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Brief Communication

Low-dose decitabine plus bortezomib-dexamethasone therapy is well-tolerated and highly effective on first-relapsed multiple myeloma: a single-center phase 2 trial

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Abstract: An open-label, single-center, phase 2 trial of a second-line therapy comprising low-dose decitabine (DAC) plus bortezomib (Bort) and dexamethasone (DXM) (Dvd) in relapsed and/or refractory multiple myeloma (RRMM) patients was conducted to screen available and inexpensive agents, aiming to work synergistically with other existing anti-melanoma drugs at reasonable prices, and effectively treat Bort and/or Len-refractory patients. Forty-seven patients were included according to the inclusion criteria, with only 1 withdrawal due to premature death. After 17.2 (range: 0.5-24.1) months of median follow-up, all the 46 cases had halted or completed DVd therapy per protocol, with an overall response rate (ORR) of 87.0%. Meanwhile, DVd was indicated to induce high, deep, and lasting responses, dependent of prior treatment or baseline characteristics. The results revealed that DVd is well-tolerated and highly effective in the treatment of first-relapsed RRMM (including those with Bort-refractory disease) patients.

Keywords: Phase 2 trial, decitabine, bortezomib, dexamethasone, multiple myeloma

Introduction

Currently, no clear consensus has been achieved concerning the optimal second-line treatment for relapsed and/or refractory multiple myeloma (RRMM), an approach that plays a particularly important role in the treatment of the disease [1-6]. Recent large randomized studies have reported impressive results in subset analyses of the use of daratumumab, pomalidomide, or carfilzomib-based triple combinations in first-relapsed RRMM patients [4-6]. Yet in many parts of the world, including China, these aforementioned novel drugs are not available or affordable. In addition, given that bortezomib (Bort) and/or lenalidomide (Len) based triplet regimens are the major first-line treatments for newly diagnosed multiple myeloma (MM) patients in China now and in the coming years, there is an urgent need for effective therapies for patients refractory to Bort and/or Len. Thus, the screening of available and affordable agents that can work synergistically with other existing affordable antimyeloma agents, while targeting the MM clones and tumor microenvironment (TME), is a priority both in China and the world as a whole.

Hypermethylation at the pd-DMR gene locus significantly lowers the response to antimyeloma therapy and disrupts the interaction between myeloma cells and the MM TME. While being a demethylating agent, decitabine (DAC) is able to validly reduce pd-DMR gene methylation [7]. Furthermore, in MM, DAC can synergistically increase myeloma cells' sensitivity to Bort and deplete myeloid-derived suppressor cells (MDSCs), which are critical for tumor cells' immune escape and survival in the TME [8-10]. Conclusively, the addition of DAC to readily available and affordable antimyeloma therapies has the potential to lead to the development of new, highly cost-efficient therapies for first-relapsed RRMM.

Table 1. Baseline clinical-demographic features

Characteristics	Cases (n = 47)
Age, y	
Median (range)	61 (36-73)
Distribution, n (%)	
<65	32 (68.1)
65-73	15 (31.9)
Median (range) time since initial diagnosis, y	1.8 (0.6-5.9)
ECOG performance status, n (%)	
0	27 (57.4)
1	17 (36.2)
2	3 (6.4)
Myeloma type, n (%)	
IgG	26 (55.3)
IgA	19 (40.4)
Light chain only	2 (4.3)
ISS disease stage, no (%)	
I	14 (29.8)
II	18 (38.3)
III	15 (31.9)
Cytogenetic profile, n (%)*	
Standard risk	20 (42.6)
High risk	13 (27.7)
The first-line therapy, n (%)	
VD	8 (17.0)
VCD	13 (27.7)
PAD	5 (10.6)
VTD	2 (4.3)
Rd	19 (40.4)
Disease status, n (%)	
Primary refractory	0 (0)
Relapsed but non-refractory to Bort	20 (42.6)
Relapsed and Refractory to Bort	8 (17.0)
Relapsed but non-refractory to Len	10 (21.3)
Relapsed and Refractory to Len	9 (19.1)
Previous ASCT, n (%)	14 (29.8)
Treatment-free interval, n (%)	
>12 months	21 (44.7)
≤12 months	26 (55.3)
>6 months	28 (59.6)
≤6 months	19 (40.4)
Median neutrophil count, $\times 10^9$/L (range)	1.9 (1.3-5.7)
Median platelet count, $\times 10^9$/L (range)	98 (87-356)
Median haemoglobin level, g/L (range)	101 (92-154)

ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; VD, bortezomib + dexamethasone; VCD, bortezomib + cyclophosphamide + dexamethasone; PAD, bortezomib + doxorubicin + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone; Rd, lenalidomide + dexamethasone; Bort, bortezomib; Len, lenalidomide. *Fluorescence in situ hybridization or karyotyping performed cytogenetic status determination with the presence of ≥1 of the following abnormalities as high-risk: del17p, t(14;16), t(4;14), or 1q21.

Methods

Herein, we conducted an open-label, single-center, phase 2 trial (Registration Number: ChiCTR-OPC-17013860; www.chictr.org.cn) to clarify the effectiveness and safety profile of a second-line therapy comprising LD-DAC plus Bort-dexamethasone (DXM) (DVd) in RRMM patients [1]. The design, implementation and reporting of the study followed the International Council for Harmonisation guidelines for Good Clinical Practice, the applicable local regulations, the Declaration of Helsinki, and the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The trial participants were all first-relapsed RRMM patients who were aged over 18 years, with measurable disease and adequate heart, kidney and liver function (**Table 1**). These eligible patients were given DVd treatment for no more than 8 cycles. DAC (5 mg/m^2, SFDA Approval Number: H20140051, Qilu Pharmaceutical (Hainan) Co. LTD) was given on days 1-5 followed by Bort (1.3 mg/m^2, SFDA Approval Number: H20183101, Qilu Pharmaceutical Co. LTD) on days 1, 4, 8, 11, both via intravenous administration. And on days 1, 2, 4, 5, 8, 9, 11, 12 every 4 weeks, 20 mg DXM was administered per os. Of the 47 cases included, only 1 withdrew due to premature death. The primary outcome measure was progression-free survival (PFS) assessed by investigators, and the secondary outcome measures were overall response rate (ORR) and patient safety.

Results

In this trail, the clinical cut-off was February 12, 2020. After 17.2 (range: 0.5-24.1) months of median follow-up, all the 46 response-measurable cases had halted or completed DVd therapy per protocol, with an overall response rate (ORR) of 87.0%, of which 30.4% achieved

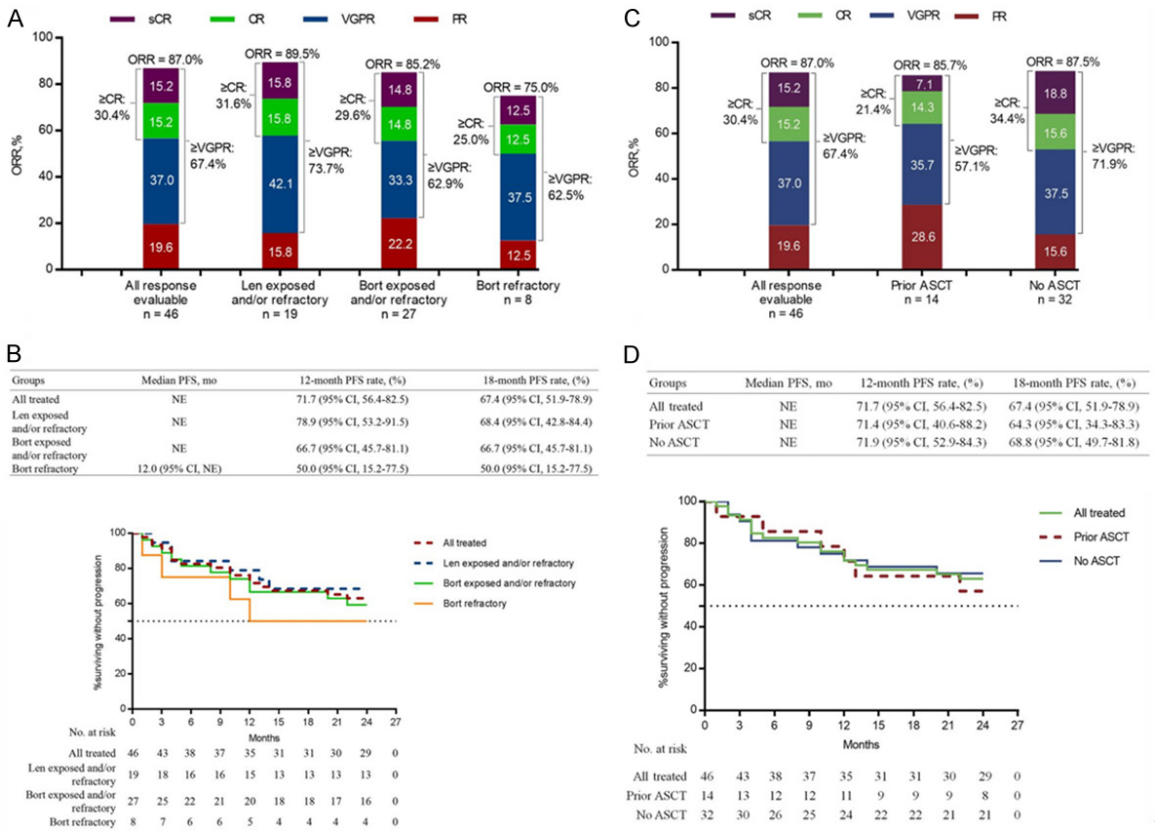

Figure 1. Clinical benefits of low-dose DAC + Bort-DXM therapy. A: Clinical response rates including ORR, sCR, CR, VGPR, and PR, and PFS; B: Clinical response rates in all response-measurable subjects and subgroups who received prior Bort/Len therapy; C: Response rates including ORR, sCR, CR, VGPR, and PR, and PFS; D: Response rates in all response-assessable subjects and subgroups based on previous ASCT. DAC, decitabine; Bort, bortezomib; DXM, dexamethasone; PFS, progression-free survival; Len, lenalidomide; NE, not estimable; ORR, overall response rate; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response.

CR or better, and 67.4% achieved VGPR or better (**Figure 1**). As to the prior Bort treatment cohort, the ORR was 85.2%, with those achieving CR or better and VGPR or better accounting for 29.6% and 62.9%, respectively (**Figure 1**). High and deep responses were also found in subgroups grouped based on prior Len therapy, prior ASCT, ISS disease stage, ECOG performance status, myeloma type, and age (**Figures 1-3**). The 12- and 18-month PFS rates of all the measurable population were 71.7% and 67.4%, respectively, failing to reach the median PFS (**Figure 1**). Nor had the prior Bort treatment cohort reaced the median PFS, with both the 12- and 18-month PFS rate being 66.7% (**Figure 1**). Subgroups based on prior Len treatment, prior ASCT, ISS disease stage, ECOG performance status, myeloma type, and age also demonstrated lasting responses (**Figures 1-3**). No evident differences were observed in PFS among all the aforementioned subgroups (**Figures 1-3**).

Thrombocytopenia (12/46, 26.1%), anemia (6/46, 13%), and pneumonia (5/46, 10.9%) were the most commonly seen grade 3/4 adverse events (AEs). Three cases (6.5%) terminated treatment because of peripheral neuritis. There were no deaths due to AEs.

Discussion

The results obtained in this study are remarkable for the following reasons. To begin with, the AEs meet the documented safety profile of Bort, without increasing toxic reactions after the addition of LD-DAC [4, 11]. Second, DVd was indicated to induce high, deep, and long-lasting responses, dependent of baseline characteristics or prior treatment. The PFS data in

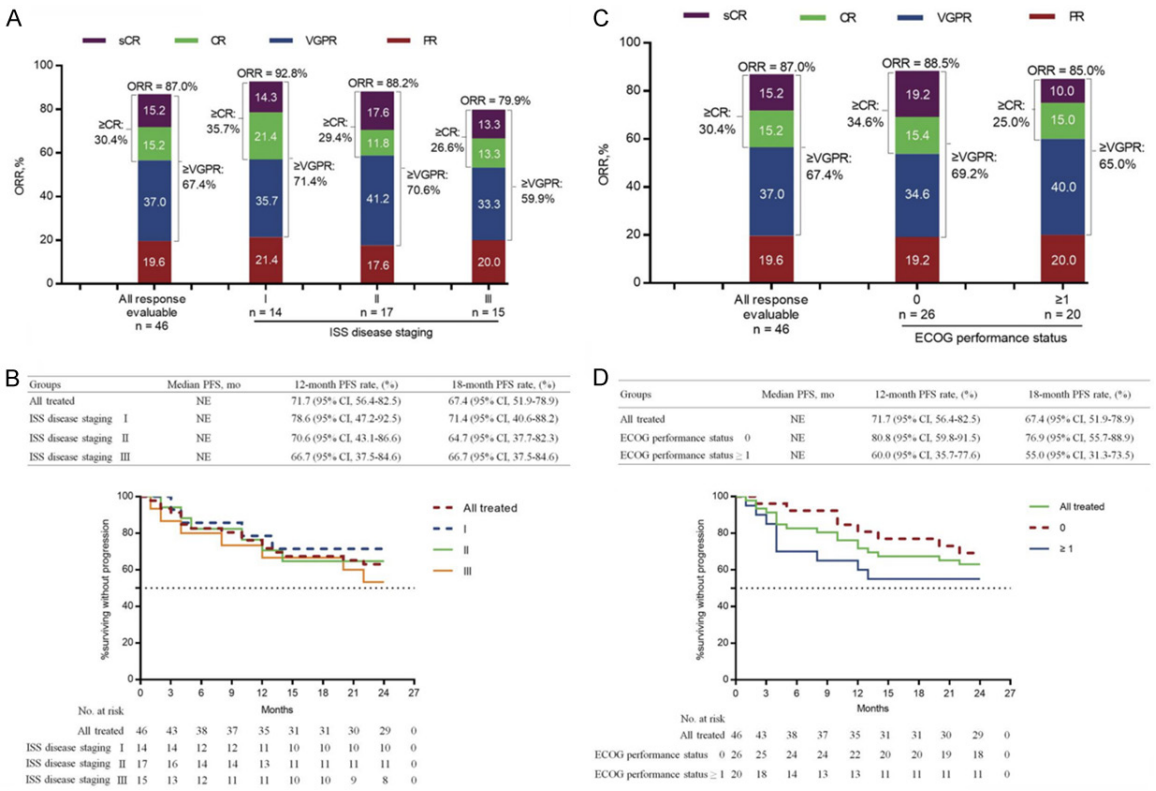

Figure 2. Clinical benefits in patients with low-dose DAC + Bort-DXM therapy. A: Response rates including ORR, sCR, CR, VGPR, and PR, and PFS; B: Response rates in all response-assessable subjects and subgroups based on ISS disease staging; C: Response rates including ORR, sCR, CR, VGPR, and PR, and PFS; D: Response rates in all response-assessable subjects and subgroups based on ECOG performance status. DAC, decitabine; Bort, bortezomib; DXM, dexamethasone; PFS, progression-free survival; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

our study are particularly encouraging, considering that the corresponding data in first-relapsed patients in the CASTOR trial were 77.5% and 68.0%, respectively [4, 12]. Third, the efficacy was consistent across subgroups irrespective of prior Bort/Len treatment, prior ASCT therapy, ISS disease stage, ECOG performance status, myeloma type, or age, suggesting promising results compared favorably with Bort-containing regimens in other studies [4, 12, 13].

In conclusion, in addition to being cost-effective, Bort and DXM in combination with LD-DAC for first-relapsed RRMM patients is a well-tolerated triplet protocol that produces a high quality response regardless of prior treatment or baseline patient characteristics, and may serve as a post-treatment alternative for those with first-line Len and/or Bort therapy.

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Disclosure of conflict of interest

None.

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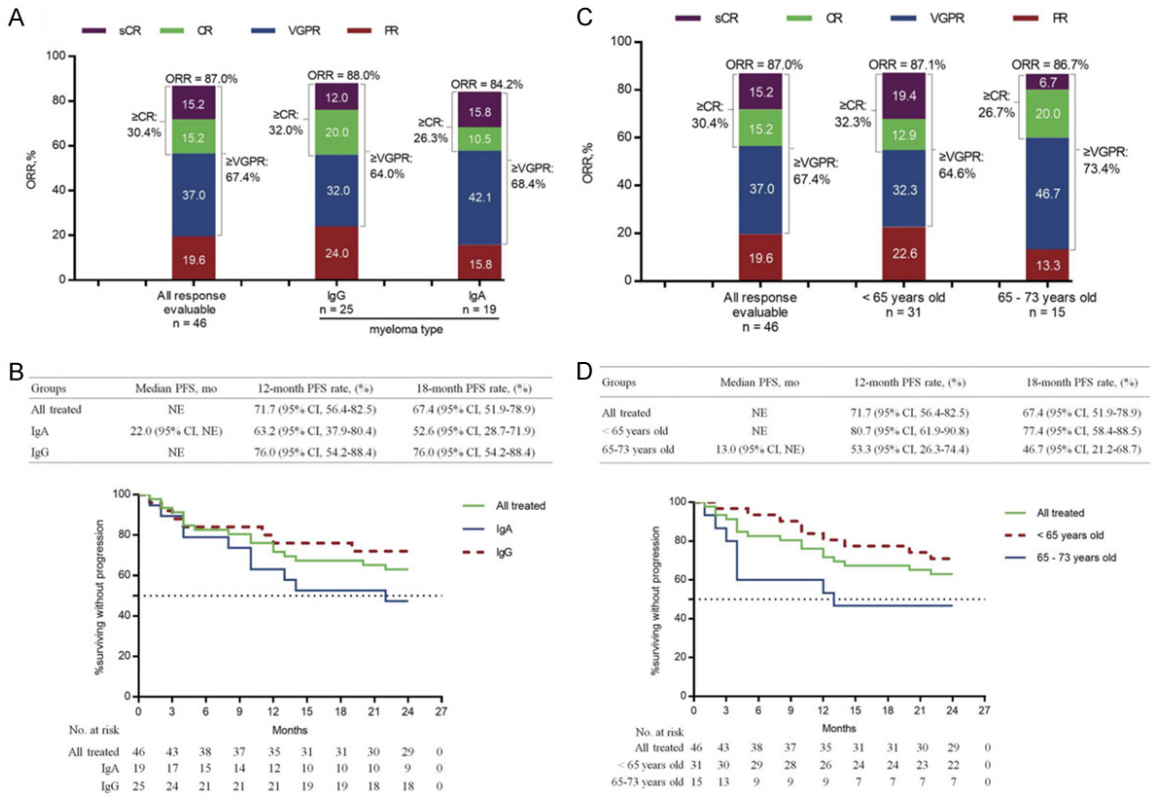

Figure 3. Clinical benefits in patients with low-dose DAC + Bort-DXM therapy. A: Response rates including ORR, sCR, CR, VGPR, and PR, and PFS; B: Response rates in all response-evaluable subjects and subgroups based on myeloma type; C: Response rates including ORR, sCR, CR, VGPR, and PR, and PFS; D: Response rates in all response-evaluable subjects and subgroups based on age. DAC, decitabine; Bort, bortezomib; DXM, dexamethasone; PFS, progression-free survival; CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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