MAK HILL Publications Research Journal of Medical Science

Research Article
doi: 10.59218/makrjms.2023.8.42.46

OPEN ACCESS

Key Words
Daratumumab, multiple myeloma, real world

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Received: 17 August 2023
Accepted: 25 August 2023
Published: 2 September 2023

Citation: Damodar Das, Jina Bhattacharyya and Sonal Paul, 2023. Daratumumab in Multiple Myeloma Patients: A Real World Single Center Experience. Res. J. Med. Sci., 17: 42-46, doi: 10.59218/makrjms. 2023.8.42.46

Daratumumab in Multiple Myeloma Patients: A Real World Single Center Experience

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ABSTRACT
Daratumumab is a monoclonal IgG1K antibody that targets CD38, which is overexpressed in myeloma cells. It works by causing complement-mediated cytotoxicity, antibody-dependent cell cytotoxicity and apoptosis. We enrolled 20 patients in our study: 7 newly diagnosed (NDMM) and 13 relapsed refractory patients. The patients were 58 years old on average. Daratumumab was given to six NDMM patients in conjunction with bortezomib, cyclophosphamide and dexamethasone (VCD) and one patient in combination with VR (lenalidomide) D. The 13 patients with relapsed refractory (RRMM) illness had previously had a median of three prior regimens, including proteasome inhibitors (PI) and immunomodulatory medicines (ImiD). All of the newly diagnosed (NDMM) patients displayed high-risk features. After four cycles, the overall response rate (ORR) for NDMM patients was 71% and 76% for RRMM patients. Stringent complete response (sCR) was attained by 28.5% (2/7) of NDMM patients and 7% (1/13) of RRMM patients. Unfortunately, five individuals died as a result of many comorbidities and advanced illness stage. Daratumumab-based regimens were well tolerated, with no reports of grade 3/4 adverse events.

INTRODUCTION

Daratumumab is a human IgG-kappa monoclonal antibody that specifically targets the CD38 antigen found on cancer plasma cells (PCs). It causes cell-mediated cytotoxicity, antibody-dependent phagocytosis and apoptosis in PCs. It also has immunomodulatory properties, since it depletes CD38+ immunosuppressive lymphoid and myeloid cells while increasing cytotoxic T-lymphocyte activity[1-3]. Daratumumab has been shown in many trials to be both safe and effective as a single agent in relapsed and refractory multiple myeloma (RRMM), as well as in combination therapy[4-7]. Daratumumab was added to backbone regimens that included bortezomib, thalidomide and dexamethasone (VTD); bortezomib, melphalan and prednisolone (VMP) and pomalidomide and dexamethasone and it resulted in enhanced effectiveness with no extra toxicity[8,9]. Quadruplet regimens with daratumumab are also showing excellent results in high-risk newly diagnosed multiple myeloma.

In the CASSIOPEIA trial, the combination of daratumumab with bortezomib, thalidomide and dexamethasone (Dara-VTD) demonstrated superior response rates, progression-free survival (PFS) and a trend toward improved overall survival (OS) compared to VTd[10]. Similarly, the GRIFFIN trial revealed that daratumumab combined with VRD (Dara-VRD) led to increased response rates, deeper response levels and prolonged PFS when compared to VRD[11].

The goal of this trial is to demonstrate the safety and effectiveness of daratumumab in normal clinical practise among Indians with newly diagnosed and relapsed refractory multiple myeloma.

Aims and objectives:

- To study the efficacy of Daratumumab in Newly diagnosed and relapsed refractory multiple myeloma patients in our population
- To study the tolerability and adverse effects of Daratumumab

MATERIALS AND METHODS

This research comprised patients who got Daratumumab medication at our tertiary care medical centre between February 2021 and June 2022. Before starting medication, all patients had a verified diagnosis of multiple myeloma (MM) using the criteria set by the International Myeloma Working Group (IMWG)[12,13]. A review of outpatient records was used to collect data, which was then analysed to look at patient demographics, illness features, previous therapies, responsiveness to daratumumab-based combination therapy, timing of disease progression and outcomes. Patients who had relapsed or were resistant to their previous line of treatment and had received at least 4 weeks of daratumumab were eligible. Based on consensus criteria, relapsed and refractory MM were identified.[14] Interphase fluorescence in-situ hybridization (iFISH) on bone marrow plasma cells was used to classify individuals as high-risk [presence of t(4;14), t(14;16), t(14;20), or del(17p)] or standard-risk[15].

Daratumumab was given intravenously in dosages of 16 mg per kilogramme of body weight every week for the first eight weeks, every two weeks for the next 16 weeks and then monthly after that. In conjunction with daratumumab, patients received one of the following treatments: Pomalidomide and dexamethasone, lenalidomide and dexamethasone (RD), bortezomib, cyclophosphamide and dexamethasone (Dara-VCD), bortezomib, lenalidomide and dexamethasone (Dara-VRD), or carfilzomib and dexamethasone (Dara-KD), carfilzomib and pomalidomide (Dara-KP) and pomalidomide, carfilzomib and dexamethasone (Dara-KPD).

The 2016 IMWG criteria were used to assess response to daratumumab-based combination regimens. The overall response rate (ORR) was calculated as the percentage of patients who achieved at least a partial response (PR) as the best response. The National Cancer Institute Common Toxicity Criteria for Adverse Events were used to analyse and grade adverse events. The study was carried out after gaining institutional ethical approval.

RESULTS

The research comprised 20 patients (7 with newly diagnosed MM and 13 with relapsed/refractory MM), with a median age of 58 years (range from 44-81). Daratumumab was given to six newly diagnosed patients in conjunction with bortezomib, cyclophosphamide and dexamethasone (VCD) and one patient received it in combination with bortezomib, lenalidomide and dexamethasone (VRD). The 13 patients with relapsed/refractory MM received a median of three prior regimens, including proteasome inhibitors (PI) and immunomodulatory medicines (IMID). Two patients relapsed after autologous transplantation and were treated with Dara-RD and Dara-KD, respectively. One of the remaining 11 relapsed/refractory patients received Dara-KD, while the others received a quadruplet regimen. Dara-VCD was given to six patients, whereas Dara-VRD was given to four. All of the newly identified MM patients had high-risk features. The average period of follow-up was 12.2 months. Table 1 shows the study population's baseline characteristics.

Patients in the Dara-VRD group began lenalidomide and dexamethasone at median dosages of 25 mg day^{-1} (range: 10-25 mg) and 40 mg $week^{-1}$ (range: 20-40 mg), respectively. Lenalidomide was

Table 1: Baseline characteristics of study population

	NDMM (n = 7)		R/R MM (n = 13)			
Patient characteristics	Dara-VCD (n = 6)	Dara-VRD (n = 1)	Dara-VCD (n = 6)	Dara-VRD (n = 4)	Dara-KD (n = 2)	Dara-RD (n = 1)
Age, years	58 (43-81)	52	65 (46-72)	56 (43-67)	54 (44-64)	64
Male, n (%)	4 (67)	1 (100)	4 (67)	3 (75)	1 (50)	1 (100)
Time from diagnosis to starting dose, years	NIL	NIL	4.1 (0.4-6)	4.1 (0.4-5.2)	4.4 (4.2-4.6)	5.1
Haemoglobin (g dL^{-1})	8.7 (7-10)	10.8	9.6 (7-11)	9.1 (6.8-11.6)	9 (7.8-10.2)	4.3
Calcium	8.8 (8-11)	8.6	8.4 (7.8-10.2)	9 (8.2-10.4)	9.4 (8.4-10.5)	8.7
Creatinine (mg dL^{-1})	2.1 (0.4-6)	1	2.2 (0.4-5.8)	1.1 (0.7-1.3)	1 (0.8-1.2)	1
Serum M Spike (g dL^{-1})	0.7 (0-4.7)	2.8	1.7 (1-4.3)	1.0 (0-5.8)	1.5 (1-2)	1.2
Cytogenetic abnormalities, n (%)						
t (4;14)	2 (33.3)	1 (100)	2 (33.3)		1 (50)	
t (14;20)	1 (16.7)			2 (50)		
del (17p)	2 (33.3)		2 (33.3)	1 (25)		
del 13	1 (16.7)	1 (100)				

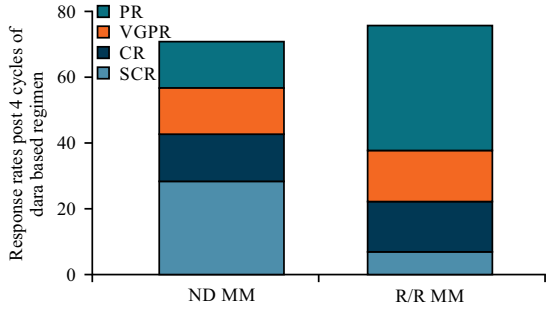

Fig. 1: Response rates post 4 cycles of dara based regimen

administered throughout the first 21 days of a 28-day cycle. The Dara-VCD group received oral cyclophosphamide at a weekly dosage of 300 mg m^{-2} body surface area, combined with bortezomib and dexamethasone. Bortezomib was started at a dosage of 2 mg per dose and given on days 1, 4, 8 and 11 of a 28-day cycle, or on days 1, 8, 15 and 22 at the discretion of the treating physician. Bortezomib was given to all patients subcutaneously. Carfilzomib at a dosage of 56 mg m^{-2} was delivered weekly to Dara-KD patients.

The overall response rate was 71% in newly diagnosed multiple myeloma (NDMM) patients and 76% in relapsed and refractory multiple myeloma (RRMM), with 28.5% (2 out of 7) of NDMM patients attaining stringent complete response (sCR) and 7% (1 out of 13) of RRMM patients achieving sCR (Fig. 1).

In Dara-VCD-treated newly diagnosed multiple myeloma (NDMM) patients, 33.3% (2 out of 6) achieved severe complete response (sCR), 16.6% (1 out of 6) obtained complete response (CR) and 16.6% (1 out of 6) achieved partial response (PR). Unfortunately, two individuals died as a result of the disease's progression. One patient who had the quadruplet Dara-VRD regimen from the start obtained a very good partial response (VGPR).

Two patients in the relapsed/refractory (R/R) group achieved full response (CR) and one patient reached VGPR with Dara-Rd. In the Dara-VCD subgroup, 16.6% (1 of 6) attained sCR, 33.3% (2 of 6) achieved VGPR and 3 patients died owing to disease progression (2 of 6) and other reasons such as diabetic ketoacidosis with pneumonia (1 of 6) that could not be ascribed to neutropenia. 25% (1 out of 4) of the Dara-VRD subgroup attained CR, 25% (1 out of 4) reached PR and 50% (2 out of 4) obtained VGPR.

As of the data cut-off, 5 patients have died, including 2 newly diagnosed and 3 RRMM patients. Except for one case of diabetic ketoacidosis with pneumonia, all deaths were ascribed to progressing illness.

Surprisingly, our sample had no substantial haematological adverse effects. Two individuals experienced moderate grade 1 infusional responses and no grade 3-4 infusional events were noted. Other documented adverse effects included infections (pneumonia) in 5% of patients, weariness in 15% of patients and diarrhoea in 10% of patients.

Overall, the DARA-based regimens were well tolerated by the patients in our study.

DISCUSSIONS

Daratumumab has been shown to be beneficial in previously treated multiple myeloma (MM) patients, both as a stand-alone therapy and in combination with other medicines, since 2015. The GEN501 and SIRIUS trials were the first to report on the effectiveness and safety of daratumumab as a stand-alone treatment for patients with relapsed and refractory (R/R) MM. Daratumumab monotherapy was approved as a consequence of the findings of these trials for patients who had received at least three prior lines of treatment, including an immunomodulatory medication (IMiD) and a proteasome inhibitor (PI), or who were doubly resistant to an IMiD and a PI[4-6].

Following the phase I/II GEN503 experiment, the combination of daratumumab with lenalidomide and dexamethasone (Dara-RD) outperformed lenalidomide and dexamethasone alone (RD) in the phase III POLLUX trial for R/R MM patients[16,17].

The median period from diagnosis to daratumumab beginning in CASTOR and POLLUX was 3.9 years (range from 0.7-21) and 3.5 years (ranging from 0.4-27), respectively, compared to almost 4 years (ranging from 0.4-13.0) in our research[18]. Our study

group reflects a real-world clinical practise scenario in which Dara-based regimens are used after numerous viable treatments have been exhausted. The finding that 28.5% of newly diagnosed MM patients achieved strict complete response (sCR), compared to 7% in relapsed refractory situations, shows that using Daratumumab earlier in the disease course, before a patient becomes multi-refractory, may result in improved outcomes. Dara-Kd had an ORR of 84% in the CANDOUR trial, with 69% of patients attaining very good partial response (VGPR) or better whereas in our investigation, both patients (100%) who received Dara-KD had complete response (CR)[19].

Dara-VCD was given to 86 newly diagnosed MM patients and 14 RRMM patients in the LYRA trial, with a median duration from diagnosis to daratumumab beginning of 2.22 years for RRMM, compared to 4 years in our research. The RRMM group achieved VGPR and better at a rate of 64.3%, with 21.4% reaching CR and an ORR of 71.4%. In our group of six RRMM patients who received Dara-VCD, 16.6% had sCR, 33.3% had VGPR and the ORR was 50%.

Outside of clinical trials, there has been little experience with daratumumab-based medicines. Lakshman *et al*.[20] from the Mayo Clinic looked at 126 RRMM patients who were treated with Dara-based combination regimens and found an overall response rate of 47% with a median follow-up of 5.5 months. The ORR in our group of 13 RRMM patients was 76%. The median age at the start of the daratumumab regimen was 67 years, compared to 59.7 years a decade earlier, most likely due to the earlier onset of MM in the Indian population. There is limited evidence from India on the use of Daratumumab, with the first trial by Ahmed *et al*.[21] using dara-based combination treatment in 7 RRMM patients who had received a median of two prior lines of therapy. The ORR was 42.7%, which was much lower than what we saw in our group. The most prevalent hazard was haematological, with two patients having grade 3-4 thrombocytopenia, two experiencing grade 3-4 neutropenia and two fatalities attributable to gram-negative sepsis and H1N1. There were no haematological toxicities in our patient group.

The percentage of VGPR and above was 44.2% in the LYRA study, which included 86 newly diagnosed MM patients treated with Dara-VCD, with 4.7% reaching CR[22]. After four rounds of induction, the ORR was 79.1%, whereas in our cohort of six newly diagnosed MM patients using Dara-VCD, 49.9% achieved CR or better, with treatment ORR of 66.6%. Gryphon, a randomised phase II trial, found that daratumumab with VRD (Dara-VRD) enhanced the rate and depth of response to treatment and extended progression-free survival when compared to VRd.[11] By the completion of induction, 12.5% had achieved CR and 42% had reached sCR, with 47% achieving minimum residual disease negativity. We have one newly diagnosed MM patient who obtained VGPR after Dara-VRd induction, perhaps because to high-risk cytogenetics [t(4,14) and del13q].

Contrary to the findings of other trials, no grade 3 or 4 haematological adverse events or infusional responses were identified in our patient population.

More research is needed to determine the treatment's safety and efficacy in the Indian population.

CONCLUSION

Most clinical studies confirm the current real-world experience that Dara-based regimens give increased effectiveness with adequate tolerability for both newly diagnosed MM and advanced RRMM patients. More study using this medicine in real-world situations is required to assess its safety and effectiveness in the Indian subcontinent.

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