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EVALUATION OF THE EFFICACY OF ANTI-CD38 ANTIBODIES IN THE TREATMENT OF MULTIPLE MYELOMA: RESULTS OF RETROSPECTIVE STUDY

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ABSTRACT

Relevance: *A breakthrough in managing multiple myeloma is associated with introducing monoclonal antibodies, significantly increasing overall response rates and improving progression-free survival. Combination regimens with monoclonal antibodies and immunomodulators demonstrate high efficacy even in patients resistant to previous lines of therapy.*

The study aimed to *evaluate the efficacy of anti-CD38 monoclonal antibodies (daratumumab) in patients with multiple myeloma after one or more prior therapy lines with other drugs.*

Methods: *A retrospective medical data analysis was conducted on 22 patients with refractory or relapsed MM who received daratumumab from February 2018 to November 2023. Patients received daratumumab either as monotherapy or in combination with other agents. The efficacy assessment was performed using the criteria of the International Myeloma Working Group (IMWG).*

Results: *The overall response rate to daratumumab treatment was 59.1%. The overall survival rate was 100% at two years and 95% by the end of the analysis period. Disease progression was observed in 22.7% of patients. The safety profile was acceptable, with mild to moderate side effects predominating, including thrombocytopenia, anemia, and neutropenia.*

Conclusion: *Daratumumab is an effective treatment for patients with refractory or relapsed MM who have undergone multiple prior lines of therapy. Treatment with daratumumab leads to significant improvements in clinical outcomes and progression-free survival. These data support the feasibility of using daratumumab in MM therapy and highlight the need for further study of its combination regimens and predictive factors for better therapeutic response.*

Keywords: *multiple myeloma, relapsed/refractory multiple myeloma, anti-CD38 antibodies, monoclonal antibodies, daratumumab, treatment efficacy.*

Introduction: Multiple myeloma (MM) is a neoplastic hematopoietic system disease characterized by uncontrolled proliferation of plasma cells in the bone marrow. The proliferation of monoclonal plasma cells in the bone marrow disrupts the normal process of hematopoiesis, leading to anemia. In addition, malignant plasma cells secrete monoclonal immunoglobulin, the so-called paraprotein or M-protein, and infiltrate other vital organs [1]. It should be noted that MM is the longest-diagnosed type of cancer in the world due to the various spectrum of clinical symptoms, in particular, back and bone pain, which often leads to late referral to oncologists and hematologists [2].

MM accounts for 1-2% of all oncological diseases and 17% of all oncohematological pathologies. On a global scale, over 180,000 cases and 121,000 deaths due to MM are reported annually among men and women of all ages [3]. The incidence in men is higher than in women, and several authors have noted ethnic and racial differences. For example, MM is twice as common in people of Aframerican origin [4-7]. According to the National Cancer Institute, MM's 5-year overall survival (OS) in 2013–2019 composed 59.8% [8].

The use of proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies (MAs), and new therapies has significantly improved progression-free survival and overall survival in patients with multiple myeloma over the past decades [1, 9]. One of the effective drugs for MM treatment is IG1kappa MA, which binds to CD38 glycoprotein [10]. CD38 induces cell adhesion and cytokine release and is highly expressed on the surface of myeloma cells, making it a target for MA IG1kappa.

One of the initial indications for MA use was daratumumab monotherapy in pre-treated patients with MM who had received several prior lines of therapy, including proteasome inhibitors and immunomodulators, as well as in patients with refractory to proteasome inhibitors and immunomodulators [11]. A retrospective analysis of 34 cases with primary and repeated use of MA and immunomodulators in patients previously treated with these drugs and refractory to them and in patients previously not treated with these drugs showed that the use of MA in combination with immunomodulators was effective not only in patients not taking these agents but also demonstrat-

ed a clinical response in a third of patients who received repeated treatment with these drugs [12]. The clinical trial data that studied the efficacy of anti-CD38 MA monotherapy showed an overall response rate (ORR) in 31% of cases and a median OS of 20.1 months [13]. Besides, according to the Phase 2 SIRIUS clinical trial, which assessed the efficacy of MA as a monotherapy, the ORR was 30.4%, and the mean OS was 20.5 months [14, 15].

Two phase 3 clinical trials (CASTOR and CANDOR) assessed the efficacy of MA in combination with proteasome inhibitors in patients with relapsed/refractory MM. The final analysis of OS in a 6-year follow-up of patients treated with daratumumab in the CASTOR study showed that OS was significantly higher in the group with IG1kappa MA, and the mean OS in this group composed 49.6 months, and in the control group was – 38.5 months [16]. According to the final analysis of the CANDOR study, the progression-free survival (PFS) in patients treated with IgG1k MA was 28.4 months after a 50-month follow-up, compared to a control group (15.8 months) [17].

In a similar POLLUX study using MA combined with immunomodulators, the 12-month PFS amounted to 64.8%, and the ORT composed 92.9% [18].

The results of the aforesaid studies on the use of CD38-directed MA in treating patients with MM have shown the efficacy of various treatment regimens. In this respect, further study of the efficacy of anti-CD38 MA in patients with refractory/relapsed MM is needed [11-18].

The study aimed to evaluate the efficacy of anti-CD38 monoclonal antibodies (daratumumab) in patients with multiple myeloma after one or more prior therapy lines with other drugs.

Materials and Methods: A retrospective analysis of medical data was carried out in 22 patients with MM registered with the City Clinical Hospital No. 7 in Almaty, with 1 or more previous lines of therapy, who received daratumumab in monotherapy and/or in combination with other agents in the period from February 2018 to November 2023.

The study included 9 men and 11 women. The average age of patients at enrollment was 62±11.9 years, and 50% were over 65 years old. The study group included 59% of women and 41% of men. The time from diagnosis to initiation of IG1kappa MA therapy ranged from 3 to 62 months, with a median of 30.3 months. Notably, 50% of patients received more than three lines of therapy before initiation of MA treatment, and all patients received proteasome inhibitors. The data are presented in Table 1.

Table 1 – Clinical characteristics and refractory status of patients enrolled in the study (n=22)

Indicator	Value, n (share, %)
Number of patients	22 (100)
Median age at study entry, year (range)	62 (38-87)
Age >65 years	11 (50)
Sex	
Men	9 (41)
Women	13 (59)
Time from diagnosis to the start of daratumumab therapy, months (range)	30.3 (3-62)
Average number of prior therapies (range)	3.3 (1-6)
>3 lines of prior therapy	11 (50)
Prior autologous hematopoietic stem cell transplantation	2 (9.1)
Prior proteasome inhibitor therapy	22 (100)
Prior therapy with immunomodulators	12 (54.4)

Treatment regimen: Within the frames of monotherapy, patients received daratumumab 16 mg/kg IV or 1800 mg SC once weekly at 1-8 weeks, once every 2 weeks at 9-24 weeks, and once every 4 weeks from week 25 onwards until progression or intolerance development.

In cases of combination therapy with other agents, the following dosages of drugs have been used:

Daratumumab – 16 mg/kg IV or 1800 mg SC once a week at 1-8 weeks, once every 2 weeks at 9-24 weeks, and once every 4 weeks from week 25 onwards until progression or until intolerance development.

Bortezomib – 1.3 mg/m^2 subcutaneously or intravenously, days 1,4,8,11 (cycles 1-8).

Lenalidomide – 25 mg orally, days 1-21.

Pomalidomide – 4 mg once daily orally, days 1-21.

Dexamethasone – 20 mg orally or intravenously, days 1,2,4,5,8,9,11,12 (cycles 1-8) when used with Bortezomib, or Dexamethasone 40 mg orally or intravenously when used with Lenalidomide/Pomalidomide [19].

In order to assess the response, the International Myeloma Working Group (IMWG) criteria have been used [20]. The Overall Response Rate (ORR) was obtained by patients achieving a strict complete response, a complete objective response, a very good partial objective response, a partial objective response, a minimal response, and stabilization of the process. The OS was defined as the time from registration to death for any reason. Progression-free survival (PFS) was defined as the time from initiation of treatment with IG1kappa MA to disease progression or death from any cause. The analysis of OS and PFS was carried out using the Kaplan-Meier method. The MedCalc Software, Belgium, was used for statistical analysis.

Results: According to our study, the ORR of patients with MM for treatment with daratumumab composed 59.1%. Of

these, 13.6% of patients achieved a complete objective response, 18.2% achieved a very good partial response, and 13.6% achieved a partial response. In 13.6% of patients, a minimal response was noted. However, 22.7% of patients experienced the disease progression, including patients who underwent autologous hematopoietic stem cell transplantation (auto-HSCT). The distribution of patients depending on the response to IG1kappa MA therapy is presented in Table 2.

Table 2 – Response rate to treatment with anti-CD 38 MA

Response to anti-CD 38 MA therapy	Number of patients	
	Abs.	%
Overall response rate	13	59.1
Strict full response	0	0
Complete objective response	3	13.6
Very good objective partial response	4	18.2
Partial objective response	3	13.6
Minimal response	3	13.6
Stabilization of the disease	2	9.1
Disease progression	5	22.7
Death	2	9.1
Overall survival (OS) rate		95.45
Progression-free survival		72.73

After two years of follow-up, the OS amounted to 100%; by the end of the follow-up period, it declined to 95% (Figure 1).

In patients with a history of auto-HSCT, the OS composed 100%, but 50% experienced the disease progression on the IG1kappa MA therapy after an average of 2 years of follow-up (Figure 2).

Figure 2 – Progression-free survival (PFS) of patients on daratumumab therapy (n=22).

The findings highlight the importance of daratumumab as an effective tool for managing refractory or relapsed forms of the disease. The high rates of ORR and PFS indicate this drug's potential to improve patients' long-term outcomes.

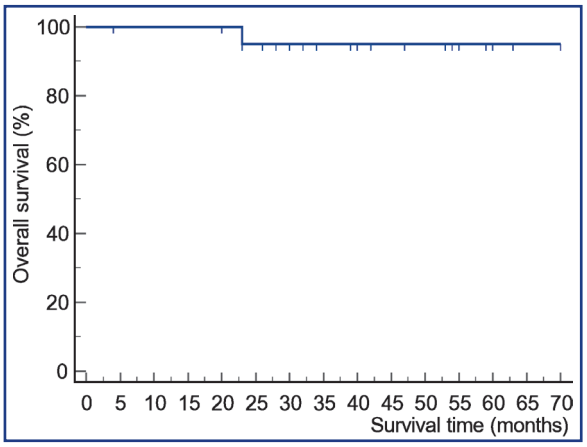

Figure 1 – Overall survival of patients with daratumumab therapy (n=22)

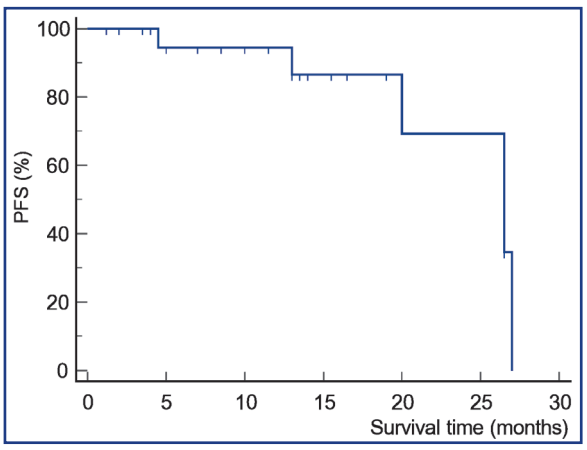

Рисунок 2

Safety profile: 72.8% of patients developed adverse reactions to daratumumab. According to Table 3, the most common side effects of anti-CD38 MA therapy were thrombocytopenia (9 patients) and anemia (7 patients). Neutropenia was observed in 5 patients, infectious complications in 2 patients, and severe neutropenia with fever in one patient required temporary treatment discontinuation. A reaction to the infusion was observed in 3 patients only at the first drug administration and did not require therapeutic intervention. This safety profile confirms that anti-CD 38 MA is a relatively safe drug, with a predominance of mild to moderate side effects. The incidence of serious adverse events was low, and most reactions did not require significant therapy changes.

Table 3 – Most common adverse events associated with Anti-CD38 MA treatment

Adverse Events Associated with Anti-CD38 MA Treatment	Total number of patients	
	Abs.	%
Neutropenia	5	22.7
Anemia	7	31.8
Thrombocytopenia	9	40.9
Pneumonia	1	4.5
Infection	2	9.1
Reaction to infusion	3	13.6

Discussion: The study results demonstrate that IG-1kappa MA is an effective treatment for patients with refractory or relapsed disease, including those who have received 3 or more lines of prior therapy, including a history of auto-HSCT [21,22]. The analysis of data from a retrospective study of 22 patients showed that the use of anti-CD38 MA both in monotherapy and in combination with other agents leads to significant improvements in clinical outcomes, including high rates of ORR and PFS. The MA safety profile was acceptable, predominating mild to moderate adverse reactions that did not require treatment discontinuation. The data of our study correlate with the world data on the therapy of refractory and relapsed MM using various treatment regimens with the inclusion of IG1kappa MA.

The studies of the MA efficacy in combination with proteasome inhibitors and immunomodulators in patients with newly diagnosed MM showed a significant improvement in PFS, complete response achievement, and a negative outcome of minimal residual disease in patients treated with daratumumab, compared to the control group [21-24]. The findings support the use of daratumumab in patients with refractory and relapsed forms of the disease and as a first-line therapy to improve clinical response and patient survival.

Conclusion: The efficacy of daratumumab in treating MM is currently beyond doubt. The use of anti-CD38 monoclonal drugs in first-line therapy has been shown to improve the OS and PFS. Numerous studies also support the potential for expanding indications, including regimens in combination with daratumumab. The analysis of the results of daratumumab use in combination regimens may provide additional evidence of its efficacy and safety, allowing for even wider use of this drug in clinical practice. Besides, further studies to identify factors that determine response to therapy and possible failures are noteworthy, which will facilitate the personalization of treatment and improvement of outcomes for patients with MM.

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АҢДАТПА

КӨПТІК МИЕЛОМАНЫ ЕМДЕУДЕ АНТИ-CD38 АНТИДЕНЕЛЕРІНІҢ ТИІМДІЛІГІН БАҒАЛАУ: РЕТРОСПЕКТИВТІК ЗЕРТТЕУДІҢ НӘТИЖЕЛЕРІ

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Өзектілігі: *Көптік миеломаны емдеудегі серпіліс моноклоналды антиденелерді қолданудың басталуымен байланысты, бұл жалпы жауап жиілігін едәуір арттырып, аурудың үдеуінсіз өмір сүру көрсеткіштерін жақсартады. Моноклоналды антиденелер мен иммуномодуляторларды біріктіріп қолдану, алдыңғы терапияның бірнеше жолдарына төзімді науқастарда да жоғары тиімділігін көрсетеді.*

Зерттеу мақсаты *– басқа препараттар кластарымен бір немесе бірнеше алдыңғы терапия жолдарынан өткен көптік миеломасы бар науқастарда анти-CD38 моноклоналды антиденесі (даратумумабты) қолдану тиімділігін зерттеу.*

Әдістері: *2018 жылдың ақпанынан 2023 жылдың қарашасына дейін даратумумаб алған рефрактерлі немесе рецидивті көптік миелома диагнозы қойылған 22 пациенттің медициналық деректеріне ретроспективті талдау жасалды. Науқастар даратумумабты монотерапия түрінде де, басқа агенттермен комбинацияда да қабылдады. Тиімділікті бағалау Миелома*

бойынша Халықаралық (IMWG) жұмыс тобының критерийлеріне сәйкес жүргізілді.

Нәтижелері: *Даратумумабпен емдеуге жалпы жауап жиілігі 59,1%-ды құрады. Екі жылдан кейінгі жалпы өмір сүру деңгейі 100%, талдау кезеңінің соңында – 95% болды. Аурудың үдеуі пациенттердің 22,7%-ында байқалды. Қауіпсіздік профилі қанағаттанарлық болды, негізгі жанама әсерлер – тромбоцитопения, анемия және нейтропения сияқты жеңіл және орташа ауырлықтағы асқынулар.*

Қорытынды: *Даратумумаб рефрактерлі немесе рецидивті көптік миелома диагнозы қойылған және бірнеше алдыңғы терапия жолдарынан өткен науқастарды емдеудің тиімді құралы болып табылады. Даратумумабпен емдеу клиникалық нәтижелерді және аурудың үдеуінсіз өмір сүруді айтарлықтай жақсартады. Бұл мәліметтер даратумумабты көптік миелома емінде қолданудың орындылығын және оның біріктірілген режимдерін әрі қарай зерттеу қажеттілігін қолдайды.*

Түйін сөздер: *көптік миелома, қайталанған/рефрактерлік көптік миелома, анти-CD38 антиденелері, моноклоналды антиденелер, даратумумаб, емдеудің тиімділігі.*

АННОТАЦИЯ

ОЦЕНКА ЭФФЕКТИВНОСТИ АНТИ-CD38 АНТИТЕЛ В ЛЕЧЕНИИ МНОЖЕСТВЕННОЙ МИЕЛОМЫ: РЕЗУЛЬТАТЫ РЕТРОСПЕКТИВНОГО ИССЛЕДОВАНИЯ

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Актуальность: *Прорыв в лечении множественной миеломы (ММ) связан с началом использования моноклональных антител, которые значительно повышают частоту общего ответа (ЧОО) и улучшают выживаемость без прогрессирования (ВБП). Комбинированные схемы с моноклональными антителами (МА) и иммуномодуляторами демонстрируют высокую эффективность у пациентов с ММ, в том числе и с рецидивирующей и рефрактерной ММ.*

Цель исследования *– изучение эффективности использования анти-CD38 моноклонального антитела у пациентов с множественной миеломой после одной или/и нескольких предшествующих линий терапии другими классами препаратов.*

Методы: *Проведен ретроспективный анализ медицинских данных 22 пациентов с рефрактерной или рецидивирующей формой ММ, получавших анти-CD 38 МА в период с февраля 2018 по ноябрь 2023 года. Пациенты получали препарат как в монотерапии, так и в комбинации с другими агентами. Оценка эффективности проводилась с использованием критериев Международной рабочей группы по миеломе (IMWG).*

Результаты: *ЧОО на лечение препаратом анти-CD 38 МА составила 59,1%. Общая выживаемость через два года составила 100%, к концу периода анализа – 95%. Прогрессирование заболевания наблюдалось у 22,7% пациентов. Профиль безопасности был допустимым, с преобладанием легких и умеренных побочных эффектов, включая тромбоцитопению, анемию и нейтропению.*

Заключение: *Препарат анти-CD 38 МА является эффективным средством для лечения пациентов с рефрактерной или рецидивирующей формой ММ, прошедших несколько линий предшествующей терапии. Лечение с использованием МА анти-CD -38 приводит к значительному улучшению клинических результатов и ВБП. Эти данные поддерживают целесообразность использования анти-CD 38 МА в терапии ММ и необходимость дальнейшего изучения его комбинированных режимов и факторов, предсказывающих лучший ответ на терапию.*

Ключевые слова: *множественная миелома, рецидивирующая/рефрактерная множественная миелома, анти-CD38 антитела, моноклональные антитела (МА), даратумумаб, эффективность лечения.*

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