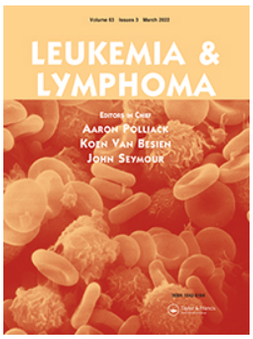

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ORIGINAL ARTICLE

A prospective, multicenter study of bortezomib, cyclophosphamide, and dexamethasone in relapsed/refractory iMCD

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ABSTRACT

Relapsed and refractory (R/R) idiopathic Multicentric Castleman disease (iMCD) is a clinical challenge with few treatment options. In this first multicenter, prospective trial which implemented the recently published CDCN response criteria, we evaluated the efficacy and safety profiles of bortezomib-cyclophosphamide-dexamethasone (BCD) regimen in 24 R/R iMCD patients. By 6 months, 15 patients (62.5%) achieved overall treatment responses; four patients (16.7%) had stable disease and five patients (20.8%) suffered from progression of disease. Even when considering all patients, there were significant ($p < .05$) improvements in median symptom score, hemoglobin, platelet count, C-reactive protein (CRP) erythrocyte sedimentation rate (ESR), IL-6, albumin, and immunoglobin G (IgG) after treatment. The regimen was well tolerated without grade 3 or higher adverse events. Estimated 1-year progression-free survival (PFS) and overall survival (OS) were 79% and 92%, respectively. BCD regimen is an effective and safe treatment option for R/R iMCD patients. This trial was registered at www.chictr.org.cn as # ChiCTR1800019342.

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KEYWORDS
Idiopathic multicentric castleman disease; bortezomib; treatment

Introduction

First described by Benjamin Castleman and his colleague in the 1950s [1], Castleman disease (CD) is now considered as a group of rare, heterogeneous lymphoproliferative disorders which are divided into unicentric CD (UCD) and multicentric CD (MCD). The latter is further divided into human herpesvirus-8 (HHV-8) associated MCD, which is caused by uncontrolled HHV-8 infection in immunocompromised patients (e.g. HIV-positive individuals), and HHV-8 negative MCD which is also termed as idiopathic MCD (iMCD) due to unknown etiology [2]. iMCD involves multiple regions of enlarged lymph node with characteristic histopathological features as well as life-threatening disease inflammatory symptoms, cytopenias, and multiple organ dysfunction due to a cytokine storm often including interleukin-6 (IL-6) [3]. The constellation of characteristic histopathological features is often subdivided into hyaline vascular (HV), plasmacytic (PC), and mixed histopathological subtypes. Due to limited understanding of iMCD pathogenesis and few treatment options, the published five-year mortality rate is approximately 23–49% [4–6]. Though IL-6 inhibition with siltuximab is effective in 34–45% of iMCD patients based on data from a randomized controlled trial [7] and it is recommended first-line for iMCD [8], there are still many unmet needs, especially for patients with refractory or relapsed diseases. Unlike first-line treatment recommendations, treatment options for refractory or relapsed patients (e.g. Rituximab with or without immunomodulators for non-severe patients and cytotoxic chemotherapy for severe patients) were mostly based on case reports or small series which were considered as category 2B evidence [8]. The lack of rigorous evaluation for these currently recommended second- or third-line treatments highlights the value of further exploration of

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

treatment options for refractory or relapsed iMCD patients.

Bortezomib, a therapeutic proteasome inhibitor, is a promising agent for patients with iMCD. First, this drug is believed to exert its effect through blockade of NF-κB-dependent production of cytokines, such as IL-6 [9,10] which is vital for the pathogenesis of iMCD. Second, bortezomib has been safely utilized to treat POEMS syndrome [11], a disease very closely related to iMCD as 15–25% POEMS patients have documented concurrent diagnosis of CD [12,13]. Third, bortezomib has been reported to successfully treat several iMCD cases [14–16] including relapsed patients, suggesting a potential role of bortezomib in iMCD patients. These abovementioned clues suggested that further evaluation for this drug was warranted. Moreover, subcutaneous administration of bortezomib has been shown to offer non-inferior efficacy to standard IV administration with an improved safety profile [17] which could be a convenient choice for iMCD, a disease requiring long-term treatment.

Aside from bortezomib, cyclophosphamide, and glucocorticoids have been reported to be effective in iMCD patients [8,18,19] due to their antimitotic and anti-inflammatory properties as well as modulation of T cells [19]. Subcutaneous bortezomib, along with oral cyclophosphamide and dexamethasone (BCD regimen), a drug combination whose safety profiles have been well demonstrated in myeloma patients [17], is therefore a promising and convenient treatment approach for iMCD. Therefore, we performed this prospective, multicenter study to further illuminate the efficacy and safety profiles of BCD regimen for relapsed and refractory (R/R) iMCD patients.

Materials and methods

Study design and participants

This prospective, multicenter, single-arm, phase 2 trial was conducted in Peking Union Medical College Hospital (Beijing, China) and Peking University First Hospital (Beijing, China) as registered in chictr.org (ChiCTR1800019342). All enrolled patients provided signed informed consent before study entry. The study was performed in accordance with the Declaration of Helsinki, with prior approval of the institutional review board and the ethics committee of the local hospital.

According to the international, evidence-based consensus diagnostic criteria for iMCD [2], adult patients (≥18 y/o) who met both major criteria and at least 2 of 11 minor criteria, and did not meet any of the exclusion criteria were diagnosed as iMCD. Patients were further classified as severe or non-severe diseases according to the Castleman Disease Collaborative Network (CDCN) severity classification [8]: severe iMCD should have at least 2 of the 5 following criteria: ECOG ≥ 2, stage IV renal dysfunction, anasarca, hemoglobin ≤ 80 g/L, pulmonary involvement/interstitial pneumonitis with dyspnea.

Relapsed disease was defined as: patients who ever achieved overall partial response (PR) or complete response (CR) with prior lines of therapy and then suffered from progressive disease (PD) [8]. Refractory disease was defined as: newly diagnosed iMCD patients who never achieved PR or CR with the first-line treatment but suffered from PD during treatment.

Relapsed or refractory (R/R) adult (≥18 y/o) iMCD patients who met the following criteria were considered as eligible candidates for this study: 1) Eastern Cooperative Oncology Group performance status (ECOG-PS ≤ 2); 2) Neutrophil count > 0.8×10^9/L and platelet count > 50×10^9/L; 3) HHV-8 negative confirmed by blood PCR or latency-associated nuclear antigen (LANA-1) staining by immunohistochemistry (IHC) and HIV negative confirmed by serology test. Exclusion criteria included known malignancies or other severe concurrent diseases (e.g. POEMS syndrome, systemic lupus erythematosus), known hypersensitivity to study agents, pregnancy or breastfeeding, and plans to become pregnant within 2 years after enrollment were excluded.

Procedures

BCD regimen (bortezomib 1.3 mg/m^2 weekly subcutaneously, oral cyclophosphamide 300 mg/m^2 weekly, oral dexamethasone 40 mg weekly for a 28-d cycle) was administered for 9 cycles; after 9 cycles of BCD treatment, BD regimen (bortezomib 1.3 mg/m^2 twice a month subcutaneously, dexamethasone 20 mg twice a month) was used as maintenance for the next 1 year. Treatment was discontinued after 1 year of maintenance or until 'treatment failure' which was defined as death or PD. Acyclovir was given as prophylactic antiviral therapy for prevention of herpes zoster reactivation; other treatments targeting iMCD were not allowed. Hematological and non-hematological toxicities requiring dose delays and/or modification were recorded. All patients were assessed for the response criteria every 3 months until 'treatment failure'. Symptom's assessment including fatigue, anorexia, fever, and body weight change as well as biochemical parameters testing and computerized tomography

imaging were carried out at baseline and at each response criteria evaluation.

Outcomes

The primary endpoint of the study was the treatment response (including overall response, biochemical response, lymph node response, and symptomatic response) at 6 months. Treatment responses were evaluated according to the CDCN criteria [8]. An overall CR was defined as normalization of laboratory tests (complete biochemical response), and inflammation-related symptoms (fatigue, anorexia, fever, and weight loss) along with a complete lymph node response. An overall PR required nothing less than a PR across all categories: improvement in all four symptoms, $>$ 50% improvement in biochemical tests, and $>$ 50% reduction of the mass. An overall stable disease (SD) required no PD in any of the categories and not meeting the criteria for overall CR or overall PR. An overall PD was considered when any category has a PD at the assessment for treatment response which was carried out every 3 months.

The secondary endpoints of the study included treatment responses at 3 and 12 months and during the study period; the trend of biochemical parameters and change in MCD-related overall symptom score which was a published score calculated as the sum of the toxicity grades of the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0 terms [7] (A total score of 34 symptoms from five categories was calculated as the sum of the toxicity grades); progression-free survival (PFS) which was defined as the time to PD or death; and overall survival (OS) which was defined as the time to patients' death.

Safety data were collected until 1 month after the last dose of study drugs, except for secondary primary malignancies (which were defined as any malignancy observed after initiation of BCD regimen), which were assessed throughout the duration of follow-up. Adverse events were graded as per NCI-CTCAE version 4.03.

Statistical analysis

Analyses were performed with SPSS version 22 (SPSS, Inc., Chicago, IL). The independent samples Student t-test (for parameters with normal distribution) and Mann–Whitney test (for parameters that were not normally distributed) were used for comparison of baseline characteristics between responders (patients who achieved at least PR at any evaluation timepoint during the follow-up period) and non-responders. The Wilcoxon signed-rank test was used to compare parameters before and after the BCD and BD regimen. For patients who were evaluated as PD, the time of PD was considered as the end of treatment. OS and PFS were calculated from the date of treatment. For PFS analyses, death or PD was considered as events; for OS analyses, death was considered as events. OS and PFS were calculated from the date of treatment. For PFS analyses, death or 'treatment failure' were considered as events. Survival curves were plotted with the Kaplan–Meier method. $p < .05$ was considered statistically significant. The final follow-up date was 1 July 2020.

Results

Patients' characteristics

A total of 24 R/R iMCD patients from two hospitals participated in this multicenter study from May 2018 to July 2020. All patients enrolled in this study were followed up for at least 6 months. Baseline demographic and disease characteristics are listed in Table 1. The median age was 42 years (22–65), with a male: female ratio of 1.2:1. Eight patients (33.3%) were classified as 'refractory' and sixteen patients (66.7%) were defined as 'relapsed'. The median prior treatment lines were 1 (1–4). Prior treatment included thalidomide-based regimen ($n = 18$), steroids monotherapy ($n = 2$), interferon ($n = 1$), cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP)-like regimen ($n = 5$), rituximab-containing regimen ($n = 3$), IL-6 targeting therapy ($n = 2$), and lenalidomide ($n = 1$). No patient fulfilled the criteria for TAFRO syndrome [20]. Eight patients (33.3%) were considered as 'severe' iMCD. The distribution of histopathological subtypes was 20.8% (hyaline-vascular subtype, HV): 66.7% (plasmacytic subtype, PC): 12.5% (mixed subtype). The median MCD-related overall symptom score at baseline was 7 (2–22) and median baseline IL-6 level was 21.4 pg/mL (2.1–128) (normal range $<$ 5.9 pg/mL). As for symptoms evaluated for the treatment response criteria: fever (16.7%), weight loss (41.7%), anorexia (58.3%), and fatigue (91.7%). Median hemoglobin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum albumin (Alb), serum creatinine (SCr), and immunoglobin G (IgG) levels were 94.5 g/L (44–135), 70.54 mg/L (2.63–183.38), 96.5 mm/h (22–140), 30.1 g/L (24–42), 68.85 μmol/L (33.0–652.0), and 23.3 g/L (7.63–66.19), respectively.

Table 1. Baseline characteristics of refractory and relapsed iMCD patients treated with the BCD regimen ($n = 24$).

Characteristics	Normal range	ALL patients, $n = 24$	Responders, $n = 16$	Non-responders, $n = 8$	p
Age, median (range), y		42 (22–65)	42 (29–65)	42 (22–64)	.600
Sex, male, *n* (%)		13 (54.2%)	9 (56.3%)	4 (50%)	1.000
Refractory, *n* (%)		8 (33.3%)	6 (37.5%)	2 (25.0%)	.667
Relapsed, *n* (%)		16 (66.7%)	9 (62.5%)	6 (75.0%)	
Prior treatment lines, median (range)		1 (1–4)	1 (1–4)	1 (1–3)	.976
Histology					.209
Hyaline vascular		5 (20.8%)	2 (12.5%)	3 (37.5%)	
Plasmacytic		16 (66.7%)	11 (68.8%)	5 (62.5%)	
Mixed		3 (12.5%)	3 (18.8%)	0 (0%)	
Severe iMCD, *n* (%)		8 (33.3%)	5 (31.3%)	3 (37.5%)	1.000
ECOG-PS					.328
0		7 (29.2%)	6 (37.5%)	1 (12.5%)	
1		13 (54.2%)	7 (43.8%)	6 (75.0%)	
2		4 (16.7%)	3 (18.8%)	1 (12.5%)	
Symptom score, median (range)		7 (2–22)	7 (2–22)	9 (5–15)	.718
Fever, *n* (%)		4 (16.7%)	2 (12.5%)	2 (25.0%)	.578
Weight loss, *n* (%)		10 (41.7%)	6 (37.5%)	4 (50.0%)	.673
Anorexia, *n* (%)		14 (58.3%)	10 (62.5%)	4 (50.0%)	.673
Fatigue, *n* (%)		22 (91.7%)	15 (93.8%)	7 (87.5%)	1.000
Peripheral lymphadenopathy, *n* (%)		23 (95.8%)	15 (93.8%)	8 (100%)	1.000
Splenomegaly, *n* (%)		8 (33.3%)	5 (31.3%)	3 (37.5%)	1.000
Skin involvement, *n* (%)		7 (29.2%)	1 (6.3%)	6 (75.0%)	.001
Pulmonary involvement, *n* (%)		5 (20.8%)	5 (31.3%)	0 (0%)	.130
Anasarca, *n* (%)		5 (20.8%)	5 (31.3%)	2 (25.0%)	1.000
IL-6, median (range), pg/mL	<5.9	21.4 (2.1–128.0)	21.8 (9.7–52.6)	16.6 (2.1–128.0)	.508
Hemoglobin, median (range), g/L	Male, 120–160; female, 110–150	94.5 (44–135)	91.5 (44.0–120.0)	98.5 (64.0–135.0)	.719
Platelet count, median (range), 109/L	100–350	337.5 (108.0–612.0)	368.0 (108.0–548.0)	283.5 (139.0–612.0)	.929
Serum creatinine, median (range), µmol/L	Male, 59–104; female, 45–84	68.85 (33.0–652.0)	66.85 (39.0–527.0)	113.1 (33.0–652.0)	.610
CRP, median (range), mg/L	0–8	70.54 (2.63–183.38)	77.65 (5.49–183.38)	36.4 (2.63–173.1)	.108
Albumin, median (range), g/L	35–52	30.1 (24–42)	30.1 (24.7–39.0)	31.1 (24.0–42.0)	.488
*ESR, median (range), mm/h	Male, 0–15; female, 0–20	96.5 (22–140)	101 (33–140)	79.5 (22.0–140.0)	.166
IgG, median (range), g/L	7.00–17.00	23.3 (7.63–66.19)	25.82 (7.63–62.11)	17.56 (10.66–66.19)	.489

*values of > 140 mm/h were considered as 140 mm/h.
iMCD = idiopathic Multicentric Castleman Disease; IL-6 = interleukin-6; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IgG = immunoglobin G.

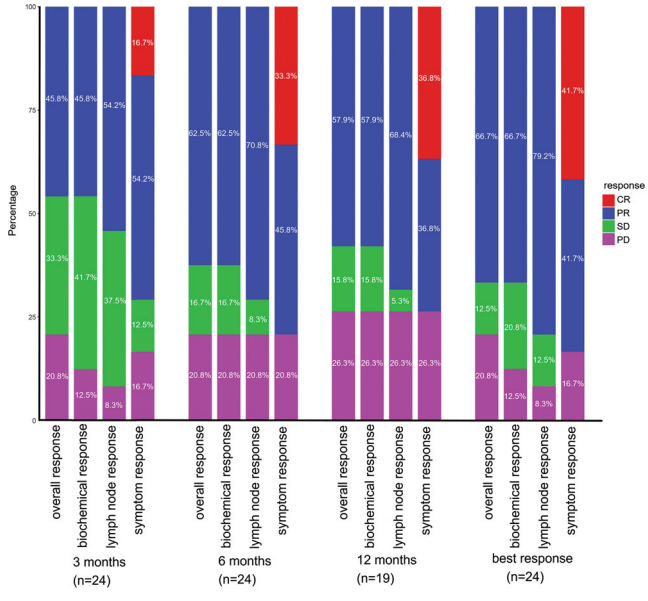

Figure 1. Evaluation of treatment responses according to CDCN criteria.

Response

At 6 months, 62.5% ($n = 15$) patients achieved overall treatment responses with all PR; 16.7% ($n = 4$) patients achieved SD and 20.8% ($n = 5$) patients suffered from PD (Figure 1). Of 62.5% patients achieved biochemical responses (all PR), 70.8% patients had lymph node

responses (all PR) and 79.1% patients achieved symptom responses (CR 33.3%, PR 45.8%) at 6 months. Similar proportions of patients achieved these response criteria at 3 months (45.8%) and 12 months (57.9%), suggesting the relative short time response and durability (Figure 1). As for best response, a total of 16 patients (66.7%) achieved overall treatment responses (all PR) after BCD treatment and were defined as 'responders'. Comparison of baseline parameters between the 16 responders and the 8 non-responders demonstrated similarities across all parameters except for a higher frequency of skin involvement ($p = .001$) and a trend toward lower CRP ($p = .108$) in non-responders (Table 1). When looking across all 24 patients who received the BCD regimen, the median symptom score declined significantly from 7 (2–22) at baseline to 2 (0–26) at 3 months ($p = .002$). Moreover, significant improvements were seen in the median hemoglobin level ($p = .001$), platelet count ($p = .002$), CRP ($p < .001$), ESR ($p = .001$), IL-6 ($p < .001$), Alb ($p < .001$), and IgG ($p = .006$) after 3 months of BCD treatment even when combining all patients (including those who did not achieve treatment response at 3 months) in the analysis (Table 2). SCr, which had a median level in the normal range before BCD, did not change significantly with treatment. Similar trends were observed for symptom score and biochemical parameters by 6 months (Table 2). The differences were even more striking when these parameters were assessed among the 16 patients who experienced treatment responses (at least PR) after BCD regimen.

A total of 10 patients experienced PD during the study period and the median time to disease progression was 9 months (3–33) for these patients. During the study period, two deaths occurred. Both patients died from disease progression at 4 months after cessation of BCD regimen due to PD at 3 months. For the other eight patients who suffered from PD, six patients had PD during the BCD treatment phase and were transferred to next line of treatment; two patients experienced PD after completion of the treatment phase of this trial. These two patients, who experienced PD at 24 and 33 months, respectively, were treated with BCD regimen again as they previously responded well to it. Both patients responded to the treatment again and achieved PR after re-initiation of the drugs.

Safety

With regards to safety, no patients suffered from grade 3 or higher adverse events and no patients died due to treatment-related toxicity. Grade 1 or 2 irregular menstruation (18.2% among female patients), insomnia (16.7%), constipation (16.7%), nausea (16.7%), upper respiratory infection (12.5%),peripheral sensory neuropathy (12.5%) were the most common adverse events. Other documented adverse events included grade 1 or 2 diarrhea (8.4%), glucose intolerance (8.4%), alanine aminotransferase (ALT) elevation (8.4%), thrombocytopenia (4.2%), neutropenia (4.2%), and vomiting (4.2%). The summary of adverse events following the BCD regimen administration is listed in Table 3. No herpes zoster reactivation was observed during follow-up and no secondary primary malignancies were documented.

Table 2. Characteristics at baseline and 3 and 6 months for all patients ($n = 24$) and for responders ($n = 16$).

Characteristics		Baseline, median (range)	3 months, median (range)	p*	6 months#, median (range)	p*
Symptom score	All patients	7 (2–22)	2 (0–26)	.002	1 (0–2)	<.001
	Responders	7 (2–22)	1.5 (0–7)	<.001	1 (0–2)	<.001
Hemoglobin, g/L	All patients	94.5 (44–135)	109.5 (72–152)	.001	116 (87–152)	.001
	Responders	91.5 (44–120)	116 (93–152)	.001	118.5 (97–152)	.001
Platelet counts,10○9/L	All patients	337.5 (108–612)	258.5 (57–652)	.005	220 (69–379)	.002
	Responders	368 (108–548)	258.5 (122–378)	.005	235 (109–379)	.007
CRP, mg/L	All patients	70.54 (2.63–183.38)	19.08 (4.44–132)	<.001	16.25 (3.4–63.26)	<.001
	Responders	77.65 (5.49–183.38)	17.74 (4.44–77.00)	<.001	15.37 (3.31–63.26)	<.001
ESR, mm/h	All patients	96.5 (22–140)	64 (7–120)	.001	62 (3–124)	.002
	Responders	101 (33–140)	64.0 (7–104)	.001	62 (3–99)	.006
IL-6, pg/mL	All patients	19.95 (2.1–128)	6.75 (2–250)	.005	4.5 (2–15.8)	<.001
	Responders	21.6 (8.9–52.6)	5.2 (2–23.4)	<.001	5.45 (2.5–15.8)	<.001
Albumin, g/L	All patients	30.1 (24–42)	37.5 (26.0–47.0)	<.001	39 (34–49)	<.001
	Responders	30.1 (24.7–39.0)	38.0 (28.1–47.0)	.001	38.5 (30.0–49.0)	.001
Serum creatinine, μmol/L	All patients	68.85 (33–652)	75 (46–525)	.909	81.5 (48–595)	.378
	Responders	66.85 (39.0–527.0)	65.0 (46–227.4)	.518	70.5 (48–124)	.329
IgG, g/L	All patients	23.3 (7.63–66.19)	23.0 (3.70–43.80)	.006	20.16 (3.43–35.85)	.001
	Responders	25.82 (7.63–62.11)	24.22 (3.70–43.80)	.004	20.28 (3.43–35.85)	.001

*Compared with baseline; #$n = 19$ (data from five patients who were evaluated as PD at 3 months was not included).
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; IgG = immunoglobin G.

Table 3. Summary of adverse events.

Adverse events	*N* (%)
Hematological toxicity	
Thrombocytopenia	
Grade 2	1 (4.2)
Neutropenia	
Grade 1	1 (4.2)
Nonhematological toxicity	
Peripheral sensory neuropathy	
Grade 1	3 (12.5)
Nausea	
Grade 1	4 (16.7)
Diarrhea	
Grade 1	2 (8.4)
Constipation	
Grade 1	4 (16.7)
Upper respiratory infection	
Grade 1	2 (8.4)
Grade 2	1 (4.2)
Glucose intolerance	
Grade 1	2 (8.4)
Irregular menstruation[a]	
Grade 1	2 (18.2)
Vomiting	
Grade 1	1 (4.2)
Insomnia	
Grade 1	4 (16.7)
ALT elevation	
Grade 1	2 (8.4)

[a]Among 11 female patients.
ALT: alanine aminotransferase

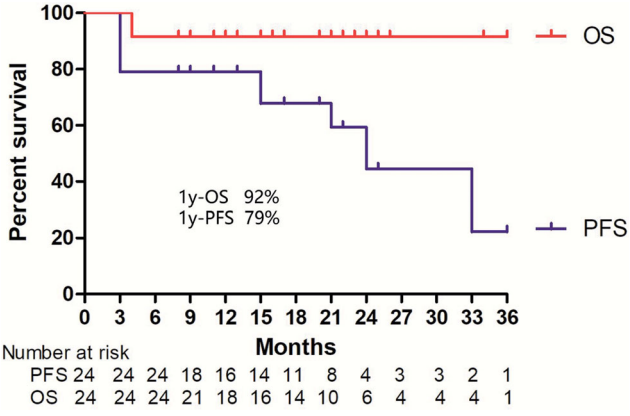

Figure 2. Overall survival (OS) and progression-free survival (PFS) of 24 relapsed/refractory iMCD cases with BCD therapy.

Survival

The median duration of follow-up was 20 months (range 8–38 months). Ten patients suffered from PD during follow-up. No patients died during the treatment period and two patients died during follow-up phase due to disease progression after cessation of BCD treatment. The median OS was not reached; the median PFS was 24 months. The estimated 1-year PFS and OS were 79 and 92%, respectively (Figure 2). Though the number of patients who have completed the 21-month course is small, PFS declines notably after cessation of BCD treatment.

Discussion

We report the results of the first prospective, multicenter trial for the treatment of R/R iMCD patients with subcutaneous administration of BCD regimen. This is also one of the first endeavors to prospectively explore the efficacy and safety profiles of agents other than IL-6 blockade therapy in R/R iMCD. According to our knowledge, this is also the first prospective trial which implemented the recently published CDCN treatment response criteria [8] for R/R iMCD as study endpoints. BCD regimen induced treatment responses in 62.5% of patients at 6 months, significantly ameliorated symptoms, and significantly improved biochemical parameters. Moreover, a total of 66.7% patients (defined as 'responders') achieved overall treatment responses at some point after BCD treatment.

Considering that a 34% treatment response for at least 18 weeks in the RCT of siltuximab in iMCD led to regulatory approvals and consensus [8] recommendation worldwide and that 0% of patients receiving placebo plus best supportive care inclusive of corticosteroids achieved treatment response criteria, BCD regimen showed a meaningful clinical benefit of more than 60% treatment response in R/R iMCD patients with at least one prior line of treatment. Compared to other potential second- or third-line treatment for iMCD as rituximab-containing therapy or combination chemotherapy [8] whose efficacy still requires more rigorous investigation, BCD regimen has an important benefit of convenient oral administration of cyclophosphamide and dexamethasone as well as subcutaneous administration of bortezomib which has shown desirable cost-effectiveness [21] and safety profiles [17]. This treatment combination provides a possibility of drug administration at home, which is especially important for iMCD which requires long-term treatment. Moreover, a durable symptom, lymph node, and biochemical improvement were observed for BCD regimen in R/R iMCD patients, with a median PFS of 2 years. Even when combining the entire study population which included both 'responders' and 'non-responders' for analysis, the median symptom score and key biochemical parameters including hemoglobin, platelet count, CRP, ESR, albumin, IL-6, and IgG improved significantly after BCD treatment (Table 2). No significant improvement was observed for SCr, which was likely due to a low proportion of patients having elevated creatinine at enrollment (8/24). Among 'responder' and 'non-responder' patients who had elevated SCr at baseline, the median SCr level decreased significantly from 178 μmol/L

(132–652) to 124 μmol/L (90–595) ($p = .028$) by 6 months.

Another key finding of this study is that no significant difference in treatment response was observed among patients with different histopathological subtypes (Table 1). Although bortezomib-based regimen was initially utilized for plasma cell disorders such as multiple myeloma [17,22,23] and light-chain amyloidosis [24], its notable that bortezomib-based regimens seem to be effective in patients with POEMS syndrome [11] who often demonstrate HV histopathological features [13] as well as previous reports of iMCD patients with HV [16], PC [9], or mixed histopathological subtypes [15]. In this study, BCD regimen demonstrated benefit for all three histopathologic subtypes of R/R iMCD. The response rates for patients with HV, PC, or mixed subtypes were 40.0, 68.8, and 100%, respectively. Bortezomib-related blockade of NF-κB-dependent induction of vascular endothelial growth factor (VEGF)-associated pathways [25] might play role in these HV patients whose lymph nodes are highly vascularized.

The BCD regimen was also well tolerated. Several anticipated side effects seen in myeloma patients [22,23], such as thrombocytopenia, neutropenia, glucose intolerance, and peripheral neuropathy were observed at low frequencies and in low grades. This might be due to the following reasons: 1) patients in this study were much younger than the multiple myeloma patients who received BCD [22,23]; 2) platelet counts in patients of this study were relatively high at baseline (median 338×10^9/L, range 108–612); 3) the subcutaneous administration of bortezomib utilized in this study has been reported to have an improved safety profile compared with intravenous administration [17]. Lastly, no herpes zoster reactivation was reported, possibly due to prophylactic antiviral therapy.

Several pretreatment clinical manifestations or laboratory parameters have been previously reported to be associated with treatment response in iMCD patients. For example, Morra et al. found that inflammatory biomarkers, such as CRP, fibrinogen, and albumin were associated with treatment response to siltuximab [26]; Zhang et al. reported that fever and absence of pulmonary involvement were associated with treatment response to thalidomide, cyclophosphamide, and prednisone (TCP) regimen [18]. In this study, response to the BCD regimen was associated with a decreased proportion of patients with skin involvement and possibly a trend toward presence of pulmonary involvement and higher CRP. Seven patients with skin involvement, including one patient with paraneoplastic pemphigus (PNP) and six patients with other skin lesions (violaceous papules and patches with pigmentation) were enrolled in this study and only one patient (6.3%) responded to BCD regimen. The patient with PNP suffered from progression of disease after three months of BCD treatment. The BCD regimen may be most appropriate for R/R iMCD patients without skin involvement.

Although IL-6 targeting therapy has been recommended as a major treatment option for iMCD patients [8], treatments directed at targets other than IL-6 need to be investigated as IL-6-targeting therapy is not available everywhere (e.g. siltuximab is not available in the market of China and tocilizumab is expensive in China) and is not effective for over one-half of patients. Patients with R/R iMCD need more treatment options. Treatment approaches directed against a target other than IL-6 signaling (e.g. TCP regimen and sirolimus [27], BCD) have been made in recent years. In this study, among two patients who previously received IL-6 targeting therapy, one showed a response. More research is needed to determine if BCD regimen is a good option for both patients who do not have access to IL-6 targeting therapy as well as R/R iMCD patients after IL-6 targeting treatment.

This study has several limitations. First, this multicenter trial includes a small number of patients from a single ethnic group. Considering the rarity of the target disease and previously published clinical trials, the sample size should be sufficient to evaluate the efficacy and safety profiles of the BCD regimen in R/R iMCD. Second, no control arm was included. As siltuximab is not available in China and there is no standard treatment for R/R iMCD according to the recently published treatment guidelines [8], an optimal control arm was not available. On the other hand, placebo, which was utilized as control arm in Phase 2 siltuximab trial in iMCD [7], would be unethical considering that 0% of those patients on placebo and best supportive care, which included corticosteroids, responded and the clinical course of R/R iMCD can be quite severe. Third, although BCD regimen had been reported to be effective in TAFRO clinical subtype of iMCD [16], no participants with the TAFRO clinical syndrome of iMCD were enrolled in this study. Therefore, the efficacy and safety profiles of BCD for iMCD-TAFRO were not evaluated in this trial. Lastly, the observation period is relatively short. On the one hand, as shown by Figure 2, PFS declines notably with time, especially after cessation of BD maintenance. In fact, two of the six patients who have completed the 21-month treatment

phase already suffered from disease progression by July 2020. The time to PD after treatment cessation for these patients was 3 and 12 months, respectively. Both patients responded again to bortezomib-containing therapy which might support a long-term maintenance strategy as currently applied for bortezomib in myeloma [28]. On the other hand, long-term sequalae of exposure to the BCD regimen in iMCD still needs further observation (e.g. cyclophosphamide might increase the risk of myelodysplastic syndrome and/or acute myeloid leukemia). We will continue to collect efficacy and safety data and extend the time of follow-up to determine the long-term benefit and risks of this regimen, particularly after treatment is discontinued.

In conclusion, BCD regimen, a convenient therapy which can be given at home, is an effective and safe treatment option for relapsed/refractory iMCD patients.

Author contribution

Contribution: L.Z., X.-x.C., D.-b.Z., Y-j.D., and J.L. recruited the patients; L.Z., Y-j.D., and J.L. designed the study; L.Z., M.-y.Z., Y-j.D., and J.L. collected the data; L.Z. performed the analysis; L.Z., Y-j.D., J.L., and D.C.F. interpreted the data and wrote the manuscript; and all authors had access to primary clinical trial data and gave final approval to submit for publication.

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