BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Effect of Bortezomib Treatment in Multiple Myeloma on Blood Coagulation Function, Renal Function, Immune Function, and the NF-κB Pathway-Associated Indicators

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Abstract

Aims/Background Multiple myeloma (MM) presents several underlying mechanisms of immune dysfunction. Advanced research on these mechanisms has introduced new drugs for MM into clinical practice. However, several challenges occur, particularly in cases of relapsed and refractory MM. In recent years, bortezomib has been recognized, for its anti-myeloma effect in both newly identified and refractory MM patients, but its mechanism of action on MM remains unexplored. Consequently, this study aims to explore the influence of bortezomib on coagulation function, renal function, immune function, and related indexes of nuclear transcription factor-κB (NF-κB) pathway in MM patients.

Methods This retrospective study analyzed 120 MM patients admitted to the First People's Hospital of Nantong, China, between August 2018 and August 2023. Based on different treatment methods, patients were divided into a control group (thalidomide, cyclophosphamide, and dexamethasone (TCD), 58 cases) and an observation group (TCD regimen and bortezomib, 62 cases). The therapeutic efficacy of the drug was observed, and the levels of blood indexes, coagulation function indexes, NF-κB related indexes, renal function indexes and immunosuppressive factors were compared between the groups both before and after treatment.

Results There were no significant differences in disease control rate (DCR) between the two groups ($p > 0.05$). After treatment, the objective response rate (ORR) and the hemoglobin levels were significantly higher in the observation group than in the control group, with lower M protein levels ($p < 0.05$). Furthermore, the prothrombin time (PT), the activated partial thromboplastin time (APTT), fibrinogen (FIB) values, *NF-κB* expression levels, β2-microglobulin (β2-MG) levels, blood urea nitrogen (BUN), serum creatinine (Scr), transforming growth factor-β (TGF-β), interleukin-6 (IL-6) and interleukin-17 (IL-17) levels were substantially decreased in the observation group compared to the control group ($p < 0.001$). Additionally, the progression-free survival rate was significantly higher in the observation group than in the control group ($p < 0.001$). However, no significant difference was observed in the overall survival (OS) rate between the two groups ($p > 0.05$). Moreover, the median progression-free survival (PFS) time was 11.95 months in the observation group and 9 months in the control group, while the median OS time was 11.7 months in the control group.

Conclusion In summary, bortezomib treatment improves coagulation and renal function in MM patients. Furthermore, it helps reduce immune suppression, prolong survival time, and inhibit the NF-κB pathway activation.

Key words: bortezomib; multiple myeloma; coagulation function; renal function; immune function; NF-κB

Submitted: 27 September 2024 Revised: 20 January 2025 Accepted: 22 January 2025

How to cite this article:
Tao J, Wang L, Gu Z, Zhang L. Effect of Bortezomib Treatment in Multiple Myeloma on Blood Coagulation Function, Renal Function, Immune Function, and the NF-κB Pathway-Associated Indicators. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0701

Introduction

Multiple myeloma (MM) is characterized by plasma cell dysplasia within the bone marrow. The majority of MM patients present with various clinical manifestations, such as multiple lytic lesions, anemia, hypercalcemia, and renal damage manifestations (Bruno et al, 2024). Presently, treatment approaches include surgery and chemotherapy. However, achieving an adequate therapeutic response remains challenging for some patients (Pasvolsky et al, 2022). In recent years, bortezomib, a new proteasome inhibitor targeting myeloma cells, has shown efficacy by reducing the degradation of nuclear transcription factor-κB (NF-κB) inhibitor, inhibiting the expression of proliferation-related genes, and alleviating the levels of adhesion factors, ultimately promoting myeloma cell apoptosis (Zhou et al, 2020).

Research has revealed that bortezomib mediates anti-myeloma effects by inhibiting the activation of NF-κB and directly inducing apoptosis in drug-resistant and relapsed MM cells (Lobbes et al, 2018). While its anti-myeloma effect is newly diagnosed and refractory MM is well recognized, the specific underlying mechanism remains unexplored. Hence, this study aims to explore the therapeutic effect of bortezomib in MM by assessing its impact on coagulation function, renal function, immune function, and the NF-κB pathway.

Methods

Recruitment of Study Participants

This retrospective study recruited 120 MM patients admitted to Nantong First People's Hospital, China, between August 2018 and August 2023. Based on treatment differences, patients were divided into a control group (thalidomide, cyclophosphamide, and dexamethasone (TCD), 58 cases) and an observation group (TCD regimen and bortezomib, 62 cases). All patients provided informed consent, and this study followed the guidelines of the Declaration of Helsinki. Furthermore, this study was approved by the Medical Ethics Committee of the First People's Hospital of Nantong (Approval number: 2024KT130).

The sample size was estimated using PASS software 15.0.5 (NCSS Co., Kaysville, UT, USA), applying an independent sample t-test. The effect size for dynamic functional connectivity was 0.5, with a significance level (α) of 0.05 and a statistical power of (1-β) of 0.8. Hence, the required sample size was calculated to be 55 cases per group and considering a potential loss rate of 5%–10%, a cohort of 120 MM patients was included in the final analysis.

Inclusion and Exclusion Criteria

The inclusion criteria were set as follows: (1) Individuals diagnosed as MM patients using the criteria established by the Chinese Medical Doctor Association Hematology Physicians Branch et al (2017), qualifying at least one of the following: bone marrow plasma cells $>$15% with primitive or naive plasma cells, biopsy confirmation of plasma cell neoplasm, or urinary clonal immunoglobulin light chain $>$1 g/24 hours. (2) Age ranged from 40 to 70 years. (3) Patients with international

staging system (ISS) stage I or II. (4) Patients gave informed consent and had complete clinical data. (5) Newly diagnosed patients.

However, patients with (1) coagulation disorders, (2) severe cardiovascular diseases, (3) drug allergies, (4) liver and kidney diseases unrelated to MM, (5) primary renal disease, (6) autoimmune diseases, (7) a history of bortezomib treatment, and (8) history of surgical treatment were excluded from the study cohort.

Treatment Protocols

The control group underwent routine treatment with a TCD regimen, including cyclophosphamide (Jilin Haitong Pharmaceutical Co., Ltd., Tonghua, China), dexamethasone (Chongqing Kerui Pharmaceutical (Group) Co., Ltd., Chongqing, China) and thalidomide (Dandong medical innovation Pharmaceutical Co., Ltd, Dandong, China). The treatment protocol was as follows: thalidomide (100 mg/d) and cyclophosphamide (300 mg/m^2) were administered on day 1, 8, and 15, while dexamethasone (40 mg) on day 1, 8, 15, and 22. The treatment continued for 12 cycles, with each cycle lasting 28 days. Additionally, maintenance treatment included thalidomide 100–200 mg/ day, administered once every 2 weeks. However, the observation group received bortezomib in addition to TCD treatment. Bortezomib (Xi'an Janssen Pharmaceutical Co., Ltd., Xi'an, China) was infused subcutaneously at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of each cycle.

Evaluation of Clinical Efficacy

The clinical efficacy was evaluated based on IMWG criteria (Durie et al, 2006).

Complete response (CR) patients were assessed as follows: negative serum and urine immunofixation electrophoresis, disappearance of soft tissue plasmacytomas, bone marrow plasma cells less than 5%, and normal serum-free light chains (FLC) ratio.

Partial response (PR) patients had serum M protein reduction of $\geq$50% and 24-hour urinary M protein reduction of $>$90% or $<$200 mg. If serum and urine M protein were not detectable, a reduction of $>$50% in the difference between involved and uninvolved serum-free light chains were used as an alternative criterion. If serum and urine M protein and serum FLC were undetectable and the baseline bone marrow plasma cell ratio exceeded $>$30%, a reduction of $>$50% in bone marrow plasma cells was used as an alternative to replace the M protein criterion. Additionally, for patients with baseline soft tissue plasmacytomas, a reduction of $>$50% in the sum of the products of perpendicular diameters (SPD) of measurable lesions was required.

Patients with a progressive disease (PD) had serum M protein increased by 25%. If the lowest M protein value was $\geq$5 g/dL, an absolute increase of $>$1 g/dL was required. Urinary M protein increased by 25%, and the difference between involved and uninvolved serum FLC increased by 25%, with an absolute increase of $>$10 mg/dL. PD patients exhibited a 25% increase in bone marrow plasma cell proportion, with an absolute increase of $\geq$10%. Patients with newly emerged lesions or $>$50% increase in the sum of the SPD of existing measurable lesions compared

to the lowest value, or an increase of $\geq$1 cm in existing lesions were considered. Furthermore, they had a >50% increase recorded in circulating plasma cells.

In the case of stable disease (SD), the reduction in target lesions didn't reach the criteria for PR, and the increase didn't qualify as PD, placing the patient between these two categories.

Finally, the response rate was assessed as follows: Objective response rate (ORR) = CR + PR, disease control rate (DCR) = CR + PR + SD.

Observational Indicators

Observational indicators assessed across the study cohort were as follows:

(1) Immunophenotypic analysis: Immunophenotyping was conducted using the Epics XL flow cytometry (Beckman Coulter Trading, Shanghai, China).

(2) Blood parameters: Serum hemoglobin and M protein levels were determined using the BK-400 fully automatic biochemical analyzer (Biobase, Jinan, China).

(3) Coagulation function indexes: Serum prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB) levels were detected using the CA-7000 automatic coagulation analyzer (Sysmex, Shanghai, China).

(4) NF-κB related indicators: Within 24 hours of admission, 3 mL of fasting venous blood sample was collected and centrifuged at a rate of 3000 r/min. The white blood cells from the middle buffy coat layer were collected using a sterile dropper, resuspended in 5 mL of sterile phosphate buffer solution (PBS), and mixed with 15 mL of lymphocyte separation fluid. After that, the cloud-like buffy coat was carefully obtained and transferred to a new sterile centrifuge tube. Following the addition of 10 mL sterile PBS, the samples were centrifuged to obtain mononuclear cells.

The expression levels of *NF-κB* mRNA in mononuclear cells were assessed using qRT-PCR. Total RNA was extracted using TRIzol reagent (Invitrogen, V13241, Waltham, MA, USA) and reverse-transcribed into cDNA employing a reverse transcription kit (Dalian Bao Bioengineering Co., Ltd., KB37030, Dalian, China). qRT-PCR was performed using the IQ5 fluorescence quantitative PCR instrument ABI7500 (Bio-Rad, Hercules, CA, USA). qRT-PCR reagents were obtained from Bio-Rad Laboratories, Inc (4316567, Bio-Rad, Hercules, CA, USA) and the primer sequences were synthesized by Shanghai Bioengineering Technology Co., Ltd. (Table 1). The reaction conditions were as follows: 95 °C for 30 seconds (1 cycle) followed by 45 cycles of 95 °C for 5 seconds and annealing at 60 °C for 30 seconds. *β-actin* was used as the internal reference gene, and *NF-κB* mRNA expression levels were quantified using the $2^{-\Delta\Delta ct}$ method. For NF-κB protein expression analysis, peripheral blood mononuclear cells were isolated from 2 mL heparin-added venous blood using lymphocyte separation solution followed by nuclear protein isolation employing a nuclear protein extraction reagent under ice bath condition. In the following step, nuclear proteins were quantified, and NF-κB activity was determined using TransAMTM-P65 ELISA Kits (Active Motif, 573019, Carlsbad, CA, USA).

(5) Renal function indicators: serum creatinine (SCr) and blood urea nitrogen (BUN) were assessed using the automatic biochemical analyzer, and serum β2-

Table 1. Primer sequences used in qRT-PCR.

	Forward (5′-3′)	Reverse (5′-3′)
NF-κB	CAAGGACATGGTGGTCGGCTTC	CGCCTCTGTCATTCGTGCTTCC
β-actin	CCTGGCACCCAGCACAAT	GGGCCGGACTCGTCATAC

Note: *NF-κB*, nuclear transcription factor-κB.

microglobulin (β2-MG) was determined using ELISA (E-ELH1123; E-ELH1475; E-ELH0359, Merck & Co., Inc., Kenilworth, NJ, USA).

(6) Immunosuppressive factors: interleukin-6 (IL-6), interleukin-17 (IL-17), and transforming growth factor-β (TGF-β) levels were detected using ELISA before and after treatment (E-ELH0196, E-ELH2438, E-ELH1476, Merck & Co., Inc., Kenilworth, NJ, USA).

(7) Prognosis: All patients were followed for 12 months from the time of enrollment, or until death. The progression-free survival (PFS) rate and overall survival (OS) rate were determined for both groups, with the median PFS and median OS times recorded. PFS was defined as the time between the start of treatment and disease progression or patient's death. OS survival time was defined as the time from death due to any cause.

(8) Adverse reactions: The incidence of adverse reactions such as diarrhea, nausea, neuropathic pain, and abdominal pain during treatment were also documented.

Statistical Analysis

Statistical analysis was conducted using SPSS 22.0 software (International Business Machines Corporation, Armonk, NY, USA). Categorical data were expressed as n (%), and the differences between groups were compared using the χ^2 test or chi-square correction test. The Shapiro-Wilk Test was applied to determine whether the measurement data followed a normal distribution. Normally distributed data were expressed as ($\bar{x} \pm$ s), with a *t*-test applied for group comparisons, an independent sample *t*-test for inter-group comparison, and paired sample *t*-test for intra-group comparison. The Kaplan-Meier survival curve was generated using GraphPad Prism 5 software (GraphPad software Corporation, San Diego, CA, USA). The cumulative survival between groups was compared using the log-rank χ^2 test. A *p*-value of <0.05 was considered statistically significant, and all tests were two-sided.

Results

Comparison of Baseline Data between the Two Groups

As detailed in Table 2, no significant differences were observed in immunophenotype as well as in other clinical data between the two groups ($p > 0.05$).

Comparison of the Clinical Efficacy between the Two Groups

The ORR in the observation group was significantly higher than in the control group ($p = 0.030$). However, no significant difference in DCR was observed between the two groups ($p = 0.079$, Table 3).

Table 2. Comparison of baseline data between the two groups ($\bar{x} \pm s$), n (%).

Baseline characteristic	Observation group (n = 62)	Control group (n = 58)	χ^2/t	p
Gender			0.089	0.765
Male	39 (62.90)	38 (65.52)		
Female	23 (37.10)	20 (34.48)		
Age ($\bar{x} \pm s$)	57.52 ± 6.03	58.19 ± 6.47	0.587	0.558
BMI (kg/m^2)	21.53 ± 1.79	21.85 ± 1.82	0.971	0.334
ISS stage			0.294	0.588
I stage	33 (53.23)	28 (48.28)		
II stage	29 (46.77)	30 (51.72)		
Immunophenotyping			0.338	0.845
IgG	29 (46.77)	29 (50.00)		
IgA	19 (30.65)	15 (25.86)		
Light chain	14 (22.58)	14 (24.14)		

Note: Control group: thalidomide, cyclophosphamide, and dexamethasone (TCD) regimen treatment; Observation group: TCD regimen treatment and bortezomib treatment (same in the table below). BMI, body mass index; ISS, international staging system; IgG, immunoglobulin G; IgA, immunoglobulin A.

Table 3. Comparison of clinical efficacy between the groups (n (%)).

Experimental group	n	CR	PR	SD	PD	ORR	DCR
Observation group	62	17 (27.42)	27 (43.55)	13 (20.97)	5 (8.06)	44 (70.97)	57 (91.94)
Control group	58	12 (20.69)	18 (31.03)	17 (29.31)	11(18.97)	30 (51.72)	47 (81.03)
χ^2		0.741	2.002	1.112	3.082	4.694	3.082
p		0.389	0.157	0.292	0.079	0.030	0.079

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 4. Comparison of blood-related indexes between the two groups ($\bar{x} \pm s$, g/L).

Experimental group	n	Hemoglobin		M protein	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	62	71.39 ± 5.24	112.01 ± 15.16*	57.41 ± 9.04	18.39 ± 3.75*
Control group	58	70.46 ± 5.69	98.85 ± 17.38*	57.96 ± 9.62	23.05 ± 4.62*
t		0.932	4.428	0.323	6.084
p		0.353	<0.001	0.747	<0.001

Note: *$p < 0.05$, compared to the same group before treatment.

Comparison of Blood-Related Indexes between the Two Groups

Before treatment, blood-related indexes were comparable between the two groups ($p > 0.05$). After treatment, the hemoglobin level in both groups higher than before treatment levels ($p < 0.05$). After treatment, the levels of M protein in both groups were significantly reduced after treatment than those before treatment

Table 5. Comparison of coagulation function indexes between the two groups ($\bar{x} \pm s$).

Experimental group	n	PT (s)		APTT (s)		FIB (g/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	62	13.59 ± 1.34	11.01 ± 1.53*	36.09 ± 2.50	23.13 ± 2.19*	4.47 ± 0.59	3.64 ± 0.51*
Control group	58	13.70 ± 1.25	12.18 ± 1.76*	36.95 ± 2.43	25.02 ± 2.24*	4.50 ± 0.43	3.99 ± 0.38*
t		0.464	3.893	1.909	4.672	0.316	4.240
p		0.643	<0.001	0.059	<0.001	0.752	<0.001

Note: Control group: TCD regimen treatment; observation group: TCD regimen treatment and bortezomib treatment. PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen. *$p < 0.05$, compared to the same group before treatment.

British Journal of Hospital Medicine | 2025 | https://doi.org/10.12968/hmed.2024.0701

Table 6. Comparison of the NF-κB pathway-related indicators between the two groups ($\bar{x} \pm s$).

Experimental group	n	*NF-κB* mRNA		NF-κB (ng/μL)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	62	1.10 ± 0.25	0.29 ± 0.05*	15.13 ± 2.46	6.79 ± 1.10*
Control group	58	1.05 ± 0.18	0.51 ± 0.10*	15.08 ± 2.13	7.51 ± 0.96*
t		1.250	15.391	0.119	3.809
p		0.214	<0.001	0.906	<0.001

Note: Control group: TCD regimen treatment; observation group: TCD regimen and bortezomib treatment. *$p < 0.05$, compared to the same group before treatment.

($p < 0.05$). After treatment, the hemoglobin level in the observation group was higher than in the control group ($p < 0.001$), while the levels of M protein in the observation group were decreased ($p < 0.001$, Table 4).

Comparison of Coagulation Function Indexes between the Two Groups

There was no significant difference in coagulation function between the two groups before treatment ($p > 0.05$). After treatment, the PT, APTT values, and FIB levels in both groups were lower than before treatment levels ($p < 0.05$). After treatment, the PT, APTT values, and FIB levels were significantly reduced in the observation group than in the control group ($p < 0.001$, Table 5).

Comparison of the NF-κB Pathway-Related Indicators between the Two Groups

Before treatment, no significant differences were observed in the NF-κB pathway-related indicators between the two groups ($p > 0.05$). After treatment, the expression levels of *NF-κB* mRNA and NF-κB protein were decreased in both groups compared to before treatment ($p < 0.05$). Additionally, after treatment, the expression levels of *NF-κB* mRNA and NF-κB protein were significantly decreased in the observation group than in the control group ($p < 0.001$, Table 6).

Comparison of Renal Function Indexes between the Two Groups

Before treatment, renal function indexes were comparable between the two groups ($p > 0.05$). However, after treatment, SCr, BUN, and β2-MG levels were significantly reduced in both groups than those before treatment ($p < 0.05$). Furthermore, after treatment, SCr, BUN, and β2-MG levels were decreased in the observation group than in the control group ($p < 0.001$, Table 7).

The Levels of Disease-Related Immunosuppressive Factors in Both Groups

Before treatment, there were no significant differences in the levels of immunosuppressive factors between the two groups ($p > 0.05$). However, after treatment, the levels of IL-6, IL-17, and TGF-β were significantly lower in the two groups than those before treatment ($p < 0.05$). Additionally, after treatment, the levels of IL-6, IL-17 and TGF-β were decreased in the observation group compared to the control group ($p < 0.001$, Table 8).

Table 7. Comparison of the renal function indexes between the two groups ($\bar{x} \pm s$).

Experimental group	n	SCr (μmol/L)		BUN (mmol/L)		β2-MG (mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	62	118.54 ± 18.69	81.79 ± 6.94*	13.15 ± 1.95	6.97 ± 1.13*	11.59 ± 2.14	4.12 ± 0.86*
Control group	58	119.08 ± 18.13	89.53 ± 6.39*	13.02 ± 2.17	8.15 ± 0.98*	11.63 ± 2.06	4.78 ± 0.91*
t		0.160	6.343	0.346	6.093	0.104	4.085
p		0.873	<0.001	0.730	<0.001	0.917	<0.001

Note: SCr, serum creatinine; BUN, blood urea nitrogen; β2-MG, β2-microglobulin. *$p < 0.05$, compared to the same group before treatment.

Table 8. Comparison of disease-related immunosuppressive factors between the two groups ($\bar{x} \pm s$).

Experimental group	n	IL-6 (pg/mL)		IL-17 (pg/mL)		TGF-β (μg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	62	146.41 ± 13.05	75.95 ± 7.76*	171.38 ± 18.24	98.54 ± 18.02*	3.15 ± 0.57	1.39 ± 0.25*
Control group	58	143.09 ± 14.67	86.14 ± 7.35*	170.24 ± 17.61	119.69 ± 19.37*	3.19 ± 0.43	1.82 ± 0.31*
t		1.312	7.374	0.348	6.197	0.432	8.389
p		0.192	<0.001	0.729	<0.001	0.667	<0.001

Note: IL-6, interleukin-6; IL-17, interleukin-17; TGF-β, transforming growth factor-β. *$p < 0.05$, compared to the same group before treatment.

Table 9. Survival rate analysis in both the study groups (n (%)).

Experimental group	n	PFS rate	OS rate
Observation group	62	29 (46.77)	41 (66.13)
Control group	58	11 (18.97)	28 (48.28)
Log-rank χ^2		12.690	3.505
p		<0.001	0.061

PFS, progression-free survival; OS, overall survival.

Table 10. Comparison of adverse outcome rates between the two groups (n (%)).

Experimental group	n	Diarrhea	Nausea	Neuropathic pain	Abdominal pain and distension	Dizziness	Total incidence
Observation group	62	1 (1.61)	1 (1.61)	1 (1.61)	1 (1.61)	0 (0.00)	4 (6.45)
Control group	58	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.72)	1 (1.72)	2 (3.45)
χ^2							0.112
p							0.737

Survival Rate Analysis in Patients across Both Groups

The progression-free survival rate was substantially higher in the observation group than in the control group ($p < 0.001$, Table 7). However, no significant difference was found in the OS rate between the two groups ($p = 0.061$, Table 9). Moreover, the median PFS time was 11.95 months in the observation group and 9 months in the control group. Furthermore, the median OS time was 11.7 months in the control group, while it exceeded 50% in the observation group where the median OS time was not reached (Fig. 1).

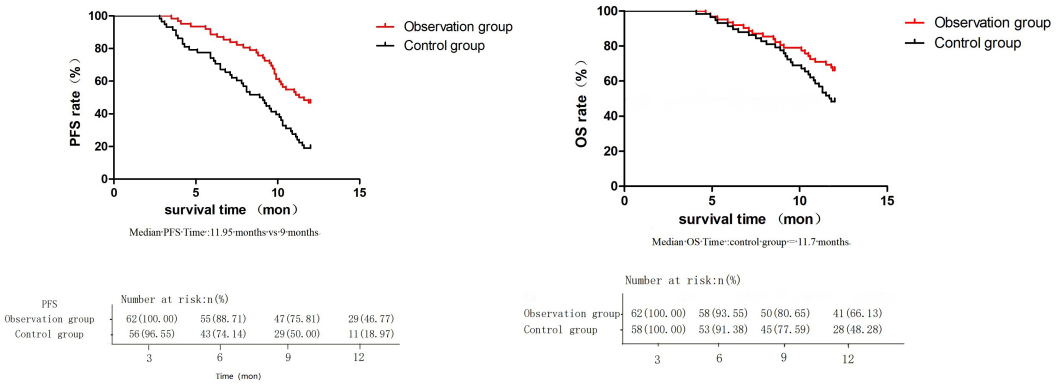

Fig. 1. Comparison of the survival rate between the two groups.

Assessing the Rate of Adverse Outcomes across Both Study Groups

These analyses revealed that the incidence of adverse outcomes was comparable between the two groups, indicating insignificant differences ($p > 0.05$, Table 10).

Discussion

In the early stage, patients with symptoms like fever, urine abnormalities, or lower back and leg pain can be misdiagnosed as respiratory diseases or nephritis, delaying accurate diagnosis and prompt intervention (Beer et al, 2021). Currently, there is no curative method for this disease. The primary treatment options include chemotherapy or surgical interventions, which focus on eliminating tumor cells and managing or alleviating clinical manifestations resulting from tumor cell proliferation (Dolph et al, 2021).

Bortezomib, a dipeptidyl borate analogue, is a synthetic and cytotoxic proteasome inhibitor that acts on the bone marrow microenvironment and ubiquitin-proteasome channel, thereby disrupting the adhesion of myeloma cells, promoting apoptosis, and impacting drug resistance (Duggan et al, 2020; Thompson et al, 2020). Previous research has revealed that novel agents such as bortezomib have improved survival outcomes in MM patients, further validating its therapeutic effectiveness (Sonneveld et al, 2024). However, our results suggest that this treatment did not substantially improve the therapeutic outcomes, which contrast with a previous study (Leleu et al, 2024). This difference may be due to the small sample size, necessitating further investigation.

In clinical practice, increased M protein levels and decreased hemoglobin levels are commonly used diagnostic criteria for MM (Hideshima et al, 2024). Moreover, a study has found that malignant plasma cells can disrupt platelet production and function either by infiltrating the bone marrow or secreting M protein (Lei et al, 2023). This study suggests that bortezomib treatment effectively reduces M protein levels and alleviates anemia in MM patients. A recent study has reported that increased activity of NF-κB is associated with the enhanced survival ability of MM cells, with chemotherapy-resistant and recurrent-prone MM cell lines demonstrating significantly elevated NF-κB activity (Walter et al, 2022). Persistent activation of NF-κB plays a crucial role in MM pathogenesis (Qu et al, 2022), as it enhances the expression of adhesion molecules, promotes myeloma precursor cell homing, and stimulates tumor cell-induced production of growth factors. Through adhesion to extracellular matrix proteins and bone marrow stromal cells, NF-κB-mediated IL-6 secretion induces various signaling pathways, promoting the extensive proliferation of myeloma cells and the progression of the disease (Yi et al, 2021). This study indicates that bortezomib inhibits NF-κB activity in MM treatment. This inhibition is likely due to bortezomib's ability to reduce the transcriptional regulatory activity of the NF-κB signaling pathway by suppressing the ubiquitin-proteasome pathway, ultimately alleviating the degradation of IkB, an NF-κB inhibitor (Yimer et al, 2019).

A recent study has shown that coagulation disorders are closely related to tumors and can directly reflect the changes of the disease, and the biological behavior of tumor cells in hypercoagulable state is more likely to become malignant (Dash et al, 2020). Thus, early identification and intervention of hypercoagulability in malignant tumors are particularly essential. PT and APTT are commonly used to evaluate the coagulation status, while fibrinogen acts as a sensitive coagulation index,

with its level reflecting the body's coagulation status (Lu et al, 2023), Research has demonstrated that fibrinogen levels are linked to the prognosis of various tumors, such as acute leukemia and lymphoma (Yu et al, 2024). Our findings indicate that bortezomib treatment effectively improves coagulation function in MM patients. This outcome is primarily due to bortezomib's ability to upregulate the expression of endothelial thrombomodulin, thereby enhancing the ability of endothelial cells to activate protein C and exerting an anticoagulant effect.

The most common and typical clinical manifestation of MM is renal damage. This occurs due to the filtration of a large number of monoclonal immunoglobulin light chains through the glomeruli, resulting in their deposition in the renal tubules, as well as hypercalcemia and other related factors, ultimately leading to renal dysfunction (Mikhael et al, 2021). Our study reveals that bortezomib treatment can improve renal function in MM patients. Bortezomib, a new targeted therapy, is a reversible inhibitor of 26S proteasome that effectively prevents the rapid degradation of intracellular proteins, thereby reducing the deposition of immunoglobulin in renal tubules. Furthermore, it impairs specific ubiquitin-proteasome channels, effectively blocking cell cycle progression and promoting apoptosis in tumor cells (Ailawadhi et al, 2024). β2-MG is a low-molecular-weight globulin secreted by platelets, lymphocytes, and white blood cells, with primary excretion through the kidneys (Atef et al, 2021). Moreover, patients with MM often experience renal failure, leading to elevated serum β2-MG levels compared to healthy individuals. When the disease improves, serum β2-MG levels decrease, indicating renal function recovery and overall clinical improvement.

Clinical data show that MM patients exhibit immune dysfunction. Immunoglobulin antibodies are abnormally secreted in MM patients, who lack immune response functionality and may even inhibit immune function to some extent (Brugnara, 2023). In this study, IL-6 and other immunosuppressive factors were selected as indicators to monitor the progression or improvement of MM. Myeloma cells are a crucial source of IL-6, a cytokine that plays a vital role in immune regulation by effectively promoting the proliferation of T cells and activated B cells (Gulubova et al, 2024). Additionally, previous research has indicated that IL-17 in the serum promotes tumor cell growth through receptor-mediated adhesion to stromal cells, highlighting its role in both tumor progression and anti-tumor immunity (Yi et al, 2021). Furthermore, TGF-β, an immunosuppressive factor secreted by cancer cells and regulatory T cells, reflects the degree of tumor-induced tumor inhibition (Ludwig et al, 2021). This study indicates that bortezomib treatment for MM reduces immunosuppression, a critical mechanism underlying its anti-tumor effects. By reducing immunosuppressive microenvironment, bortezomib alleviates immune suppressive and ultimately reduces tumor burden.

A previous study has indicated an increased rate of adverse effects with bortezomib treatment in MM patients (Lobbes et al, 2018). However, the results of this study differ from previous studies, which may be due to the small sample size (Lobbes et al, 2018). Therefore, further investigations involving large sample sizes are warranted to validate these findings and reduce potential biases.

Conclusion

In summary, bortezomib treatment improves coagulation and renal function in MM patients. Furthermore, it reduces immune suppression, prolongs survival time, and inhibits the NF-κB pathway activation, emerging as a primary therapeutic option.

Key Points

- Bortezomib improves coagulation function in patients with multiple myeloma.
- Bortezomib improves renal function in patients with multiple myeloma.
- Bortezomib in treating multiple myeloma reduces the level of immunosuppression.
- Bortezomib inhibits NF-κB pathway activation in the treatment of multiple myeloma.

Availability of Data and Materials

The data analyzed are available upon request from the corresponding author.

Author Contributions

JT conceived the study. LW and ZYG performed the research. JT and LYZ analyzed the data and JT drafted the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All patients provided informed consent. This study conforms to the Declaration of Helsinki and has been approved by the Medical Ethics Committee of Nantong First People's Hospital (Approval number: 2024KT130).

Acknowledgement

Not applicable.

Funding

This study is supported by Youth project of Nantong Municipal Health Commission (No. QN2022019), Nantong University clinical medicine special research fund (NTUB2023B77), Research Project of Nantong Municipal Health Commission (MSZ2024026) and Nantong University Special Research Fund for Clinical Medicine (Grant No. 2024JY001).

Conflict of Interest

The authors declare no conflict of interest.

References

Ailawadhi S, Lee HC, Omel J, Toomey K, Hardin JW, Gasparetto CJ, et al. Impact of lenalidomide-bortezomib-dexamethasone induction on patients with newly diagnosed multiple myeloma and renal impairment: Results from the Connect® MM Registry. Blood Cancer Journal. 2024; 14: 198. https://doi.org/10.1038/s41408-024-01177-6

Atef M, Zayed N, Salama R, Abdel Alem S, Yousof H, Saber M, et al. Is urinary β2-microglobulin a reliable marker for assessment of renal tubular dysfunction in chronic hepatitis B patients receiving tenofovir therapy? European Journal of Gastroenterology & Hepatology. 2021; 33: e992–e998. https://doi.org/10.1097/MEG.0000000000001977

Beer H, Routledge D, Joyce T, Furphy EJ, Combe N, Ritchie D, et al. The development of a home-based therapeutic platform for multiple myeloma. Expert Review of Hematology. 2021; 14: 1129–1135. https://doi.org/10.1080/17474086.2021.2022471

Brugnara C. Immune Therapies in the Treatment of Multiple Myeloma. American Journal of Hematology. 2023; 98 Suppl 2: S3. https://doi.org/10.1002/ajh.26851

Bruno T, Catena V, Blandino G, Fanciulli M, Di Agostino S. Molecular insights unlocking therapeutic potential for multiple myeloma and bone disease management. Journal of Experimental & Clinical Cancer Research. 2024; 43: 322. https://doi.org/10.1186/s13046-024-03248-9

Chinese Medical Doctor Association Hematology Physicians Branch, Chinese Medical Association Hematology Branch, Chinese Medical Doctor Association Multiple Myeloma Professional Committee. 2017 Chinese guidelines for Diagnosis and Treatment of multiple myeloma (revised in 2017). Chinese Journal of Internal Medicine. 2017; 56: 866–870. (In Chinese)

Dash AB, Zhang J, Shen L, Li B, Berg D, Lin J, et al. Clinical benefit of ixazomib plus lenalidomide-dexamethasone in myeloma patients with non-canonical NF-κB pathway activation. European Journal of Haematology. 2020; 105: 274–285. https://doi.org/10.1111/ejh.13435

Dolph M, Tremblay G, Leong H. US Budget Impact Model for Selinexor, Bortezomib, and Dexamethasone for the Treatment of Previously Treated Multiple Myeloma. ClinicoEconomics and Outcomes Research. 2021; 13: 493–502. https://doi.org/10.2147/CEOR.S305830

Duggan P, Reece DE, Song K, Jimenez-Zepeda V, Mccurdy A, Louzada M, et al. Is Tandem ASCT Needed in MM Patients with High Risk Cytogenetics in the Era of Maintenance Therapy? Results from the Canadian Myeloma Research Group (CMRG) Database. Blood. 2020; 136: 18–19. https://doi.org/10.1182/blood-2020-139689

Durie BGM, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467–1473. https://doi.org/10.1038/sj.leu.2404284

Gulubova M, Chonov D, Aleksandrova E, Ivanova K, Ignatova MM, Vlaykova T. Interleukin-6-Positive Immune Cells as a Possible New Immunologic Marker Associated With the Colorectal Cancer Prognosis. Applied Immunohistochemistry & Molecular Morphology. 2024; 32: 233–243. https://doi.org/10.1097/PAI.0000000000001198

Hideshima T, Podar K, Chauhan D, Ishitsuka K, Mitsiades C, Tai YT, et al. Editorial Expression of Concern: p38 MAPK inhibition enhances PS-341 (bortezomib)-induced cytotoxicity against multiple myeloma cells. Oncogene. 2024; 43: 3018. https://doi.org/10.1038/s41388-024-03147-5

Lei X, Zhang T, Deng Z, Jiang T, Hu Y, Yang N. Coagulation markers as independent predictors of prostate cancer aggressiveness: a retrospective cohort study. Scientific Reports. 2023; 13: 16073. https://doi.org/10.1038/s41598-023-43427-w

Leleu X, Hulin C, Lambert J, Bobin A, Perrot A, Karlin L, et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. Nature Medicine. 2024; 30: 2235–2241. https://doi.org/10.1038/s41591-024-03050-2

Lobbes H, Grobost V, Lemal R, Rieu V, Le Guenno G, Ruivard M. Efficacy of bortezomib in non-IgM type I cryoglobulinaemic vasculitis: a single-centre retrospective case series. European Journal of Haematology. 2018; 101: 635–642. https://doi.org/10.1111/ejh.13154

Lu S, Gao W, Li M, Xu Q, Rong J, Song Y, et al. Thromboelastography Parameters Change Significantly in Patients with Endometrial Cancer and Uterine Fibroids. Clinical Laboratory. 2023; 69. https://doi.org/10.7754/Clin.Lab.2022.220408

Ludwig N, Wieteska Ł, Hinck CS, Yerneni SS, Azambuja JH, Bauer RJ, et al. Novel TGFβ Inhibitors Ameliorate Oral Squamous Cell Carcinoma Progression and Improve the Antitumor Immune Response of Anti-PD-L1 Immunotherapy. Molecular Cancer Therapeutics. 2021; 20: 1102–1111. https://doi.org/10.1158/1535-7163.MCT-20-0944

Mikhael J, Singh E, Rice MS. Real-world renal function among patients with multiple myeloma in the United States. Blood Cancer Journal. 2021; 11: 99. https://doi.org/10.1038/s41408-021-00492-6

Pasvolsky O, Yeshurun M, Fraser R, Estrada-Merly N, Rozovski U, Shargian-Alon L, et al. Maintenance therapy after second autologous hematopoietic cell transplantation for multiple myeloma. A CIBMTR analysis. Bone Marrow Transplantation. 2022; 57: 31–37. https://doi.org/10.1038/s41409-021-01455-y

Qu J, Hou Y, Chen Q, Chen J, Li Y, Zhang E, et al. RNA demethylase ALKBH5 promotes tumorigenesis in multiple myeloma via TRAF1-mediated activation of NF-κB and MAPK signaling pathways. Oncogene. 2022; 41: 400–413. https://doi.org/10.1038/s41388-021-02095-8

Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. The New England Journal of Medicine. 2024; 390: 301–313. https://doi.org/10.1056/NEJMoa2312054

Thompson JF, Teh Z, Chen Y, Gardiner J, Bednarz JM, Thompson GN, et al. A costing study of bortezomib shows equivalence of its real-world costs to conventional treatment. British Journal of Haematology. 2020; 189: e76–e79. https://doi.org/10.1111/bjh.16484

Walter LO, Maioral MF, Silva LO, Speer DB, Campbell SC, Gallimore W, et al. Involvement of the NF-kappa B and PI3K/Akt/mTOR pathways in cell death triggered by stypoldione, an o-quinone isolated from the brown algae Stypopodium zonale. Environ Toxicol. 2022; 37: 1297–1309. https://doi.org/10.1002/tox.23484

Yi H, Liang L, Wang H, Luo S, Hu L, Wang Y, et al. Albendazole inhibits NF-κB signaling pathway to overcome tumor stemness and bortezomib resistance in multiple myeloma. Cancer Letters. 2021; 520: 307–320. https://doi.org/10.1016/j.canlet.2021.08.009

Yimer H, Melear J, Faber E, Bensinger WI, Burke JM, Narang M, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. British Journal of Haematology. 2019; 185: 492–502. https://doi.org/10.1111/bjh.15806

Yu CR, Liao YA, Chiang CN, Chen JM, Pan HB, Pan CY, et al. Doxorubicin synergizes bortezomib-induced multiple myeloma cell death by inhibiting aggresome formation and augmenting endoplasmic reticulum/Golgi stress and apoptosis. Journal of Translational Medicine. 2024; 22: 1095. https://doi.org/10.1186/s12967-024-05920-2

Zhou Y, Liu X, Xue J, Liu L, Liang T, Li W, et al. Discovery of Peptide Boronate Derivatives as Histone Deacetylase and Proteasome Dual Inhibitors for Overcoming Bortezomib Resistance of Multiple Myeloma. Journal of Medicinal Chemistry. 2020; 63: 4701–4715. https://doi.org/10.1021/acs.jmedchem.9b02161