The infection rate in new diagnosis and relapsed/refractory multiple myeloma patients who had bortezomib-based chemotherapy and relationship between development of infection and lymphocyte/monocyte ratio

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ABSTRACT

Objectives: Multiple Myeloma (MM) is a disease caused by the clonal proliferation of plasma cells. In recent years, proteozom inhibitors, immunomodulatory agents and monoclonal antibodies have been used in the treatment of MM. In this study, the relation of bortezomib, one of the proteozoma inhibitors used in the treatment of MM, with the development of infection was investigated.
Methods: We retrospectively evaluated 56 patients who had MM treated with bortezomib-based regimen. We tried to determine the relationship between infection with immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, neutrophil absolute value at the time of chemotherapy, lymphocyte absolute values at the time of infection, monocyte absolute value at the time of infection, and the lymphocyte/monocyte (L/M) ratio at the time of infection. The effects of L/M ratio on progression free survival (PFS) and overall survival (OS) were also examined.
Results: Thirty (53.6%) of the 56 patients were newly diagnosed, 26 (46.4%) of 56 patients were relapsed/refractory MM. The bortezomib-based regimen was given to all patients. Of the 56 patients included in the study, 21 (37.5%) were female, 35 were male (62.5%). The ages of the patients was 28-79 years (median: 58.5 years). No infection attack was observed in 31 (55.4%) patients. Disease stage (R-ISS) ($p = 0.032$), presence or absence of co-morbid disease ($p = 0.035$), disease status during an infection attack ($p < 0.01$), lymphocytopenia at the time of chemotherapy ($p = 0.003$), absolute value of lymphocytopenia at the time of infection attack ($p < 0.01$) and L/M ratio ($p < 0.01$) had a significant relation with development of infection. Lymphocytopenia at the time of infection attack ($p < 0.01$, OR < 1, 94.6% CI) and L/M ratio ($p < 0.01$, OR < 1, 91.1% CI) had been found significant in univariate logistic regression analysis. Lymphocytopenia at the time of infection attack ($p = 0.002$, OR < 1, 95% CI) and L/M ratio ($p = 0.003$, OR < 1, 95% CI) had been found significant in multivariate logistic regression analysis. L/M ratio had a significant effect on OS ($p < 0.017$) but not on PFS ($p > 0.05$).
Conclusions: It was determined that L/M ratio has an effect on OS and it is also an independent factor on the development of infection. OS was decreasing and the risk of developing infection was increasing, when the L/M ratio was low.
Keywords: bortezomib, infection, lymphocyte/monocyte ratio

Muliple Myeloma (MM) is a disease caused by clonal proliferation of plasma cells. It constitutes 10% of hematological cancers. For diagnosis, ≥ 10% clonal bone marrow plasma cells in bone marrow or a biopsy proven plasmacytoma plus evidence of one or more multiple myeloma defining events (MDE) namely CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions). Plasma cell disorder defined as bone marrow clonal plasmacytosis ≥ 60%, serum involved/uninvolved free light chain (FLC) ratio ≥ 100 (provided involved FLC is ≥ 100 mg/L), or > 1 focal lesion on magnetic resonance imaging (MRI) [1].

Many chemotherapeutic agents are used in the treatment of MM. The use of melphalan in the treatment of MM was a revolution in the 1950s [2], and then the demonstration of the effect of high-dose melphalan and autologous stem cell transplantation on progression-free survival changed the standard treatment approaches in MM [3] In the last 10 years, immunomodulatory drugs such as Thalidomide, Lenalidomide, Pomalidomid (IMID) and proteasome inhibitors such as Bortezomib have been started to use [4, 5]. Subsequently, CD38-targeted monoclonal antibody 'Daratumumab' was added in the MM patients' treatment [6]. Bortezomib is still being the first treatment option in MM in Turkey.

With the use of high-dose melphalan and bortezomib and new agents in the IMID group, there was a dramatic change in the mean survival in MM patients. Overall survival had been extended from 3 years to 8-10 years. This increase in efficacy also led to changes in the spectrum of side effects. Humoral immunodeficiency has been usually seen in MM patients. After using these drugs in the MM patients' treatment, they began to affect cellular immune functions, and changing infectious complication processes were begun [7, 8].

Bortezomib is a molecule that reversibly and selectively inhibits the 26S proteasome and shows its effect through nuclear factor-kB (NF-kB) [7, 9-11]. It causes apoptosis by inhibition of NF-kB. It also performs T cell suppression through the same mechanism. Therefore, T cells containing high levels of NF-kB are more sensitive to bortezomib treatment. CD4^{+} T cells affected by bortezomib treatment produce less IFN-gamma and IL-2 [10]. This explains the anti-inflammatory and immunomodulatory effect of bortezomib [7].

Hematological side effects occur due to the anti-inflammatory and immunomodulating effects of bortezomib. The most important of these are neutropenia and thrombocytopenia [7]. Monocytopenia and lymphocytopenia (T-cell suppression) associated with bortezomib treatment may also occur [8, 9].

In this study, it is aimed to reveal the relationship between infection development with variables such as absolute lymphocyte value, lymphocyte/monocyte ratio (L/M), and IgG level in newly diagnosed and relapsed/refractor MM patients who had treated with bortezomib-based chemotherapy. At the same time, the L/M ratio and overall survival relationship had been determined.

METHODS

We retrospectively evaluated 56 patients who had MM treated with bortezomib based regimen. Type of Infection were determined. Lymphocyte absolute values at the time of diagnosis, immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, neutrophil value at the time of chemotherapy, lymphocyte absolute values at the time of infection, and monocyte absolute value at the time of infection were recorded from the file information. The L/M ratio of the patients at the time of infection were calculated and transferred to the SPSS database. We tried to determine the relationship between infection with immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, lymphocyte absolute values at the time of infection, monocyte absolute value at the time of infection, and the L/M ratio at the time of infection. The effects of L/M ratio on progression free survival (PFS) and overall survival (OS) were also examined.

Gazi University Faculty of Medicine ethical committee has approved this study on 12/09/2014 with the number of 25901600-3086.

Determinations
International staging system (ISS):
- Stage-I: serum beta - 2 microglobulin level < 3.5 mg/dl and serum albumin level ≥ 3.5 g/dl
- Stage-II: out of ISS stage I and stage III criteria

- Stage-III: serum beta-2 microglobulin level ≥ 5.5 mg/L [12].

Revised International Staging System (R-ISS):

- R-ISS I: serum β2-microglobulin level < 3.5 mg/L, serum albumin level ≥ 3.5 g/dL, no high-risk cytogenetic anomaly (CA) [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range)

- R-ISS II : out of ISS stage I and stage III criteria

- R-ISS III: serum β2-microglobulin level > 5.5 mg/L and high-risk CA or high LDH level [13].

Table 1. **Patients' MM subtypes, M protein level, ISS and R-ISS stages and Co-morbidity at the diagnosis**

	Number of the patients	%
MM subtypes		
IgG kappa	24	42.9
IgG lambda	13	23.2
Ig A kappa	3	5.4
Ig A lambda	4	7.1
Ig D lambda	3	5.4
kappa light chain	4	7.1
lambda light chain	4	7.1
non-secretory	1	1.8
M protein level		
< 3 g/dl	13	23.2
>3g/dl	43	76.8
ISS stage		
stage-1		21.4
stage-2	10	17.9
stage-3	34	60.7
R-ISS stage		
stage-1	10	17.9
stage-2	29	51.8
stage-3	17	30.4
Co-morbidity		
no co-morbidity	22	39.3
DM	9	16.1
CRF	10	17.9
HT	9	16.1
AHD	3	5.4
COPD	1	1.8
HF	1	1.8
ARF+SM+COPD+HT	1	1.8

MM = multple myeloma, ISS = international scoring system, R-ISS = revised international scoring system, DM = diabetes mellitus, CRF = chronic renal failure, HT = hypertension, AHD = atherosclerotic heart disease, COPD = chronic obstructive pulmonary disease, HF = heart failure, ARF = acute renal failure, SM = secondary malignancy

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation and median (minimum-maximum) for numerical variables, and as percentages for categorical variables. The normal distribution of parametric values was determined by the Shapiro-Wilk Test. For determining the significance In statistical analysis, the T-test was used for parametric variables, Mann Whitney U test was used for non-parametric variables. Pearson Chi-Square Test was used to comparing two categorical variables. Univariate and multivariate logistic regression analyzes were performed for advanced statistical analysis. Log-Rank test was used to calculate survival analysis. All statistical evaluations were made using the Statistical Package for Social Sciences (SPSS) for Windows 16 (IBM SPSS Inc., Chicago, IL) program. Statistical significance p-value was accepted as < 0.05 in all analyzes.

RESULTS

Of the 56 patients included in the study, 21 (37.5%) were females and 35 (62.5%) were males. The median age of the patients was 58.5 years (min-max: 28-79 years). Thirty (53.6%) of 56 patients were newly diagnosed, 26 (46.4%) of 56 patients were relapsed/refractor MM. Table 1 show the patients' MM subtypes, M protein level, ISS and R-ISS stages and co-morbidity at the time of diagnosis. The bortezomib-based regimen was given to all patients. Accordingly, 43 (76.8%) patients had bortezomib 1.3 mg/m2 sc (1, 8, 15, and 22 days), cyclophosphamide 300 mg/m2 PO (1, 8, 15, and 22 days) and dexamethasone 40 mg (1, 8, 15, and 22 days) (VCD) regimen, 13 patients

(23.2%) had bortezomib 1.3 mg/m^2 sc (Days 1, 8, 15, and 22), melphalan 9 mg/m2 PO, (1-4 Days) and prednisone 60 mg/m^2 PO, (Days 1-4) (VMP) chemotherapy regimen.

Thirty-one (55.4%) patient did not have any infection. Pulmonary infection was seen in 17 (30.4%) patients, urinary system infection was seen in 3 (5.4%) patients, lung and urinary system infection was seen in 2 (3.6%) patients, cellulitis was seen in 1 (1.8%) patient, psoas abscess was seen in 1 (1.8%) patient, the unknown origin of fever was seen in 1 (1.8%) patient. Twelve (21.4%) of the patients had an infection in the first cycle, others had an infection in the second or more cycles. Infection agents could be isolated in only 7 (12.5%) patients. Accordingly: E. Coli infection was seen in 5 (8.9%) patients, viral infection was seen in 1 (1.8%) patient, and coagulase-negative staphylococcal infection was seen in 1 (1.8%) patient. While the patients received bortezomib-based chemotherapy, the median neutrophil values was 0 /mcL (min-max: 0-4000/ mcL). In 8 (14.3%) patients; neutrophil level was ≤ 1000 /mcL, and in 48 (85.7%) patients; neutrophil level was > 1000 /mcL. Before starting chemotherapy, median basal lymphocyte absolute values was 14051/ mcL (min-max: 320-3190 /mcL). The median lymphocyte values measured while receiving chemotherapy was 636/mcL (min-max: 32-1890 mcL). The median lymphocyte absolute values of the patients in the infection attack was 1775/mcL (min-max: 30-4000/mcL). In twenty (35.7%) patients; lymphocyte values was ≤1000/mcL, in 36 patients (64.3%) lymphocyte values was >1000/mcL. The median monocyte absolute values of the patients in the infection attack was 434/mcL (min-max: 80-1000/mcL). The median IgG value at diagnosis was 3000 mg/dl

Table 2. Value of age, median level of Ig G level at diagnosis, lymphocytopenia at the time of chemotherapy and L/M ratio

	Infection negative	Infection positive	*p* value
Age	55.87±11.0	61.6±112.2	0.07t
Ig G level at diagnosis	3325 (305-10800)	3000 (141-13800)	0.93MU
Lymphocytopenia at the time of chemotherapy	780 (50-1890)	300 (32-1780)	0.003MU
L/M ratio	4.6 (1.5-45)	0.88 (0.04-5)	0.00MU

Data are shown as mean ± standard deviation or median (min-max). L/M = lymphocyte/monosyte
T-test, MU: Mann Whitney U test

Table 3. **Variables that are found to be statistically significant/not statistically significant**

	Infection negative	Infection positive	p value
Gender, n (%)			
Female	12 (38.7)	9 (36)	0.83x2
Male	19 (61.3)	16 (64)	
Total	31 (100)	25 (100)	
Subtypes of MM, n (%)			
Ig G kappa	15 (48.4)	9 (36)	0.35x2
Others	16 (51.6)	16 (64)	
Total	31 (100)	25 (100)	
ISS, n (%)			
Stage-I	8 (25.8)	4 (16)	0.29x2
Stage -II	7 (22.6)	3 (12)	
Stage -III	16 (51.6)	18 (72)	
Total	31 (100)	25 (100)	
R-ISS, n (%)			
Stage -I	6 (19.4)	4 (16)	0.032 x2
Stage-II	20 (64.5)	9 (36)	
Stage-III	5 (16.1)	12 (48)	
Total	31 (100)	25 (100)	
Co-morbidity, n (%)			
No	16 (51.6)	6 (24)	0.035 x2
Yes	15 (48.4)	19 (76)	
Total	31 (100)	25 (100)	
Diesea state, n (%)			
CR	31 (100)	1 (4)	< 0.01 x2
Others	0	24 (96)	
Total	31 (100)	25 (100)	
Levelof M protein, n (%)			
< 3gr/dl	9 (29)	4 (16)	0.25x2
> 3 gr/dl	22 (71)	21 (84)	
Total	31 (100)	25 (100)	
Level of creatinin			
< 2mg/dl	22 (71)	14 (56)	0.24x2
> 2 mg/dl	9 (29)	11 (44)	
Total	31 (100)	25 (100)	
Typeofchemotherapy			
VCD	25 (80.6)	18 (72)	0.44x2
VMP	6 (19.4)	7 (28)	
Total	31 (100)	25 (100)	
Number of Bortezomib cycles			
≤ 4 cycle	27 (87.1)	21 (88)	0.53x2
> 4 cycle	4 (12.9)	4 (12)	
Total	31 (100)	25 (100)	
Neutropenia			
< 1000	2 (6.5)	6 (24)	0.06x2
> 1000	29 (93.5)	19 (76)	
Total	31 (100)	25 (100)	
Lymphocytopenia			
< 1000	0	20 (80)	< 0.01 x2
> 1000	31 (100)	5 (20)	
Total	31 (100)	25 (100)	

L/M = lymphocyte/monosyte, ISS = international scoring system, R-ISS = revised- international scoring system, VCD = bortezomib, cyclophosphamide, dexamethasone, VMP =bortezomib, melphalan, prednisolone, x2: chi-quare test

Table 4. Univariate and multivariate analysis of variables

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	95% CI	p value	OR	95% CI	*p* value
Co-morbidity	3.37	1.06-10.7	0.039	0.4	0.17-1.29	0.146
Diseade State	0.99	0.99-1	< 0.01	3.6	0-1	0.95
Lymphocytopenia at the time of chemotherapy	0.99	0.99-1	0.018	0.96	0.06-15	0.99
Lymphocytopenia	0.99	0.994-0.998	< 0.01	0.99	0.99-1	0.002
L/M ratio	0.173	0.065-0.45	< 0.01	0.007	055-0.88	0.003

L/M = lymphocyte/monosyte, CI = confidental interval, OR = odss ratio

(min-max: 141-13800 mg/dl). The median value of L/M ratio was 2.00 (min-max: 0.04-45).

A statistically significant correlation was seen in disease stage (R-ISS) ($p = 0.032$), presence or absence of co-morbid disease ($p = 0.035$), disease status during an infectious attack ($p < 0.01$), lymphocytopenia at the time of chemotherapy ($p = 0.003$), absolute value of lymphocytopenia at the time of infection ($p < 0.01$) and the L/M ratio ($p < 0.01$) with the development of infection. According to the R-ISS, patients who had stage 3 and in the presence of co-morbid disease had a higher infection risk while the infection rates were low in patients who had a complete response. Lymphocytopenia was related to the development of infection. Especially, patients who had ≤ 1000 /mcL ($p < 0.01$) lymphocyte level and who had a low L/M ratio (< 2) had a high risk of development of infection. Variables that are found to be statistically significant (or not statistically significant) relation with development of infection are shown in Table 2 and Table 3.

Disease status during infection ($p < 0.01$, OR<1, 98.2% CI), lymphocytopenia at the time of infection ($p < 0.01$, OR < 1, 94.6% CI) and L/M ratio ($p < 0.01$, OR < 1, 91.1% CI) were significant in univariate logistic regression analysis. Infection rate was lower in

patients with complete response. Accordingly, infection rates increase in patients who had lymphocytopenia and in patients who had a low level of L/M ratio. Significant parameters in univariate analysis were re-evaluated in multivariate logistic regression analysis, lymphocytopenia at the time of infection and L/M ratio were found significant (respectively: $p = 0.002$, OR < 1, 95% CI; $p = 0.003$, OR < 1, 95% CI). The variables that are significant in univariate and multivariate analysis are shown in Table 4.

When the effects of the independent variable of L/M ratio on PFS and OS were examined; L/M ratio had no significant effect on PFS ($p > 0.05$), while had a significant effect on OS ($p < 0.017$). The mean OS was 33 ± 2.7 months (min-max: 27.53-38.47 months). The cut-off value of the L/M ratio was 2 (this is the median value of the L/M ratio). Mean OS survival of patients who had L/M ≥ 2 was 37 ± 2.5 months (min-max: 32- 41.96 months), mean OS of patients who had L/M < 2 was 28 ± 3.2 months (min-max: 21.7-34.27/ months). Fig. 1 show relationships between the OS and the L/M ratio.

DISCUSSION

It has been reported in the literature that the frequency of viral infections is high in MM patient who had a bortezomib therapy. Especially, it has been emphasized that there is a relationship between bortezomib and Herpes Zoster infection [10, 11, 14]. As we have been stated, the relationship between bortezomib and infection development is due to the lymphocytopenia-inducing effect of bortezomib [6]. The result we obtained in this study also supports these findings. It has been shown that lymphocytopenia and the decrease in the L/M ratio are independent variables on
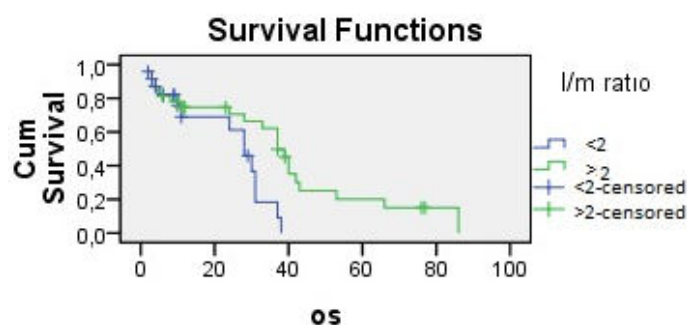
Fig. 1. Relationship between lymphocyte/monosyte (L/M) ratio and survival.

the development of infection. We also find that R-ISS, co-morbidity, disease state have significant affect on development of infection in MM patients, however, were not found an independent factors.

Pang *et al*. [15] claimed that neutrophile+monocyte/lymphocyte ratio (NMLR) is an independent variable on progression-free survival. Newly diagnosed patients who received VCD chemotherapy regimen were included in this study. The NMLR ratio was calculated for each patient and a value of 1.9 was taken as the cut-off value. It has been shown that immune restructuring is more effective and disease exacerbation is less in patients who had a NMLR < 1.9. On the other hand, it is known that the microenvironment is important in the course of the disease in MM patients. Neutrophils, lymphocytes and monocytes are being in this microenvironment [16, 17]. In some studies, it has been shown that the ratio of absolute neutrophil value to absolute lymphocyte value and the ratio of absolute lymphocyte value to absolute monocyte value are effective in immune remodeling in MM patients, and this affects progression-free survival [16, 18, 19]. It is also emphasized that the cells that are particularly effective in the microenvironment of MM are neutrophils and monocytes, and the treatment options may change according to the neutrophil lymphocyte ratio and the lymphocyte-monocyte ratio in patients with MM [20]. In recent years, the use of immunomodulatory drugs and the use of CAR-T cell therapy, especially in patients with relapsed / refractory MM, have shown the importance of immune abnormality in the course of the disease in patients with MM. In vivo balance to be established in the immune environment affects the course of the disease [21].

It has been shown that absolute neutrophil value, absolute lymphocyte value, and absolute monocyte value and their ratio to each other are independent variables in solid tumors and hematological cancers and in the course of the disease after autologous stem cell transplantation [22-26]. In most of these studies, it was shown that high neutrophil/lymphocyte ratio and low lymphocyte/monocyte ratio were associated with poor prognosis. On the contrary, there are studies in the literature that showing the neutrophil/lymphocyte ratio is not effective on survival [19]. Romena *et al*. [20], showed that the monocyte ratio is effective on the microenvironment in myeloma bone marrow. Especially, it is emphasized that it enables growth in

myeloma cells. When all these are taken into consideration, it is emphasized that neutrophil, lymphocyte and monocytes and especially NMLR parameter are effective on survival in MM patients. The reason for better progression-free survival in patients with a low NMLR rate may be due to the low monocyte ratio that enables the growth of the myeloma cell. There are also studies claiming that the increase in the L/M ratio is associated with a good prognosis [26] It is still unknown how the changes in lymphocyte and monocyte ratio affect the risk of infection. However, absolute lymphocyte value, absolute monocyte value and L/M ratio are closely related to the immune system [27]. It is also known that alloreactive T lymphocytes are suppressed, especially in bortezomib-based regimens [10]. As a result of all these, it can be said that absolute lymphocyte and monocyte values and L/M ratio might be occurred predisposition for infections. It is also known that bortezomib prevents the growth of myeloma cells with causing to monocytopenia.

Decreasing in the L/M ratio, in other words, higher monocyte value relative to lymphocyte value, might be associated with infection in bortezomib-based regimens. If bortezomib-based regimen is used in relapsed refractory cases or newly diagnosed cases of MM, lymphocytopenia should be tried to prevent. On the other hand, it is necessary to keep the monocyte value at certain rates in order to prevent tumor growth. Yang *et al*. [27], examined the relationship between L/M ratio and OS. The median L/M ratio in our study is the 2. Overall survival was longer in patients who had L/M ratio ≥ 2.

CONCLUSION

It was determined that L/M ratio has an effect on OS and it is also an independent factor on the development of infection. OS was decreasing and the risk of developing infection was increasing, when the L/M ratio was low. We have to say that; there is some restriction in this study such as number of patients and power effect of lymphocytopenia in multivariate analysis. Therefore; more studies which are including more patients, are needed for claiming the lymphocytopenia and L/M ratio are an independent variable on the development of infection and L/M ratio has an effect on OS. After then, L/M will be a follow-up pa-

rameter in the development of infection in bortezomib-based regimens and it will be considered as an effective parameter on OS.

Authors' Contribution

Study Conception: MP, NAB, MSP; Study Design: MP, NAB, MSP; Supervision: MP, NAB, MSP; Funding: MP, NAB, MSP; Materials: MP, NAB, MSP; Data Collection and/or Processing: MP, NAB, MSP; Statistical Analysis and/or Data Interpretation: MP, NAB, MSP; Literature Review: MP, NAB, MSP; Manuscript Preparation: MP, NAB, MSP and Critical Review: MP, NAB, MSP.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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