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Original Article

Daratumumab Plus Carfilzomib: An Optimistic Approach in Relapsed/Refractory Multiple Myeloma

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Abstract

Background: Although with the introduction of novel agents, clinical outcomes have significantly improved in patients of multiple myeloma (MM); however, nearly all relapse, requiring subsequent treatment. Patients who have been heavily treated for relapsed/refractory MM (RRMM) have limited options and poor survival outcomes. Carfilzomib plus daratumumab combination have been evaluated in a phase 1b study in patients of RRMM progressing after 1–3 lines of therapies including bortezomib and an immune-modulatory drug. However, data are lacking evaluating the efficacy of this combination in RRMM patients who have progressed or have suboptimal response on either of these drugs (carfilzomib or daratumumab). **Methods:** Prospective analysis of data of 19 RRMM patients who progressed after multiple lines of therapy (including bortezomib and lenalidomide/pomalidomide) and had suboptimal response/stable/progressive disease after receiving carfilzomib or daratumumab based combination as last therapy. All patients received combination of carfilzomib plus daratumumab along with dexamethasone (DKd) after prior consent. Daratumumab (16 mg/kg IV) was administered weekly (days 1, 8, 15, and 22) during cycles 1 and 2, every 2 weeks (days 1 and 15) during cycles 3–6, and every 4 weeks thereafter. Carfilzomib was administered weekly on days 1, 8, and 15 of each 28-day cycle. Patients received an initial carfilzomib dose of 20 mg/m^2 on day 1,2; 27 mg/m^2 on day 8, 9, 15, 16 of cycle 1, which increased to 70 mg/m^2 on day 1, 8, 15 from cycle 2 onwards if deemed tolerable. Dexamethasone was given as fixed-dose of 40 mg weekly. **Results:** Eighteen of 19 patients (including 3 high risk cytogenetics) to DKd (CR-4, very good partial response-10, partial response-02). After median follow-up of 16 months, progression-free survival (PFS) was 95%. Median PFS was not reached. Three patients who were transplant eligible received high-dose chemotherapy followed by autologous stem-cell transplantation and achieved minimal residual disease negativity. The most frequent all grade side effects were hematological, which included neutropenia 30%, anemia 70%, and thrombocytopenia 42%. Most frequent non hematological side effects were nausea 40%, vomiting, cough, respiratory tract infections, asthenia, and loss of appetite. **Conclusion:** Carfilzomib plus daratumumab based combination in RRMM patients has shown promising results in phase Ib study, where patients with prior exposure to either of these drugs were excluded. Our data show similar or better response of this combination in patients who had progressive disease/stable disease/minimal response to either of carfilzomib or daratumumab. This combination can be a better option in heavily treated RRMM (with prior exposure to either of carfilzomib or daratumumab) producing deeper and durable responses. A larger study may be required to prove this benefit.

Keywords: *Carfilzomib, daratumumab, multiple myeloma, relapsed/refractory*

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Introduction

Multiple myeloma (MM) is an incurable disease, accounting for 1% of all cancers and 15% of all hematological malignancies. It is characterized by recrudescing patterns of remissions and relapses warranting subsequent therapy.[1] Though with the introduction of novel therapies, the outcome has dramatically improved in patients of MM, but the widespread use of lenalidomide early in course of disease either as a component of initial therapy or as maintenance emphasizes the need to explore more effective combinations among patients with relapsed/refractory MM (RRMM).[2]

Daratumumab and carfilzomib have got approval in many countries both as monotherapy as well as incorporating them individually with standard of care regimens, based on their rapid and durable responses in patients with RRMM. Both these drugs individually as monotherapy or

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in combination with other standard therapy has significantly resulted in reduced disease progression or death by inducing rapid, deep, and durable responses in patients of RRMM.[3-5] However, majority of these trials either excluded lenalidomide refractory patients (POLLUX and ASPIRE) or bortezomib refractory patients (CASTOR), making it difficult to extrapolate results of these studies in patients who are refractory to both bortezomib and lenalidomide.[3,6,7] Second, the patients in these trials who had received only one or two prior lines of treatment were significantly higher in number as compared to those who received 3 or more lines of prior therapy (80% vs. 20%). Prognosis of patients who had received multiple lines of treatment remains dismal in view of poor and short-term responses to subsequent therapy and thus demands exploring the more effective combination therapies.

Favorable toxicity profiles and better tolerability of these drugs in triplet- and quadruple-based regimes has led to explore daratumumab and carfilzomib as combination therapy in multiarm phase 1b MMY1001. The combination of these two drugs have resulted in better and durable responses fetching 12 months progression-free survival (PFS) of 75% in patients with RRMM after 1–3 lines of therapy. As it is common practice to add or replace one or more drugs of regimen, to which disease is not responding, but there is lack of data for the outcome of this combination in patients progressing or poor/suboptimal responses to either of these drugs. We present data of nineteen patients who after inadequate (minimal response or stable disease [SD]) response to either carfilzomib or daratumumab based regime and received a combination of these drugs as subsequent therapy.

Methods

Patients diagnosed with MM and either having progressive or SD as per international myeloma working congress (IMWG) to either daratumumab or carfilzomib based regime in addition to at least one prior line of therapy, received combination therapy of daratumumab, carfilzomib, and dexamethasone. Patients received this combination between June 2017 and August 2018. All patients were treated in 28-day cycles until disease progression (cycle 1 was 29 days). Daratumumab (16 mg/kg IV) was administered weekly (days 1, 8, 15, and 22) during cycles 1 and 2, every 2 weeks (days 1 and 15) during cycles 3–6, and every 4 weeks thereafter. Carfilzomib was administered weekly on days 1, 8, and 15 of each 28-day cycle as a 30-min infusion (before daratumumab on days when both were administered). Patients received an initial carfilzomib dose of 20 mg/m^2 on day 1, 2; 27 mg/m^2 on day 8, 9, 15, 16 of cycle 1, which increased to 70 mg/m^2 on day 1, 8, 15 from cycle 2 onward if deemed tolerable. Post 16 weeks of daratumumab (08 weekly and 08 fortnightly doses) and 12 cycles of carfilzomib, patients continued receiving maintenance daratumumab monthly (16 mg/kg) and carfilzomib every 2 weeks (56 mg/m^2). Dexamethasone was given as fixed-dose of 40 mg weekly, later modified to every 2 weeks as per the maintenance schedule. Premedication included diphenhydramine, acetaminophen, and ranitidine. Patients also received zoledronic acid 4 mg or denosumab 120 mg on day 1 of each cycle.

Response to treatment and disease progression were evaluated according to the IMWG response criteria at the end of each treatment cycle. M protein measurements in serum were assessed by a central laboratory. Serum immunofixation electrophoresis was performed at screening and when complete response (CR) was suspected. Minimal residual disease (MRD) assessment was done at CR in all patients and post 3 months of high dose chemotherapy (HDT) followed by autologous stem cell rescue in patients who were undertaken for the same.

Results

A total of 19 patients received DKd combination therapy. Baseline characteristics, as well as prior therapies, are presented in Table 1. The median age of patients was 56 years (39–68), and the median number of prior therapies received was 3 (2–5). Fifteen (80%) patients received 3 or more lines of therapy. The median duration of illness in patients before this study was 38 months. None of the patients had undergone prior autologous stem-cell transplantation (ASCT), and three had high-risk cytogenetics. All patients received bortezomib and lenalidomide as prior therapy. Five (26%) patients had the extramedullary disease. All patients received carfilzomib

Table 1: Base line characteristics and prior treatment history

Characteristics	Number
Gender (male/female)	13/06
Median age (years)	56
ECOG PS	
0-1	11
2	8
Prior therapies	3
Median	
2	6
3	6
≥4	7
Prior bortezomib	19
Refractory	3
Prior lenalidomide	19
Refractory	7
Prior pomalidomide	8
Refractory	8
Prior carfilzomib (median number of doses)	6
Prior daratumumab (median number of doses)	6
Last therapy	
Carfilzomib + pomalidomide + dexamethasone	11
Daratumumab + pomalidomide + dexamethasone	8

ECOG PS-Eastern Cooperative Oncology Group performance status

or daratumumab as last therapy (carfilzomib-11, daratumumab-08) and had progressive disease (PD), minimal response (MR) or SD as best response (PD-02, MR-04, SD-13). All but one patient responded to DKd (CR-4, very good partial response [VGPR-10], partial response-02). After the median follow-up of 16 months, PFS was 95% irrespective of prior therapies. All standard-risk patients and two of 3 high-risk patients achieved VGPR or better. Three patients (including one high-risk cytogenetics) who were transplant eligible received HDT followed by ASCT and achieved MRD negativity.

The most frequent all-grade side effects [Table 2] were haematological which included neutropenia 30%, anemia 70%, and thrombocytopenia 42%. Most frequent non-hematological side effects were nausea 40%, vomiting 15%, cough 35%, respiratory tract infections 30%, asthenia 45%, and loss of appetite 50%. The most frequent grade — adverse events were anemia, lymphopenia, and pneumonia. Infusion-related reactions were observed in only two patients, which subsided on stopping the infusion and re-challenging them after repeat pre-medication.

Discussion

MM is an incurable disease, characterized by recurring patterns of remissions and relapses requiring subsequent therapy.[1] Though with the advent of novel therapeutic options, outcome has drastically improved, due to limited options, these drugs should be sequenced in a manner to achieve maximal benefits deep and durable responses. Since the depth of response has prognostic value, patients achieving higher responses have superior PFS and overall survival (OS); thus selection of effective combination therapy is paramount.[8-10]

Results from individual studies of daratumumab as well as carfilzomib-based combination have resulted in deep and durable responses and significantly reduced risk for disease progression or death. However, most of the patients in these trials received one or two lines of prior therapy and also excluded those who were refractory to lenalidomide or bortezomib, making it difficult to extrapolate results of these studies in patients who are heavily treated or are refractory to both bortezomib and lenalidomide.[3,6,7] In this study, nineteen patients who had relapsed/refractory disease following two to five prior lines of therapy, (including bortezomib and lenalidomide/pomalidomide) and had PD, suboptimal response (MR/SD, which cannot be considered as surrogate of response as per IMWG) with either carfilzomib or Daratumumab-based regimes received DKd and have shown significant and promising results. The ORR was whopping 94%, with only one patient not responding to therapy.

Table 2: Common adverse events

Adverse event	Any grade	Grade 3/4
Anemia	15 (80)	5 (25)
Neutropenia	6 (30)	3 (15)
Lymphopenia	13 (68)	8 (42)
Thrombocytopenia	8 (42)	4 (20)
Asthenia	9 (45)	5 (25)
Fatigue	14 (70)	5 (25)
Fever	3 (15)	0
Cough	12 (60)	0
Bronchitis	4 (20)	1 (05)
Nausea	8 (20)	0
Vomiting	3 (15)	0
Diarrhea	6 (30)	1 (15)

Multiple studies incorporating targeted therapies support an aggressive treatment paradigm so as to maximize the benefit in terms of quality of response as well as minimizing the burden of the malignant clone.[11-13] Multiple literature have correlated improved responses (CR and VGPR) with improvements in PFS and OS, suggesting to attain early quality responses to drive the response further during subsequent treatment. This holds good even in relapsed refractory setting where in pooled analysis of phase II studies showed an association between the level of response and OS with a median OS of >70 months for achievement of ≥ VGPR, 35 months for PR and 11.7 months or nonresponse ($P < 0.001$).[14] Depth of response before transplant also harmonizes with quality of response post-ASCT and is predictive of long term PFS and OS after ASCT. Thus, a well-selected triplet driving a quick and deep response may increase the likelihood of ASCT in transplant eligible patients of RRMM, and also achieving MRD negativity. Four patients out of 19, after achieving CR received HDT followed by ASCT and achieved MRD negative status.

Our results are comparable to multicenter multiarm phase Ib study of daratumumab plus carfilzomib but limitations being very small sample size and short follow-up. Furthermore, patients in our study had progressed or suboptimal response to either carfilzomib or daratumumab, for which literature on using a combination of both these drugs in such subset of patients is not available. Its common practice to add or replace drugs of the regimen to which the disease is not responding, which becomes paramount in patients who are heavily treated considering the limited number of left out options to maintain control over the disease leading to better PFS and OS. Minimal response or SD as per IMWG can not be considered as an indicator of response, requiring substitution of drugs of the ongoing regime. A similar approach was adopted in this study, where 17 patients had SD/MR, and two had PD with last received therapy (carfilzomib or daratumumab), and achieved noteworthy pronounced results.

Conclusion

To summarize, combination of daratumumab plus carfilzomib is a promising regime in heavily treated

patients of MM progressing on either of these drugs with fabulous response rates and manageable toxicity profile. Although the drug combination seems to be very expensive, considering the cost-benefit ratio in a patient of RRMM (post 3–5 lines of therapy) in terms of mitigating the disease burden and improving the depth and duration of response, seems to be fruitful bid warranting a sincere consideration. This combination can be a better option in heavily treated RRMM (with prior exposure to either of carfilzomib or daratumumab) producing deeper and durable responses which can be further complemented by ASCT in transplant eligible patients. Large study with longer follow-up time is required to prove this benefit.

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Conflicts of interest

There are no conflicts of interest.

References

1. Orlowski RZ, Lonial S. Integration of novel agents into the care of patients with multiple myeloma. Clin Cancer Res 2016;22:5443-52.
2. Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, *et al*. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. Leukemia 2012;26:149-57.
3. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, *et al*. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319-31.
4. Moreau P, Mateos MV, Berenson JR, Weisel K, Lazzaro A, Song K, *et al*. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): Interim analysis results of a randomised, phase 3 study. Lancet Oncol 2018;19:953-64.
5. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, *et al*. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518-28.
6. Spencer A, Lentzsch S, Weisel K, Avet-Loiseau H, Mark TM, Spicka I, *et al*. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: Updated analysis of CASTOR. Haematologica 2018;103:2079-87.
7. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, *et al*. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66.
8. Munshi NC, Avet-Loiseau H, Rawstron AC, Owen RG, Child JA, Thakurta A, *et al*. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: A meta-analysis. JAMA Oncol 2017;3:28-35.
9. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 1996;335:91-7.
10. Gay F, Oliva S, Petrucci MT, Conticello C, Catalano L, Corradini P, *et al*. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomised, multicentre, phase 3 trial. Lancet Oncol 2015;16:1617-29.
11. Lahuerta JJ, Mateos MV, Martínez-López J, Rosiñol L, Sureda A, de la Rubia J, *et al*. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: Sequential improvement of response and achievement of complete response are associated with longer survival. J Clin Oncol 2008;26:5775-82.
12. Moreau P, Attal M, Pégourié B, Planche L, Hulin C, Facon T, *et al*. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood 2011;117:3041-4.
13. Harousseau JL, Avet-Loiseau H, Attal M, Charbonnel C, Garban F, Hulin C, *et al*. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: Long-term analysis of the IFM 99-02 and 99-04 Trials. J Clin Oncol 2009;27:5720-6.
14. Quach H, Mileshkin L, Seymour JF, Milner A, Ritchie D, Harrison S, *et al*. Predicting durable remissions following thalidomide therapy for relapsed myeloma. Leuk Lymphoma 2009;50:223-9.