ULOGA DARATUMUMABA U LEČENJU MULTIPLOG MIJELOMA

RAD PO POZIVU

INVITED PAPER

DARATUMUMAB FOR THE TREATMENT OF MULTIPLE MYELOMA

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SAŽETAK

Daratumumab je prvo odobreno monoklonsko antitelo koje se vezuje za CD38 protein na površini ćelija mijeloma. Istorijski gledano, standardni antimijelomski protokol bio je oralni melfalan uz prednizolon. Nešto više od dve decenije nakon toga počinje primena visokodoznog melfalana praćenog autolognom transplantacijom matičnih ćelija, što postaje standard lečenja mlađih pacijenata sa mijelomom. Istovremeno, sprovodi se profilaksa čestih i razornih skeletnih komplikacija intravenskom primenom bisfosfonata. U narednim godinama počela je nova era značajnih poboljšanja u terapiji mijeloma sa uticajem na preživljavanje starijih i/ili "frail" pacijenata imunomodulatornim lekom talidomidom, što je nastavljeno primenom njegovog manje toksičnog i efikasnijeg analoga lenalidomida. Istovremeno je u terapijske protokole uveden bortezomib, prvi u klasi inhibitora proteazoma. Uprkos poboljšanju u preživljavanju, prognoza je ostala loša za pacijente sa relapsom nakon terapije bortezomibom i lenalidomidom sa srednjim ukupnim preživljavanjem od samo 9 meseci.

Zatim se nakon početnih dozno eskalacionih studija, utvrđuje da daratumumab dovodi do produženog preživljavanja u odsustvu značajnog "ubijanja" tumorskih ćelija kroz modulaciju imunskog sistema ili mikrookruženja koštane srži. Primena daratumumaba samog ili u kombinaciji poboljšala je ishod lečenja svih pacijenata sa mijelomom bez značajnog povećanja toksičnosti. Zahvaljujući ovakvom pristupu, pacijenti sa mijelomom žive duže i imaju bolji kvalitet života. uz dalje napore za njihovo izlečenje, što predstavlja glavni terapijski cilj.

Ključne reči: daratumumab, multipli mijelom, terapija, prognoza

ABSTRACT

Daratumumab is the first approved monoclonal antibody that targets the CD38 protein on the surface of myeloma cells. Historically, a well-established anti-myeloma protocol included oral melphalan and prednisolone as the standard of care. Apart from this, in a bit longer than two decades the high dose of melphalan followed by autologous stem cell transplantation became the standard for young and fit myeloma patients. Simultaneously, the prophylactic treatment of frequent and devastating skeletal complications was improved using intravenous bisphosphonate. In the following years, there came an era of significant improvements in anti-myeloma treatment that had an impact on survival rate of elderly and/or frail myeloma patients. The treatment included immunomodulatory drug thalidomide followed by the development of a less toxic and more effective analogue lenalidomide. At the same time, bortezomib, a first-in-class proteasome inhibitor, was introduced in the therapeutic protocols. Despite these improvements in survival, the prognosis remained poor for patients relapsing after treatment with bortezomib and lenalidomide with a median overall survival of only 9 months.

After the initial dose escalation studies daratumumab resulted in a prolonged survival in the absence of significant killing of tumor cells through modulation of the immune system or the bone marrow microenvironment. The emerging picture showed that the addition of daratumumab alone or in combination improved the outcome in all myeloma patients without adding significantly to toxicity. Owing to this approach, myeloma patients live longer and have a better quality of life and there are further efforts to cure them which represents the main therapeutic goal.

Key words: daratumumab, multiple myeloma, therapy, prognosis

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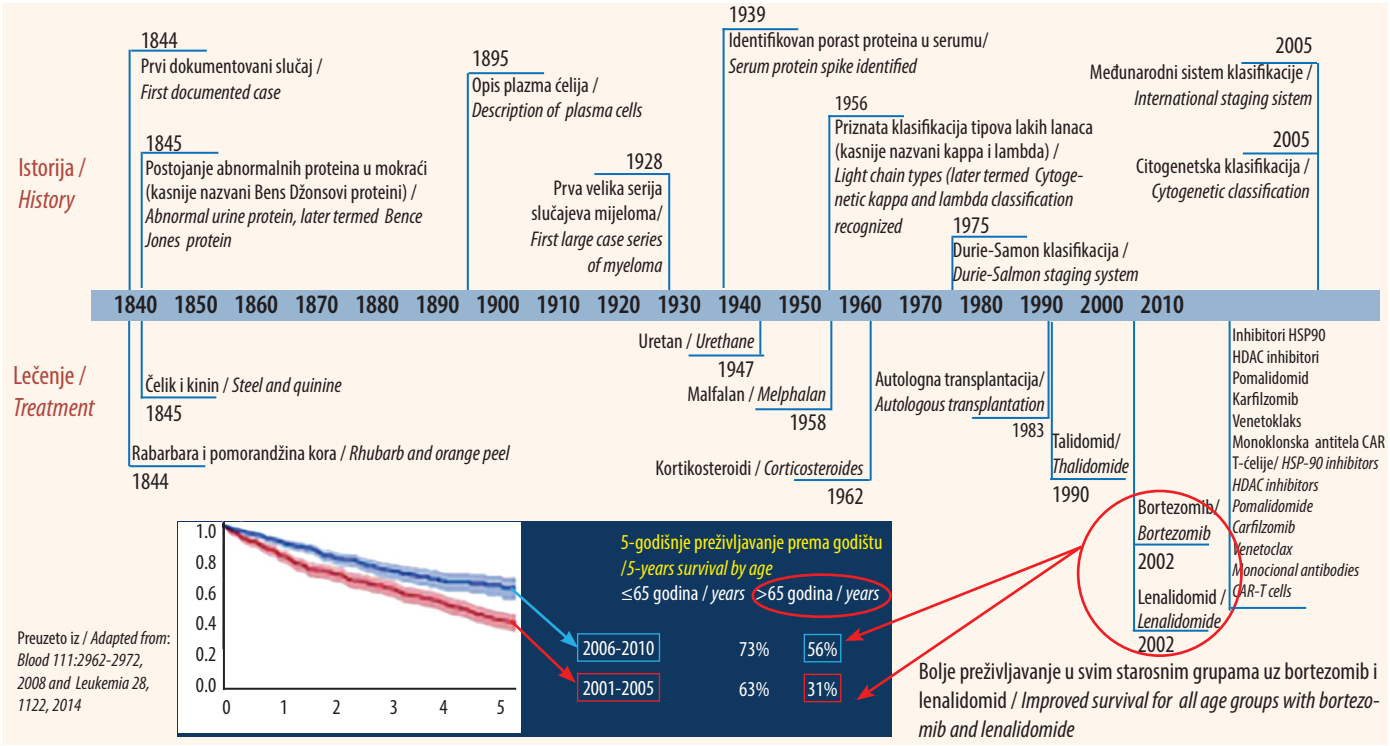
Tokom nešto više od dve decenije svedočimo velikoj promeni u lečenju multiplog mijeloma. Naslanjajući se na dobro uspostavljen režim koji podrazumeva korišćenje melfalana i prednizolona, *InterGroup Francophone du Myelome* je poboljšala ishode kod mladih i fizički zdravih pacijenata sa mijelomom koji su dobro podnosili toksičnost velikih doza melfalana [1,2]. Istovremeno, profilaktička terapija čestih i razarajućih koštanih komplikacija koje nastaju usled multioplog mijeloma unapređena je intravenskom upotrebom bisfosfonata [3]. Naredne prekretnice u unapređenju lečenja mijeloma koje bi imale uticaja na preživljavanje starijih i/ili slabih pacijenata koji boluju od mijeloma (Slika 1) najavljene su posmatranjem efekta koji je talidomid imao na lečenje mijeloma nakon čega je usledio razvoj njemu analognog lenalidomida koji je manje toksičan i efikasniji [4,5]. Istovremeno je bortezomib, prvi proteazomni inhibitor, pokazao obećavajući učinak u lečenju mijeloma [6,7].

Uprkos napretku u preživljavanju, prognoza je ostala loša za pacijente kod kojih dolazi do relapsa nakon lečenja bortezomibom i lenalidomidom, pri čemu njihovo srednje preživljavanje iznosi svega 9 meseca [8]. Lekari koji su se bavili lečenjem mijeloma sanjali su o pronalaženju antitela koje bi u potpunosti promenilo ishod kod pacijenata koji boluju od mijeloma, slično onome što je rituksimab učinio za pacijente obolele od malignog limfoma. Jedna mala dansko-holandska biotehnološka kompanija, Genmab, 2006. godine je predložila kliničko testiranje antitela CD38 (daratumu-

In a matter of a little more than two decades, we have witnessed a tremendous change in the treatment of multiple myeloma. Building on the well-established regimen of oral melphalan and prednisolone the *InterGroup Francophone du Myelome* improved the outcomes of young and fit myeloma patients that could tolerate the toxicity of high-dose melphalan [1,2]. At the same time, prophylactic treatment of frequent and devastating skeletal complications of multiple myeloma was improved by the use of intravenous bisphosphonate [3]. The next milestones of improvements of anti-myeloma treatment that would also have impact on the survival of elderly and/or frail myeloma patients (Figure 1) was heralded by the observation of anti-myeloma activity of thalidomide followed by the development of less toxic and more effective analog lenalidomide [4,5]. Simultaneously bortezomib, a first-in-class proteasome inhibitor, showed promising activity in myeloma [6,7].

Despite these improvements in survival, prognosis remained poor for patients relapsing after the treatment with bortezomib and lenalidomide with a median overall survival of only 9 months [8]. Myeloma doctors were dreaming of an antibody that could transform the outcomes for myeloma patients in a manner similar to what rituximab had accomplished for patients with malignant lymphomas. In 2006 Genmab, a small Danish-Dutch biotech company, came forward with a proposal to test a CD38 antibody (daratumumab) clinically in relapsed-refractory myeloma. The ra-



Slika 1. Istorijat i lečenje multiplog mijeloma od 1844. godine do danas

Figure 1. History and treatment of multiple myeloma from1844 to the present

maba) kod relapsirajućeg refraktornog mijeloma. To su obrazložili postojanjem jake ekspresije CD38 u ćelijama mijeloma i dokazane sposobnosti ovog antitela da *in vitro* ubije ćelije mijeloma uz postojanje sinergističkog anti-mijelomskog dejstva kada se kombinuje sa lanalidomidom ili bortezomibom [9,10]. Međutim, visoka ekspresija muktifunkcionalnog molekula CD38 u ljudskom telu i nedostatak pogodnih životinjskih modela za prekliničko testiranje potencijalne toksičnosti izazvali su zabrinutost. Situaciju je dodatno zakomplikovala nedavna katastrofa koja se dogodila prilikom kliničkog ispitivanja antitela CD38 koja je vlastima skrenula pažnju na potencijalnu opasnost koju može da izazove korišćenje monoklonskih antitela u vidu terapije [11]. Bilo je jasno da početna testiranja daratumumaba u okviru kliničkog istraživanja moraju biti pažljivo isplanirana. Kada se počelo sa testiranjem 2008. godine primenjena je strategija koja je podrazumevala davanje veoma male početne doze jednom po jednom pacijentu, uz dovoljno dugačak period posmatranja kako bi se otkrili eventualni neželjeni efekti, i malo povećanje doze antitela svakoj narednoj grupi pacijenata. Pošto je polje istraživanja bilo potpuno novo, prvobitni protokol GEN501 je dosta prilagođavan, u hodu, a do kraja je uneto čak 14 izmena. Spor napredak je bio neizbežan, a Genmab se istovremeno, poput mnogih drugih malih biotehnoloških kompanija, borio da preživi usled finansijskih problema. Tokom prve četiri godine, u istraživanje je uključeno svega 23 pacijenta.

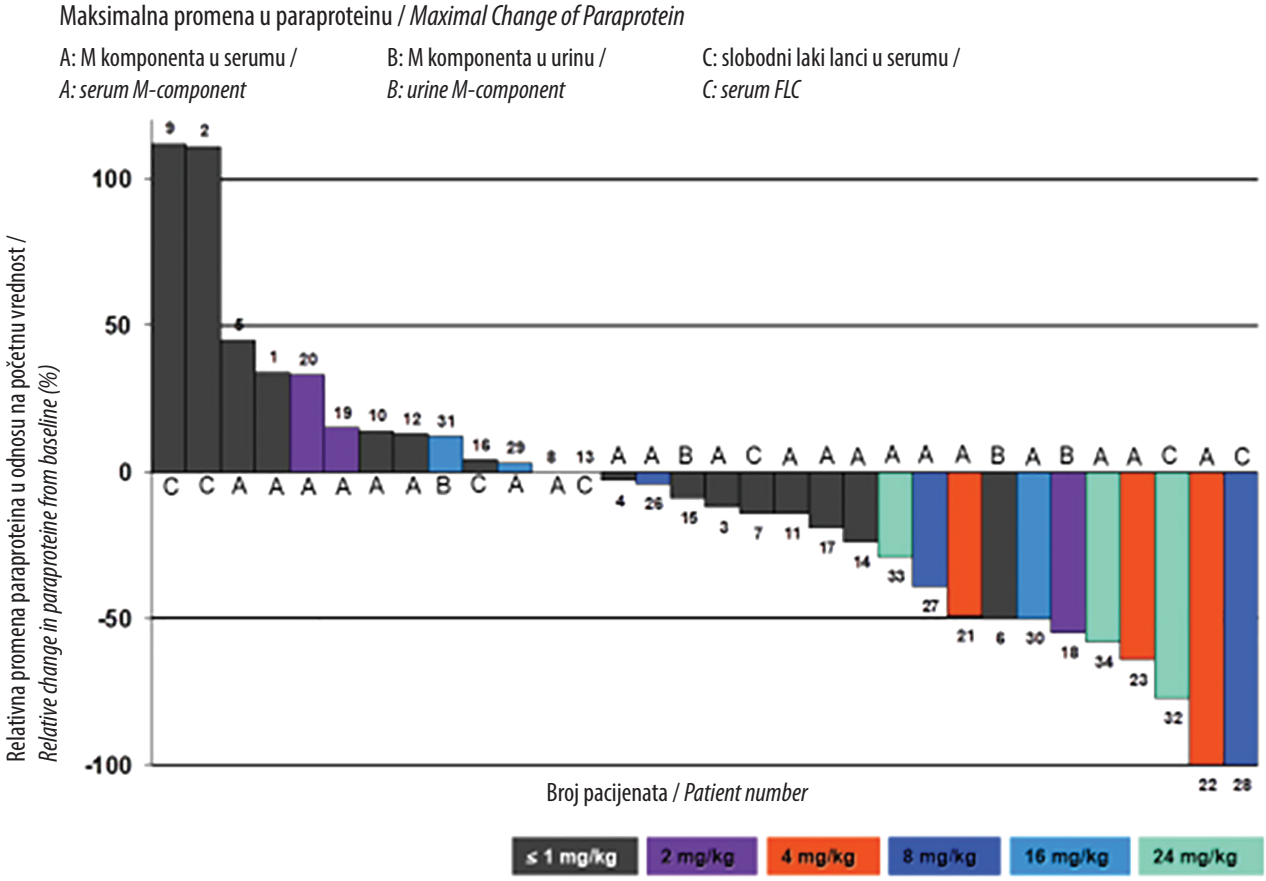
Uprkos postovanju zajedničkog sna o tome da će jednoga dana biti pronađen „rituksimab za mijelom", prevladao je skepticizam i kada su predstavljeni prvi rezultati iz GEN501na ASH 2011 za njih je pokazano veoma malo interesovanje, a citiranost je bila na nuli. Naredne godine, doza daratumumaba je porasla na 2 i 4 mg/kg telesne težine i odgovor je počeo da se nazire. To je promenilo celokupnu sliku i na ASH 2012 rezultati iz GEN501 privukli su znatnu pažnju, a bilo je 23 citata (Grafikon 1) (Genmab: Podaci u dosijeu). Shodno tome, ubrzano je uključivanje pacijenata u istraživanje, a u Severnoj Americi započeto je prateće istraživanje (SIRIUS), kao i kombinovane studije sa lenalidomidom i bortezomibom.

Monoterapija daratumumabom značajno je poboljšala preživljavanje. Ciljana populacija je imala srednje preživljavanje 20 meseci, ali još je zanimljivija činjenica da je daratumumab produžio ukupno preživljavanje 52% pacijenata kod kojih nije bilo formalnog odgovora prema kriterijumima koje je propisala IMWG (International Myeloma Working Group), već samo stabilizacije bolesti ili minimalnog odgovora, na 18.5 meseci [12-14] (Grafikon 2). Ovo je bilo dvotruko veće preživljavanje od očekivanog u to vreme za pacijente

tionale was a strong expression of the CD38 target by myeloma cells and demonstration of the ability of the antibody to kill myeloma cells in vitro along with synergistic anti-myeloma activity when combined with lenalidomide or bortezomib [9,10]. However, wide expression of the multifunctional CD38 molecule in the human body and a lack of suitable animal models for preclinical testing of potential toxicities caused worries. Furthermore, the situation was complicated by a recent disaster in a clinical trial of a CD28 antibody that alerted the authorities to the potential danger of using monoclonal antibodies for therapy [11]. It was clear that the initial testing of daratumumab in a clinical trial had to be planned with great care. A very low starting dose, one patient included at a time with a sufficient observation period to detect potential side effects, and small increments of the dose of antibody from each cohort of patients to the next was the strategy, when starting up in 2008. Since the field was entirely new, many adjustments of the first protocol GEN501 had to be made along the way coming up to a total of 14 amendments to the protocol. Slow progress was inevitable and at the same time, Genmab, like many small biotech companies, was fighting for its life due to financial constraints. In the first 4 years of the trial only 23 patients were enrolled.

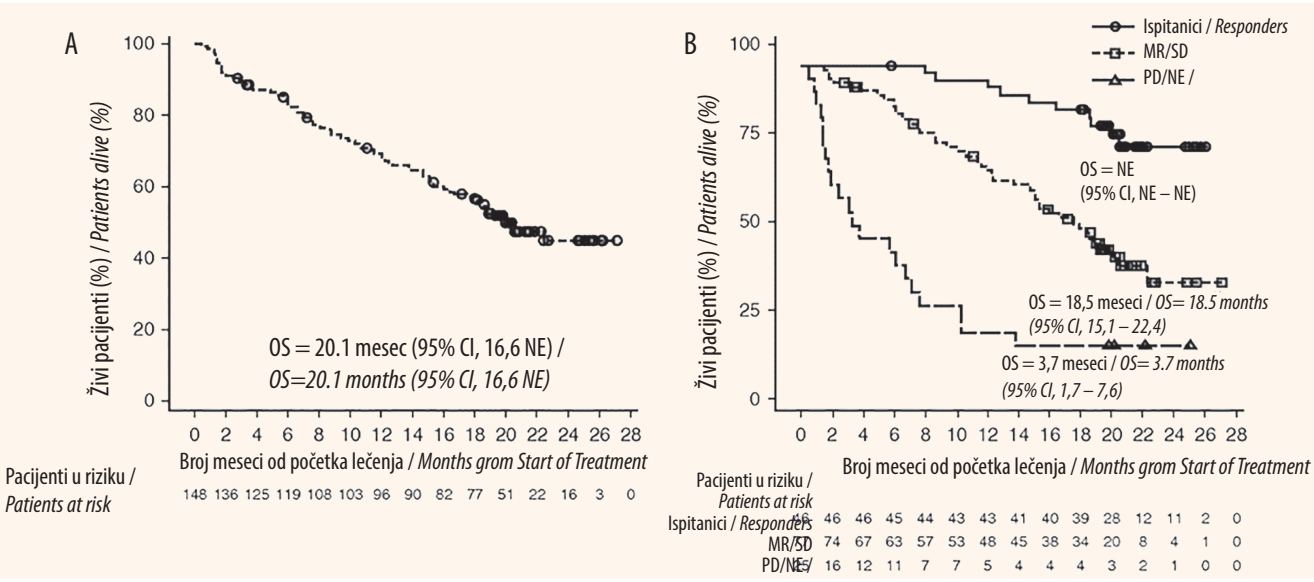
Despite a common dream of having a "rituximab for myeloma" one day, skepticism prevailed, and when the first data from GEN501 were presented at ASH 2011 it received very little interest and zero citations. The following year, dosing of daratumumab passed 2 and 4 mg/kg of body weight and the first signs of a response started to appear. This changed the whole picture, and at ASH 2012 the results of GEN501 received considerable interest and 23 citations (Chart 1) (Genmab: Data on file). Consequently, enrolment of patients into the trial accelerated and a companion study (SIRIUS) in North America and combination studies with lenalidomide and bortezomib were launched.

As monotherapy, daratumumab improved survival considerably. The intention to treat population had a median overall survival of 20 months, but perhaps most interestingly, daratumumab also prolonged the overall survival of the 52% of patients that did not obtain a formal response according to IMWG criteria, but only stable disease or a minor response, to 18.5 months [12-14] (Chart 2). This was a doubling of the survival that could be expected at that time for patients refractory to bortezomib and lenalidomide [8]. The reason for this extension of survival in the absence of significant killing of tumor cells is not well understood, but modulation of the immune system or the bone marrow microenvironment are likely explanations.



Grafikon 1. Prvo kliničko istraživanje upotrebe daratumumaba na ljudima GEN501 započelo je u martu 2008. godine. Regrutacija je u početku išla veoma sporo i samo 23 pacijenta uključeno je u projekat tokom prve četiri godine. Sa prvim znacima kliničke aktivnosti pri dozi od 2 i 4 mg/kg koja je predstavljena na ASH 2012 interesovanje je značajno poraslo, ubrzano je uključivanje novih pacijenata i prateće istraživanje (SIRIUS) pokrenuto je u Severnoj Americi (Genmab: Podaci u dosijeu).

Chart 1. The first human clinical trial with daratumumab GEN501 started in March 2008. The recruitment was initially very slow with only 23 patients enrolled in 4 years. With the first sign of clinical activity at 2 and 4 mg/kg presented at ASH 2012 interest increased considerably, recruitment for the trial accelerated and a companion study (SIRIUS) was initiated in North America (Genmab: Data on file)



Grafikon 2. Monoterapija daratumumabom poboljšala je ukupno preživljavanje i kod ispitanika i kod pacijenata kod kojih je odgovor bio minimalan (MR) ili je došlo do stabilizacije bolesti (SD) (52%)

Chart 2. Daratumumab monotherapy improved overall survival both for responders (31%) and for patients obtaining only MR or SD (52%)

otporne na bortezomib i lenalidomid [8]. Razlog za ovo produženje preživljavanja uprkos činjenici da ćelije tumora nisu ubijene nije potpuno jasan, ali moguća objašnjenja mogu biti modulacija imunog sistema ili koštano mikrookruženje.

Narednih godina bismo mogli biti svedoci veoma aktivnog razvoja programa za upotrebu daratumumaba zahvaljujući saradnji kompanija Genmab i Janssen. Daratumumab je korišćen u svim terapijskim linijama i u kombinaciji sa svim najvažnijim lekovima koji se koriste za lečenje mijeloma. Pokazalo se da je uvođenje daratumumaba u terapiju poboljšalo ishod lečenja u svim slučajevima bez značajnijeg povećanja toksičnosti. Utvrđeno je da je rizik od razvoja pojave neutropenije i infekcija u blagom porastu, ali stvari se mogu dovesti u ravnotežu uz pomoć adekvatne nege. Reakcije izazvane infuzijom bile su prisutne kod otprilike polovine pacijenata prilikom prve primene infuzije, ali nakon togsu se retko javljale, i bile su blage. Dostupnost subkutanog daratumumaba povoljno je uticala na reakcije usled primene infuzije i olakšala je primenu leka.

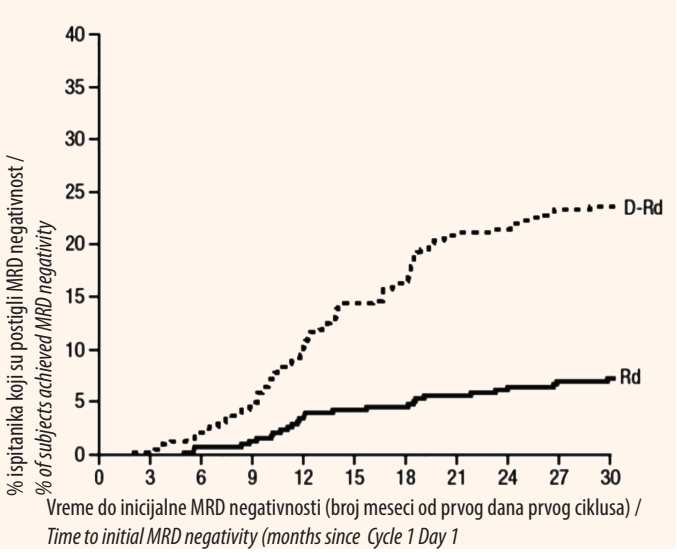
Kako trenutno postoji više opcija za lečenje pacijenata sa relapsnim refraktornim mijelomom sve je teže prikazati poboljšanje ukupnog preživljavanja u kliničkim istraživanjima, iako je nedavno otkriveno da postoji korist za preživljavanje kod pacijenata koji primaju daratumumab u istraživanjima ALCYONE, POLLUX, CASTOR i MAIA [15-18].

Zabrinutost da bi sveukupna korist za preživljavanje ostvarena u jednoj liniji terapije mogla loše da se odrazi na ishod naredne linije terapije nije potvrđena u praksi. Naprotiv, korist za preživljavanje dobijena upotrebom daratumumaba preneta je u sledeću liniju terapije kao što je pokazano u PFS-2 u okviru istraživanja MAIA (Slika 3) [18]. Takođe se pokazalo da produženo lečenje daratumumabom dovodi do progresivnog produbljivanja remisije što se odražava negativnošću minimalne rezidualne bolesti (MRD) (Grafikon 4) [19].

U okviru studije CASSIOPEIA pokazano je da se dodavanjem daratumumaba indukcionom tretmanu pre autologne transplantacije matičnih ćelija, kao i kasnije terapiji održavanja povećava preživljavanje bez progresije (PFS) i stopa negativnosti minimalne rezidualne bolesti (MRD) [20].

Pored potrebe za dugoročnim lečenjem, važno je primetiti da se tokom lečenja daratumumabom kvalitet života postepeno popravlja [21]. Pošto se daratumumab veoma dobro podnosi, i kao jedini lek i u kombinaciji sa drugim lekovima, i oslabljeni stariji pacijenti mogu imati koristi od lečenja.

Daratumumab deluje na više različitih načina, ali nije poznato koji načini su najvažniji, dok su razlozi za izostanak odgovora na lečenje daratumumabom ili



Grafikon 3. Stopa MRD negativnosti u rendomiziranom istraživanju MAIA

Chart 3. Rate of MRD negativity (10-5) in the intention to treat population of the MAIA trial.

In the following years, we could witness a very active development program for daratumumab owing to collaboration between Genmab and Janssen. Daratumumab was used in all lines of therapy and in combination with all most important drugs used for the treatment of myeloma. The emerging picture showed that the addition of daratumumab improved the outcome in all cases without adding significant toxicity. A slight increase in the risk of neutropenia and infections has been found, but this can be counterbalanced by appropriate supportive care. Infusion-related reactions were seen in about half of the patients during the first infusion but rarely thereafter and were mild in nature. The infusion -related reactions and the ease of administration have been improved by the availability of a subcutaneous formulation of daratumumab.

In the present scenario of multiple treatment options for patients with relapsed refractory myeloma it is increasingly difficult to demonstrate improved overall survival in clinical trials, but recently an overall survival benefit was found for patients receiving daratumumab both in the ALCYONE, the POLLUX, the CASTOR, and the MAIA trial [15-18].

Worries that an overall survival benefit in one line of therapy might translate into a poorer outcome of the subsequent line of therapy were not supported. On the contrary, the survival benefit from daratumumab was carried forward into the subsequent line of therapy as shown by the PFS-2 of the MAIA trial (Figure 2) [18]. It has also been shown that prolonged treatment with daratumumab will result in progressive deepening of remission as reflected by MRD negativity (Figure 3) [19].

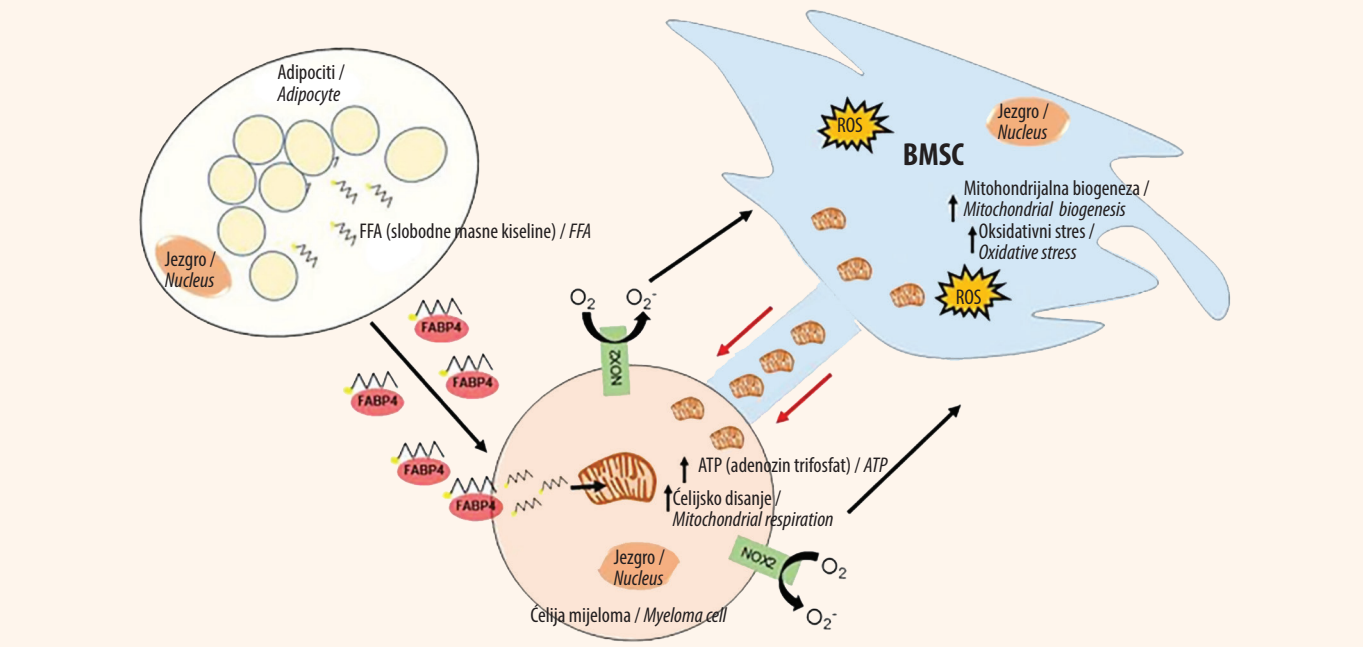
nestanak početnog odgovora nejasni. Neki od načina delovanja daratumumaba (citotoksičnost zavisna od komplementa (CDC), ćelijska citotoksičnost zavisna od antitela (ADCC) i ćelijska fagocitoza zavisna od antitela (ADCP)) zavise od jačine ekspresije CD38. Slaba ekspresija CD38 može negativno da utiče na ove načine delovanja, a do nje može doći vremenom s obzirom na to da primena leka daratumumab smanjuje ekspresiju CD38 u ćelijama mijeloma [22,23]. S druge strane, smanjen nivo CD38 može imati i pozitivan efekat. Stvaranje imunosupresivnog adenozina je ometeno u mikrookruženju koštane srži [24]. Oslabljeno je potencijalno zaštitno pričvršćivanje ćelije mijeloma za stromu [25]. Osim toga, blokirno je stvaranje nanotuba koje povezuju stromalne ćelije sa ćelijama mijeloma i prenose mitohondrije koje daju energiju ćelijama mijeloma (Slika 2) [26].

U kliničkoj praksi, brz početni odgovor na daratumumab je često praćen dugim periodom sporog ali postojanog opadanja M-proteina. U teoriji, za brz početni odgovor na daratumumab mogu biti zaslužni CDC, ADCC i ADCP koje najbolje funkcionišu kada je ekspresija CD38 visoka. Nakon toga može uslediti dug period u kojem značajniju ulogu imaju reprogramiranje imunog sistema i modulacija mikrookruženja do kojih dolazi zahvaljujući smanjenom stvaranju adenozina, slabijem pričvršćivanju ćelija mijeloma za stromu, ometanju stvaranja nanotuba i eleminaciji regulatornih T, B i M ćelija [27].

The CASSIOPEIA study has revealed that adding DARA to the induction treatment before autologous stem-cell treatment and to the consolidation treatment afterwards increases the PFS and the rate of MRD negativity [20].

Along with a need for a long-term treatment it is important to notice that the quality of life is improving over time during treatment with Daratumumab [21]. Since daratumumab is so well tolerated both as a single agent and combined, frail elderly patients obtain benefits from the treatment as well.

Daratumumab has multiple modes of action but it is unknown which are the most important and the reason for failure to respond to treatment with daratumumab or loss of response are obscure. Some of daratumumab´s modes of action (complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)) depend on the level of CD38 expression. These modes of action may be impaired by a low level of expression of CD38, which may occur with time as treatment with daratumumab reduces the expression of CD38 by myeloma cells [22,23]. On the other hand, the reduced level of CD38 may also be beneficial. The formation of immunosuppressive adenosine is inhibited in the bone marrow microenvironment [24]. Potentially protective adhesion of myeloma cells to stroma is impaired [25]. Apart from this, the formation of nanotubes connecting stromal cells with myeloma



Slika 2. Mitohondrije se prenose od stromalnih ćelija do ćelija mijeloma putem međusobno povezanih nanotuba koje obezbeđuju energiju i jačaju maligni fenotip ćelija mijeloma. Stvaranje nanotuba zavisi od CD38 i može biti blokirano od strane CD38 antitela (prilagođeno i preuzeto iz Oncoscience 4, 173, 2017).

Figure 2. Mitochondria are transferred from stromal cells to myeloma cells trough interconnecting nanotubes providing energy and boosting the malignant phenotype of the myeloma cell. The formation of nanotubes is dependent on CD38 and may be blocked by CD38 antibody (modified and reprinted from Oncoscience 4, 173, 2017)

Uvođenje daratumumaba u protokol lečenja pacijenata sa mijelomom predstavlja retku kombinaciju efikasnog načina lečenja i lečenja koje se dobro podnosi. Zajedno sa imunomodulatornim lekovima i proteazomnim inhibitorima, daratumumab predstavlja prvi veliki korak dalje od staromodne terapije zasnovane na alkilatorima ka novom dobu u kome je imuni sistem podešen tako da može da se bori protiv mijeloma. Kao rezultat toga, pacijenti oboleli od mijeloma živeće duže i bolje kako se budemo sistematski kretali ka svom cilju izlečenja mijeloma.

Sukob interesa: Nije prijavljen.

cells and transferring energizing mitochondria to the myeloma cells is blocked (Figure 2) [26].

In clinical practice, a rapid initial response to daratumumab is often followed by a long period with a slow but steady decline of the M-protein over time. In theory, the rapid initial response to daratumumab could be due to CDC, ADCC and ADCP that work best when CD38 expression is high. This may be followed by a long period where reprogramming of the immune system and modulation of the microenvironment by reduced formation of adenosine, impaired adhesion of myeloma cells to stroma, inhibition of formation of nanotubes and elimination of regulatory cells of the T, B and M cell systems become more important [27].

The introduction of daratumumab in the treatment of patients with myeloma offers a rare combination of a very efficient and well-tolerated new treatment modality. Together with the immunomodulatory drugs and proteasome inhibitors, it represents the first major step away from old-fashioned alkylator based therapy towards a new era where the immune system is tuned to cope with myeloma. As a result, myeloma patients will survive longer and live better lives as we systematically move forward towards the goal of curing myeloma.

Conflict of interest: None declared.

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