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Original Article

Evaluation of immunomodulatory drugs in multiple myeloma: single center experience

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Abstract: Objective: Multiple myeloma (MM) comprises 1% of all cancers and 10% of hematologic malignancies and known as an incurable disease. The introduction of immunomodulatory drugs (IMiDs) has brought a major shift in therapeutic paradigm in the treatment of newly diagnosed and relapsed/refractory MM patients. The aim of this study was to evaluate the relationship between response status and hematological parameters in patients with MM treated with thalidomide or lenalidomide. Methods: Sixty-eight patients who were treated with IMiDs in Ege University, School of Medicine, Department of Hematology, between 2005 and 2012, were evaluated, retrospectively. Results and Conclusion: We could not find any difference between the hematological parameters before and after the treatment neither with thalidomide nor lenalidomide. However, the heterogenity of our groups, the difference in treatment strategies and potential side effects would have an impact on this result. It is needed to perform prospective clinical trials to prove that whether correction of hematological parameters would reflect the response status in patients with myeloma that treated with IMiDs.

Keywords: Multiple myeloma, immunomodulatory drugs, thalidomide, lenalidomide

Introduction

The therapeutic circumstance of multiple myeloma (MM) that improve patient outcomes has changed in recent years, with the introduction of new drugs into routine clinical use, increased use of autologous stem cell transplantation (ASCT) and improved supportive care [1, 2]. Thalidomide and lenalidomide are immunomodulatory drugs (IMiDs) that are approved for treatment of newly diagnosed or relapsed/refractory MM patients, combination with steroids, proteosome inhibitors and alkilayting agents. Pomalidomide, like the others, has potent immunomodulatory activity and has been approved by the US Food and Drug Administration for the treatment of relapsed/refractory MM.

Thalidomide is a potent antiangiogenic agent that also stimulates primary human T-cells and natural killers, modulates cytokines, and increases IL-2-mediated T-cell proliferation and IFN-γ production by T-cell receptor complex [3]. Thalidomide was shown to bind to cereblon, which is the substrate-recognition component of a cullin-dependent ubiquitin ligase, and to inhibit its autoubiquitination activity. CRBN depletion is initially cytotoxic to human myeloma cells [4, 5].

Efficacy of thalidomide was firstly evaluated by Singhal et al. as an single agent in MM patients who were relapsed after high-dose chemotherapy and indicated that thalidomide is an effective treatment for relapsed/refractory MM patients with 22±5% event-free survival (EFS) and 58±5% median overall survival (OS) [6, 7]. Also, thalidomide maintenance therapy has been shown to increase progression-free survival (PFS) after conventional therapy and ASCT, but high rates of discontinuation of the drug due to toxicities and decrease in quality of life has been reported [8, 9].

Although thalidomide is an effective agent, its adverse side-effects and dose-limiting toxicities including fatigue, somnolence, constipation, skin problems, neuropathy and increased incidence of thrombosis are confusing. Therefore, some researches were initiated to explore more potent and safer drugs. Lena-

Tabel 1. The main characteristics of the patients

	Thalidomide	Lenalidomide
Number of patients	34	34
Median age	58.8 (39-78)	61.3 (45-78)
Sex (Male/Female)	23/11	22/12
Stage		
I (A+B)	1 (2.9%)	2 (5.8%)
II A	2 (5.8%)	4 (11.8%)
III (A+B)	31 (91.1%)	28 (82.3%)
Ig type		
G based (-kappa or -lamba)	22 (66.8%)	28 (82.3%)
G	3 (8.8%)	-
A based (-kappa or -lambda)	4 (11.6%)	5 (14.7%)
A	4 (11.7%)	-
Kappa	1 (2.9%)	-
Lambda	-	1 (2.9%)
Median IMiD dose	285 mg/day (50-400)	18.3 mg/day (5-25)
Time from diagnosis to IMiD use	26.1 months	33.1 months
Line of therapy		
First	-	-
Second	15 (44.1%)	9 (26.4%)
Third	15 (44.1%)	17 (50.0%)
Fourth	4 (11.8%)	8 (23.5%)
ASCT*	17 (50.0%)	15 (44.1%)
Median duration of IMiD use	20 months	7 months
OS**	60.5 months	44 months
PFS***		
1-year	64.7%	76.4%
3-year	29.4%	-
5-year	5.9%	-
1-year mortality	17.6%	0%
Side effects		
Thrombosis	1 (2.9%)	0%
Neuropathy	13 (38.2%)	0%
Pneumonia	2 (5.8%)	4 (11.8%)
Cytopenias	9 (26.5%)	8 (23.5%)
Constipation	16 (47.1%)	0%
Rash	3 (8.8%)	0%

*ASCT: Autologous Stem Cell Transplantation, **OS: Overall Survival, ***PFS: Progression-free Survival.

lidomide was derivated from thalidomide and it is more effective in mediating direct cytokine-related and immunmodulatory effects [10] with much less severe side-effects [2]. Most common grade 3-4 adverse effects of lenalidomide are cytopenias, fatigue, rash, infections and venous thromboembolism.

Thalidomide appears to have more antiangiogenic potential than lenalidomide, whereas lenalidomide has greater immunomodulation and tumor inhibiting properties than thalidomide [11, 12].

Lenalidomide and dexamethasone combination was found effective in newly diagnosed MM patients with 91-95% overall response and 32-38% very good partial response (VGPR) or better rates [13].

A comprehensive meta-analysis of randomized controlled trials signified that the addition of lenalidomide to conventional therapy has no impact on survival but can improve PFS compared with conventional therapy alone in newly diagnosed MM patients [14].

Hematological parameters which are performed as a part of routine investigations are easily available and cheaper than serum/urine electrophoresis, bone marrow biopsy and β2 microglobulin levels which are expensive, invasive and require high technical set up [15]. There are also very few studies that evaluate hematologic parameters as an early predictor of response to IMiDs.

The aim of this study is to share experience of our centre in myeloma patient groups in terms of demographic features and clinical status treated with thalidomide or lenalidomide and the potential predictive value of improvement or regression in hemoglobin (Hb), hematocrit (Htc), white blood count (WBC) and platelet levels before and during IMiD therapy.

Methods

The data of 68 MM patients who were treated with IMiDs and followed up at Hospital of Ege University School of Medicine, Adult Hematology

Table 2. Laboratory values of patients before and after IMiDs

	Thalidomide	Lenalidomide
Before treatment		
Hb*	11.6	11.9
Htc*	34.8	35.9
WBC*	4.58	6.44
Plt*	182	209
1st month		
Hb	11.5	11.6
Htc	35.2	35.2
WBC	4.43	5.58
Plt	197	205
2nd month		
Hb	11.8	11.6
Htc	35.2	35.1
WBC	4.65	5.21
Plt	212	172
3rd month		
Hb	12.0	11.5
Htc	36.2	34.4
WBC	4.73	4.56
Plt	212	169

*Hb g/dL, *Htc%, *WBC mm^9, *Plt mm^9.

Department, between January 2005 and July 2012 was analyzed, retrospectively. The patient data and variables related to treatment strategies (age, sex, first and second chemotherapy regimens, daily IMiD doses, side effects, OS, PFS and mortality) were obtained from the records of the hematology clinic (**Table 1**). The hemogram levels were compared at the beginning, during the therapy and if ceased, at the end of therapy. For evaluation, hemoglobin and hematocrit levels, leukocyte and platelet counts were extracted from patients files which were performed at the beginning and first, second and third months of the treatment. These values are classified based on the patients' response status and also evaluated separately for each patient individually. The first 3 months' values and responses were allowed for evaluation.

We analyzed the relationship between IMiDs use and hematologic parameters with a multivariate test (logistic regression). *P* values less than 0.05 were considered significant. The data were analyzed using computer software (SPSS 16.0, SPSS, Inc., Chicago, IL).

Results

Thirty-four MM patients who were treated with thalidomide between 2005 and 2012 were analyzed. The median age of the patients was 58.8 years (39-78 years), and of 23 (67.6%) males and 11 (32.4%) females. According to Durie-Salmon staging 31 (91.1%) patients were stage 3 (A+B), 2 (5.8%) were stage 2A and 1 (2.9%) of the patients was stage 1A. Twenty-two (64.7%) of the patients were Ig G based (-kappa or lambda) myeloma, 4 (11.7%) were Ig A, 3 (8.8%) were Ig G, 2 (5.8%) were Ig A based (-kappa or -lambda) (8.7%) and 1 (2.9%) patient was kappa myeloma. Autologous stem cell transplantation (ASCT) was performed to 17 (50.0%) patients before the thalidomide treatment. Age, performance status and co-morbidities were the reasons of avoiding from transplantation in the rest of the patients. None of the patients were transplanted after the thalidomide treatment. Lenalidomide could not be used before the thalidomide treatment due to regulatory issues but 10 (29.4%) patients were treated with lenalidomide after thalidomide, sequentially due to disease progression. Thalidomide was combined with methylprednisolone in 8 (23.5%) patients and with dexamethasone in 4 (11.8%) patients. The time from diagnosis to use of thalidomide was 26.1 months. Thalidomide could not be used as first-line therapy in any patient. It was used as second-line treatment in 15 (44.1%) patients, third-line treatment in 15 patients (44.1%) and fourth-line treatment in 4 (11.8%) patients. The median thalidomide dose was 285 mg/day (50-400 mg) and the median duration of thalidomide use was 20 months. Acetylsalicylic acid (ASA) and/or low-molecular weight heparin (LMWH) or warfarin were given to prevent thrombosis in patients with potential risk of thrombosis. Only one (2.9%) deep venous thrombosis was detected during the treatment period.

Median overall survival was 65.5 months. One-year OS was 85.3%, 3-year OS was 64.7% and 5-year OS was 14.7%. One-year PFS was 64.7%, 3-year PFS was 29.4% and 5-year PFS was 5.9%. 1-year mortality was 17.6%. Most prominent side effects were as follows: constipation in 16 (47.1%) patients, neuropathy in 13 (38.2%), cytopenias in 9 (26.5%), rash in 3 (8.8%) and pneumonia in 2 (5.8%) patients. Thalidomide was ceased in 17 (50.0%) patients

because of disease progression and in 2 (5.8%) patients because of severe neuropathy. Three (8.8%) patients died under thalidomide treatment. Five (14.7%) patients left the follow-up. Thalidomide treatment still continues in 7 (20.5%) patients. 18 patients died during the follow-up (**Table 1**).

The median values of the patients before thalidomide use, first, second and third month after initiation of thalidomide has been shown in **Table 2**. Improvement in values was observed but there were no statistically significant difference in hemoglobin levels, hematocrit, platelet and WBC counts before, during and after thalidomide treatment (**Table 2**).

We have added the data of 34 patients who were treated with lenalidomide between 2010 and 2012 for further evaluation. The median age of the patients was 61.3 years (45-78 years), and of 22 (64.7%) males and 12 (35.2%) females. According to Durie-Salmon staging system: 28 (82.3%) patients were stage 3 (A+B), 5 (14.7%) were 2 (A+B), and 1 (2.9%) of the patients was stage 1A. Twenty-eight (52.9%) of the patients were Ig G based (-kappa or -lambda) myeloma, 5 (14.7%) were Ig A based (-kappa or -lambda), and 1 (2.9%) patient was lambda myeloma. ASCT was performed in 15 (44.1%) patients before the lenalidomide treatment. No patients could move to ASCT after the lenalidomide treatment. Age, performance status and co-morbidities were the reasons of avoiding from transplantation in the rest of the patients. Median time from diagnosis to use of lenalidomide was found to be as 33.1 months. Acetylsalisilic acid (ASA) and/or low-molecular weight heparin (LMWH) or warfarin was used to prevent from thrombosis due to thrombosis risk of patients. No thrombosis was observed. In all cases, lenalidomide was combined with dexametasone at doses appropriate to patient age and co-morbidities. Thalidomide was used in 10 (29.4%) patients before the lenalidomide treatment and thalidomide was stopped due to disease progression in all patients. Lenalidomide could not be used as first-line therapy in any patient becouse of regulatory issues. It was used as a second-line therapy in 9 (26.4%) patients, as a third-line treatment in 17 (50.0%) patients and as a fourth-line therapy in 8 (23.5%) patients. The median lenalidomide dose was 18.3 mg/day (5-25 mg) and the median duration of lenalidomide treatment was 7 months (**Table 1**).

Median overall survival was 44 months. One-year OS was 100%, 1-year PFS was 76.4% and 1-year mortality was 0%. Most seen side effects were persistent cytopenias in 8 (23.5%) patients and, pneumonia in 4 (11.7%) patients. Lenalidomide stopped in 4 (11.7%) patients because of disease progression and in 4 (11.7%) patients because of persistent cytopenias. One (2.9%) patient died under lenalidomide treatment. Lenalidomide treatment has been still continuing in 25 (73.5%) patients.

Small decrease was observed but there was no statistically significant difference in terms of Hb, Htc, WBC and platelet levels before, during and after lenalidomide treatment. The median values of the patients before lenalidomide use, first-second and third month after initiation of lenalidomide has been shown in **Table 2**.

Discussion

According to our results, thalidomide and lenalidomide have been used in our patients at least after 2 or 3 prior therapies. Thalidomide has lesser efficacy and relatively high side effects. Lenalidomide seems to be more effective and have less side effects but it seems to be more expensive in Turkey health policies. This study could not compare the drugs directly because of patient heterogenity. OS of thalidomide seems better than lenalidomide but OS rates can not be compared because of different follow-up times. But 1-year PFS and 1-year mortality rates can indicate that lenalidomide can be a better option in relapsed/refractory MM with less side effects.

A comparative, retrospective analysis which aimed to evaluate the efficacy and toxicity of lenalidomide plus dexamethasone (len/dex) versus thalidomide plus dexamethasone (thal/dex) as an initial therapy for newly diagnosed 411 MM patients indicated that lenalidomide is a more effective treatment than thalidomide with similar grade 3 or 4 but more tolerable adverse events [16].

Decreased number of plasma cells in bone marrow and increased Hb levels were detected by Singhal et al. in relapsed/refractory patients with thalidomide treatment [4]. Uppal et al.

reported that Hb, WBC, absolute neutrophil count (ANC) and platelet levels all showed an improving trend within 2 months with thalidomide treatment [13]. Waage et al. indicated that Hb concentration showed a different time course, with a significant increase after 3 months and further increases continued for up to 12 months in their study that include 65 patients treated with thalidomide [17]. In evaluation of laboratory values of our patients; improvement was observed with thalidomide treatment but there were no statistically significant difference in Hb, Htc, WBC and platelet levels before and after the treatment. But our follow-up period comprimise a short period after start of IMiDs.

On the other hand regression in blood values with lenalidomide treatment was found in our study. This can be a predictor of myelosuppressive (hypocellularity) effect of lenalidomide. Prior lenalidomide treatment is associated with an increased risk of peripheral blood stem cell collection (PBSC) failure. Bhutani et al. reported that the median number of PBSCs collected in the lenalidomide treatment group was significantly less than the lenalidomide naive group. In addition, the median number of apheresis sessions required for adequate PBSCs collection was significantly more in the lenalidomide treatment group as compared to lenalidomide naive group. Also there was a negative correlation between PBSCs number and prior number of cycles of lenalidomide treatment [18]. PBSC has to be planned before or in early cycles of lenalidomide treatment.

Although there was no difference in our patients with stable and progressive disease status under treatment with thalidomide and lenalidomide in terms of blood levels, it is needed to have more patients and longer follow-up period. Blood levels might be a good indicator for evaluation of response to thalidomide therapy for patients treated for longer period.

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Disclosure of conflict of interest

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