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An Experience on Pomalidomide in Patients within Relapsed/Refractory Multiple Myeloma - A Multicenter Study in Turkey

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Authors' contributions

This work was carried out in collaboration among all authors. Author MAE, AS, SK and FA designed the study. Author MAE, MSD, MB, AB and SD wrote the protocol. Author FH, JY, MB, SN, MM, DO, SK and BE managed the analyses of the study. Author OE, MSD, TH, AB, EG, MM, BS, SD, DO, TU, BE and FA managed the literature searches. Author JY, MHD and TU performed the statistical analysis. Author AS wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Pomalidomide is a new generation thalidomide analogue. Effectiveness as a single agent or combination with low dose dexamethasone has been in the treatment of relapse/refractory Multiple Myeloma (MM). The aim of the present study was to share the experience of different oncology centres with pomalidomide treatment in patients with relapsed/refractory MM.
Materials and Methods: Seventy-three patients from 16 centres were enrolled into the study. The patients were followed for a median of 6 months. Relapsed/refractory MM patients who received at least one line of treatment before pomalidomide were included into the study. ISS, R-ISS and Eastern Cooperative Oncology Group (ECOG) scores of the patients and treatment-related side effects were evaluated.
Results: As a result of the median follow-up for 6 months, 36% (26/72) of the patients presented progression. The estimated median PFS was found 29 months. The Cox regression analysis revealed that ECOG affected PFS only, myeloma subtype; ISS and R-ISS scores did not affect PFS. The most common side effects with pomalidomide treatment in our population include neutropenia, infections, anaemia and thrombocytopenia.
Conclusion: In our study, it was statistically shown that the ECOG score was effective in survival in relapsed / refractory MM patients treated by pomalidomide. Therefore, we recommend evaluation of the ECOG score for each patient before treatment in eligible cases.

Keywords: Multiple myeloma; pomalidomide; ECOG; neutropenia; immunomodulatory drugs.

1. INTRODUCTION

Multiple myeloma (MM) is a B-cell neoplasm characterized by neoplastic proliferation of plasma cells that produce a monoclonal immunoglobulin. Increased plasma cells in the bone marrow may cause bone pain, lytic bone lesions, and pathological fractures. It is estimated that the incidence of MM disease with a median age of over 70 years of age at diagnosis would increase by 80% in the next 20 years with the increase in the elderly population [1].

The revised International Staging System, in which increased beta-2 microglobulin and decreased albumin levels are poor prognostic values, is used for risk assessment in MM patients. Detection of t (4; 14), t (14; 20), t (14; 16), del17p13, or gain 1q by FISH; lactate dehydrogenase (LDH) level as 2-times higher than the upper limit in biochemistry, and presence of primary plasma cell leukaemia are high risk indicators in MM [2]. However, it is known that not all of these chromosome abnormalities are valid for R-ISS.

Autologous hematopoietic cell transplantation (HCT) was reported to prolong both event-free and overall survival (OS) in comparison to chemotherapy alone for treatment of MM [3]. Autologous HCT is needed because MM cannot be cured by chemotherapy alone. In a randomized trial comparing autologous HCT with chemotherapy alone, autologous HCT was reported to improve event-free survival (EFS) and OS [4,5].

Almost all patients with MM will present relapse and require further treatment. Treatment options for patients with relapse/refractory MM include HCT, repetition of the previous chemotherapy regimen, or implementation of a new chemotherapy regimen. Although very good responses can be obtained with induction therapies, especially with the combination of proteasome inhibitors and immunomodulatory drugs, no modern induction approach is superior to consolidation therapy with autologous HCT. It has been shown that autologous HCT increases the likelihood of remission and prolongs progression-free and overall survival (OS) in MM patients [6]. There are various chemotherapeutic drugs used for relapse/ refractory MM patients. The factors to be considered for treatment selection include the previous treatments, responses of patients to these treatments, co-morbidities, and risk scoring of the patient.

The main drugs that may be used for treatment of relapse/refractory MM are proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), monoclonal antibodies (daratumumab, elotuzumab, isatuximab), alkylating agents, anthracyclines, and corticosteroids as a single agent or usually in combinations of two to three drugs. Patients who

relapse after lenalidomide therapy may respond to a regimen involving pomalidomide [7].

Pomalidomide is a new generation thalidomide analogue. Pomalidomide was shown to be effective as a single agent or in combination with low dose dexamethasone for treatment of relapse/refractory MM [8,9]. Positive efficacy of pomalidomide-dexamethasone combination was reported on progression-free survival (PFS) and OS [10]. Pomalidomide-Proteasome Inhibitor-Dexamethasone (P-VD) Combination, Pomalidomide-Cyclophosphamide-Dexamethasone (PCycloD) Combination and Pomalidomide–Antibody (Daratumumab)–Dexamethasone Combination therapies are widely used for treatment of MM [11,12].

The aim of the present study was to share the experience of different oncology centres with pomalidomide treatment in patients with relapsed/refractory MM.

2. MATERIALS AND METHODS

Patients who received at least one line of treatment before pomalidomide were included into the study. All patients in this study received lenalidomide treatment prior to pomalidomide. The patients were followed for a median of 6 months. Seventy-three patients from 16 centres were enrolled into the study. The data of the patients included in the study were obtained from electronic information system of the hospital and patient records.

Pomalidomide 4 mg was given orally on daily basis in days 1 to 21 of each 28-day cycle with low-dose dexamethasone. All patients received only pomalidomide / dexamethasone combination. The dose of pomalidomide in hemodialysis patients was revised to 3 mg / day. The International Staging System (ISS) and Revised International Staging System (R-ISS) are used to classify patients [13]. The ISS was staged as follows; Stage I: β2-microglobulin <3.5 mg/L with a serum albumin of 3.5 g/dL or more; Stage II: Either of these 2 criteria: β2-microglobulin between 3.5 mg/L and 5.5 mg/L and albumin <3.5 g/dL; Stage III: β2-microglobulin >5.5 mg/L. The R-ISS was staged as follows; Stage I: Serum β2 microglobulin < 3.5 mg/L, Serum albumin ≥ 3.5 g/dl, Standard-risk chromosomal abnormalities (CA) and Normal LDH; Stage II: Not R-ISS stage I or III; Stage III: Serum β2 microglobulin ≥ 5.5 mg/L and either, High-risk CA by FISH or High LDH.

Anaemia is defined as serum Hemoglobin (Hb) levels of<13 and <12 g/dL in men and women, respectively. Neutropenia was graded as follows; Grade 1 neutropenia: absolute neutrophil count (ANC) < 2,000 cells/mm^3; Grade 2 neutropenia: ANC 1,000 to 1,500 cells/mm^3; Grade 3 neutropenia: ANC 500 to 1,000 cells/mm^3; Grade 4 neutropenia: ANC < 500 cells/mm^3. Grade 1 thrombocytopenia is defined as platelet count of 75 to 150 × 10^3 /µL; Grade 2 thrombocytopenia is defined as platelet count of 50to 75 × 10^3 /µL; Grade 3 thrombocytopenia is defined as platelet count of 25to 50 × 10^3 /µL; Grade 4 thrombocytopenia is defined as platelet count < 25 × 10^3 /µL.

Elevations in aminotransferases are graded according to the WHO classification as follows: grade 0 within normal limits, grade 1 > upper limit normal (ULN) to 2.5 times ULN, grade 2 > 2.5 times ULN-5 times ULN, grade 3 >5 times ULN-20 times ULN, grade 4 >20 times ULN.

2.1 Statistical Analysis

Normality analysis of the data and other statistical analyses were performed using IBM SPSS 25.0 version. After the normality analysis was performed with the Shapiro-Wilk test, the data were given as median (min-max). Cox regression analysis was performed to determine the factors affecting progression.

3. RESULTS

A total of 73 patients from 16 different cancer centres were included in the study (33 males, 40 females). The demographic and characteristic characteristics of the patients before pomalidomide treatment are summarized in Table 1.

ISS and R-ISS scores of 73 myeloma patients included in the study are given in Table 2.

The most common side effects with pomalidomide treatment in our population were neutropenia, infections, anaemia, and thrombocytopenia. The incidence of side effects seen in our patients is provided in Table 3.

As a result of the median follow-up of 6-month period, 36% (26/72) of the patients presented progression. The estimated median PFS was found 29 months. As a result of univariate analysis; it was found that only ECOG affected PFS (table 4). However, ECOG's effect on overall survival could not be demonstrated.

Table 1. Demographic and clinical characteristic features of patients

Gender	
Male	33 (45,2%)
Female	44 (54,8%)
Age, median (min-max)	67 (47-94)
Number of previous treatment lines median(min-max)	3 (1-6)
Follow-up time (months) median(min-max)	6 (2-34)
Hemoglobin, before pomalidomide median(min-max)	10.1 (6.2-14.8)
Neutrophil, before pomalidomide median(min-max)	2.39 (0.44-9.9)
Thrombocyte, before pomalidomide median(min-max)	139 (17-232)
LDH, before pomalidomide median(min-max)	210 (73-1477)
GFR median(min-max)	74 (7-114)
Beta-2 microglobulin median(min-max)	5.2 (1.9-33)
Myeloma subtype	
IgA	42 (57.5%)
IgG	17 (23.3%)
Light Chain	14 (19.2%)
Eastern Cooperative Oncology Group (ECOG)	
0	6 (8.2%)
1	42 (57.5%)
2	18 (24.7%)
3	7 (9.6%)

Table 2. Distribution of patients according to ISS and R-ISS prognostic scoring systems

ISS	
1	9 (12.3%)
2	31 (42.5%)
3	32 (43.8%)
Unknown	1 (1.4%)
R-ISS	
1	7 (9.6%)
2	50 (68.5%)
3	13 (17.8%)
Unknown	3 (4.1%)

Table 3. Side effects during treatment with pomalidomide

Dermatologic eruption (%)	5/66 (7.6%)
Neutropenia (%)	42/66 (63.6%)
Anemia (%)	33/66 (50%)
Thrombocytopenia (%)	29/66 (43.9%)
Diarrhoea (%)	4/66 (6.1%)
Constipation (%)	8/66 (12.1%)
Pneumonia (%)	17/66 (25.7%)
Hypertension (%)	9/66 (13.6%)
Other infections (%)	21/66 (31.8%)
Bleeding (%)	1/66 (1.5%)
Hepatotoxicity (%)	4/66 (6,1%)
Neutropenic fever (%)	17/66 (25,7%)
Oedema	6/66 (9,1%)

4. DISCUSSION

Pomalidomide is an analogue of thalidomide with immunomodulatory, anti-angiogenic and anti-apoptotic characteristics used for treatment of MM. It is available in oral form used in the treatment of relapsed/refractory MM. It has been reported that pomalidomide prolongs PFS and OS in relapsed/refractory MM patients who have received 2 lines of any previous therapy (≥2 cycles of both bortezomib and lenalidomide) [14]. EMA and FDA approved the Pomalidomide / dexamethasone combination therapy in relapsed / refractory MM patients in 2013 [15].

Table 4. Factors that affect the progression (p value)

Parameters	p value
R-ISS	0.653
ISS	0.747
Myeloma subtype	0.330
Number of treatments received before pomalidomide	0.727
ECOG (Before pomalidomide)	0.013

Sixty relapsed/refractory MM patients were evaluated in the first phase II study of pomalidomide in combination with low-dose dexamethasone for treatment of relapsed or refractory multiple myeloma. In this trial, pomalidomide was given at a dose of 2 mg daily in days 1 through 28 of a 28-day cycle. In

addition, 40 mg of dexamethasone was given on daily basis in days 1, 8, 15, and 22 of each cycle. Consequently, 38 patients (63%) achieved a response including complete response in three patients, very good partial response in 17 patients, and partial response in 18 patients. The median PFS time was 11.6 months. Pomalidomide therapy was frequently well tolerated in this trial. Toxicity is mainly caused by myelosuppression. Grade 3 or 4 hematological toxicity occurred in 23 patients, and consisted of neutropenia (32%), anemia (5%) and thrombocytopenia (3%) [16].

Two different dosing regimens of pomalidomide and dexamethasone were evaluated in advanced MM in a multi-centres, phase 2, randomized study. Pomalidomide (4 mg) was administered in days 1 to 21 or continuously over a 28-day cycle in addition to dexamethasone which was administered weekly. The median overall survival was similar to two different regimens. Among the patients, 57% (similar in 2 arms) and 44% (49% arm 21/28 days and 39% arm continuously group) of patients were alive after 12 months and 18 months of pomalidomide therapy, respectively. In this trial, grade 3 and 4 adverse events were neutropenia by 62%, anaemia by 36%, thrombocytopenia by 27%, pneumonia by 13%, dyspnoea by 12%, bone pain by 11%, renal failure by 11%. As a result of this trial, it has been demonstrated that the combination of pomalidomide and low dose dexamethasone is highly active and well tolerated for treatment of relapsed and refractory MM [9].

A previous phase III (MM-003; NIMBUS) trial evaluated the clinical benefit of the pomalidomide / dexamethasone combination (pomalidomide 4 mg 21/28 plus low dose dexamethasone) versus high dose dexamethasone (320 mg per cycle) in relapsed/refractory MM patients against bortezomib and lenalidomide treatment [10]. In the study in which 455 patients were randomly recruited, superiority of pomalidomide / dexamethasone arm was reported when compared to the high-dose dexamethasone arm in PFS (median 2 months) and OS (median 5 months) at the end of 10 months. In the pomalidomide / dexamethasone arm of the aforesaid study, grade 3-4 neutropenia was reported by 48% and grade 3-4 infection by 30%. Similar to this study, neutropenia (63.6%) and infection (57.6%) were observed in the majority of the patients in our study.

A phase IIIb study (MM-010; STRATUS) trial also investigated the efficacy and safety of low-dose dexamethasone plus pomalidomide in relapsed/refractory MM patients. After a median follow-up of 16.8 months, treatment with pomalidomide plus low dose dexamethasone was associated with an average PFS of 4.6 months, an average OS of 11.9 months, an overall response rate of 33%. The most common haematological side effects in patients include neutropenia detected in approximately half of the patients, and anaemia detected in approximately one third of the patients [17]. Moreau et al. reported the most common side effects during pomalidomide treatment as neutropenia (56% of patients), anemia (32%), thrombocytopenia (26%) and febrile neutropenia (6%) [18]. Similarly, in our population, the most common haematological side effects are neutropenia (63.6%) and anaemia (50%). In our study, the median progression period was 29 months in patients with a median follow-up period of 6 months. No progression was observed under pomalidomide treatment in 63% of the patients included in our study.

In a non-randomized phase 2 study conducted on 100 MM patients who were initially treated with bortezomib and lenalidomide, and treated with pomalidomide-cyclophosphamide-dexamethasone (PCD) at first relapse, 91% of patients had partial or better response after 4 cycles of PCD. As a result of an univariate analysis, it was found that immunoglobulin type and ISS score did not affect the response of the patients to pomalidomide treatment [11]. Similarly, in our study, it was found that myeloma type, ISS and R-ISS scores did not affect progression time, only ECOG affected PFS.

In a multi-centred, retrospective study on 117 relapsed / refractory MM patients, the efficacy and toxicity of pomalidomide were examined. The median treatment line previously received by the patients of the study was 5 (2-11). In this study, the median PFS of the patients was 5.6 months, and the median OS was 8.4 months [19]. In our study, the estimated median PFS was determined as 29 months. The reason for the better median PFS in our study may be related to the fact that patients received 3 (1-6) lines of treatment before pomalidomide.

Since myeloma subtype, ISS, and R-ISS scores were not statistically correlated with PFS, this may be explained by low number of patients and retrospective nature of the study.

5. CONCLUSION

In our study, it was found that myeloma type, ISS and R-ISS scores did not affect progression time, only ECOG affected PFS. It was statistically shown that the ECOG score was effective in survival in relapsed / refractory MM patients treated by pomalidomide. Therefore, we recommend evaluation of the ECOG score for each patient before treatment in eligible cases.

CONSENT AND ETHICAL APPROVAL

The ethics committee of Inonu University approved our study (approval number: 2020/1051). As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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