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RESEARCH ARTICLE

The Efficacy and Safety Analysis of the Bendamustine, Pomalidomide, and Dexamethasone (BPD) Combination Treatment for Patients with Proteasome Inhibitor Intolerance and/or Relapsed Multiple Myeloma

Yiming Zhao[1,2,#], Wanlu Tian[1,2], Fengbo Jin[1,2], Lei Jiang[1,2], Rui Zhang[1,2], Wei Qian[1,2], Leiming Xia[1,2] and Mingzhen Yang[1,2,*]

[1]*Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Hefei, China;* [2]*Anhui Public Health Clinical Center, Hefei, China*

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Abstract: ***Background*:** Multiple Myeloma (MM) is a hematologic malignancy that often progresses to a refractory relapse, posing significant treatment challenges due to prior treatments, drug response duration, clinical and molecular characteristics, comorbidities, and adverse reactions.

***Methods*:** This single-center and single-arm study assessed the BPD regimen, which includes bendamustine, pomalidomide, and dexamethasone, for its efficacy and safety in 21 patients with Relapsed and Refractory Multiple Myeloma (RRMM), including those who were intolerant to prior bortezomib treatment.

***Results*:** The Overall Response Rate (ORR) after 1-8 cycles of BPD treatment was 58.8%. The 6-month Progression-Free Survival (PFS) was 70.5%, and the 12-month PFS was 52.9%. The 1-year Overall Survival (OS) rate was 82.35%. Hematologic toxicities were the main adverse reactions, with grade 3 or higher adverse events mainly linked to hematologic toxicity and infections.

***Conclusion*:** The BPD regimen has shown to be highly effective, with a favorable ORR and survival rate in RRMM patients, indicating it a relatively safe and well-tolerated treatment option.

Keywords: Multiple myeloma, bendamustine, pomalidomide, dexamethasone, proteasome inhibitor intolerance, relapse.

1. INTRODUCTION

Multiple Myeloma (MM) is a hematologic malignancy originating from plasma cells. Monoclonal plasma cells in the bone marrow secrete monoclonal proteins, leading to complications such as lytic bone lesions, hypercalcemia, anemia, and renal impairment [1]. In the United States, the median age at diagnosis for this tumor is approximately 69 years, with an incidence rate of around 6.3 cases per 100,000 individuals per year [2, 3]. MM accounts for approximately 1% to 10% of all hematologic malignancies, and in 2021, an estimated 34,920 new cases and 12,410 deaths are projected in the United States [4]. Over the past few decades, survival rates for MM patients have significantly improved, especially with the introduction of new drugs such as immunomodulatory agents (*e.g.*, lenalidomide, pomalidomide), proteasome inhibitors (*e.g.*, bortezomib, carfilzomib, ixazomib), histone deacetylase inhibitor panobinostat, nuclear export inhibitor selinexor, and monoclonal antibodies (*e.g.*, daratumumab, isatuximab, elotuzumab) [3, 5]. In recent years, the widespread use of various drugs, including Proteasome Inhibitors (PI), Immunomodulatory Drugs (IMiDs), and Monoclonal Antibodies (MoAbs), has significantly contributed to improving patient survival. The VRD regimen (bortezomib + lenalidomide + dexamethasone) as a first-line treatment has been widely used in China [6]. However, given that conventional treatments cannot cure MM, nearly every patient eventually experiences a relapse. Once relapsed, the high cost of new drugs, including monoclonal antibodies, makes them financially burdensome for many patients, preventing sustained use [7]. Additionally, some patients, even if free from relapse for a short period, may discontinue treatment due to intolerable peripheral neuropathy caused by the use of proteasome inhibitors [8, 9].

Therefore, optimizing the current treatment strategies for patients with Relapsed and Refractory Multiple Myeloma (RRMM) is an urgent clinical challenge.

Bendamustine is a cytotoxic agent with dual activity, possessing both alkylating and purine analog properties, similar to fludarabine. It demonstrates activity in solid tumors such

* Address correspondence to this author at the Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Hefei, China; Anhui Public Health Clinical Center, Hefei, China;
E-mail: yangmz89@163.com
# *This author contributed equally to this work and share the first authorship.*

as ovarian and breast cancer, as well as hematologic malignancies like lymphoma, chronic lymphocytic leukemia, and multiple myeloma. Importantly, *in vitro* studies indicate that bendamustine does not exhibit cross-resistance or only partial cross-resistance with cyclophosphamide, melphalan, and cisplatin. This characteristic makes bendamustine a suitable choice for treating patients with RRMM [10, 11]. The European Medicines Agency (EMA) was the first to approve bendamustine, in combination with dexamethasone, for the treatment of newly diagnosed multiple myeloma patients [12]. In real-world settings, bendamustine has shown impressive and promising therapeutic outcomes in patients with relapsed/refractory extramedullary plasmacytoma [13]. In these studies, the BPD regimen has demonstrated outstanding efficacy and a relatively safe toxicity profile.

Pomalidomide, an oral immunomodulatory agent, exhibits more potent and direct antitumor effects as well as immune-enhancing properties compared to lenalidomide [14]. Despite belonging to the same class of drugs as lenalidomide, pomalidomide maintains its antitumor and immunomodulatory effects even in lenalidomide-resistant cell lines and animal activity models [15, 16]. The combination of pomalidomide and dexamethasone is considered the standard treatment option for patients with RRMM and provides survival benefits in cases of lenalidomide resistance.

In this study, we aim to explore the potential of combination therapy with these two drugs in RRMM patients, with a focus on their efficacy and safety.

2. MATERIALS AND METHODS

2.1. Study Design

This study was a single-center, single-arm study, and all patients signed informed consent before treatment.

2.2. Patient Selection and Data Collection

In this study, we primarily focused on 17 patients with RRMM, excluding 4 patients who were intolerant to bortezomib. A total of 17 RRMM patients were collected between November 2021 and May 2023, all of whom were from the First Affiliated Hospital of Anhui Medical University. All patients had previously received two or more treatment regimens. Patient information, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance score, number of previous treatment lines, R-ISS staging at the time of diagnosis, extramedullary involvement, cytogenetics/molecular biology findings, autologous stem cell transplantation, prior treatment drugs, treatment response, and efficacy, was recorded.

2.3. Treatment Protocol

The specific BPD treatment regimen was as follows: bendamustine 70-90mg/m^2 on days 1-2, pomalidomide 4 mg orally once daily on days 1-21, and dexamethasone 40 mg orally on days 1, 8, 15, and 22 (dose reduced to 20 mg for patients aged >75 years or those with frailty) with a 28-day cycle. Patients received eight cycles of bendamustine and continued to receive Pomalidomide-Dexamethasone (PD) treatment to reduce the risk of bendamustine-related toxicity and secondary malignancies. BPD treatment continued until unacceptable toxicity or disease progression.

2.4. Clinical Endpoints

Progression-Free Survival (PFS) was defined as the time from the start of BPD to disease progression or death for any reason. The primary endpoint was PFS. Secondary endpoints included Objective Response Rate (ORR), Overall Survival (OS), safety, and others.

2.5. Response Criteria and Adverse Event Assessment

This study used the IMWG 2016 response criteria, categorizing responses as stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minimal Response (MR), Stable Disease (SD), and Disease Progression (PD). The ORR was defined as the sum of sCR, CR, VGPR, and PR rates. Adverse Events (AEs) were assessed according to the NCI CTC AE V 4.0 criteria.

2.6. Ethical Approval

The research protocol received approval from the Ethics Committee of the Fourth Affiliated Hospital of Anhui Medical University (Approval Number: PJ-YX2021-022, dated November 26, 2021). The study adheres to the principles of the Helsinki Declaration and Good Clinical Practice guidelines issued by the International Conference on Harmonisation.

2.7. Statistical Methods

The distribution of subgroups will be represented using the number of cases and proportions and analyzed using Prism 9 and SPSS 26.0. Simple Survival Analysis (Kaplan-Meier) will be employed to analyze patient survival curves.

3. RESULTS

3.1. Patient Characteristics

In this study, 17 patients with RRMM were enrolled, ranging in age from 41 to 76 years, with a median age of 57 years. Patients over 65 years old accounted for 29.4% (5 cases). Among them, there were 11 males (64.7%) and 6 females (35.3%). The ECOG score was 0-1 in 88.2% of patients. Regarding M protein types, there were 7 cases of IgG, 5 of IgA, 1 of IgD, 3 light-chain types, and 1 other type. Extramedullary plasmacytoma was present in 5 out of 17 patients, with 2 cases having 17p deletion and 1 case with t(4;14) at diagnosis. According to the R-ISS staging, there was 1 patient in stage 1, 10 in stage 2, and 6 in stage 3. Prior to enrollment, all patients had received bortezomib, 16 out of 17 had used lenalidomide, 2 out of 17 had used anti-CD38 monoclonal antibodies, and 3 out of 17 had undergone autologous stem cell transplantation. Eight patients had previously received a third-line treatment regimen, and the other 9 had received a last-line regimen. See Table (**1**) for details.

Table 1. Baseline characteristics and short-term efficacy of included patients.

-	Cases	Percentage
Gender	-	-
Male	11	64.70%
Female	6	35.30%
Age (years)	-	-
The median age	57	-
>65	5	29.40%
Type of M Protein	-	-
IgG	7	41.10%
IgA	5	29.40%
IgD	1	5.90%
Light chain type	3	17.60%
Other	1	5.90%
ISS-R Periodization	-	-
I	1	5.90%
II	10	58.80%
III	6	35.20%
Cytogenetics features at the times of diagnosis	-	-
1q21	7	41.10%
Comon	2	11.70%
P53 /Del 17P	2	11.70%
complex chromosomal karyotype	2	11.70%
t(4;14)	1	5.90%
t(14;16)	1	5.90%
unkonw	2	11.70%
Pre-treatment	-	-
Previous use of bortezomib	17	100%
Previous use of lenalidomide	16	94.10%
Previous use of target drugs (Kafezomi,Dara,selinexor)	2	11.70%
ASCT	3	17.60%
Number of treatment lines	-	-
3-line	8	47%
Last-line	9	53%
Treatment response status	-	-
CR	2	11.70%
VGPR	5	29.40%
PR	4	23.50%
SD	5	29.40%
PD	1	5.88%
Extramedullary	-	-
No	12	70.50%
Yes	5	29.40%

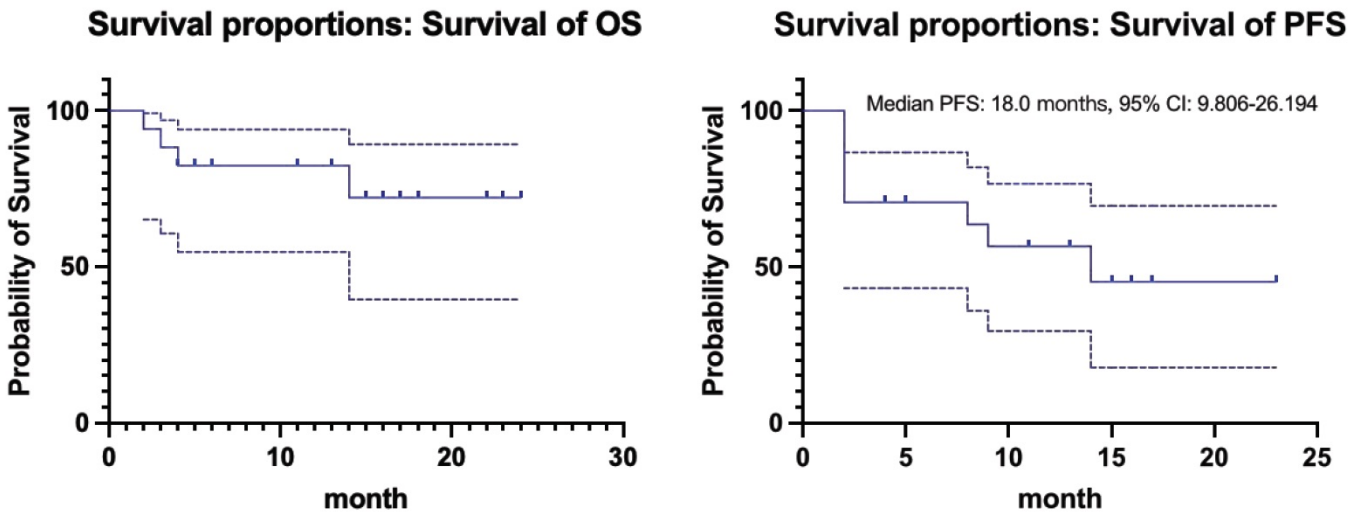

Fig. (1). OS and PFS curves of included patients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2. Efficacy Analysis

In the recent efficacy analysis, after 1-8 cycles of BPD treatment, the ORR was 58.8%, including 0 cases of sCR, 2 of cCR, 5 of VGPR, 4 of PR, 5 of PD, and 1 of SD. Three patients' creatinine levels returned to normal after using the BPD regimen, and among those who achieved ORR, 2 successfully bridged to autologous stem cell transplantation. See Table (**1**) for details.

In the long-term efficacy analysis over a follow-up period of up to 24 months, we found that the median PFS was 18.0 months, with a 95% CI of 9.806-26.194. The 6-month and 12-month PFS rates were both 75.5%, and the median OS was not reached, with both 6-month and 12-month OS rates at 82.4%. Details are present in Fig. (**1**).

3.3. Safety

In the safety analysis, we found that the BPD regimen was generally well-tolerated. The most common grade 3 or higher AEs were hematologic toxicities, including neutropenia (58.8%), anemia (35.2%), thrombocytopenia (47%), and leukopenia (82.3%). Six patients developed pulmonary infections, including one definite case of PCP. Three patients experienced agranulocytosis with infection. Two cases of grade 3 or higher infection AEs were observed. No grade 3 or higher non-hematologic toxicities such as nausea, fatigue, liver damage, or neuropathy were reported. Bendamustine showed certain safety advantages in renal function [17]. Particularly, noteworthy is that 4 patients experienced renal impairment while using the BPD regimen, of which 3 were due to disease progression, and only 1 was considered related to the BPD regimen. This was a transient increase and returned to normal after treatment. See Table (**2**) for details.

Table 2. Adverse reactions of included patients.

-	All Grades	Grade≥3
Neutropenia	10(58.8%)	3(17.6%)
Anemia	6(35.2%)	1 (5.9%)
Thrombocytopenia	8(47%)	4 (23.5%)
Infection	27 (52%)	10 (19%)
Gastrointestinal toxicity	7 (41%)	0 (0%)
Thromboembolism	0(0%)	0 (0%)
Neuropathy	0 (0%)	0 (0%)
Renal function impairment	1(5.9%)	0 (0%)
Hepatic toxisity	2(11.7%)	0 (0%)
Hypertension	0(0%)	0(0%)

4. DISCUSSION

In the treatment of RRMM, various therapeutic strategies are available. The ideal treatment for each patient should be tailored based on disease-related factors, responses to prior treatments, clinical and biochemical characteristics, patient comorbidities, and known adverse reactions to treatments. Most patients receive drug combinations, including previously unutilized Proteasome Inhibitors (PI), immunomodulatory drugs (IMiDs), monoclonal antibodies, and histone deacetylase inhibitors, among other novel agents [18, 19]. However, alkylating agents remain an important choice in the treatment of myeloma, and their combination with novel drugs has been proven effective for both newly diagnosed and relapsed/refractory myeloma. Bendamustine, integrating the mechanisms of alkylators and purine analogs [20], demonstrates synergy in overcoming non-cross resistance in RRMM patients and is more accessible due to its cost-effectiveness.

Recent studies have shown that combinations of bendamustine with bortezomib, carfilzomib, and lenalidomide exhibit effective outcomes in RRMM patients. For instance, a

regimen of bendamustine combined with carfilzomib and dexamethasone demonstrated a promising ORR of 88%, a median PFS of 15.1 months, and a median OS of 56.3 months in RRMM patients [21]. Another trial with bendamustine combined with isatuximab and dexamethasone in RRMM patients showed a median PFS of 5.2 months, a median OS of 23.2 months, and an ORR of 61% [22].

An open-label phase I/II trial of the combination of pomalidomide, bendamustine, and dexamethasone has demonstrated its efficacy as a treatment choice for patients with RRMM, achieving an ORR of 61%, with median PFS and OS of 9.6 months and 21.3 months, respectively [23]. Kumar *et al.* conducted a phase II clinical trial using a regimen of bendamustine, pomalidomide, and dexamethasone in RRMM [16]. This phase II study observed the efficacy of the BPD (Bendamustine, Pomalidomide, Dexamethasone) treatment in RRMM patients, with a notable response in patients with Extramedullary Myeloma (EMM). The prevalence of EMM in our study was not high, yet all patients benefited from the BPD regimen.

Musto *et al.* investigated the use of bendamustine in RRMM, emphasizing its potential role in patients who have exhausted other treatment options [24]. The study highlighted that the combination therapy, including bendamustine can synergistically overcome non-cross resistance in RRMM patients. The most common side effect observed was hematologic toxicity, with 56% of patients experiencing grade 3-4 hematologic toxicity. It has been noted that treatment methods based on bendamustine combinations have acceptable toxicity profiles.

The high ORR and PFS rates in this study might be related to the patients' lesser prior exposure to various new drugs (such as carfilzomib, CD38 monoclonal antibodies, and selinexor). Among the 17 RRMM patients in the study, only three had undergone autologous stem cell transplantation, none had received CAR-T cell therapy, and there was a higher proportion of third-line treatments. The proportion of patients in the ISS-R3 stage and those with EMM was not high, which might have contributed to the better outcomes observed in this study compared to previous research. In terms of safety, the most common adverse effect of bendamustine was hematologic toxicity. The study showed that after more than 3-4 cycles of the BPD regimen, hematologic toxicity was almost inevitable, with pulmonary and bloodstream infections being the most common infections. No treatment-related deaths were observed [25]. Regarding renal function impairment, during the BPD regimen, four patients experienced increased creatinine levels, three of which were related to disease progression, and only one case was considered drug-related AEs, which were transient and returned to normal after dose adjustment. Among the 21 patients studied, four were intolerant to bortezomib, primarily due to severe peripheral neuropathy. These four patients switched to the BPD regimen and showed good disease control, remaining stable until one patient experienced disease progression in the 19th month of follow-up, which was then controlled again with a carfilzomib-based regimen. No worsening of peripheral neuropathy was observed in these four patients. None of the 17 RRMM patients experienced an exacerbation of peripheral neuropathy.

This study demonstrates that the bendamustine-based BPD triplet regimen is effective and well-tolerated in treating RRMM patients, with the main adverse reaction being hematologic toxicity. The use of granulocyte colony-stimulating factors can significantly reduce the incidence of infections. Despite the emergence of various new drugs with promising efficacy, their high cost limits their use domestically. The BPD regimen shows good effectiveness and economic benefits in RRMM patients with renal impairment and extramedullary disease. More extensive data validation will require larger sample sizes and longer follow-up periods [9].

CONCLUSION

The BPD regimen, as demonstrated in this study, provides a promising therapeutic approach for patients with RRMM. With an ORR of 58.8% and a 1-year OS rate of 82.35%, the BPD regimen has shown significant efficacy. Despite the occurrence of hematologic toxicities, the treatment was generally well-tolerated, suggesting a favorable safety profile. These findings warrant further investigation and potentially the broader application of the BPD regimen in the clinical management of RRMM. Future studies should aim to confirm these results in larger, multicenter trials and explore strategies to mitigate the observed toxicities.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: MY; data collection: FJ, LJ; analysis and interpretation of results: RZ, WQ, LX. Author, YY. Author. ZZ. Author; draft manuscript: YZ, WT. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AEs	=	Adverse Events
CR	=	Complete Response
ECOG	=	Eastern Cooperative Oncology Group
EMA	=	European Medicines Agency
EMM	=	Extramedullary Myeloma
IMiDs	=	Immunomodulatory Drugs
MM	=	Multiple Myeloma
MoAbs	=	Monoclonal Antibodies
MR	=	Minimal Response
ORR	=	Overall Response Rate
OS	=	Overall Survival
PD	=	Pomalidomide-Dexamethasone

PFS = Progression-Free Survival

PI = Proteasome Inhibitors

PR = Partial Response

RRMM = Relapsed and Refractory Multiple Myeloma

sCR = stringent Complete Response

SD = Stable Disease

VGPR = Very Good Partial Response

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research protocol received approval from the Ethics Committee of the Fourth Affiliated Hospital of Anhui Medical University, Hefei, China (Approval Number: PJ-YX2021-022, dated November 26, 2021).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013, and Good Clinical Practice guidelines issued by the International Conference on Harmonisation.

CONSENT FOR PUBLICATION

All patients signed informed consent before treatment.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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