Research Article

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Title: Anti-CD38 monoclonal antibody daratumumab enhances the overall response rate in patients with multiple myeloma.

Short title: Daratumumab improves overall response rate in multiple myeloma patients.

Abstract

Purpose: New medicines employed in recent years have resulted in significant increases in survival rates for Multiple Myeloma (MM). Daratumumab, a monoclonal antibody against CD38, is utilized in both first-line myeloma treatment and relapsed/refractory illness. Our study aims to assess the clinical features, response to treatment and factors influencing response to treatment in patients who received daratumumab monotherapy or combination therapy at our center.

Materials and methods: In the Pamukkale University Faculty of Medicine Hematology clinic between June 2022 and June 2023, 21 patients who were treated with daratumumab after receiving a multiple myeloma diagnosis were included. Demographic features of the patients, disease stage, prior therapies, characteristics of daratumumab treatment, and response rates to treatments were retrospectively analyzed.

Results: The patients median age was 65±9.7 years (42-80), with a female/male ratio of 11/10. Treatment with daratumumab: 61.9% was used after two lines of therapy, 23.8% was used in first-line therapy, and 14.28% was used in second-line therapy. The average number of cycles was 4.05±5.06. Of the patients treated with daratumumab, 4.76% were treated as a single agent; 61.9% were treated in combination with immunomodulatory medications, cyclophosphamide and/or melphalan; and 33.4% were treated in conjunction with chemotherapy. When the response to treatment was evaluated, 38.1% of the patients passed away, 38.1% had a very good partial response (VGPR) or better, and 23.8% had a partial response (PR). 42.9% of patients who received daratumumab along with chemotherapy died. With daratumumab-containing regimens, overall response rates increased significantly as the number of cycles increased (ORR) (p=0.026).

Conclusion: When daratumumab-containing protocols are used in the treatment of multiple myeloma, it has been observed that overall response rates improve and treatment success increases in direct proportion to the number of cures.
Keywords: Daratumumab, multiple myeloma, treatment.

Makale başlığı: Multipl miyelomda Anti-CD38 monoklonal antikoru daratumumab tedavisi genel yanıt oranını arttırır.

Kısa başlık: Daratumumab multipl miyelom hastalarında genel yanıt oranını iyileştirir.

Öz

Amaç: Son yıllarda kullanılan yeni ilaçlar Multipl Miyelom (MM) hastalığında sağkalım oranlarında önemli artışlara yol açmıştır. CD38'e karşı geliştirilmiş monoklonal antikor olan Daratumumab hem birinci basamak miyelom tedavisinde hem de nükseden/dirençli hastalıkta kullanılmaktadır. Çalışmamız, merkezimizde daratumumab monoterapisi veya kombinasyon tedavisi alan hastaların klinik özelliklerini, tedaviye yanıt ve yanıtı etkileyen faktörleri değerlendirmeyi amaçlamaktadır.

Gereç ve yöntem: Pamukkale Üniversitesi Tıp Fakültesi Hematoloji kliniğinde Haziran 2022 ile Haziran 2023 tarihleri arasında multipl miyelom tansı ile takip edilen ve daratumumab tedavisi alan 21 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, evreleri, daha önce aldıkları tedaviler, daratumumab tedavisinin özellikleri ve tedaviyle elde edilen yanıt oranları retrospektif olarak incelendi.

Bulgular: Hastaların ortanca yaşı 65±9,7 yıl (42-80), kadın/erkek oranı 11/10 idi. Daratumumab tedavisi hastaların %61,9'da iki basamak tedavi sonrasında, %23,8'inde birinci basamak tedavide ve %14,28'de ikinci basamak tedavide kullanıldı. Ortalama siklus sayısı 4,05±5,06 idi. Daratumumab ile tedavi edilen hastaların %4,76'sında tek ajan, %61,9'u immünomodülatör ilaçlar, siklofosfamid ve/veya melfalan ile kombinasyon halinde ve %33,4'ü ise kemoterapi ile kombinasyon halinde kullanıldı.

Tedaviye yanıt değerlendirildiğinde; hastaların %38,1'inin kaybedildiği, %38,1'inin çok iyi kısmi yanıt (ÇİKY) ve üzeri yanıt ile %23,8'inin stabil hastalık (SH) ile tedaviye devam ettiği görüldü. Kemoterapiyle birlikte daratumumab alan hastaların %42,9'u kaybedildi. Daratumumab içeren rejimler ile kür sayısı arttıkça genel yanıt oranlarının anlamlı bir şekilde arttığı görüldü (p=0,026).

Sonuç: Multiple miyelom tedavisinde daratumumab içeren protokoller kullanıldığında kür sayısı ile doğru orantılı olarak genel yanıt oranlarının iyileştiği ve tedavi başarısının arttığı görülmüştür.

Anahtar kelimeler: Daratumumab, multiple miyelom, tedavi.

Introduction

It is widely accepted, multiple myeloma (MM) is an extremely challenging form of hematological malignancy. Despite the difficulties of treatment, significant gains in response rates have been made with novel drugs employed in recent years, as well as great success in progression-free survival and overall survival [1].

Daratumumab, a monoclonal antibody created against CD38 produced in myeloma cells, is one of the novel treatment used for MM. Daratumumab displays cytotoxicity that is reliant on complement, cytotoxicity that is dependent on antibodies, cellular phagocytosis that is dependent on antibodies, and immunomodulatory effects [2-4]. In view of its shown performance in monotherapy or combination treatment protocols in clinical trials, daratumumab is replacing MM patients' previous treatment methods. Even in patients with poor prognostic features who had received multiple lines of therapy, 20.1-month overall survival was achieved with daratumumab treatment administered as monotherapy [5]. Many studies in newly diagnosed and relapse-refractory patients have shown that triple and quadriple treatment regimens with the inclusion of daratumumab have significant survival succsess [6-9]. The aim of this study was to examine the parameters influencing the clinical course and response rates to daratumumab treatment in patients with newly diagnosed or relapsed refractory myeloma (MM) at our clinic.

Materials and methods

The study included patients with multiple myeloma who were followed up in the hematology clinic of Pamukkale University Faculty of Medicine. Retrospective analysis was done on the data of newly diagnosed or relapsed refractory multiple myeloma patients treated with daratumumab as a single agent or in combination regimen. Patients were diagnosed as multiple myeloma according to the diagnostic criteria established by the International Myeloma Study Group (IMWG) [10].

Newly diagnosed or relaps/refractory multiple myeloma patients who received daratumumab as a single agent or combination therapy between June 2022 and June 2023 were included in study. Demographic features of the patients, paraprotein type, laboratory results, stage of the disease according to international staging system (ISS) [10], prior treatments (if any), treatment line and treatment protocol of daratumumab, response to treatment and survival of the patients were obtained from electronic data system. Response to treatment was determined according to IMWG treatment response criteria [10].

Treatments in practice and assessment of response: Daratumumab was infused intravenously at a dose of 16 mg/kg and given weekly infusions in first 8 weeks, then every two weeks, and then monthly infusions according to treatment protocol. First dose of daratumumab was given as splited dose in two consecutive days. Premedication including antihistaminic, dexamethasone and montelukast was administered before infusion of daratumumab. According to manufacturer suggestions; the first infusion was started at 50 ml/h, followed by dose escalation up to 200 ml/h, in the absence of infusion-related reactions (IRRs). Subsequent infusions were diluted in 500 ml and started from 50 ml/h in second infusion or 100 ml/h in subsequent infusions with an increase up to 200 mL/h Infusion-related side effects were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [11].

Treatment responses were assessed in accordance with the IMWG [10]. Serum free kappa and lambda levels, immunoglobulin levels, and serum/urine protein electrophoresis were evaluated every month for response assessement; serum and urine immunoelectrophoresis were evaluated bimonthly. Any elevation in M protein or clinical progression of myeloma-associated end-organ damage during this period was considered treatment resistance. In addition to laboratory and clinical assessment, bone marrow aspiration and biopsy was performed after 3 or 4 cycles of treatment. Furthermore, individuals with initial extramedullary myeloma, lytic bone lesions or plasmocytoma underwent response evaluation with magnetic resonance imaging or 18 Fluorodeoxyglucose Positron Emission Tomography (F-18 FDG PET). Responses to treatment were classified as complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD) according to IMWG response criteria [10].

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Pamukkale University on June 13, 2022, with the reference number 168199, and informed consents were obtained patients.

Statistical analysis

The data were analysed with SPSS 25.0 package program. Continuous variables were given as mean ± standard deviation and categorical variables as number and percentage. Mann-Whitney U test was used to compare independent group differences. The correlations between continuous variables were analysed by Pearson correlation analyses and the differences between categorical variables were analysed by Chi-square analysis. Logistic regression analysis was used to determine the factors affecting response to treatment.

Results

Data of 21 patients who met the inclusion criteria were analyzed. The median age of the patients was 65±9.7 (42-80) years, with an 11/10 female to male ratio. Among the patients, 66.7% were ISS stage III (advanced stage) and 47.5% had IgG kappa paraproteinaemia. Clinical characteristics of patients were shown in Table 1.

Extramedullary-paraosseous myeloma was present in in 42.9% of the patients. Daratumumab is administered as first-line therapy in 23.8% of cases, as second-line therapy in 14.28% of cases, and following second-line treatment in 61.9% of cases. Median follow-up time was 5.15 months (0.36-23). The mean number of cycles was 4.05±5.06.

When we looked at treatment regimens; five patients received daratumumab-bortezomib-thalidomide-dexamethasone (D-VTD); seven patients received D-VTD+chemotherapy (cyclophosphamide-etoposide-cisplatin-doxorubicin; all or some of them); one patient received daratumumab-bortezomib-cyclophosphamide-dexamethasone (D-VCD); one patient received daratumumab-melphalan-prednisolone (D-VMP); five patients received daratumumab-lenalidomide-dexamethasone (D-RD); one patient received daratumumab monotherapy; and one patient received daratumomab-bortezomib-dexamethasone (D-VD).

Analysis of the response rates revealed that the overall response rate (ORR) was 66%; of these, 6 patients (28.6%) had a complete response (CR), 3 patients (14.3%) had a very good partial response (VGPR), 5 patients (23.8%) had a partial response (PR), and 7 patients (33.3%) had progressive disease (PD) (Table 1).

When the factors that may affect response to treatment were analyzed, it was observed that age, gender, stage, presence of extramedullary-paraosseous myeloma, treatment line and response to previous treatments had no statistically significant effect on daratumumab response (p>0.05) (Table 2). All patients who received more than 3 cycles of daratumumab-containing therapy achieved VGPR and better response. In patients who received ≤3 cycles of daratumumab containing therapy only 25% (n:4) of patients achieved VGPR and better response. Comparison of these two groups shows that giving more than 3 cycles of daratumumab-containing therapy significantly increases response rates (p=0.026) (Table 2).

Drug-related infusion reaction was seen in only 2 patients and treatment was discontinued in one of these patients because of grade 4 reaction. In the other patient, a grade 2 infusion reaction developed, the infusion was interrupted, controlled with an additional dose of dexamethasone and then resumed.

When the final status of the patients was evaluated, it was observed that 38.1% of patients were died, 38.1% continued treatment with VGPR or higher response, and 23.8% (n:5) continued treatment with PR. Among the 7 patients who received D-VTd+chemotherapy, 3 (42.9%) died due to progressive disease and one patient could not complete the treatment due to acute heart failure that developed during treatment.

Analysis of potential treatment-affecting factors revealed that age, gender, stage, extramedullary-paraosseous myeloma existence, treatment step, and prior therapies did not significantly impact response (p>0.05). When patients receive more than 3 cycles of daratumumab, the rate of obtaining very good partial response and better response (VGPR and CR) increased and this effect was found to be statistically significant (p=0.026) (Table 2). Neverthless none of these factors appeared to have an impact on the response to treatment, according to multivariate analysis.

Discussion

Multiple myeloma treatment remains difficult even with the new drugs that have been developed and made available recently, as well as the consolidation with autologous bone marrow transplantation—an essential component of treatment for eligible patients. Survival is particularly poor in patients with an aggressive course, high risk and resistant to proteasome inhibitors (PIs) or immunomodulatory agents (IMIDs). Our study showed that Daratumumab containing regimens improve the response rates especially after 3 cycles of therapy. VGPR and CR rates increased when the patients recieved more than 3 cycles of daratumumab containing therapy.

Numerous clinical studies demonstrate the effectiveness of daratumumab, a monoclonal antibody directed against CD38, in the treatment of myeloma through both monotherapy and various combination regimens [5-9]. In the 2016 study by Usmani et al. demonstrating the effectiveness of daratumumab monotherapy in relapsed refractory multiple myeloma patients, the total response rate was 31% among patients who had previously undergone at least two lines of treatment, comprising IMID and/or PI. In this study, patients received daratumumab at a dose of 16mg/kg for the first 8 doses once a week, then 8 doses twice a month and then once a month until progression [5]. As a single agent this success in patients who had previously received multiple lines of treatment, led to studies showing the efficacy of combinations of daratumumab with IMID and/or PI in R/R patients; POLLUX (D-Rd), CASTOR (D-Vd), and in newly diagnosed patients CASSIOPEIA (D-VTd), ALCYONE (D-VMP). As a result, it is now used to treat MM patients who are both transplant-ineligible and transplant-eligible [6-9].

In our study, daratumumab monotherapy and combination therapies were used in 5 newly diagnosed and 16 relapsed/refractory MM patients in our center and these treatment protocols are similar to the protocols whose efficacy has been shown by clinical studies in the literature; D-VTd, D-VCd, D-VMP, D-Rd, D-Vd and daratumumab monotherapy. Different from the literature, D-VTd+chemotherapy protocol was applied in 7 relapsed/refractory (R/R) patients. Although the protocols of our patients were different, we found that complete response rates (CR) increased significantly if the patient receives more than 3 cycles of daratumumab-containing cycles (p=0.026). According to the results of phase 3 studies in which daratumumab was used as monotherapy and with combination regimens, it is seen that the rates of undetectable minimal residual disease (MRD) and complete response rate increase with the duration of treatment [5-9]. With D-Rd, the response rates after more than three years of follow-up were CR 56.6% and ORR 92.9% in the POLLUX trial, which comprised 559 relapsed refractory MM patients [7]. MRD negative was found in 64% of patients at the 100-day evaluation following autologous stem cell transplantation in the CASSIOPEIA research, which administered the D-VTd regimen to 543 newly diagnosed MM patients [8].

In a retrospective study by Zhou et al. [12], the total survival was determined to be 8.4 months, and the total response rate was 70%. The study included 38 R/R MM patients who were given D-KRd-PACE, of which 30% were found to be nonresponsive. However, in our study, mortality rate was 42.9% in patients who received D-VTd+chemotherapy combination. Patients who underwent D-VTd-chemotherapy had a high mortality rate, which might be explained by the fact that some of them were frail patients who had run out of choices, that their disease was developing quickly, and that they previously had many therapies before receiving daratumumab treatment. Although promising results have been obtained in the treatment of MM with daratumumab, loss of response may be observed due to the development of resistance to daratumumab by different mechanisms. Studies on understanding the mechanisms of resistance development and solutions to be developed for prevention are ongoing [13,14].

The most important limitations of this study was the insufficient number of patients and the analysis of a heterogeneous patient group. Due to the small number of patients, separate statistical evaluation could not be performed in newly diagnosed and relapsed refractory patients. In addition, because our center has been using regimens including daratumumab for the last several years, the patients' follow-up periods were short, making it unable to undertake a survival study. With multicenter studies that include more patients, offer long-term follow-up, and analyze real-world data, it appears feasible to experience varying clinical outcomes.

In conclusion, it is obvious that different daratumumab combinations play a significant role in the treatment of multiple myeloma, both as salvage therapy for patients who have previously received several lines of treatment and as the first line for newly diagnosed and high-risk patients. Consequently, an increase in response rates can have a substantial impact on the course of treatment as the number of cycles with Daratumomab administration increases.

Conflict of interest: No conflict of interest was declared by the authors.

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The study was previously presented as a paper at the 2nd Leukaemia Lymphoma Myeloma Congress and was awarded the "Best 7 Paper Award".

Ethics committee approval: Pamukkale University's Non-Interventional Clinical Research Ethics Committee approved the study on June 13, 2022, with the reference number 168199.

Authors' contributions to the article

O.E. contributed to data collection, literature review and article writing, N.A.A. contributed to the creation of the study design, checking the accuracy of the data, statistical analysis of the data, literature review and article writing, V.E. and I.C.K. contributed to data collection, and N.G contributed to the creation of the study design and literature review.

Table 1. Patients' clinical characteristics and treatments

Variable	n (%) or Median
Median Age (years)	65±9.7 (42- 80)
Gender	
• Female	11(52.4)
• Male	10 (47.6)
ISS stage	
• Stage 1	5 (23.8)
• Stage 2	2 (9.5)
• Stage 3	14 (66.7)
Paraprotein Tipi	
• IgG lambda	6 (28.6)
• IgG kappa	10 (47.6)
• Lambda mild chain	1 (4.8)
• Kappa mild chain	2 (9.5)
• IgA lambda	2 (9.5)
• Disease status	
• New Diagnosis	5 (23.8)
• Relapse-Refractory	16 (76.2)
Number of Previous Treatments	
• 0	5 (23.8)
• 1	3 (14.3)
• 2	5 (23.8)
• ≥3	8 (38.1)
Extramedullary disease	
• Yes	9 (42.9)
• No	12 (57.1)
Treatment regimes	
• D-VTd	5 (23.8)
• D-VTd+ Chemotherapy	7 (33.3)
• D-VCd	1 (4.8)
• D-VMP	1 (4.8)
• D-Rd	5 (23.8)
• D-Vd	1 (4.8)
• Daratumumab monotherapy	1 (4.8)
Daratumumab-related reactions	
• Yes	2 (9.5)
• No	19 (90.5)
Response Status	
• CR	6 (28.6)
• VGPR	3 (14.3)
• PR	5 (23.8)
• PD	7 (33.3)
Mortality	8 (38.1)
• Due to disease progression	4 (19.05)
• Due to sepsis	4 (19.05)

ISS: International staging system, CR: Complete Response, PR:Partial Response
VGPR: Very Good Partial Response, PD: Progressive Disease
D-VTd: Daratumumab-Bortezomib-Thalidomide-Dexamethasone
D-VCd: Daratumumab-Bortezomide-Cyclophosphamide-Dexamethasone
D-VMP: Daratumumab-Bortezomib-Melphalan-Dexamethasone
D-Rd: Daratumumab-Lenalidomide-Dexamethasone
D-Vd: Daratumumab-Bortezomib-Dexamethasone

Table 2. Treatment response rates according to clinical characteristics

Variable	Response Rate		*P* value
	≥ VGPR n (%)	<VGPR n (%)	
Age			0.256
>65	7 (70)	3 (30)	
≤65	6 (54.5)	5 (45.59	
Gender			0.056
Female	2 (20)	8 (80)	
Male	7 (63.6)	4 (36.4)	
Stage ISS			0.155
I	1 (20)	4 (80)	
II	0 (0)	2 (80)	
III	6 (42.9)	8 (57.1)	
Number of Cycles			**0.026**
>3	5 (100)	0 (0)	
≤3	4 (25)	12 (75)	
Extramedullary Myeloma			0.445
Yes	3 (33.3)	6(66.7)	
No	6 (50)	6(50)	
PI refractory			0.309
Yes	4 (33.3)	8 (66.7)	
No	5 (55.6)	4 (44.4)	
IMID refractory			0.604
Yes	5 (38.5)	8 (61.5)	
No	4 (50)	4 (50)	

ISS: International Staging System, VGPR: Very Good Partial Response, PI: Proteasome Inhibitor
IMID: Immunomodulatory Drug, $p<0.05$ was considered statistically significant

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Özde Elver, M.D. Pamukkale University Faculty of Medicine Department of Haematology, Denizli, Türkiye, e-mail: ozde.elver@gmail.com (https://orcid.org/0000-0002-1731-946X) (Corresponding Author)

Nevin Alayvaz Aslan, Asst. Prof. Pamukkale University Faculty of Medicine Department of Haematology, Denizli, Türkiye, e-mail: nevinalayvaz@gmail.com (https://orcid.org/0000-0003-3292-8519)

Veysel Erol, M.D. Kahramanmaraş Necıp Fazıl Cıty Hospıtal Hematology Clınıc, Kahramanmaraş, Türkiye, e-mail: verol55@hotmail.com (https://orcid.org/0000-0001-5244-3733)

İsmail Can Kendir, PhD. Pamukkale University Faculty of Medicine Department of Haematology, Denizli, Türkiye, e-mail: can_kendir@hotmail.com (https://orcid.org/0000-0003-4372-7149)

Nil Güler, Prof. Pamukkale University Faculty of Medicine Department of Haematology, Denizli, Türkiye, e-mail: nilvecay@yahoo.com (https://orcid.org/0000-0003-0604-6475)

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