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Journal of Hematology and Allied Sciences

Original Research

Relationship between first-line treatment response and bone marrow fibrosis in newly diagnosed multiple myeloma

Aysun Halacoglu[1]

[1]Department of Hematology, Medicana Bahcelievler, İstanbul, Turkey.

***Corresponding author:**
Aysun Halacoglu,
Department of Hematology,
Medicana Bahcelievler,
İstanbul, Turkey.

aysunhalacoglu@hotmail.com

Received: 08 December 2021
Accepted: 07 February 2022
EPub Ahead of Print: 05 March 2022
Published: 19 April 2022

DOI
10.25259/JHAS_30_2021

Quick Response Code:

ABSTRACT

Objectives: Multiple myeloma (MM) occurs with uncontrolled and clonal increase proliferation of plasma cells in the bone marrow. Myelofibrosis can be primary or can be secondary when associated with other malignant or non-malignant diseases. MM is a malignant disease in which both collagen and reticulin fibrosis can be detected together at the time of diagnosis.The aim of this study is to investigate the relationship between bone marrow fibrosis at diagnosis and response to after first-line treatment in newly diagnosed MM.

Material and Methods: In this study, 95 newly diagnosed MM patients were analyzed retrospectively. Demographic characteristics, complete blood count, biochemical examinations, bone marrow fibrosis grades, and first-line treatment response of the patients were retrieved from records as it is a retrospective study. Patients were divided into 2 groups according to their response to first- line treatment. Patients who have a strict complete response (sCR), complete response (CR) or a very good partial response (VGPR) responses to first-line therapy were included in the first group. Patients who gave partial response (PR), minimal response (MR) or progressive disease (PD) responses to the first-line therapy were included in the second group.

Results: There were 72 patients in the Group I (good response group) and 23 patients in Group II (poor response group). Between the good response group and poor response group myeloma type, platelet count at diagnosis, β2 microglobulin, lactate dehydrogenase, erythrocyte sedimentation rate, bone marrow plasma cell ratio, R-ISS, and first-line treatment were not statistically significant ($P > 0.05$). Age was statistically significantly lower in the good response group ($P = 0.04$). In male gender, a better response was obtained ($P = 0.02$). At the time of diagnosis, hemoglobin levels in the good response group were found high compared to the poor response group ($P = 0.02$). Bone marrow fibrosis was found to be lower at the time of diagnosis in the group that responded good response to first-line treatment ($P = 0.01$).

Conclusion: In this study, it was shown that bone marrow fibrosis at diagnosis is an important factor affecting the response to first-line treatment.The degree of bone marrow fibrosis detected at the time of diagnosis in MM may guide the selection of targeted therapy in first-line treatment.

Keywords: Multiple myeloma, Bone marrow, Fibrosis, Newly diagnosed, First-line treatment

INTRODUCTİON

Multiple myeloma (MM) is a malignant disease that occurs with uncontrolled and clonal increased proliferation of plasma cells in the bone marrow.[1] As myelofibrosis can be primary, it also can be secondary for malignant and non-malignant diseases. For the formation of bone marrow fibrosis, stimulants for fibroblast proliferation such as transforming growth factor-β, epidermal

growth factor (EGF), platelet-derived, and endothelial cell growth factor (PD-ECGF) that affect the platelet formation conversion factor released from megakaryocytes and platelets are required.[2] Myelofibrosis includes the increased deposition and qualitative composition of fibers (reticulin or collagen) in the bone marrow.[3] MM is a malignant disease where both collagen and reticulin fibrosis are detected together.[4,5] In the previous studies, the detection of bone marrow fibrosis in MM has been associated with a poor prognosis.[6,7]

The aim of this study is to investigate the relationship between bone marrow fibrosis at diagnosis and with response to first-line therapy in newly diagnosed MM.

MATERIAL AND METHODS

This study includes that 95 MM patients who received treatment in the hematology department of my hospital between January 2015 and June 2020 were diagnosed with MM according to the diagnostic criteria of the International Myeloma Working Group (IMWG). Bone marrow fibrosis was diagnosed and graded according to the criteria of a European consensus on the grading of bone marrow fibrosis.[3] Demographic characteristics, complete blood count, biochemical examinations, bone marrow fibrosis grades, and first-line treatment response of the patients were retrieved. Hematologic response assessment was carried out per IMWG consensus response criteria.[8]

Patients were divided into two groups according to their response to first-line treatment with IMWG response criteria.[8] Patients who gave a strict complete response (sCR), CR, or a very good partial response (VGPR) to first-line therapy were included in the first group. Patients who gave PR, minimal response (MR), or PD responses to the first-line therapy were included in the second group.

There were 72 patients in Group I (good response group) and 23 patients in Group II (poor response group).

All of the ethical considerations had been strictly followed in accordance with the Helsinki Declaration.

Statistical analysis

SPSS statistics 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Comparisons of categorical variables in groups were tested by Chi-square or Fisher exact tests. Percentage change rates of parameters were used for correlation analysis. The confidence interval was 95% and $P < 0.05$ was considered statistically significant.

RESULTS

In this study, 95 newly diagnosed MM patients were included and analyzed. About 43 (45.3%) of the patients were female and 52 (54.7%) were male. The age range was 37–86 years and the median age was 64 years.

Protein electrophoresis, serum, and 24-h urine immunoelectrophoresis were performed in all patients. IgG kappa was detected in 31 (32.6%) patients, IgG lambda in 22 (23.1%) patients, IgA kappa in 22 (23.1%) patients, IgA lambda in 6 (6.3%) patients, IgM kappa in 4 (4.2%) patients, 2 (2.1%) IgM lambda type, lambda light chain type in 7 (7.5%) patients, and kappa light chain type paraproteinemia in 1 (1.2%) patient. Non-secretory myeloma was not seen in any of the patients.

According to the R-ISS, 27 (28.4%) patients were Stage 1, 34 (35.8%) patients were Stage 2, and 34 (35.8%) patients were Stage 3.

First-degree bone marrow fibrosis was detected in 48 (50.5%) patients and second-degree fibrosis in 33 (34.7%) patients. Fibrosis was not detected in 14 (14.8%) patients. Grade 3 fibrosis was not seen present in any of the patients. No relation was seen between the percentage of plasma cells and BM fibrosis.

About 55 (57.8%) patients in the first-line treatment received PAD (bortezomib, adriamycin, and dexamethasone), 19 (20%) patients received VCD (bortezomib, cyclophosphamide, and dexamethasone), 9 (9.5%) patients received Vel-dex (bortezomib and dexamethasone), 5 (5.3%) patients received Thal-dex (thalidomide/dexamethasone), 4 (4.2%) patients received VRD (bortezomib, lenalidomide, and dexamethasone), and 3 (3.2%) patients received VAD (vincristine, adriamycin, and dexamethasone) [Table 1].

After the 2–4 course of first-line treatment, 6 (6.3%) patients gave sCR, 39 (41%) patients gave CR, 27 (28.5%) patients gave VGPR, 12 patients (12.6%) gave PR, 7 patients (7.4%) gave MR, and 4 (4.2%) patients gave PD.

Between the good response group and poor response group myeloma type, platelet count at diagnosis, β2 microglobulin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate, bone marrow plasma cell ratio, R-ISS, and first-line treatment were not statistically significant ($P > 0.05$). Age was statistically significantly lower in the good response group ($P = 0.04$). In the male gender, a better response was obtained ($P = 0.02$). At the time of diagnosis,

Table 1: First-line treatment regimens.

PAD	55 (57.8%)
VCD	19 (20%)
Vel-Dex	9 (9.5%)
Thal-Dex	5 (5.3%)
VRD	4 (4.2%)
VAD	3 (3.2%)

hemoglobin levels in the good response group were found high to poor response group (P = 0.02). Bone marrow fibrosis was found to be lower at the time of diagnosis in the group that gave a good response to first-line treatment (P = 0.01) [Table 2].

DISCUSSION

The first-line treatment response is very important because patients with an adequate response, age, and performance status after first-line treatment are eligible candidates for autologous stem cell transplantation (ASCT) in MM. In a study in the literature, after first-line treatment, rates of VGPR or better were as follows: 42% after four cycles.[9] In this study, an average of 2–4 cycles after the first-line treatment, 6.3% patients sCR, 41% patients CR, and 28.5% patients VGPR were obtained.

In a previous study[10] in MM first-line treatment 60% CTD (cyclophosphamide, thalidomide, dexamethasone) and 7% CyBorD (cyclophosphamide, bortezomib and dexamethasone) were used. In this study, first-line treatment of 57.8% patients PAD 20% patients VCD treatment was given. Good response was 78.2% in the group with PAD and 68.4% in the group with VCD.

There was statistical significance between first-line treatment response to light chain disease, Stage III disease, hemoglobin <10 g/dl, creatinine >2 mg/d, calcium >11 mg/dL, β2 microglobulin >5.5 mg/mL, and albumin <3.5 g/dL. There was no statistically significant relationship between age, LDH, and first-line treatment response.[9] In this study, no statistically significant relationship was found between the type of myeloma, the number of platelets at the time of diagnosis, β2 microglobulin, LDH, erythrocyte sedimentation rate, bone marrow plasma cell ratio, stage of the disease, and first-line treatment. However, in this study, a statistically significant relationship was found between age, sex, hemoglobin level, and first-line treatment response.

The previous studies have shown that some patients with MM have increased connective tissue in the bone marrow as a result of cytokine release and this has a prognostic significance.[11] In addition, the detection of fibrosis in the bone marrow at the time of diagnosis has been associated with a poor prognosis in MM. In this study, less bone marrow

Table 2: Relationship between first-line treatment response and other parameters.

	Good response group (n=72)	Poor response group (n=23)	P-value
Median age (range)	63 (37-86)	68 (53-83)	0.04
Sex, n (%)			
Female	28(38.8%)	15 (65.2%)	0.02
Male	44 (61.2%)	8 (34.8%)	
Myeloma type, n (%)			
Ig G/kappa	22 (30.5%)	9 (39%)	0.95
Ig G/lambda	17 (23.5%)	5 (21.9%)	
Ig A/kappa	18 (25%)	4 (17.6%)	
Ig A/lambda	5 (7%)	1 (4.3%)	
Ig M/kappa	3 (4.2%)	1 (4.3%)	
Ig M/lambda	1(1.4%)	1 (4.3%)	
Kappa	1 (1.4%)	-	
Lambda	5 (7%)	2 (8.6%)	
Time of diagnosis			
Hb (g/dl) (range)	9.9±1.5	9±1.9	0.02
Thrombocytes(mm^3) (median)	212,000	249,000	0.13
β2-microglobulin (mg/L) (range)	5.1±3.5	5.5±2.1	0.63
LDH (U/L) (range)	178±75	215±93	0.09
Sedimentation (range)	106±19	103±18	0.51
Bone marrow plasma cell ratio (range)	43±16	48±19	0.26
Stage (R-ISS), n (%)			0.97
I	24 (33.3%)	3 (13%)	
II	26 (36.1%)	8 (34.8%)	
III	22 (30.6%)	12 (52.2%)	
Bone marrow fibrosis, n (%)			0.01
Grade 1	39 (54.1%)	9 (39.1%)	
Grade 2	19 (26.4%)	14 (60.9%)	
No Fibrosis	14 (19.5%)	-	

fibrosis was found in the group with good first-line treatment response, and more bone marrow fibrosis was detected in the bone marrow biopsy performed at the time of diagnosis in the group with poor first-line treatment response. First-line treatment response was good in all patients who had no bone marrow fibrosis.

The fact that bone marrow fibrosis was found to be lower at the time of diagnosis in the group that responded good to first-line treatment may be especially important in terms of prognostic classifications. Increased bone marrow fibrosis at the time of diagnosis in MM is an important factor affecting the response to the treatment.

CONCLUSION

The relationship between first-line treatment response and bone marrow fibrosis at the time of diagnosis was evaluated in this study. It was shown that bone marrow fibrosis at diagnosis is an important factor affecting the response to first-line treatment. The degree of bone marrow fibrosis detected at the time of diagnosis in MM may guide the selection of targeted therapy in first-line treatment. Particularly, the addition of CD38 targeted therapy, daratumumab, to the first-line treatment of patients with increased bone marrow fibrosis at the time of diagnosis and who may be candidates for ASCT due to age and performance status may be considered. This study results need to be supported by randomized, prospective, and histopathological studies with the large number of patients.

Compliance with ethical standards

All of the ethical considerations had been strictly followed in accordance with the Helsinki Declaration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Halacoglu A. Relationship between first-line treatment response and bone marrow fibrosis in newly diagnosed multiple myeloma. J Hematol Allied Sci 2021;1:107-10.