PLAZMOCITNA LEUKEMIJA

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PLASMA CELL LEUKEMIA

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SAŽETAK

Plazmocitna leukemija je veoma retka i agresivna forma plazmocitne diskrazije koju odlikuje loša prognoza, kratko preživljavanje i loš odgovor na primenjenu terapiju. Kliničke manifestacije su različite, ali se najčešće sreće ekstramedularna forma bolesti, hiperkalcemija, anemija, trombocitopenija, oštećenje bubrežne funkcije i povećanje koncentracije laktat dehidrogenaze. Postoje brojne citogenetske abnormalnosti koje dovode do veće proliferacije, inhibicije apoptoze, promene u ekspresiji adhezivnih molekula i hemokinskih receptora. I pored uvođenja novih terapijskih modaliteta zasnovanih na primeni bortezomiba i imunomodulatornih lekova, kao i primeni biološke terapije, terapijski ishod je još uvek nezadovoljavajući.

Ključne reči: plazmocitna leukemija, citogenetske abnormalnosti, imunomodulatorni lekovi

ABSTRACT

Plasma cell leukemia (i.e., plasmacytic leukemia) is a very rare and aggressive form of plasma cell dyscrasia characterized by a poor prognosis, short survival time, and a poor response to the administered therapy. Clinical manifestations vary, however, the extramedullary form of the disease is the most common, as are hypercalcemia, anemia, thrombocytopenia, impaired renal function, and increased lactate dehydrogenase concentration. Numerous cytogenetic abnormalities lead to greater proliferation, inhibition of apoptosis, and changes in the expression of adhesion molecules and chemokine receptors. Despite the introduction of new therapeutic modalities based on bortezomib, immunomodulatory drugs, and biological therapy, the therapeutic outcome is still unsatisfactory.

Keywords: plasma cell leukemia, cytogenetic abnormalities, immunomodulatory drugs

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UVOD

Plazmocitna leukemija predstavlja retku i veoma agresivnu formu plazma ćelijske diskrazije. U većini plazma ćelijskih diskrazija maligni plazmociti naseljavaju koštanu srž gde stupaju u brojne ćelijske i humoralne interakcije za mikro sredinom koštane srži [1]. Povremeno, plazmociti mogu da napuste koštanu srž i da se nađu u perifernoj krvi, odakle potencijalno mogu da nasele i parenhimatozne organe. Nalaz plazmocita u perifernoj krvi nije ujedno i dovoljan kriterijum za postavljanje dijagnoze plazmocitne leukemije. Naime, ranije definisani dijagnostički kriterijumi za plazmocitnu leukemiju, kao što je postojanje najmanje 20% plazmocita među leukocitima periferne krvi ili više od 2 x 10^9/L plazmocita u perifernoj krvi, redefinisani su nedavno, pa je tako, od 2013. godine, Međunarodna radna grupa za mijelom (engl. *Interenational Myeloma Working Group – IMWG*) potvrdila da je za dijagnozu neophodno najmanje 5% plazmocita u perifernoj krvi [2,3]. Incidencija plazmocitne leukemije u Evropi je oko 0,04 pacijenta na 100.000 stanovnika, a takođe se sreće kod 2%–4% obolelih od multiplog mijeloma [1,4]. Bolest se karakteriše kratkim periodima remisije i ranim relapsima. Stoga je i očekivano kratko preživljavanje – petogodišnje preživljavanje je oko 10%, uz napomenu da je nešto bolje kod pacijenata sa primarnom plazmocitnom leukemijom [5].

Plazmocitna leukemija može biti primarna – javlja se kao „de novo" bolest (1%–2% bolesnika sa multiplim mijelomom) i sekundarna – predstavlja leukemijsku transformaciju refraktornog multiplog mijeloma ili se javlja kod relapsa multiplog mijeloma (incidencija 2%–9%) [6]. Bez obzira da li se radi o primarnoj ili sekundarnoj plazmocitnoj leukemiji, prognoza je veoma loša. Biologija i kliničke manifestacije primarne i sekundarne plazmocitne leukemije se razlikuju (Tabela 1). Naime, pacijenti sa primarnom plazmocitnom leukemijom pokazuju bolji terapijski odgovor ako se leče agresivnom hemioterapijom i autologom transplantacijom matičnih ćelija hematopoeze ali se, na žalost, vrlo brzo registruju i recidivi bolesti koji su najčešće refraktorni na terapiju [4]. Sa druge strane, sekundarna plazmocitna leukemija pokazuje znatno lošiji terapijski odgovor (manje od 50% pacijenata) sa vrlo brzim fatalnim ishodom [1]. Kao posledica uvođenja novih terapijskih modaliteta i povećanja prosečne dužine života pacijenata obolelih od multiplog mijeloma, učestalost sekundarne plazmocitne leukemije je u porastu [4]. Ovaj porast učestalosti sekundarne plazmocitne leukemije se može objasniti i povećanom prevalencijom obolelih od multiplog mijeloma, što je posledica produžetka dužine života, kao i primenom više terapijskih linija u toku lečenja multiplog mijeloma, što može doprineti

INTRODUCTION

Plasma cell leukemia (i.e., plasmacytic leukemia) is a rare and exceptionally aggressive form of plasma cell dyscrasia. In most plasma cell dyscrasias, malignant plasma cells infiltrate the bone marrow, engaging in numerous cellular and humoral interactions with the bone marrow microenvironment [1]. Occasionally, plasma cells can leave the bone marrow and enter the peripheral blood, where they can potentially colonize parenchymal organs. The finding of plasma cells in the peripheral blood is not a sufficient criterion for establishing a diagnosis of plasma cell leukemia. Namely, previously defined diagnostic criteria for plasma cell leukemia, such as the existence of at least 20% of plasma cells among peripheral blood leukocytes or more than 2 x 10^9/L plasma cells in peripheral blood, have been redefined recently, consequently, as of 2013, the International Myeloma Working Group (IMWG) has confirmed that the presence of at least 5% of plasma cells in peripheral blood is necessary for diagnosis [2,3]. The incidence of plasma cell leukemia in Europe is about 0.04 patients per 100,000 inhabitants, and it is also found in 2%–4% of patients with multiple myeloma [1,4]. The disease is characterized by short periods of remission and early relapses. Therefore, a short survival time is expected - the five-year survival is around 10%, however, it should be noted that it is slightly better in patients with primary plasma cell leukemia [5].

Plasma cell leukemia can be primary, occurring as a *de novo* disease (1%-2% of patients with multiple myeloma) and secondary, representing the leukemic transformation of refractory multiple myeloma or occurring in relapsed multiple myeloma (incidence 2%-9%) [6]. Regardless of whether it is primary or secondary plasma cell leukemia, the prognosis is poor. The biology and clinical manifestations of primary and secondary plasma cell leukemia differ (Table 1). Namely, patients with primary plasma cell leukemia show a better therapeutic response if they are treated with aggressive chemotherapy and autologous hematopoietic stem cell transplantation. However, unfortunately, relapses of the disease, which are most often refractory to therapy, are also registered within a short space of time [4]. On the other hand, secondary plasma cell leukemia shows a significantly worse therapeutic response (less than 50% of patients) with a swift fatal outcome [1]. Due to the introduction of new therapeutic modalities and the increase in the average life expectancy of patients suffering from multiple myeloma, the frequency of secondary plasma cell leukemia is increasing [4]. This increase in the frequency of secondary plasma cell leukemia can be explained by the higher prevalence of patients with multiple myeloma, which is a conse-

Tabela 1. Revised Cardiac Risk Index-Lee kriterijumi

	Primarna plazmocitna leukemija	Sekundarna plazmocitna leukemija
Epidemiologija	Javlja se u mlađem životnom dobu	Javlja se u starijem životnom dobu
Kliničke i laboratorijske karakteristike	- Česta ekstramedularna bolest - Visoka koncentracija kreatinina - Visoka koncentracija beta-2-mikroglobulina	- Česta koštana bolest
Molekularne karakteristike	- Uglavnom hipodiploidna - Česta translokacija 11;14	- Uglavnom hiperdiploidna - Česte translokacije 11;14, 4;14, 14;16
Preživljavanje	Duže	Kraće

Table 1. Revised Cardiac Risk Index-Lee Criteria

	Primary plasma cell leukemia	Secondary plasma cell leukemia
Epidemiology	Occurs at a younger age	Occurs in old age
Clinical and laboratory characteristics	- Frequent extramedullary disease - High creatinine concentration - High concentration of beta-2-microglobulin	- Frequent bone disease
Molecular characteristics	- Mostly hypodiploid - Frequent translocation 11;14	- Mostly hyperdiploid - Frequent translocations 11;14, 4;14, 14;16
Survival	Longer	Shorter

klonskoj selekciji i novim genetskim promenama [7]. Ipak, i pored toga, primarna plazmocitna leukemija je češća forma bolesti i čini oko 60%–70% pacijenata [2].

Biologija plazmocitne leukemije

Jedna od osnovnih karakteristika većine plazma ćelijskih diskrazija je proliferacija malignih plazmocita uglavnom u koštanoj srži. Zahvaljujući adhezivnim molekulima eksprimiranim na plazmocitima i ćelijskim interakcijama sa mikrosredinom koštane srži, ovi maligni plazmociti ostaju najčešće locirani u koštanoj srži. Kod plazmocitne leukemije, zbog promenjene ekspresije pojedinih adhezivnih molekula, maligni plazmociti lako napuštaju koštanu srž, ulaze u perifernu krv i naseljavaju parenhimatozne organe [8]. Ćelije plazmocitne leukemije pokazuju smanjenu ekspresiju *NCAM* (*neural cell adhesion molecule CD56*) molekula, kao i *LFA* (*leukocyte function associated antigen-1*), *VLA-5* (*very late antigen 5*), *CD9, CD82* i drugih adhezivnih molekula, čime se smanjuje vezivanje ćelija plazmocitne leukemije za stromalne ćelije koštane srži i tako olakšava migracija u perifernu krv [9,10].

Postojanje brojnih citogenetskih aberacija je tipično za ćelije plazmocitne leukemije. Naime, ćelije plazmocitne leukemije su najčešće diploidne ili hipoploidne (oko 80%) dok su plazmociti u multiplom mijelomu najčešće hiperdiploidni [3,5]. Najčešće citogenetske aberacije koje se javljaju u ćelijama plazmocitne leukemije su delecija hromozoma 13 i monozomija i sreću se kod više od 85% obolelih [5,10]. Abnormalnost hromozoma 1 (delecija ili amplifikacija) su takođe če-

quence of the extension of life expectancy, as well as the use of more therapeutic lines during the treatment of multiple myeloma, which can contribute to clonal selection and new genetic changes [7]. Nevertheless, primary plasma cell leukemia is the more common form of the disease and accounts for about 60%–70% of patients [2].

Biology of plasma cell leukemia

One of the main characteristics of most plasma cell dyscrasias is the proliferation of malignant plasma cells mainly into the bone marrow. Due to adhesion molecules expressed in plasma cells and cellular interactions with the bone marrow microenvironment, these malignant plasma cells most often remain in the bone marrow. In plasma cell leukemia, due to the altered expression of certain adhesion molecules, malignant plasma cells easily migrate from the bone marrow, enter the peripheral blood, and inhabit parenchymatous organs [8]. Plasmacytic leukemia cells show a reduced expression of NCAM molecules (neural cell adhesion molecule CD56), as well as of LFA (leukocyte function associated antigen-1), VLA-5 (very late antigen 5), CD9, CD82, and other adhesion molecules, thereby reducing the binding of plasmacytic leukemia cells to bone marrow stromal cells and consequently facilitating migration into the peripheral blood [9,10].

The presence of numerous cytogenetic aberrations is typical for plasmacytic leukemia cells. Namely, plasmacytic leukemia cells are most often diploid or hypoploid (about 80%), while plasmacytes in multiple

ste kod obolelih od plazmocitne leukemije, naročito kod primarne forme bolesti [5,11,12]. Kod većine ćelija plazmocitne leukemije se sreće translokacija t(14;16) i delecija 17p, čime se objašnjava i česta translokacija IgH kao i ekspresija ciklina D1 [4]. Translokacije t(11;14) i t(4;14) se javljaju sa približno istom učestalošću kao kod obolelih od multiplog mijeloma [4]. Primenom najsavremenijih metoda molekularnog ispitivanja utvrđena je visoka učestalost mutacija TP53 i K/NRAS gena [5]. Značaj svake od ovih detektovanih citogenetskih abnormalnosti je još uvek nedovoljno poznat, mada se smatra da su povezane sa agresivnijim kliničkim tokom bolesti i lošijom prognozom.

Kliničke manifestacije

Klinička slika obolelih od plazmocitne leukemije se u izvesnoj meri razlikuje od multiplog mijeloma. Prosečna starost obolelih od plazmocitne leukemije je 61 godina, što je oko 10 godina manje nego prosečna starost obolelih od multiplog mijeloma [4]. Većina obolelih od plazmocitne leukemije ima veliku tumorsku masu koja uzrokuje gubitak u telesnoj težini, povremeno noćno preznojavanje, simptome bubrežne insuficijencije, anemije, te hemoragijski sindrom. Naime, zbog velike tumorske mase i najčešće masivne infiltracije koštane srži pacijenti imaju izraženu anemiju i trombocitopeniju. Pored toga, veoma često postoji infiltracija perifernih organa pa se javljaju hepatosplenomegalija i limfadenopatija, kao i infiltracija pluća, pleure, testisa, centralnog nervnog sistema i mišića uz postojanje simptoma i kliničkih znakova tipičnih za infiltrovana tkiva [3-6,8-10]. Bol u kostima i osteolizne lezije se javljaju nešto ređe nego kod obolelih od multiplog mijeloma [3-6,8-10].

Laboratorijski nalaz

Zbog infiltracije koštane srži, najveći broj obolelih od plazmocitne leukemije pokazuje postojanje normocitne anemije (oko 80%) i trombocitopenije (oko 60%), a često postoji i leukocitoza uz apsolutnu plazmocitozu (iznad 2 x 10^9/L) [4,6]. Kod većine obolelih javlja se *rouleaux* fenomen u perifernom razmazu [4,6].

U biohemijskim analizama, najčešće se registruju povećana serumska aktivnost laktat dehidrogenaze i beta-2-mikroglobulina, hiperkalcemija i povećanje serumske koncentracije kreatinina i uree [6,7]. Kod većine bolesnika se registruje postojanje M-komponente u serumu i to najčešće u klasi IgG (oko 50%), kao i IgA (oko 15%), dok su IgD i IgE veoma retki [6]. Kod oko 80% obolelih od plazmocitne leukemije sreće se Bens Džonsova proteinurija [6].

Biopsija koštane srži obično pokazuje masivnu infiltraciju ćelijama plazmocitne leukemije uz potiski-

myeloma are most often hyperdiploid [3,5]. The most common cytogenetic aberrations that occur in plasmacytic leukemia cells are deletion of chromosome 13 and monosomy which are found in more than 85% of patients [5,10]. Chromosome 1 abnormalities (deletion or amplification) are also common in patients with plasma cell leukemia, especially in those with the primary form of the disease [5,11,12]. Translocation t(14;16) and deletion 17p are found in the majority of plasmacytic leukemia cells, which explains the frequent translocation of IgH as well as the expression of cyclin D1 [4]. Translocations t(11;14) and t(4;14) occur with approximately the same frequency as in patients with multiple myeloma [4]. Using the most modern molecular testing methods, a high frequency of TP53 and K/NRAS gene mutations has been determined [5]. The significance of each of these detected cytogenetic abnormalities is still insufficiently known, although they are believed to be associated with a more aggressive clinical course of the disease and a poorer prognosis.

Clinical manifestations

The clinical presentation of patients with plasma cell leukemia differs to some extent from the one found in multiple myeloma. The average age of patients with plasma cell leukemia is 61 years, which is about 10 years less than the average age of patients with multiple myeloma [4]. Most patients with plasma cell leukemia have a large tumor mass that causes weight loss, occasional night sweats, symptoms of kidney failure, anemia, and hemorrhagic syndrome. Namely, due to the large tumor mass and most often massive infiltration of the bone marrow, patients have severe anemia and thrombocytopenia. In addition, there is very often infiltration of peripheral organs, resulting in hepatosplenomegaly and lymphadenopathy, as well as infiltration of the lungs, pleura, testicles, central nervous system, and muscles with the presence of symptoms and clinical signs typical of infiltrated tissues [3-6,8-10]. Bone pain and osteolytic lesions occur somewhat less often than in patients with multiple myeloma [3-6,8-10].

Laboratory findings

Due to bone marrow infiltration, the largest number of patients with plasmacytic leukemia show the existence of normocytic anemia (about 80%) and thrombocytopenia (about 60%), and there is often leukocytosis with absolute plasmacytosis (above 2 x 10^9/L) [4,6]. In the majority of patients, the rouleaux phenomenon is present in the peripheral blood smear [4,6].

Biochemical analyses most often register increased serum activity of lactate dehydrogenase, and beta-2-microglobulin, as well as hypercalcemia, and an

vanje ostalih loza hematopoeze. Kod pojedinih bolesnika, morfologija plazmocita nije promenjena, ali kod drugih dominiraju nezrele forme sa izrazito bazofilnom citoplazmom, dva jedra, velikim jedarcetom i perinuklearnim haloom [1,6,8].

Dijagnoza

Dijagnoza bolesti postavlja se primenom protočne citometrije periferne krvi. Naime, imunofenotipski, ćelije plazmocitne leukemije su CD38 i CD138 pozitivne kao i u multiplom mijelomu, ali u odnosu na plazmocite u multiplom mijelomu, pokazuju veću ekspresiju molekula CD20, CD23, CD28, CD44, CD43, uz sniženu ekspresiju molekula CD9, CD56, CD71, CD117 i HLA-DR (Tabela 2) [5,8]. Detekcijom najmanje 5% plazmocita sa gore navedenim imunofenotipom među leukocitima periferne krvi, postavlja se dijagnoza plazmocitne leukemije. Po postavljenoj dijagnozi, neophodno je učiniti radiografiju skeleta ili primeniti druge radiološke metode, poput kompjuterizovane tomografije - skenera (*CT*), nuklearne magnetne rezonance (NMR) ili pozitronske emisione tomografije (PET skener) čitavog tela, radi detekcije ekstramedularne bolesti. Takođe je neophodno, primenom fluorescentne *in situ* hibridizacije (engl. *fluorescence in situ hybridization - FISH*), utvrditi postojanje citogenetskih aberacija sa naročitim osvrtom na postojanje delecije hromozoma 17p, delecije hromozoma 13q, delecije hromozoma 1p, translokacije hromozoma 14 (t(11;14), t(4;14), t(14;16)) [8].

Prognostički faktori

Loši prognostički faktori obolelih od plazmocitne leukemije su starost preko 60 godina, trombocitopenija ispod 100 x 10^9/L, broj plazmocita u perifernoj krvi veći od 20 x 10^9/L, niska serumska koncentracija albumina, hiperkalcemija, povećana koncentracija laktat dehidrogenaze i beta-2-mikroglobulina, lošiji *performance* status, kao i izostanak terapijskog odgovora na indukcionu terapiju [10,12-15]. Pored toga, postojanje hipodiploidije, kompleksnog kariotipa, delecije 13q, delecije 17p, delecije 1p i amplifikacije 1q udruženo je sa lošijim ukupnim preživljavanjem [11,12]. Do uvođenja novih agenasa i autologe transplantacije prosečno preživljavanje obolelih od plazmocitne leukemije iznosilo je od 4–11 meseci [9]. Uvođenje novih terapijskih modaliteta, kao i transplantacije matičnih ćelija hematopoeze, produžilo je prosečno preživljavanje obolelih i ono sada iznosi 2–3 godine [16].

Terapija

Uzimajući u obzir agresivnost bolesti, terapiju je neophodno započeti odmah po postavljenoj dijagnozi. Postoje izvesne razlike u lečenju primarne i sekundar-

increase in serum creatinine and urea concentrations [6,7]. In most patients, the presence of the M-component in the serum is registered, most often of the IgG class (about 50%), as well as IgA (about 15%), while IgD and IgE are very rare [6]. About 80% of patients with plasma cell leukemia have Bence-Jones proteinuria [6].

Bone marrow biopsy usually shows massive infiltration by plasmacytic leukemia cells with suppression of other hematopoietic lineages. In some patients, the morphology of plasmocytes is not changed, but in others, immature forms dominate, with a distinctly basophilic cytoplasm, two nuclei, a large nucleolus, and a perinuclear halo [1,6,8].

Diagnosis

The diagnosis of the disease is established using flow cytometry of peripheral blood. Namely, immunophenotypically, plasmacytic leukemia cells are CD38 and CD138 positive as is the case in multiple myeloma, but compared to plasma cells in multiple myeloma, they show a higher expression of CD20, CD23, CD28, CD44, and CD43 molecules, with reduced expression of CD9, CD56, CD71, CD117 and HLA-DR molecules (Table 2) [5,8]. By detecting at least 5% of plasma cells with the above-mentioned immunophenotype among peripheral blood leukocytes, the diagnosis of plasma cell leukemia is established. After the diagnosis is made, it is necessary to take radiography of the skeleton or apply other radiological methods, such as computerized tomography (CT), nuclear magnetic resonance imaging (NMRI), or positron emission tomography (PET) of the whole body, to detect extramedullary disease. It is also necessary to determine, using fluorescence in situ hy-

Tabela 2. Tumačenje risk skora

Table 2. Interpretation of risk score

	Plazmocitna leukemija / *Plasma cell leukemia*
CD38	Slična / *Similar*
CD138	Slična / *Similar*
CD20	Povećana / *Elevated*
CD23	Povećana / *Elevated*
CD28	Povećana / *Elevated*
CD44	Povećana / *Elevated*
CD43	Povećana / *Elevated*
CD9	Snižena / *Decreased*
CD56	Snižena / *Decreased*
CD71	Snižena / *Decreased*
CD117	Snižena / *Decreased*
HLA-DR	Snižena / *Decreased*

ne plazmocitne leukemije. Odabir terapijskog režima uglavnom zavisi od činjenice da li je pacijent kandidat za autologu transplantaciju ili ne.

Primena konvencionalne hemioterapije u lečenju primarne plazmocitne leukemije nije dala zadovoljavajuće rezultate, pa je indukciona terapija plazmocitne leukemije, bez obzira da li je pacijent kandidat za autologu transplantaciju ili ne, zasnovana na primeni proteazomnih inhibitora i/ili imunomodulatornih lekova [15,17]. Terapijski režimi zasnovani na primeni bortezomiba u lečenju primarne plazmocitne leukemije rezultiraju ukupnim terapijskim odgovorom (engl. *overall response rate – ORR*) od 76%–80% [2,17]. Primena lenalidomida u kombinaciji sa deksametazonom takođe daje ohrabrujuće rezultate u lečenju [16]. Još bolje rezultate beleži lečenje primenom kombinacije bortezomiba, lenalidomida i deksamezatona uz dodatak elotuzumaba [7]. Uvođenje karfilzomiba (druga generacija proteazomnih inhibitora), u kombinaciji sa lenalidomidom i deksametazonom, dovodi do ukupnog terapijskog odgovora kod 93% bolesnika uz postizanje kompletnih remisija kod 33% obolelih [18].

Ako je pacijent kandidat za autologu transplantaciju matičnih ćelija, posle indukcione visokodozne hemoterapije primenjuje se melfalan u visokim dozama kao režim kondicioniranja i sprovodi autologa transplantacija. Primenom ove terapije postiže se kompletna remisija kod do 40% obolelih [19]. Za mlađe pacijente koji imaju podudarnog donora postoji mogućnost da se lečenje nastavi primenom i alogene transplantacije matičnih ćelija hematopoeze [20,21]. Posle završene indukcione terapije i/ili transplantacije matičnih ćelija hematopoeze, preporuka je primeniti terapiju održavanja primenom lenalidomida, bortezomiba ili deksametazona do progresije bolesti [8].

Prilikom primene indukcione terapije postoji rizik od nastanka sindroma lize tumora. Velika tumorska masa i visok proliferativni potencijal malignih plazmocita su faktori rizika za ovu komplikaciju lečenja. Stoga je preporučeno da se u ovoj fazi lečenja primenjuje adekvatna rehidratacija uz urikosupresore uz neprekidni monitoring pacijenta [9]. Osim toga, usled primene proteazomnih inhibitora i imunomodulatornih lekova, savetuje se primena i profilaktičke antivirusne i antikoagulantne terapije [9].

Terapija relapsa primarne plazmocitne leukemije zavisi od starosti pacijenta, *performance* statusa, terapijskog odgovora na prethodnu terapiju, primenjenih prethodnih terapija, komorbiditeta i bubrežne insuficijencije. Svakako se savetuje primena kombinacije novih terapijskih agenasa ali je terapijski uspeh veoma mali [8,18,21]. Literaturni podaci o terapijskom uspehu terapijskih modaliteta zasnovanih na primeni bortezo-

bridization (FISH), the existence of cytogenetic aberrations with particular reference to the presence of the deletion of chromosome 17p, deletion of chromosome 13q, deletion of chromosome 1p, and translocation of chromosome 14 (t(11;14), t(4;14), t(14;16)) [8].

Prognostic factors

Poor prognostic factors for patients with plasma cell leukemia are as follows: age over 60 years, thrombocytopenia below 100 x 10^9/L, plasma cell count in peripheral blood greater than 20 x 10^9/L, low serum albumin concentration, hypercalcemia, increased concentration of lactate dehydrogenase and beta-2-microglobulin, poorer performance status, as well as lack of therapeutic response to induction therapy [10,12-15]. In addition, the presence of hypodiploidy, complex karyotype, 13q deletion, 17p deletion, 1p deletion, and 1q amplification is associated with worse overall survival [11,12]. Before the introduction of new agents and autologous transplantation, the average survival of patients with plasma cell leukemia was 4-11 months [9]. The introduction of new therapeutic modalities, as well as hematopoietic stem cell transplantation, has extended the average survival of patients and it is now 2-3 years [16].

Treatment

Bearing in mind the aggressiveness of the disease, it is necessary to start treatment immediately after diagnosis. There are certain differences in the treatment of primary and secondary plasma cell leukemia. The choice of therapeutic regimen mainly depends on whether the patient is a candidate for autologous transplantation or not.

The application of conventional chemotherapy in the treatment of primary plasma cell leukemia did not give satisfactory results, therefore, the induction therapy for plasma cell leukemia, regardless of whether the patient is a candidate for autologous transplantation or not, is based on the use of proteasome inhibitors and/or immunomodulatory drugs [15,17]. Therapeutic regimens based on bortezomib in the treatment of primary plasma cell leukemia result in an overall response rate (ORR) of 76%–80% [2,17]. The application of lenalidomide in combination with dexamethasone has also given encouraging results in treatment [16]. Even better results have been recorded with a combination of bortezomib, lenalidomide, and dexamethasone with the addition of elotuzumab [7]. The introduction of carfilzomib (second-generation proteasome inhibitors), in combination with lenalidomide and dexamethasone, leads to an overall therapeutic response in 93% of patients, with complete remission registered in 33% of patients [18].

miba i karfilzomiba, kao i monoklonskih antitela su vrlo oskudni. Terapija sekundarne plazmocitne leukemije zavisi od starosti bolesnika, komorbiditeta, prethodnog terapijskog odgovora i dužine trajanja terapijskog odgovora postignutog primenom prethodne terapije, pa još uvek ne postoji zlatni standard lečenja. Bez obzira na primenjeni terapijski režim, uspeh je veoma mali i preživljavanje je obično svega nekoliko meseci [4].

Uzimajući u obzir vrlo skromne rezultate u lečenju primarne i sekundarne plazmocitne leukemije, očekuje se da bi primena novih agenasa poput venetoklaksa, pomalidomida, iksazomiba, selineksora, karfilzomiba, daratumumaba, anti-CD38 monoklonskih antitela, BRAF/MEK inhibitora, CAR-T terapije i drugih, mogla dovesti do poboljšanja terapijskog odgovora [4,9]. Rezultati do sada publikovanih studija su vrlo oskudni, ali ipak obećavaju.

Sukob interesa: Nije prijavljen.

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If the patient is a candidate for autologous stem cell transplantation, after the application of induction high-dose chemotherapy, high-dose melphalan is administered as a conditioning regimen, and autologous transplantation is performed. With this therapy, complete remission is achieved in up to 40% of patients [19]. For younger patients with a matched donor, it is possible to continue treatment with allogeneic hematopoietic stem cell transplantation [20,21]. After the completion of induction therapy and/or transplantation of hematopoietic stem cells, it is recommended to apply maintenance therapy using lenalidomide, bortezomib, or dexamethasone until disease progression [8].

The application of induction therapy carries the risk of tumor lysis syndrome. A large tumor mass and high proliferative potential of malignant plasma cells are risk factors for this treatment complication. Therefore, it is recommended that in this treatment phase, appropriate rehydration and uricosuppressors should be administered with continuous monitoring of the patient [9]. In addition, due to the use of proteasome inhibitors and immunomodulatory drugs, the use of prophylactic antiviral and anticoagulant therapy is advised [9].

Primary plasma cell leukemia relapse treatment depends on the patient's age, performance status, therapeutic response to previous treatment, previously administered treatments, comorbidities, and renal insufficiency. Application of a combination of new therapeutic agents is definitely advised, but the therapeutic success is very low [8,18,21]. Literature data on the therapeutic success of modalities based on the use of bortezomib, carfilzomib, and monoclonal antibodies are very scarce. The treatment of secondary plasma cell leukemia depends on the patient's age, comorbidities, previous therapeutic response, and the duration of the therapeutic response achieved with the previous therapy, therefore, there is still no gold-standard of treatment. Regardless of the applied therapeutic regimen, success is very low, and survival is usually only a few months [4].

Bearing in mind the very limited results in the treatment of primary and secondary plasma cell leukemia, it is expected that the application of new agents such as venetoclax, pomalidomide, ixazomib, selinexor, carfilzomib, daratumumab, anti-CD38 monoclonal antibodies, BRAF/MEK inhibitors, CAR-T therapy and other agents, could lead to an improvement in therapeutic response [4,9]. The results from the studies published so far are very limited, but promising.

Conflict of interest: None declared.

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