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The Effect of Bortezomib Regimen on Multiple Myeloma Patients Infected with COVID-19

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Abstract

Background: Patients with multiple myeloma (MM) have compromised immune systems due to the nature of the malignancy and anticancer treatments. This study aims to report the effects of Bortezomib-containing chemotherapy regimens on the severity and mortality of MM patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2).

Method: This retrospective cohort study enrolled MM patients presenting with coronavirus disease 2019 (COVID-19) infection referred to Omid Hospital. Patients were divided into two groups based on whether they received any chemotherapy regimens containing Bortezomib within the last 90 days of admission or not. Clinical and laboratory characteristics, severity, and outcomes of both groups were reported and compared.

Results: Among 48 patients with MM diagnosed with COVID-19 (63% male; median age 66), 33 received chemotherapy. The most common symptoms were fever, cough, and dyspnea, and there was no significant difference between the groups. Only D-dimer had a significant difference in laboratory tests ($P = 0.03$) and was higher in the chemotherapy group. There was no significant relationship between chemotherapy and severity (risk ratio (RR) = 1.17; 95% confidence interval (CI): 0.37 to 3.71; $P = 0.79$) or chemotherapy and mortality (RR= 1.00; 95% CI: 0.39 to 2.61; $P = 0.99$), even after adjusting for baseline C-reactive protein and white blood cell counts.

Conclusion: Our study showed that receiving Bortezomib-containing chemotherapy regimens did not worsen the symptoms and prognosis of MM patients infected with COVID-19. However, further studies with larger sample sizes and longer follow-up times are needed to provide better evidence on this subject.

Keywords: COVID-19, Cancer, Hematologic neoplasms, Multiple myeloma, Bortezomib

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Introduction

Since the end of 2019, the emerging pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has raised concerns for cancer patients due to their impaired immunity and vulnerability to infections.[1] It is now known that cancer patients are at a higher risk of developing severe forms of coronavirus disease 2019 (COVID-19) and experiencing higher mortality rates, with the risk varying among different cancer types.[2, 3] Patients with hematologic malignancies are more vulnerable to COVID-19 than those with solid malignancies.[4] This increased risk poses a challenge for oncologists on whether to continue cancer treatments or not. Although vaccination reduces mortality and hospital admission rates among the general population and cancer patients, breakthrough infections have been reported in cancer patients,[5] with recent studies showing that the breakthrough infection rate is higher in cancer patients than in the general population.[6] This suggests that even after the pandemic, we may encounter cancer patients infected with COVID-19, and there is a need for evidence regarding treatments during this period.

Several studies have evaluated the effect of chemotherapy on cancer patients, resulting in systematic reviews and meta-analyses. However, there is inconsistency between the results. For instance, a meta-analysis of 16 studies by Yekeduz et al. concluded that chemotherapy within the last 30 days of diagnosis does not affect the severity, but increases the mortality rate of cancer patients.[7] In contrast, two other systematic reviews and meta-analyses by Liu et al. and Lin et al. showed that mortality has no significant difference between cancer patients under active treatment and cancer patients who are not.[8, 9] These contrasts highlight the need for studies on each specific chemotherapy regimen, as the type of cancer and chemotherapy drugs can affect the results.

Multiple myeloma (MM), the second most common hematological malignancy, is a proliferation of clonal B lymphoid cells that contribute to end-organ damage.[10] Patients with MM experience lower levels of humoral immunity due to their compromised production of proper immunoglobulins while facing over-secretion of monoclonal immunoglobulins. Moreover, the patients' cellular and innate immunity is also impaired.[11]

The standard therapy commonly used for active MM patients is triplet therapy, which is a combination of a proteasome inhibitor, an immunotherapy drug, and a corticosteroid.[12] Current evidence shows that proteasome inhibitors lead to a decreased cytotoxic T-cell response and susceptibility to viral infections.[13] Bortezomib, a proteasome inhibitor, is widely used in Iran to treat these patients.

To the best of our knowledge, no specific study has evaluated Bortezomib on cancer patients infected with COVID-19. Therefore, this study aims to assess the effects of chemotherapy regimens consisting of Bortezomib on the severity and mortality of MM patients infected with SARS-COV-2.

Material and Methods

Study design and participants

This is a retrospective cohort study of active MM patients with COVID-19 infection who were referred to Omid Hospital in Isfahan, Iran, from March 2020 to October 2021. Patients who had a positive SARS-CoV-2 test by polymerase chain reaction or lung involvement confirmed by chest computed tomography (CT) scan were included in the study. Exposure in this cohort study was defined as receiving any chemotherapy regimens that included Bortezomib within the last 90 days of admission. The control group did not receive Bortezomib within the last 90 days of admission due to Bortezomib-induced peripheral neuropathy. The decision to choose 90 days as the definition for recent chemotherapy was based on the article by Jee et al.[14] As the vaccination of cancer patients started in mid-2021 and receiving a vaccine can affect the outcomes, we excluded breakthrough infections from this study.

Data collection and follow-up

Demographic and clinical data, comorbidities such as diabetes, hypertension, cardiac disease,

Table 1. Patients' characteristics

	Total N = 48	Received chemotherapy (N = 33)	No chemotherapy (N = 15)	*P*
Demographics				
Gender (Male): n (%)	30 (63)	19 (58)	11 (73)	0.35
Age: Mean (SD)	66 (12)	65 (12)	67 (11)	0.64
Hospitalization length				
Median [Q1 – Q3]	7 [5 – 11]	7 [5 – 12]	7 [5 – 9]	0.69
ICU admission: n (%)	12 (25)	10 (30)	2 (13)	0.29
Blood products received: n (%)				
Packed cell	24 (50)	16 (48)	8 (53)	1.00
Fresh frozen plasma	11 (23)	6 (18)	5 (33)	0.28
Platelet	12 (25)	7 (21)	5 (33)	0.48
Symptoms of SARS-CoV-2 infection: n (%)				
Fever	22 (46)	14 (42)	8 (53)	0.54
Cough	15 (31)	11 (33)	4 (27)	0.75
Dyspnea	15 (31)	11 (33)	4 (27)	0.75
Weakness	10 (21)	7 (21)	3 (20)	1.00
Nausea	8 (17)	6 (18)	2 (13)	1.00
Lose olfactory or taste sense	3 (6)	3 (9)	0 (0)	0.54
Body pain	7 (15)	4 (12)	3 (20)	0.66
Underlying diseases: n (%)				
Hypertension	6 (13)	3 (9)	3 (20)	0.42
Diabetes mellitus	2 (4)	2 (6)	0 (0)	
Hyperthyroidism	1 (2)	1 (3)	0 (0)	
Baseline laboratory parameters Median [Q1 – Q3]				
CRP: mg/dL (n = 46)	47.5 [22.1 – 64]	46 [22 – 60]	53 [30.2 – 76]	0.29
D-Dimer: ng/ml (n = 40)	745.5 [423.1 – 1863]	1500 [700 – 2500]	693 [300 – 1043]	0.03
LDH: U/L (n = 45)	546[365 – 913]	529 [364 – 970]	617 [365 – 913]	0.69
WBC × 10^9: cells/L (n = 48)	4.93 [2.2 – 8.3]	5.2 [2.1 – 8.8]	4.7 [2.7 – 6]	0.81
Neutrophils × 10^9: cells/L (n = 37)	3.8 [2.0 – 6.9]	4.9 [1.9 – 7.6]	3.3 [2.0 – 3.8]	0.10
Lymphocytes × 10^9: cells/L (n = 38)	0.70 [0.44 – 1.51]	0.67 [0.36 – 1.51]	0.81 [0.53 – 1.87]	0.41
Platelets: (n = 48)	104.5 [34 – 168]	113 [37 – 180]	80 [14 – 144]	0.40
NLR (n = 37)	5.06 [2.35 – 9.51]	5.06 [2.35 – 16.96]	4.96 [1.77 – 5.66]	0.34
PLR (n = 38)	138.6 [54.0 – 224.0]	155.8 [65.8 – 295.8]	107.7 [8.9 – 178.7]	0.08
Hemoglobin: g/dL (n = 48)	9.5 [8.1 – 10.6]	9.8 [8.3 – 10.5]	8.3 [7.9 – 11.2]	0.46
Ferritin: pg/ml (n = 32)	1946 [761 – 4350]	1375 [624 – 3370]	3925 [1789 – 5180]	0.12

Fisher's exact test and Mann-Whitney U test were used to compare categorical and numeric variables, respectively. CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; N: Number

medical symptoms, and medical drug usage history were gathered from the health information system (HIS) and health records. Routine blood examinations, including complete blood count, D-Dimer, serum ferritin, lactate dehydrogenase (LDH), and C-reactive protein (CRP), were also extracted at admission. Furthermore, the physician examined the data to check for any discrepancies. The follow-up time was calculated from admission to the day of discharge or death.

Statistical analysis

This study aimed to assess the effect of chemotherapy on death and ventilation in MM patients with COVID-19 infection. Log-binomial regression was used to assess this relationship; baseline white blood cells (WBC), CRP, and platelet counts were adjusted in multivariable analysis. Moreover, the relative risk (RR) and its corresponding 95% confidence interval (CI) were presented to illustrate the magnitude of the association. The *P*-values were reported as two-tailed, and $P \leq 0.05$ was considered statistically significant. All tests were performed using Stata version 14.

Ethics approval and consent to participate

The study was carried out in accordance with the Helsinki Declaration (IV Adaptation). The study protocol was approved by the Research Ethics Committees of the Vice-Chancellor in Research, Medical University of Isfahan (approval

Table 2. Association between receiving chemotherapy and ventilation or death

Model	Ventilation		Death	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Model A[a]	1.21 (0.37 , 3.94)	0.75	1.02 (0.37 , 2.80)	0.97
Model B[b]	1.22 (0.37 , 3.96)	0.74	1.02 (0.38 , 2.76)	0.97
Model C[c]	1.17 (0.37 , 3.71)	0.79	1.00 (0.39 , 2.61)	0.99

Log-binomial regression was used to determine the relationship between chemotherapy and ventilation or death. [a]No adjustment; [b]adjustment for baseline WBC; [c]adjustment for baseline WBC and CRP; RR: Risk ratio; CI: Confidence interval; WBC: White blood cell; CRP: C-reactive protein

ID: IR.MUI.MED.REC.1400.213). In view of the retrospective nature of the study, the need for individual patient consent was waived by the research ethics committee as data protection safeguards were in place.

Results

Patients' characteristics

Our cohort comprised 48 patients, with a mean age of 66 years (standard deviation 12). 33 patients received Bortezomib within the last three months, while 15 did not. Of the total cohort, 30 patients were men, and 19 (58%) received Bortezomib. The median length of hospitalization in both groups was seven days (Table 1).

Association between receiving chemotherapy and ventilation or death

Table 2 shows that there was no significant relationship between the use of Bortezomib and ventilation (RR = 1.21; 95% CI: 0.37 to 3.94; $P = 0.75$). When adjusted for baseline WBC count, CRP, and platelet levels, the relationship became even weaker (RR = 1.18; 95% CI: 0.37 to 3.78; $P = 0.78$). Furthermore, Bortezomib use did not have a significant effect on mortality in either the crude or adjusted models (RR = 1.02; 95% CI: 0.37 to 2.80; $P = 0.97$; RR = 0.99; 95% CI: 0.38 to 2.58; $P = 0.99$, respectively).

Discussion

The results of our study showed that Bortezomib chemotherapy regimens did not affect the symptoms, severity, and mortality of patients. Previous studies have demonstrated that patients with malignancies, including MM, have a higher risk of mortality, developing severe forms of COVID-19, and requiring mechanical ventilation than the general population.[15] Cancer patients also experience shorter hospital stays, and their condition deteriorates rapidly,[16] which underscores the need for better and greater care by healthcare providers.

Our study revealed that the most common symptoms of MM patients infected with COVID-19 are fever, cough, and dyspnea. A meta-analysis by Zarifkar et al. also reported that the most common symptoms of cancer patients are non-specific, including fever and dyspnea.[3] The prevalence of non-specific symptoms like fever and dyspnea is not significantly different in cancer groups compared to the general population.[16] However, although symptoms like cough and fever have a high sensitivity for COVID-19, their specificity is low.[17] Thus, healthcare providers should not base their decision to rule in or rule out COVID-19 on symptoms alone, especially for suspected cancer patients. Our results also showed that receiving Bortezomib chemotherapy regimens did not affect the symptoms of MM patients.

The laboratory test results at admission also showed no significant differences between the groups, except for D-Dimer. D-Dimer is a biomarker that could have been affected by chemotherapy,[18] which explains why the difference between the groups was significant. Both groups had lymphopenia, which is a risk factor for severity and mortality in COVID-19. Having low lymphocytes in both groups indicates that all MM patients, regardless of whether they received Bortezomib or not, are at a higher risk of severity and mortality.[19]

Our study also demonstrated that the Bortezomib chemotherapy regimen did not affect the severity and mortality of patients. Previous studies suggest that laboratory tests such as WBC and CRP are predictors of severity and mortality in the general population and cancer patients. We

also adjusted the baseline WBC, CRP, and platelet[20,21] levels, but the results did not change, and there was no significant difference between the groups.

Most current studies have included all types of cancers or all hematological cancers together. Consequently, the proportion of each cancer type affected the results. Booth et al. and Cattaneo et al. have shown that active treatments are a risk factor for poor outcomes in patients with hematological malignancies.[22, 23] In contrast, Sanchez-Pina et al. concluded that the decisions for systemic anticancer treatment modifications or delays are case-by-case decisions.[24] A report from a tertiary center on MM patients also concluded that cancer treatments like chemotherapy did not affect mortality.[25] However, it is noteworthy that the sample size of this study was small, with only 58 patients.

Limitations

This study has limitations that should be considered. The first and major limitation of this study is the small sample size. Therefore, it is strongly recommended to conduct multi-institutional studies to create better evidence. Another limitation of the study is the short follow-up time. We only followed patients during their hospital admission. Studies with longer follow-up periods can help to determine the long-term effects of Bortezomib on the survival of patients with multiple myeloma. As many countries, including Iran, have vaccinated their communities, including cancer patients, it is recommended to conduct studies on vaccinated patients, as vaccination is an important variable that can affect the results.

Conclusion

Determining whether to continue chemotherapy in cancer patients infected with COVID-19 or not is a major concern for oncologists. Our study showed that receiving Bortezomib chemotherapy regimens did not worsen the symptoms and prognosis of multiple myeloma patients infected with COVID-19. However, more studies with larger sample sizes and longer follow-up periods are needed to create better evidence on this subject.

Availability of Data and Materials

The datasets of the study are not publicly available due to patient confidentiality, but a de-identified version will be made available from the corresponding author on reasonable request.

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Conflict of Interest

None delared.

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