.3%)
Duration of drug use, months, median (min-max)	24 (1-120)	12 (1-46)	4 (1-10)
Time to response, months, median (min-max)	2.5 (1-4)	2 (1-6)	2 (1-3)

Response to treatment, n (%)			
No response	5 (45.5%)	9 (11.5%)	4 (26.7%)
CR	2 (18.2%)	11 (14.1%)	0
VGPR	3 (27.3%)	27 (34.6%)	2 (13.3%)
PR	1 (9.1%)	31(39.7%)	9 (60.0%)
Antibiotics prophylaxis, n (%)			
None	11 (100%)	29 (37.2%)	4 (26.7%)
TMP-SMZ	0	21 (26.9%)	2 (13.3%)
Clarithromycin	0	17 (21.8%)	7 (46.7%)
TMP-SMZ + clarithromycin	0	6 (7.7%)	2 (13.3%)
TMP-SMZ + ciprofloxacin	0	3 (3.8%)	0
Ciprofloxacin	0	2 (2.6%)	0
Duration of antibiotics prophylaxis, months, median (min-max)	-	9 (1-26)	4 (1-10)
VTE prophylaxis, n (%)			
None	5 (45.5%)	0	0
5-ASA	6 (54.5%)	59 (75.7%)	10 (66.7%)
5-ASA + LMWH	0	19 (24.3%)	5 (33.3%)
Hematological adverse effects, n (%)			
None	5 (45.5%)	0	1 (6.7%)
Neutropenia	3 (27.3%)	54 (69.2%)	11 (73.3%)
Thrombocytopenia	2 (18.2%)	26 (33.3%)	3 (20.0%)
Anemia	1 (9.1%)	8 (10.3%)	0
Other adverse effects, n (%)			
None	0	0	0
Infection	2 (18.2%)	59 (75.7%)	4 (26.7%)
VTE	1 (9.1%)	8 (10.2%)	0
Neuropathy	7 (63.6%)	0	0
Hepatotoxicity	0	6 (7.7%)	0
Other	1 (9.1%)	6 (7.7%)	0
Treatment status, n (%)			
Continue	2 (18.2%)	22 (28.2%)	6 (40.0%)
Stop	9 (81.8%)	56 (71.8%)	9 (60.0%)
Reason for discontinuation of treatment, n (%)			
Death	3 (27.3%)	10 (12.8%)	5 (33.3%)
Adverse effects	4 (36.4%)	17 (21.8%)	1 (6.6%)
Relapse	1 (9.1%)	18 (23.1%)	3 (20%)
CR	1 (9.1%)	11 (14.1%)	0
Cause of death, n (%)			
Infection	2 (18.2%)	2 (2.6%)	5 (33.3%)
Stroke	1 (9.1%)	4 (5.2%)	0
Other	0	4 (5.2%)	0
IMIDs: immunomodulatory drugs; CR: complete response; VGPR: very good partial response; PR: partial response; TMP-SMZ: trimethoprim-sulfamethoxazole; 5-ASA: 5-acetylsalicilic acid; LMWH: low molecular weight heparin; VTE: venous thromboembolism			