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Effects of monoclonal antibody daratumumab combined with ixazomib-based treatment regimen on survival of patients with relapsed/refractory multiple myeloma

Efekti daratumumab monoklonskog antitela u kombinaciji sa režimom lečenja zasnovanim na iksazomibu na preživljavanje obolelih od relapsnog/refraktornog multiplog mijeloma

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Abstract

Background/Aim. Combination therapy with daratumumab and ixazomib has been previously used for the treatment of multiple myeloma (MM), but treatment outcomes of these drugs and safety have not yet been confirmed. The aim of the study was to assess the effects of monoclonal antibody daratumumab in combination with an ixazomib-based treatment regimen on the survival of patients with relapsed/refractory MM (RRMM). **Methods.** A retrospective study included the clinical data of 65 RRMM patients admitted from March 2016 to March 2019. The patients were divided according to different treatment regimens into two groups: Group A, with 31 patients, treated with a combination of ixazomib, dexamethasone, lenalidomide, and Group B, with 34 patients, treated with a combination of ixazomib, dexamethasone, lenalidomide, and daratumumab. Treatment outcomes, adverse reactions, quality of life, and survival were compared. **Results.** Groups A and B showed no significant differences in the objective response rate (70.97% vs. 85.29%) or the type and grade of adverse reactions ($p = 0.161$). The scores of all dimensions of the World Health Organization Quality of Life Brief Version of group B were higher than those of group A after treatment ($p < 0.05$). There was no significant difference in the one-year or three-year survival rate between group A (64.52%, 19.35%) and group B (73.53%, 32.35%) ($p = 0.432$ and $p = 0.234$, respectively). Still, group B had a significantly higher two-year survival rate than that of group A (61.76% vs. 35.48%) ($p = 0.034$). **Conclusion.** The combination of daratumumab and ixazomib-based treatment regimen helps improve the survival and quality of life of RRMM patients without increasing the incidence rate of adverse reactions during treatment.

Key words:
antineoplastic combined chemotherapy protocols; drug-related adverse effect and adverse reactions; immunotherapy; multiple myeloma; quality of life; survival; treatment outcome.

Apstrakt

Uvod/Cilj. Kombinovana terapija daratumumabom i iksazomibom je ranije korišćena za lečenje multiplog mijeloma (MM), ali rezultati lečenja ovim lekovima i bezbednost još uvek nisu potvrđeni. Cilj rada bio je da se procene efekti daratumumab monoklonskog antitela u kombinaciji sa režimom lečenja zasnovanim na iksazomibu na preživljavanje obolelih od relapsnog/refraktornog MM (RRMM). **Metode.** Retrospektivnom studijom obuhvaćeni su klinički podaci 65 obolelih od RRMM, primljenih u periodu od marta 2016. do marta 2019. godine. Bolesnici su podeljeni prema različitim režimima lečenja na dve grupe: na grupu A, koja je obuhvatila 31 bolesnika lečenih kombinacijom iksazomiba, deksametazona i lenalidomida i grupu B koja je obuhvatila 34 bolesnika lečenih kombinacijom iksazomiba, deksametazona, lenalidomida i daratumumaba. Upoređivani su ishodi lečenja, neželjene reakcije, kvalitet života i preživljavanje bolesnika. **Rezultati.** Nisu pokazane značajne razlike u objektivnoj stopi odgovora između grupa A i B (70,97% vs. 85,29%) niti u vrsti ili stepenu neželjenih reakcija ($p = 0,161$). Skorovi svih

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dimenzija Upitnika Svetske zdravstvene organizacije o kvalitetu života – kratka verzija (*World Health Organization Quality of Life Brief Version*) grupe B bili su viši od skorova grupe A posle lečenja ($p < 0,05$). Nije bilo značajne razlike u jednogodišnjoj i trogodišnjoj stopi preživljavanja između grupe A (64,52%, 19,35%) i grupe B (73,53%, 32,35%) ($p = 0,432$ i $p = 0,234$, redom). Ipak, grupa B imala je značajno višu stopu preživljavanja od grupe A (61,76% vs. 35,48%) ($p = 0,034$). **Zaključak.** Kombinacija daratumumaba i režima lečenja zasnovanog na iksazomibu poboljšava preživljavanje i kvalitet života obolelih od RRMM, bez povećanja stope incidencije neželjenih reakcija tokom lečenja.

Ključne reči:
lečenje kombinovanjem antineoplastika, protokoli; neželjena dejstva i neželjene reakcije; imunoterapija; multipli mijelom; kvalitet života; preživljavanje; lečenje, ishod.

Introduction

Multiple myeloma (MM) is a malignant tumor of plasma cells that cannot be cured at the moment by any treatment regimen. Most MM patients are in a remission-relapse-retreatment loop during treatment, and the disease eventually progresses into relapsed/refractory MM (RRMM) [1]. The diagnosis and treatment of RRMM aim to prolong the survival of patients and improve their quality of life (QoL).

Proteasomes are crucial for the degradation of proteins and the regulation of various signaling pathways [2]. The proliferation of tumor cells in MM patients has a close relationship with the signaling pathway regulating proteasomes [3]. The main pathway for the degradation of 80% of proteins lies in the ubiquitin-proteasome system. Proteasome activity is a determinant of the proliferation of myeloma cells, and this process can produce numerous proteins to increase the cell burden. In turn, these myeloma cells can activate the ubiquitin-proteasome system to maintain the protein homeostasis, which further induces dysfunction [4]. Hence, proteasomes may be the drug target of MM.

Proteasome inhibitors, immunomodulators, and hormones are commonly used in the maintenance treatment of RRMM. Ubiquitin-conjugating enzyme E2K (UBE2K) participates in the synthesis of K48-linked ubiquitin chains, which can be the target of some drugs used in the treatment of RRMM [5]. Inhibiting UBE2K expression can suppress myeloma cell proliferation, block the cell cycle, trigger cell apoptosis, and increase the production of reactive oxygen species, which can also regulate the genes related to mitosis and apoptosis. Ixazomib is a reversible proteasome inhibitor exhibiting high selectivity and anti-myeloma activity [6]. It can suppress chymotrypsin activity and induce the accumulation of ubiquitinated proteins by selectively binding to the β5 subunit of 20S proteasome, thereby impeding the proliferation and differentiation of tumor cells and playing an anti-myeloma role [7]. Wang et al. [8] reported that ixazomib shortened myeloma cell survival and facilitated cell apoptosis in a dose-dependent manner. Ixazomib can also extend the progression-free survival (PFS) of adult RRMM patients by 5.9 months [9]. In addition, Dimopoulos et al. [10] demonstrated that maintenance therapy with ixazomib prolonged the PFS of MM patients.

At present, ixazomib is approved for use in combination therapy with dexamethasone and lenalidomide. Daratumumab is a human monoclonal antibody specific for CD38, a key target for myeloma cells [11]. It was initially approved as monotherapy for RRMM and later for use in combination with other new myeloma therapies due to favorable toxic traits [12]. Li et al. [13] reported that 29.4% of MM patients selected the combined therapy with daratumumab and ixazomib. Nevertheless, their treatment outcomes and safety still need further validation.

In this study, the effect of daratumumab combined with an ixazomib-based treatment regimen on the survival of RRMM patients was assessed, aiming to provide more options and guidance for clinical maintenance treatment.

Methods

General data

A retrospective study included the clinical data of 65 RRMM patients treated from March 2016 to March 2019. According to different treatment regimens, these patients were assigned into two groups: group A with 31 patients and group B with 34 patients.

In group A, there were 19 males and 12 females, aged 42–69 years, with a mean of 55.48 ± 4.70 years. In terms of RRMM types, there were 8 cases of immunoglobulin (Ig) A, 18 cases of IgG, 2 cases of IgM, 1 case of lambda (λ) light chain, and 2 cases of kappa (κ) light chain. According to the Durie-Salmon staging system [14], the patients were classified into stage III (n = 15) and stage IIIA (n = 16). There were 6 cases in Revised International Staging System (R-ISS) Stage I, 14 in Stage II, and 11 in Stage III. Besides, 10 cases received one treatment line, 15 cases received two treatment lines, and 6 cases received three or more treatment lines. PFS and overall survival (OS) at the moment of starting the treatment were 18.2 ± 3.5 months and 42.5 ± 6.7 months, respectively.

Group B consisted of 20 males and 14 females aged 40–72 years, with a mean of 56.34 ± 4.02 years. Classified by RRMM types, there were 11 cases of IgA, 20 cases of IgG, 1 case of IgM, 1 case of IgD, and 1 case of λ light chain. Classified by the Durie-Salmon staging system, there were 17 cases in stage IIIA and 17 in stage IIIB. There were 7 cases in R-ISS Stage I, 16 in Stage II, and 11 in Stage III. Additionally, 11 cases received one treatment line, 16 cases received two treatment lines, and 7 cases received three or more treatment lines. The PFS and OS at the moment of starting treatment were 18.7 ± 3.8 months and 43.1 ± 6.3 months, respectively.

The general data displayed no statistically significant differences between the two groups ($p > 0.05$).

Inclusion and exclusion criteria

The inclusion criteria were the following: patients with RRMM diagnosed based on the diagnostic criteria of MM in the Guidelines for the Diagnosis and Management of Multiple Myeloma [15]; those with loci showing minimal response (MR) after receiving at least one of previous treatment regimens; those whose tumor progressed during treatment or within 60 days after the last treatment, or those whose tumor response rate was ≤ 25% after treatment; those aged ≥ 18 years; those with sufficient bone marrow reserves; those with complete clinical data.

The exclusion criteria were as follows: patients with plasma cell leukemia; those with monoclonal protein changes; those who were treated with daratumumab and ixazomib; those with abnormal organ enlargement; those with congestive heart failure; those complicated with myelodysplastic syndrome, uncontrollable hypertension, or hyperglycemia; those with an expected survival of < 3 months.

Therapeutic methods

Both groups received ixazomib-based treatment with a 28-day treatment model. Group A took orally 4 mg of ixazomib (4 mg, Takeda Pharma A/S) on the 1st, 8th, and 15th day, dexamethasone (20 mg, Chengdu Tiantaishan Pharmaceutical Co., Ltd.) on the 1st, 8th, 15th, and 22nd day, respectively, and lenalidomide (25 mg, Chia Tai Tianqing Pharmaceutical Group Co., Ltd. – CTTQ) once every three days from the 1st to 21st day. In addition to the medications for group A, 16 mg/kg daratumumab (15 mL, Cilag AG) was infused intravenously into group B on the 1st, 8th, 15th, and 22nd day, which was conducted once every two weeks from the 9th week and once every four weeks from the 25th week.

Observation of indicators

The treatment outcomes were evaluated according to the MM evaluation criteria [16]. The response status of loci was classified into complete response (CR), strict CR (sCR), very good partial response – PR (VGPR), PR, MR, stable disease, and progressive disease. Total objective response rate (ORR) = percentage of CR + sCR + VGPR + PR cases.

Adverse reactions (AR) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 published by the National Cancer Institute USA [17], and the safety of ixazomib and daratumumab was evaluated.

The World Health Organization Quality of Life Brief Version (WHO QOL-BREF) was utilized to assess QoL before treatment and one year after treatment. The WHO QOL-BREF measured four specific domains and one general domain, involving 26 questions, among which 24 questions were used to evaluate physical health (7 items), psychological health (6 items), social relationship (3 items), and environmental health (8 items), and the remaining 2 questions were employed to evaluate general health. Each domain scored 0–100 points, and the higher the score, the better QoL [18].

Survival was assessed after three years of outpatient or telephone follow-up until April 2022. One-, two-, and three-year survival rates of the patients were recorded.

Statistical analysis

All data were statistically analyzed using SPSS 23.0 software. Measurement data were compared between two groups using the independent samples *t*-test. Count data were expressed as percentages and compared with the Chi-squared (χ^2) test. The Kaplan-Meier method was used for survival analysis. The difference was statistically significant as $p < 0.05$.

Results

Treatment outcomes of patients in both groups are shown in Table 1. ORR showed no significant difference between groups A and B (70.97% vs. 85.29%) ($\chi^2 = 1.969$; $p = 0.161$).

There were no significant differences in the type or grade of AR between groups A and B ($p > 0.05$) (Table 2).

Prior to treatment, the QOL-BREF score was not significantly different between groups A and B ($p > 0.05$). After treatment, the physical health, psychological health, social relationship, environmental health, and general QoL scores in group B were significantly higher than those in group A ($p < 0.05$) (Table 3).

No statistically significant difference was detected in the one- or three-year survival rate between group A (64.52% and 19.35%) and group B (73.53% and 32.35%) ($p = 0.432$ and $p = 0.234$, respectively). Still, group B had a significantly higher two-year survival rate than that of group A (61.76% vs. 35.48%) ($p = 0.034$) (Table 4). Moreover, the median follow-up time was 20.32 months in group A and 24.74 months in group B, and the OS was compared between the two groups using the log-rank test, showing no significant difference ($\chi^2 = 2.154$, $p = 0.142$) (Figure 1).

Table 1

Treatment outcomes of patients in both groups

Group	CR	sCR	VGPR	PR	MR	SD	ORR
A (n = 31)	0 (0.00)	3 (9.68)	8 (25.81)	11 (35.48)	6 (19.35)	3 (9.68)	22 (70.97)
B (n = 34)	0 (0.00)	5 (14.71)	12 (35.29)	12 (35.29)	3 (8.82)	2 (5.88)	29 (85.29)
χ^2							1.969
p							0.161

CR – complete response; SCR – strict CR; VGPR – very good PR; PR – partial response; MR – minimal response; SD – stable disease; ORR – objective response rate.
Values are given as numbers (percentages).

Table 2

Type and grade of adverse reactions

Parameter	Grade 1–2		Grade 3–4		Total incidence rate		χ^2	p
	Group A	Group B	Group A	Group B	Group A	Group B		
Neutropenia	9 (29.03)	11 (32.35)	5 (16.13)	5 (14.71)	14 (45.16)	16 (47.06)	0.023	0.878
Lymphopenia	11 (35.48)	13 (38.24)	3 (9.68)	4 (11.76)	14 (45.16)	17 (50.00)	0.152	0.696
Thrombocytopenia	8 (25.81)	9 (26.47)	2 (6.45)	1 (2.94)	10 (32.26)	10 (29.41)	0.062	0.804
Cardiotoxicity	8 (25.81)	9 (26.47)	2 (6.45)	1 (2.94)	10 (32.26)	10 (29.41)	0.062	0.804
Anemia	11 (35.48)	10 (29.41)	3 (9.68)	4 (11.76)	14 (45.16)	14 (41.18)	0.105	0.746
Nausea	18 (58.06)	20 (58.82)	7 (22.58)	9 (26.47)	25 (80.65)	29 (85.29)	0.249	0.618
Vomiting	15 (48.39)	14 (41.18)	5 (16.13)	4 (11.76)	20 (64.52)	18 (52.94)	1.430	0.232
Peripheral neuropathy	5 (16.13)	5 (14.71)	1 (3.23)	0 (0.00)	6 (19.35)	5 (14.71)	0.249	0.618
Diarrhea	4 (12.90)	5 (14.71)	1 (3.23)	2 (5.88)	5 (16.13)	7 (20.59)	0.214	0.643
Constipation	7 (22.58)	6 (17.65)	1 (3.23)	3 (8.82)	8 (25.81)	9 (26.47)	0.004	0.951
Fatigue	19 (61.29)	21 (61.76)	8 (25.81)	11 (32.35)	27 (87.10)	32 (94.12)	0.954	0.329

Values are given as numbers (percentages).
Note: Group A consists of 31 patients and Group B of 34 patients.

Table 3

WHO QOL-BREF scores before and after treatment

Parameter	Values	t	p
Physical health			
Group A			
BT	36.86 ± 4.20	0.944	0.349
AT	59.63 ± 5.07		
Group B			
BT	35.89 ± 4.08	2.725	0.008
AT	63.25 ± 5.59		
Psychological health			
Group A			
BT	30.72 ± 3.47	0.541	0.590
AT	46.82 ± 4.75		
Group B			
BT	31.19 ± 3.53	2.858	0.006
AT	50.32 ± 5.09		
Social relationship			
Group A			
BT	32.75 ± 3.59	1.009	0.317
AT	31.89 ± 3.28		
Group B			
BT	61.58 ± 5.42	3.792	< 0.001
AT	66.91 ± 5.87		
Environmental health			
Group A			
BT	45.51 ± 4.82	0.553	0.582
AT	46.18 ± 4.93		
Group B			
BT	69.72 ± 6.45	2.286	0.026
AT	73.50 ± 6.84		
General health			
Group A			
BT	38.93 ± 4.05	0.099	0.921
AT	39.03 ± 4.10		
Group B			
BT	60.36 ± 5.03	3.316	0.002
AT	64.75 ± 5.59		

WHO QOL-BREF – World Health Organization Quality of Life Brief Version; BT – before treatment; AT – after treatment. Values are given as mean ± standard deviation.

For the results before vs. after treatment in the same group, $p < 0.05$ was considered statistically significant.

Table 4

Survival of patients

Group	1-year survival	2-year survival	3-year survival
A (n = 31)	20 (64.52)	11 (35.48)	6 (19.35)
B (n = 34)	25 (73.53)	21 (61.76)	11 (32.35)
χ^2	0.618	4.481	1.418
p	0.432	0.034	0.234

Values are given as numbers (percentages).

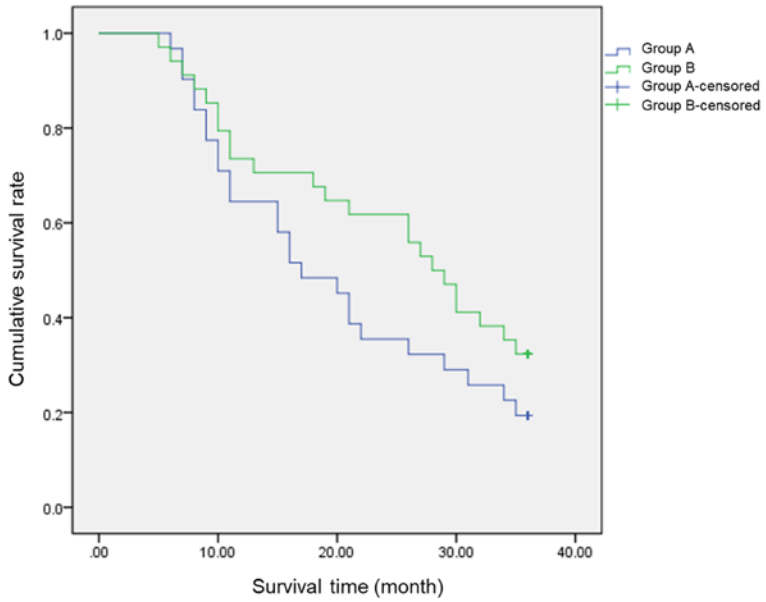

Fig. 1 – Survival curves of group A and group B.
Group A and B censored: moment when monitoring was terminated.

Discussion

In this study, groups A and B showed no significant difference in the treatment outcomes, which may be attributed to the small sample size. However, the two-year survival rate and WHO QOL-BREF score of group B were significantly higher than those of group A, which suggested that the combination of daratumumab and ixazomib-based treatment regimen can improve the prognosis of RRMM patients regarding both survival and QoL. These findings are consistent with those reported by Stege et al. [19], who observed prolonged survival and improved QoL in patients receiving ixazomib + daratumumab maintenance therapy. It is possible that daratumumab directly binds to CD38 on the surface of myeloma cells and triggers their death through multiple mechanisms [20]. As reported by Saltarella et al. [21], daratumumab resisted MM activity through the mechanisms of cytotoxicity mediated by antibody-dependent cells, antibody-dependent cell phagocytosis, complement-dependent cytotoxicity, and immunomodulation.

Ixazomib-based treatment regimen has good drug resistance in general, and the common AR include neutropenia, lymphopenia, thrombocytopenia, fatigue, nausea, and vomiting [22]. The main reason is that treatment with chemotherapy drugs for a period can inhibit the hematopoietic function of the bone marrow owing to the toxic effect [23]. Herein, we found no significant increase in the overall AR after the combination of daratumumab with an ixazomib-based treatment regimen. Similarly, Maouche et al. [24] found favorable resistance profiles with ixazomib, dexamethasone, and lenalidomide in the treatment of RRMM. Hence, the combination was safe and reliable, with most drug-related adverse events within a controllable range.

Nevertheless, this study is limited. The sample size is relatively small, so larger multicenter studies are required to investigate the observed trends further.

Conclusion

The combination of daratumumab with ixazomib-based treatment regimen can improve the survival rate and quality of life of relapsed/refractory multiple myeloma patients without leading to an obvious increase in the incidence rate of adverse reactions during treatment.

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Conflict of interest

The authors declare no conflict of interest.

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