KLINIČKE KARAKTERISTIKE I PREŽIVLJAVANJE ODRASLIH PACIJENATA OBOLELIH OD AKUTNE MIJELOIDNE LEUKEMIJE: ISKUSTVO JEDNOG CENTRA

ORIGINALNI RAD

ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS AND SURVIVAL OUTCOMES IN ACUTE MYELOID LEUKEMIA PATIENTS: SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod/Cilj: Akutna mijeloidna leukemija (AML) je heterogena bolest, po svojim biološkim karakteristikama i po odgovoru na terapiju. Brojni prognostički faktori pri dijagnozi koji su u vezi sa samom bolešću kod pacijenta, terapija i odgovor na terapiju utiču na ishod AML-a. Uprkos velikoj stopi postizanja kompletne remisije, ukupno preživljavanje (engl. *overall survival – OS*) je i dalje loše. Cilj ovog istraživanja je da se odredi kliničko-biološki profil bolesnika sa AML-om i njegov prognostički uticaj na stopu *OS* i preživljavanje bez znakova bolesti (engl. *disease-free survival – DFS*).

Materijali i metode: Retrospektivna analiza obuhvatila je 271 bolesnika sa dijagnozom akutne mijeloidne leukemije postavljenom na Klinici za hematologiju, Univerzitetskog kliničkog centra Srbije (UKCS), između januara 2018. i januara 2023. godine. Analizirani su demografski parametri, *ECOG PS* (engl. *Eastern Cooperative Oncology Group performance status*), komorbiditeti, parametri laboratorijske analize i hematološke dijagnostike AML-a, kao potencijalni faktori rizika za *OS* i *DFS*, uz korišćenje univarijantnog Koksovog regresionog modela.

Rezultati: Od ukupno 271 pacijenta, 206 (76%) je lečeno intenzivnom hemioterapijom, od kojih je bilo 108 muškaraca i 98 žena. Prosečna starost ovih ispitanika je bila 50,3 godine. Prema klasifikaciji rizika Evropske mreže za leukemiju (engl. *European LeukemiaNet – ELN*), najviše je bilo bolesnika intermedijarnog stepena rizika, odnosno 128 (62,1%) pacijenata. Najzastupljeniji podtip AML-a je bio *NOS* AML (engl. AML *not otherwise specified*), prisutan kod 123 (59,7%) bolesnika. Univarijantna analiza je pokazala da su starost od ≥ 60 godina ($p = 0,009$) i vrednost Le ≥ 30 x 10^9/l ($p = 0,031$) nepovoljni prognostički parametri za *OS*. Podtip AML-a, *MRC* (engl. *myelodysplasia-related changes*) bio je najznačajniji faktor rizika za kraće preživljavanje bez znakova bolesti ($p = 0,027$).

Zaključak: U analiziranoj grupi bolesnika sa AML-om lečenih intenzivnom terapijom, pokazali smo nisku stopu *OS,* kao i da godine starosti i *MRC* podtip AML-a predstavljaju nepovoljne faktore rizika za kraće ukupno preživljavanje, odnosno preživljavanje bez znakova bolesti.

Ključne reči: akutna mijeloidna leukemija, prognostički faktori, preživljavanje

ABSTRACT

Introduction/Aim: Acute myeloid leukemia (AML) is a heterogeneous disease, in terms of its biological characteristics and response to therapy. Numerous prognostic factors at diagnosis related to the disease itself, the treatment, and the response to treatment influence the outcome of AML. Despite the high rate of complete remission, overall survival (OS) is still poor. This study aims to determine the clinical and biological profile of patients with AML and its prognostic impact on the OS rate and disease-free survival (DFS).

Materials and methods: The retrospective analysis included 271 patients diagnosed with acute myeloid leukemia at the University Clinical Center of Serbia (UCCS) Hematology Clinic, between January 2018 and January 2023. Demographic parameters, the Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidities, and the parameters of laboratory analysis and hematological diagnosis of AML were analyzed as potential risk factors for OS and DFS, using the univariate Cox regression model.

Results: Out of a total of 271 patients, 206 (76%) were treated with intensive chemotherapy, of whom 108 were men and 98 were women. The average age of these respondents was 50.3 years. According to the European Leukemia Network (ELN) risk classification, the patients were mostly in the group with intermediate risk, i.e. 128 (62.1%) patients. The most common subtype of AML was AML NOS (AML not otherwise specified), present in 123 (59.7%) patients. Univariate analysis showed that age ≥ 60 years ($p = 0.009$) and WBC ≥ 30 x 10^9/l ($p = 0.031$) were unfavorable prognostic parameters for OS. AML subtype, MRC (myelodysplasia-related changes) was the most significant risk factor for shorter disease-free survival ($p = 0.027$).

Conclusion: In the analyzed group of AML patients treated with intensive therapy, we demonstrated a low OS rate and showed that age and the MRC subtype of AML represent unfavorable risk factors for shorter OS and DFS, respectively.

Keywords: acute myeloid leukemia, prognostic factors, survival

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UVOD

Akutna mijeloidna leukemija (AML) je heterogena maligna bolest hematopoeznog sistema koju karakteriše klonska proliferacija nediferentovanih mijeloidnih prekursora tj. blasta [1]. Usled nakupljanja nezrelih ćelija dolazi do potiskivanja i oštećenja normalnih ćelija hematopoeze, što se posledično klinički manifestuje kao infekcija, anemija i krvarenje [2]. Povremeno, AML može da ima ekstramedularnu prezentaciju, uključujući i zahvaćenost centralnog nervnog sistema (CNS) [3].

AML je bolest starijeg životnog doba – prosečna starosti pacijenata u trenutku postavljanja dijagnoze je 69 godina. Spada u retke bolesti, sa godišnjom incidencijom od 4,2 /100.000 stanovnika, i češća je kod muškaraca (M : Ž = 5,1/100.000 : 3,5/100.000) [4].

Poznato je nekoliko faktora rizika koji se dovode u vezu sa nastankom AML-a: izloženost mutagenim faktorima spoljašnje sredine, prethodna hemioterapija i druge hematološke bolesti [2]. Novija istraživanja su pokazala povezanost AML-a i urođenog nasleđivanja u okviru porodice [5,6].

Tehnološki napredak u molekularnoj dijagnostici doveo je do novih saznanja o biologiji AML-a. Prethodna klasifikacija AML-a Svetske zdravstvene organizacije (SZO), iz 2016. godine, predviđala je ≥ 20% blasta kao dijagnostički kriterijum, sa izuzetkom AML-a sa rekurentnim citogenetskim abnormalnostima (RCA) i obuhvatala je četiri glavne grupe: AML sa RCA, AML sa mijelodisplastičnim karakteristikama (engl. *AML with myelodysplasia-related changes – MRC*), AML nastala posle prethodnog lečenja (engl. *therapy-related AML – t-AML*) i *NOS* AML (engl. *AML not otherwise specified*) [5]. Međunarodna konsenzus klasifikacija (engl. *International Consensus Classification – ICC*) i klasifikacija SZO, iz 2022. godine, unapredile su prethodnu klasifikaciju AML-a, uvođenjem novih genetski definisanih entiteta za koje je granična vrednost procenta blasta snižena [6,7]. Obe klasifikacije iz 2022. godine polaze od toga da je abnormalna morfologija rezultat poremećene ćelijske biologije, koja je uzrokovana somatskim mutacijama ili ekspresijom izmenjenih gena, pa se stoga više fokusiraju na ekstenzivno genetsko profilisanje u definisanju entiteta bolesti.

Prema SZO, konačna dijagnoza AML-a se postavlja na osnovu integrisanog dijagnostičkog algoritma koji uključuje rezultate nekoliko komplementarnih metoda: citomorfološke, imunofenotipske, citogenetske i molekularno genetske analize u formi objedinjenog izveštaja [6,7].

Ishod AML je veoma heterogen i zavisi od niza faktora u vezi sa bolesnikom (godine starosti, *ECOG PS* (engl. *Eastern Cooperative Oncology Group performance status*), komorbiditeti) kao i u vezi sa samom bolešću (broj leukocita (Le) na dijagnozi, prethodni

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous malignant disease of the hematopoietic system characterized by clonal proliferation of undifferentiated myeloid precursors, i.e. blasts [1]. As a result of the accumulation of immature cells, normal hematopoietic cells are suppressed and damaged, which consequently manifests clinically as infection, anemia, and bleeding [2]. Occasionally, AML can have an extramedullary presentation, including central nervous system (CNS) involvement [3].

AML is a disease of older age – the average age of patients at the time of diagnosis is 69 years. It belongs to rare diseases, with an annual incidence of 4.2/100,000 inhabitants, and is more common in men (M : F = 5.1/100,000 : 3.5/100,000) [4].

Several risk factors are known to be associated with the development of AML: exposure to mutagenic environmental factors, previous chemotherapy, and other hematological diseases [2]. More recent studies have shown an association between AML and congenital inheritance within the family [5,6].

Technological advances in molecular diagnostics have led to new insights into the biology of AML. The previous World Health Organization (WHO) classification of AML, from 2016, required ≥ 20% blasts as a diagnostic criterion (except in AML with recurrent cytogenetic abnormalities – AML with RCA), and included four main groups: AML with RCA, AML with myelodysplasia-related changes (AML with MRC), therapy-related AML (t-AML), and AML not otherwise specified (AML NOS) [5]. The International Consensus Classification (ICC) and the WHO classification, from 2022, improved the previous classification of AML by introducing new genetically defined entities for which the threshold value of the percentage of blasts was lowered [6,7]. Both 2022 classifications are based on the assumption that abnormal morphology stems from disrupted cell biology, which is caused by somatic mutations or altered gene expression, and therefore focus more on extensive genetic profiling in defining disease entities.

According to the WHO, the final diagnosis of AML is established based on an integrated diagnostic algorithm that includes the results of several complementary methods: cytomorphological, immunophenotypic, cytogenetic, and molecular genetic analysis in the form of a unified report [6,7].

The outcome of AML is very heterogeneous and depends on several factors related to the patient (age, Eastern Cooperative Oncology Group performance status – ECOG PS, comorbidities), as well as to the disease itself (white blood cell count (WBC) at diagnosis, previous myelodysplastic syndrome (MDS), patholog-

mijelodisplačni sindrom (MDS), patološki kariotip, molekularni markeri, prethodna citotoksična terapija) [2]. Genetske abnormalnosti predstavljaju snažan faktor rizika za nepovoljnu prognozu [1,8]. Prema preporukama Evropske mreže za leukemiju (engl. *European LeukemiaNet – ELN*), stratifikacija rizika AML-a, koja se zasniva na citogenetskim i molekularnim aberacijama, obuhvata tri grupe rizika: povoljna, intermedijarna i nepovoljna [7]. Pored toga, procena merljive rezidualne bolesti (MRB) protočnom citometrijom i *PCR* (engl. *polymerase chain reaction*) metodom [7] pokazala je povezanost sa pojavom relapsa bolesti i kraćim ukupnim preživljavanjem (engl. *overall survival – OS*) [9].

Na izbor terapijskog pristupa, pored *ECOG PS* i komorbiteta utiče i prognostički molekularni profil AML-a [7]. Standard intenzivnog lečenja za bolesnike sa AML-om se sastoji od inicijalne indukcione terapije „7+3" (7 dana citarabin i 3 dana antraciklin) i postremisione konsolidacione terapije (protokoli bazirani na citarabinu), što je praćeno transplantacijom matičnih ćelija hematopoeze (TMĆH), ukoliko je indikovana [7,10,11]. U zavisnosti od godina starosti, stopa postizanja kompletne remisije (engl. *complete remission - CR*) varira. Za bolesnike starosti ≤ 60 godina prosek *CR* je 60-85%, uz petogodišnje *OS* od oko 30% [4,10], dok je za pacijente starosti > 60 godina, stopa postizanja *CR* 40-60% i *OS* je manje od 10% [10,12].

Današnji trendovi su usmereni u pravcu personalizovanog terapijskog pristupa prema specifičnom molekularnom profilu bolesti [13]. Genomska heterogenost AML-a je dovela do razvoja terapija koje direktno ciljaju mutacije, kao što su inhibitori *FLT3* (engl. *FMS-related receptor tyrosine kinase* 3) i izocitrat dehidrogenaze 1/2 (IDH1/IDH2). Ove terapije su postale deo standardnog lečenja. Pored toga, uvedeni su i drugi inovativni lekovi poput gemtuzumab ozogamicina (GO), (anti CD33 monoklonsko antitelo), i *CPX-351* (lipozomalna formulacija daunorubicina i citarabina) [7]. Uvođenjem terapija nižeg intenziteta, povećane su terapijske mogućnosti za sve bolesnike, posebno za starije pacijente ili za one koji ne ispunjavaju kriterijume za intenzivno lečenje. Tako je primena protokola sa *BCL-2* (engl. *B cell lymphoma 2*) inhibitorom u kombinaciji sa niskim dozama citarabina ili sa hipometilirajućim agensima, pokazala unapređenje u lečenju ove grupe bolesnika [14,15].

Uprkos nedavnom obećavajućem napretku i uvođenju novih terapijskih pristupa, ishod bolesnika sa AML-om i dalje nije u potpunosti zadovoljavajući [16]. U tom smislu, u toku su brojne studije inovativnih lekova, čiji preliminarni rezultati deluju ohrabrujuće, a čiji je cilj povećanje stope izlečenja AML-a.

Cilj ovog istraživanja je da se odredi kliničko-biološki profil bolesnika sa AML-om i njegov prognostički

ical karyotype, molecular markers, previous cytotoxic therapy) [2]. Genetic abnormalities are a strong risk factor for unfavorable prognosis [1,8]. According to the recommendations of the European Leukemia Network (ELN), the risk stratification of AML, which is based on cytogenetic and molecular aberrations, includes three risk groups: favorable, intermediate, and unfavorable [7]. In addition, assessment of measurable residual disease (MRD) by flow cytometry and the polymerase chain reaction (PCR) method [7] showed an association with the occurrence of disease relapse and shorter overall survival (OS) [9].

In addition to ECOG PS and comorbidities, the choice of therapeutic approach is influenced by the prognostic molecular profile of AML [7]. The standard of intensive treatment for patients with AML consists of initial "7+3" induction therapy (7 days of cytarabine and 3 days of anthracycline) and post-remission consolidation therapy (cytarabine-based protocols), which is followed by hematopoietic stem cell transplantation (HSCT), if indicated [7,10,11]. Depending on age, the rate of achieving complete remission (CR) varies. For patients aged ≤ 60 years, the average CR is 60-85%, with a five-year OS of about 30% [4,10], while for patients aged > 60 years, the CR rate is 40-60% and the OS is less than 10% [10,12].

Current trends are directed towards a personalized therapeutic approach based on the specific molecular profile of the disease [13]. The genomic heterogeneity of AML has led to the development of therapies that directly target mutations, such as FMS-related receptor tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase 1/2 (IDH1/IDH2) inhibitors. These treatments have become part of standard treatment. In addition, other innovative drugs such as gemtuzumab ozogamicin (GO), (anti CD33 monoclonal antibody), and CPX-351 (a liposomal formulation of daunorubicin and cytarabine) have been introduced [7]. With the introduction of lower-intensity therapies, the therapeutic possibilities for all patients have increased, especially for older patients or those who are not eligible for intensive treatment. Thus, the application of a protocol with the B cell lymphoma 2 (BCL-2) inhibitor in combination with low doses of cytarabine or with hypomethylating agents has shown an improvement in the treatment of this group of patients [14,15].

Despite recent promising breakthroughs and the introduction of new therapeutic approaches, the outcome of patients with AML is still not completely satisfactory [16]. Consequently, numerous studies of innovative drugs are underway aimed at increasing the cure rate of AML. Their preliminary results seem encouraging.

uticaj na stopu *OS* i na preživljavanje bez znakova bolesti (engl. *disease-free survival – DFS*).

MATERIJALI I METODE

Bolesnici

Retrospektivna analiza obuhvatila je 271 bolesnika sa AML-om, koji su dijagnostikovani i lečeni na Klinici za hematologiju Univerzitetskog Kliničkog centra Srbije, u periodu od januara 2018. do januara 2023. godine. Bolesnici sa akutnom promijelocitnom leukemijom nisu uključeni u ovo istraživanje. Dijagnoza AML-a postavljena je na osnovu integrisanog dijagnostičkog pristupa, a u skladu sa preporukama SZO iz 2016. godine [5]. Stratifikacija rizika bolesnika sa AML-om (povoljni, intermedijarni, nepovoljni) sprovedena je u skladu sa ELN preporukama [11]. U citogenetskoj analizi uzoraka koštane srži je korišćena standardna tehnika G traka [17]. Imunofenotipizacija je sprovedena metodom protočne citometrije na uzorcima koštane srži [18]. Prisustvo FLT3-ITD (engl. internal tandem duplication) i TKD (engl. tyrosine kinase domain) mutacija, kao i NPM1 (engl. nucleophosmin) mutacija je analizirano PCR metodama [19,20]. Organomegalija, limfadenopatija, hipertrofija desni i CNS infiltracija su definisane kao ekstramedularna bolest (EMB). Ispitivanje prisustva leukemijskih ćelija u likvoru sprovedeno je metodom protočne citometrije kod simptomatskih i asimptomatskih bolesnika sa karakteristikama koje su povezane sa CNS infiltracijom (laktat dehidrogenaza (LDH) ≥ 450, Le ≥ 30×10^9/l, mijelomonocitni i/ili monocitni fenotip, ekspresija CD56, FLT3-ITD/TDK mutacije i CBF (engl. core binding factor)) u AML-u [21]. Prilikom postavljanja dijagnoze evidentirano je opšte funkcionalno stanje na osnovu ECOG PS skale [22]. Takođe je određivan i značaj postojećih komorbiditeta, na osnovu HCT-CI (engl. hematopoietic cell transplantation-specific comorbidity index) skora [23]. Kod svih bolesnika analizirani su sledeći laboratorijski parametri: leukociti – Le ($x10^9$/l), trombociti – Tr ($x10^9$/l), hemoglobin – Hb (g/l), LDH (U/l), procenat blasta u perifernoj krvi i u koštanoj srži.

Terapija

Većina bolesnika (206/271) je lečena intenzivnom terapijom (daunorubicin i citarabin po šemi „3+7"), praćeno konsolidacijom uz primenu citarabina i TMĆH. Bolesnici koji nisu ispunjavali kriterijume za intenzivno lečenje (65/271) primali su neintenzivnu hemioterapiju (daunorubicin i citarabin po šemi „2+5" i „1+5", niskodozni citarabin) ili suportivnu terapiju (6-merkaptopurin, hidroksiureja), u zavisnosti od opšteg funkcionalnog stanja i komorbiditetnog indeksa. Bolesnici koji su relapsirali i oni koji su bili primarno refraktarni, lečeni

This study aims to determine the clinical and biological profile of patients with AML and its prognostic impact on OS rate and disease-free survival (DFS).

MATERIALS AND METHODS

Patients

The retrospective analysis included 271 patients with AML, diagnosed and treated at the Clinic for Hematology of the University Clinical Center of Serbia (UCCS), between January 2018 and January 2023. Patients with acute promyelocytic leukemia were not included in this study. The diagnosis of AML was established based on an integrated diagnostic approach, as per the 2016 WHO recommendations [5]. Risk stratification of patients with AML (favorable, intermediate, adverse) was carried out in keeping with ELN recommendations [11]. The standard G-banding technique was used in the cytogenetic analysis of bone marrow samples [17]. Immunophenotyping was performed by flow cytometry on bone marrow samples [18]. The presence of internal tandem duplication (FLT3-ITD) and tyrosine kinase domain (TKD) mutations, as well as of nucleophosmin (NPM1) mutations was analyzed by PCR methods [19,20]. Organomegaly, lymphadenopathy, gingival hypertrophy, and CNS infiltration were defined as extramedullary disease (EMD). Examination of the presence of leukemic cells in the cerebrospinal fluid was carried out by flow cytometry in symptomatic and asymptomatic patients with characteristics associated with CNS infiltration (lactate dehydrogenase (LDH) ≥ 450, WBC ≥ $30x10^9$/l, myelomonocytic and/or monocytic phenotype, CD56 expression, FLT3-ITD/TDK mutations and core binding factor (CBF)) in AML [21]. The general functioning status was recorded based on the ECOG PS scale [22]. The significance of existing comorbidities was also determined based on the HCT-CI (hematopoietic cell transplantation-specific comorbidity index) score [23]. The following laboratory test were performed in all patients: white blood cell count - WBC ($x10^9$/l), platelet count - PLT ($x10^9$/l), hemoglobin – Hb (g/l), LDH (U/l), percentage of blasts in peripheral blood and bone marrow.

Treatment

Most of the patients (206/271) were treated with intensive therapy (daunorubicin and cytarabine 3+7 regimen), followed by consolidation with cytarabine and HSCT. Patients who were not eligible for intensive treatment (65/271) received non-intensive chemotherapy (daunorubicin and cytarabine regimens 2+5 and 1+5, low-dose cytarabine) or supportive therapy (6-mercaptopurine, hydroxyurea), depending on their general functioning status and comorbidity index.

su protokolima spašavanja (engl. *salvage*), (fludarabin, citarabin, idarubicin, po protokolu *FLAG-Ida* ili mitoksantron, etopozid, citarabin, po protoklu *MEC*).

Procena terapijskog odgovora

Procena odgovora na terapiju definisana je prema preporukama *ELN* [11]: *CR* < 5% blasta u koštanoj srži, odsustvo cirkulišućih blasta, odsustvo EMB, apsolutni broj neutrofila ≥ 1,0×10^9/l i Tr ≥ 100 ×10^9/l. Relaps je definisan kao prisustvo ≥ 5% blasta u koštanoj srži ili pojava blasta u perifernoj krvi, kao i pojava EMB. Rana smrt je definisana kao smrt u periodu od 28 dana od otpočinjanja indukcione hemioterapije. Refraktorna bolest (RB), *OS* i *DFS* definisani su prema predloženim preporukama [11].

Statistička analiza

Za opisivanje podataka korišćene su deskriptivne analize (aritmetička sredina, medijana, standardna devijacija, učestalost). Dužina preživljavanja je analizirana pomoću Kaplan-Majerove metode, dok je log-rank test korišćen za poređenje preživljavanja među ispitivanim grupama. Univarijantni Koksov proporcionalni regresioni model je korišćen za identifikaciju faktora rizika. Statistička značajnost je definisana na $p < 0,05$. Statistički testovi su sprovedeni u softveru za statističku analizu *IBM® SPSS® Statistics V25, IBM, USA*.

REZULTATI

Kliničke karakteristike

Od ukupno 271 bolesnika sa AML-om, 206 (76%) pacijenata je lečeno primenom intenzivne hemioterapije, dok je 65 (24%) lečeno neintenzivnom terapijom. Kliničke karakteristike bolesnika lečenih intenzivnom terapijom su prikazane u Tabeli 1. Studija je obuhvatila 108 muškaraca i 98 žena (M : Ž 52,4% : 47,6%), prosečne starosti 50,3 ± 13,9 godina.

Distribucija bolesnika prema podtipu AML-a, a u skladu sa klasifikacijom SZO iz 2016. godine, bila je: AML sa RCA je imao 51 (24,76%) pacijent, od toga je bilo 32 (15,5%) bolesnika sa NPM1, 12 (5,6%) pacijenata sa inv(16) i 7 (3,4%) bolesnika sa t(8;21); *MRC* AML je imalo 27 (13,1%) pacijenata; dok je *t-AML* bila prisutna kod 5 (2,4%) bolesnika. Najviše je bilo bolesnika sa *NOS* AML, 123 (59,7%) pacijenta; bilo je 7 (7%) slučajeva AML-a sa minimalnom diferencijacijom, 21 (20%) slučaj AML-a bez sazrevanja, 26 (25%) slučajeva AML-a sa sazrevanjem, 33 (32%) slučaja akutne mijelomonocitne leukemije, 15 (15%) slučajeva akutne monoblastne i monocitne leukemije. *FLT3-ITD* pozitivnost je uočena u 38 (18,4%) slučajeva, dok je *FLT3-TKD* mutacija registrovana u 5 (2,4%) slučaja. U našoj grupi bolesnika, najPatients who relapsed and those who were primarily refractory were treated with salvage protocols (fludarabine, cytarabine, idarubicin, according to the FLAG-Ida protocol, or mitoxantrone, etoposide, cytarabine, according to the MEC protocol).

Assessment of therapeutic response

The assessment of therapeutic response was defined according to ELN guidelines [11]: CR < 5% blasts in the bone marrow, absence of circulating blasts, absence of EMD, absolute neutrophil count ≥ 1.0×10^9/l, and PLT ≥ 100 ×10^9/l. Relapse was defined as the presence of ≥ 5% blasts in the bone marrow or the appearance of blasts in peripheral blood, as well as the presence of EMD. Early death was defined as death within 28 days of starting induction chemotherapy. Refractory disease (RD), OS, and DFS were defined according to the proposed guidelines [11].

Statistical analysis

Descriptive analysis methods (arithmetic mean, median, standard deviation, frequency). were used to describe the data. The length of survival was analyzed using the Kaplan-Meier method, while the log-rank test was used to compare survival among the studied groups. The univariate Cox proportional regression model was used to identify risk factors. Statistical significance was defined at $p < 0.05$. Statistical tests were performed with the statistical analysis software IBM® SPSS® Statistics V25, IBM, USA.

RESULTS

Clinical characteristics

Out of a total of 271 patients with AML, 206 (76%) were treated with intensive chemotherapy, while 65 (24%) were treated with non-intensive therapy. The clinical characteristics of patients treated with intensive therapy are shown in Table 1. The study included 108 men and 98 women (M : F 52.4% : 47.6%) The average age of the patients was 50.3 ± 13.9 years.

The distribution of patients according to AML subtype, and per the WHO classification from 2016, was as follows: 51 (24.76%) patients had AML with RCA, of whom there were 32 (15.5%) patients with NPM1, 12 (5.6%) patients with inv(16) and 7 (3.4%) patients with t(8;21); 27 (13.1%) patients had MRC AML; while t-AML was present in 5 (2.4%) patients. The majority were patients with AML NOS, 123 (59.7%) patients; there were 7 (7%) cases of minimally differentiated AML, 21 (20%) cases of non-maturing AML, 26 (25%) cases of maturing AML, 33 (32%) cases of acute myelomonocytic leukemia, 15 (15%) of cases of acute monoblastic and monocytic leukemia. FLT3-ITD positivity was observed

veću zastupljenost pokazali su sledeći imunofenotipski antigeni na leukemijskim ćelijama: CD13 (90,7%), CD33 (93,9%), CD34 (74,4%) i CD117 (86%). Ukupno 26,1% bolesnika je imalo CD56 pozitivnu AML.

in 38 (18.4%) cases, while FLT3-TKD mutation was registered in 5 (2.4%) cases. In our group of patients, the following immunophenotypic antigens on leukemic cells showed the highest prevalence: CD13 (90.7%), CD33 (93.9%), CD34 (74.4%), and CD117 (86%). A total of 26.1% of patients had CD56-positive AML.

Tabela 1. Kliničko-biološke karakteristike bolesnika lečenih intenzivnom hemioterapijom

Table 1. Clinical and biological characteristics of patients treated with intensive chemotherapy

Karakteristike / *Characteristics*	***Value***
Starost (godine), AS±-SD / *Age (years); mean ± SD*	50.3 ± 13.9
Godine < 60 g naspram > 60 g; n (%) / *Age < 60 y vs. > 60 y; n (%)*	142 (68.9%) vs. 64 (31.1%)
EMB - limfadenopatija; n (%) / *EMD – lymphadenopathy; n (%)*	44 (21.6%)
EMB - hepatosplenomegalija; n (%) / *EMD – hepatosplenomegaly; n (%)*	61 (29.8%)
EMB - hipertrofija desni; n (%) / *EMD – gingival hypertrophy; n (%)*	21 (10.3%)
CNS infiltracija; n (%) / *CNS infiltration n (%)*	46 (22.3%)
ECOG ≥ 2 / *ECOG ≥ 2* **Da; n (%) / *Yes; n (%)*** **Ne; n (%) / *No; n (%)***	 43 (20.9%) 163 (79.1%)
HCT-CI ≥ 3 / *HCT-CI ≥ 3* **Da; n (%) / *Yes; n (%)*** **Ne; n (%) / *No; n (%)***	 11 (5.3%) 192 (93.2%)
BMI kg/m^2; AS ± SD / *BMI kg/m^2; mean ± SD*	25.9 ± 5.5
Le; medijana (x10^9/l), raspon / *WBC; median (x10^9/l), range*	6.9 (0.1-278.5)
Le > 30 x10^9/l; n (%) / *WBC > 30 x10^9/l; n (%)*	56 (27.2%)
Hb; AS ± SD (g/l) / *Hb; mean ± SD (g/l)*	95.9 ± 19.5
Tr; medijana (x10^9/l), opseg / *PLT; median (x10^9/l), range*	51.5 (2-396)
LDH; medijana (U/l), opseg / *LDH; median (U/l), range*	396 (127-12,954)
LDH ≥ 450 U/l; n (%) / *LDH ≥ 450 U/l; n (%)*	88 (43.3%)
Blasti u PK; % (opseg) / *Blasts in PB; % (range)*	19 (0-99)
Blasti u KS; % (opseg) / *Blasts in BM; % (range)*	57.5 (20-96)
SZO AML; (N, %) / *WHO AML; n (%)* **AML sa RCA / *AML with RCA*** **MRC AML / *MRC AML*** **t-AML / *t-AML*** **NOS AML / *AML NOS***	 51 (24.7%) 27 (13.1%) 5 (2.4%) 123 (59.7%)
AML/CD56; n (%) / *AML/CD56; n (%)*	46 (26.1%)
FLT3-ITD^{mut}; n (%) / *FLT3-ITD^{mut}; n (%)*	38 (18.4%)
FLT3-TKD^{mut}; n (%) / *FLT3-TKD^{mut}; n (%)*	5 (2.4%)
ELN grupa rizika; n (%) / *ELN risk group; n (%)* **Povoljan / *Favorable*** **Intermedijarni / *Intermediate*** **Nepovoljan / *Unfavorable***	 27 (13.1%) 128 (62.1%) 51 (24.8%)

Legenda: AML – akutna mijeloidna leukemija; SD – standardna devijacija; CNS – centralni nervni sistem; AS - aritmetička sredina; *ECOG* – engl. *Eastern Cooperative Oncology Group*; *ELN* – engl. *European Leukemia Net*; EMB – ekstramedularna bolest; Hb – hemoglobin; *HCT-CI* – engl. *hematopoietic cell transplantation-specific comorbidity index*; KS – koštana srž; LDH – laktat dehidrogenaza; Le – leukociti; PK – periferna krv; *BMI* – engl. *body mass index*; SZO – Svetska zdravstvena organizacija; AML sa RCA – AML sa rekurentnim citogenetskim abnormalnostima; *MRC AML* – engl. *AML with myelodysplasia-related changes*; *t-AML* – engl. *therapy-related AML*, *NOS AML* – engl. *AML, not otherwise specified*

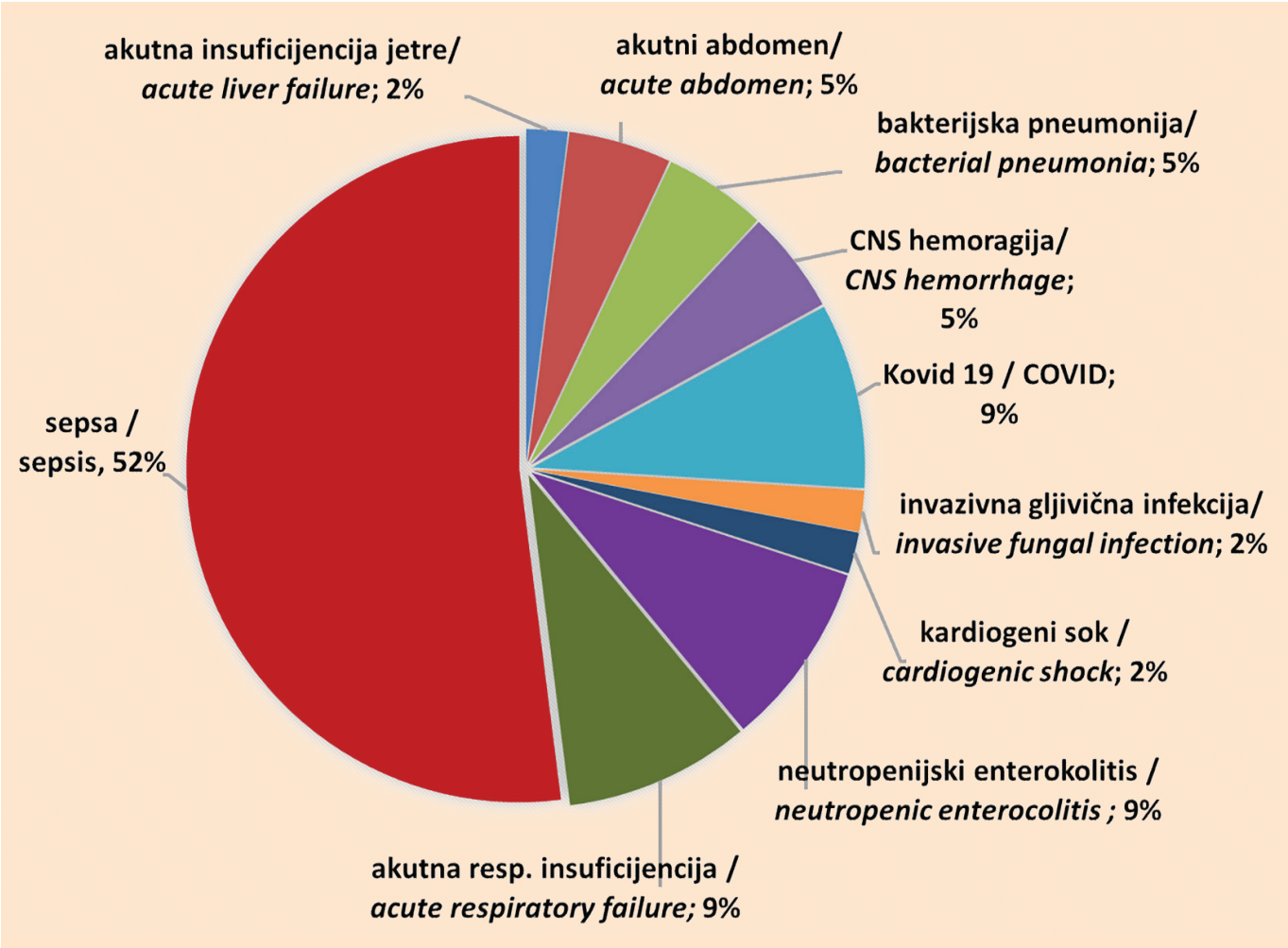
Legend: AML – acute myeloid leukemia; SD – standard deviation; CNS – central nervous system; ECOG – Eastern Cooperative Oncology Group; ELN – European Leukemia Network; EMD – extramedullary disease; Hb – hemoglobin; HCT-CI – hematopoietic cell transplantation-specific comorbidity index; BM – bone marrow; LDH – lactate dehydrogenase; WBC – white blood cell count; PB – peripheral blood; WHO – World Health Organization; BMI – body mass index; AML with RCA – AML with recurrent cytogenetic abnormalities; MRC AML – AML with myelodysplasia-related changes; AML NOS– AML not otherwise specified; t-AML – therapy-related AML

Ishod lečenja

Kompletna remisija je postignuta kod 92 od 158 (79,7%) slučajeva. Relaps bolesti je imalo 62 (67,4%) pacijenta, dok je primarno refraktornih bolesnika bilo 32 (20,3%). Rana smrt je zabeležena u 48 (23,3%) slučajeva. Glavni uzročnici rane smrti prikazani su u Grafikonu 1. Medijana *OS* je bila 12 meseci (10-13,9 meseci). Ukupno petogodišnje preživljavanje je iznosilo 19% (Slika 1. A). Medijana *DFS* je iznosila 13 meseci. Ukupno 51 od 157 (32,5%) bolesnika je lečeno transplantacijom matičnih ćelija hematopoeze. Bolesnici lečeni pomoću TMĆH su imali statistički značajno duže *OS* (medijana 20 meseci naspram 7 meseci; $p < 0,001$) u poređenju sa bolesnicima koji nisu lečeni ovom terapijom (Slika 1. B).

Treatment outcome

Complete remission was achieved in 92 out of 158 (79.7%) cases. Sixty-two (67.4%) patients had disease relapse, while 32 (20.3%) were primarily refractory patients. Early death was recorded in 48 (23.3%) cases. The main causes of early death are presented in Graph 1. Median OS was 12 months (10-13.9 months). Overall five-year survival was 19% (Figure 1. A). The median DFS was 13 months. Fifty-one out of 157 (32.5%) patients were treated with hematopoietic stem cell transplantation. Patients treated with HSCT had statistically significantly longer OS (median 20 months vs. 7 months; $p < 0.001$), as compared to patients not treated with this therapy (Figure 1. B).



Grafikon 1. Uzroci rane smrti kod bolesnika sa AML-om lečenih intenzivnom terapijom

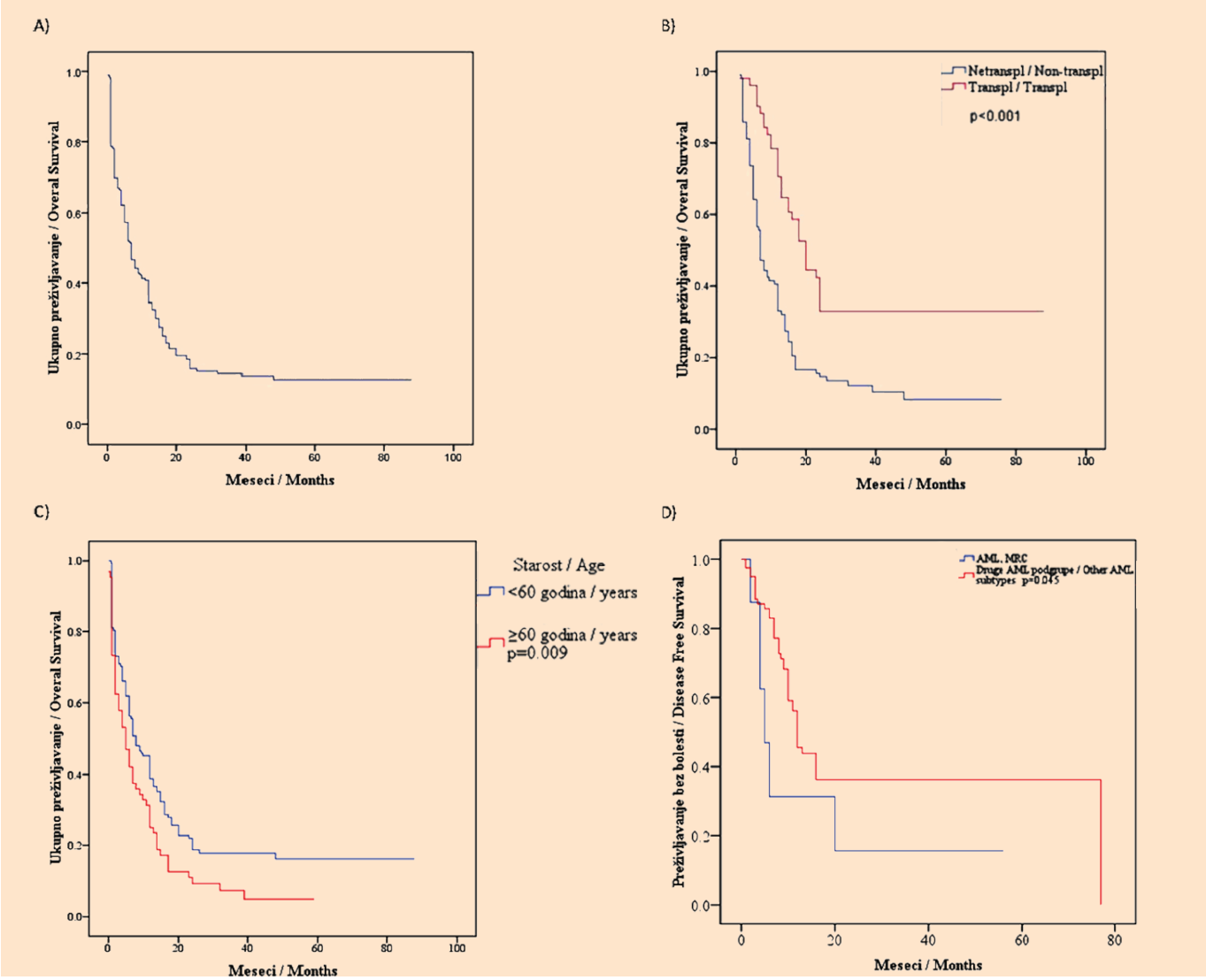
Graph 1. Causes of early death in patients with AML treated with intensive therapy

Prognostički faktori *OS* i *DFS*

Univarijantna analiza je pokazala da su sledeće ispitivane karakteristike bile značajni prediktori za kraće *OS*: godine ≥ 60 ($p = 0,009$), (Slika 1. C), Le ≥ 30 x10^9/l

Prognostic factors of *OS* and *DFS*

Univariate analysis showed that the following analyzed characteristics were significant predictors of shorter OS: age ≥ 60 ($p = 0.009$), (Figure 1. C), WBC ≥ 30 x10^9/l



Slika 1. Krive preživljavanja bolesnika sa AML-om
A) Kriva petogodišnjeg preživljavanja bolesnika sa AML-om
B) Kriva preživljavanja kod transplantiranih i netransplantiranih bolesnika
C) Kriva preživljavanja kod bolesnika < 60 g naspram > 60 g
D) Kriva preživljavanja kod bolesnika sa MRC AML-om naspram pacijenata sa drugim podtipovima AML-a

Figure 1. Survival curves of patients with AML
A) Five-year survival curve of patients with AML
B) Survival curve in transplanted and non-transplanted patients
C) Survival curve in patients < 60 years vs. > 60 years
D) Survival curve in patients with MRC AML vs. other subtypes of AML

(p = 0,031). Ostali ispitivani prognostički faktori nisu pokazali statističku značajnost (Tabela 2). Univarijantna analiza je pokazala da je loše *DFS* bilo značajno povezano sa *MRC* AML podtipom (p = 0,045) (Slika 1. D).

DISKUSIJA

AML je heterogena bolest, kako po svojim citološkim, imunofenotipskim i citogenetsko-molekularnim karakteristikama, tako i po odgovoru na standardno lečenje i preživljavanju bolesnika [1,2]. Uprkos visokoj stopi *CR* od 60-85%, prosečna stopa petogodišnjeg *OS* je niska, iznosi oko 30%, i značajno se razlikuje između različitih starosnih grupa, dostižući 50% kod mlađih bolesnika,

(p = 0.031). Other examined prognostic factors did not show statistical significance (Table 2). Univariate analysis showed that poor DFS was significantly associated with the MRC AML subtype (p = 0.045) (Figure 1 D).

DISCUSSION

AML is a heterogeneous disease, in terms of its cytological, immunophenotypical, cytogenetic, and molecular characteristics, but also with regards to patient response to standard treatment and patient survival [1,2]. Despite the high CR rate (60-85%), the average five-year OS rate is low, around 30%, and varies significantly among different age groups, reaching

Tabela 2. Univarijantna analiza faktora rizika za OS kod bolesnika sa AML-om lečenih intenzivnom terapijom

Table 2. Univariate analysis of risk factors for OS in AML patients treated with intensive therapy

Karakteristike / *Characteristics*	Univarijantna analiza / *Univariate analysis*		
	p	*HR*	*95% CI*
Starost > 60 g naspram < 60 g / *Age >60 y vs. < 60 y*	0.009	1.015	0.064-16.165
Le ≥ 30 x10^9/l naspram Le < 30 x 10^9/l / *WBC ≥ 30 x10^9/l vs. Le < 30x10^9/l*	0.031	0.079	0.003-1.829
Blasti u PK ≥ 50% / *Blasts in PB ≥ 50%*	0.237	0.998	0.158-6.291
Blasti u KS ≥ 50% / *Blasts in BM ≥ 50%*	0.761	0.972	0.155-8.201
MRC AML naspram drugi AML podtipovi / *MRC AML vs. other AML subtypes*	0.138	0.494	0.145-1.680
Flt3-ITD$^+$ naspram Flt3-ITD$^-$ / *Flt3-ITD$^+$ vs. Flt3-ITD$^-$*	0.733	0.236	0.061-0.919
ECOG ≥ 2 naspram < 2 / *ECOG ≥ 2 vs. < 2*	0.714	0.323	0.059-1.765
CNS$^+$ naspram CNS$^-$ / *CNS$^+$ vs. CNS$^-$*	0.272	1.201	0.318-4.533
Nepovoljni naspram intermedijarni i povoljni rizik / *Unfavorable vs. intermediate and favorable risk*	0.527	14.259	1.916-106.114
LDH ≥ 450 / *LDH ≥ 450*	0.697	8.390	1.241-56.711
HCT-CI ≥ 3 / *HCT-CI ≥ 3*	0.897	1.912	0.632-5.785
AML CD56 / *AML CD56*	0.223	0.437	0.055-3.444

Legenda: AML – akutna mijeloidna leukemija; CNS – centralni nervni sistem; *Flt3-ITD* – engl. *fms-related receptor tyrosine kinase 3-internal tandem duplication*; *ECOG* – engl. *Eastern Cooperative Oncology Group*; Le – leukociti; PK – periferna krv; KS – koštana srž; *MRC* – engl. *myelodysplasia-related changes*; *HCT-CI* – engl. *hematopoietic cell transplantation-specific comorbidity index*; LDH – laktat dehidrogenaza

Legend: AML – acute myeloid leukemia; CNS – central nervous system; Flt3-ITD – fms-related receptor tyrosine kinase 3-internal tandem duplication; ECOG – Eastern Cooperative Oncology Group; WBC – white blood cell count; PB – peripheral blood; BM – bone marrow; MRC myelodysplasia-related changes; HCT-CI – hematopoietic cell transplantation-specific comorbidity index; LDH – lactate dehydrogenase

Tabela 3. Univarijantna analiza faktora rizika za DFS kod bolesnika sa AML-om lečenih intenzivnom terapijom

Table 3. Univariate analysis of risk factors for DFS in AML patients treated with intensive therapy

Karakteristike / *Characteristics*	Univarijantna analiza / *Univariate analysis*		
	p	*HR*	*95% CI*
Starost > 60 g naspram < 60 g / *Age >60 y vs. < 60 y*	0.148	100.703	0.764-13,274.567
Le ≥ 30 x10^9/l naspram Le < 30 x10^9/l / *WBC ≥ 30 x10^9/l vs. Le < 30x10^9/l*	0.603	18.519	0.048-7,099.2367
Blasti u PK ≥ 50% / *Blasts in PB ≥ 50%*	0.638	0.145	0.007-3.093
Blasti u KS ≥ 50% / *Blasts in BM ≥ 50%*	0.496	60.494	0.395-9,263.056
MRC AML naspram drugi AML podtipovi / *MRC AML vs. other AML subtypes*	0.045	2.139	0.904-5.063
Flt3-ITD$^+$ naspram Flt3-ITD$^-$/ *Flt3-ITD$^+$ vs. Flt3-ITD$^-$*	0.188	1.075	0.075-15.332
ECOG ≥ 2 naspram < 2 / *ECOG ≥ 2 vs. < 2*	0.118	11.521	0.525-252.941
CNS$^+$ naspram CNS$^-$ / *CNS$^+$ vs. CNS$^-$*	0.471	1.128	0.181-7.024
Nepovoljni naspram intermedijarni i povoljni rizik / *Unfavorable vs. intermediate and favorable risk*	0.983	1.149	0.036-36.308
LDH ≥ 450 / *LDH ≥ 450*	0.873	6.929	0.231-207.864
HCT-CI ≥ 3 / *HCT-CI ≥ 3*	0.094	2.293	0.819-6.423
AML CD56 / *AML CD56*	0.911	12.887	0.26-581.361

Legenda: AML – akutna mijeloidna leukemija; CNS – centralni nervni sistem; *Flt3-ITD* – engl. *fms-related receptor tyrosine kinase 3-internal tandem duplication*; *ECOG* – engl. *Eastern Cooperative Oncology Group*; Le – leukociti; PK – periferna krv; KS – koštana srž; *MRC* – engl. *myelodysplasia-related changes*; *HCT-CI* – engl. *hematopoietic cell transplantation-specific comorbidity index*; LDH – laktat dehidrogenaza

Legend: AML – acute myeloid leukemia; CNS – central nervous system; Flt3-ITD – fms-related receptor tyrosine kinase 3-internal tandem duplication; ECOG – Eastern Cooperative Oncology Group; WBC – white blood cell count; PB – peripheral blood; BM – bone marrow; MRC myelodysplasia-related changes; HCT-CI – hematopoietic cell transplantation-specific comorbidity index; LDH – lactate dehydrogenase

dok je kod pacijenata starijih od 60 godina manja od 10% [4,10,24]. Brojni radovi su pokazali da prognostički faktori pri dijagnozi (citogenetsko-molekularni status, godine starosti, inicijalna leukocitoza, procenat blasta, podtip AML, *ECOG PS*, *HCT-CI*) imaju uticaj na ishod bolesti [1,8,25-30]. Takođe, u druge značajne prediktore ishoda ubrajaju se odgovor na primenjenu terapiju i rezistencija na lekove [8,31].

Naša grupa od 206 bolesnika koji su lečeni intenzivnom terapijom je bila mlađa, prosečne starosti 50,3 godina, u odnosu na literaturne podatke [4,26], te niskog *ECOG PS* i *HCT-CI* skora. Najviše je bilo bolesnika sa *NOS* AML-om 123 (59,7%), prema SZO klasifikaciji iz 2016. godine, a u okviru ove grupe dominirali su bolesnici sa granulocitnom diferencijacijom (80/123, odnosno 65%), a najčešći podtip je bila AML sa sazrevanjem, što odgovara literaturnim podacima [5]. U našoj grupi bolesnika, EMB pri dijagnozi je prezentovala u vidu: hepatosplenomegalije (29,8%), limfadenopatije (21,6%) i hipertrofije desni (10,3%), dok je infiltracija CNS potvrđena kod 46 (22,3%) bolesnika, što je u skladu sa nedavno objavljenim rezultatima [3].

Naši bolesnici su imali veliku stopu postizanja *CR* (79,7%), dok je primarnu refraktornu bolest imalo 32 (20,3%) bolesnika što odgovora literaturnim podacima [10,16]. Rana ili indukciona smrt se javila u 48 (23,3%) slučajeva. U kliničkim studijama, u poslednje dve decenije, uočava se smanjene smrtnosti povezane sa indukcionom terapijom sa 15-20% na manje od 5% [32]. Najčešći uzrok rane smrti bila je sepsa 52,6%. Infekcija je i inače opisana kao jedna od najčešćih uzroka rane smrti [33]. U našoj grupi, relaps se javio kod 62 (67,4%) bolesnika, što je više u odnosu na literaturne podatke [34,16]. Lečenje pomoću TMĆH je jedina metoda kojom bolesnici mogu da se izleče od AML, što su pokazali i naši rezultati – postojala je statički značajna razlika u preživljavanju između transplantiranih i netransplantiranih bolesnika [2,7,10,11].

U skladu sa brojnim drugim studijama [25,26,31], univarijantna analiza je istakla starost bolesnika pri dijagnozi kao prediktor kliničkog ishoda. Naime, rezultati naše studije pokazuju da bolesnici stariji od 60 godina nose 50% veći rizik za kraće *OS* u odnosu na mlađe. Činjenica da je medijana oboljevanja od AML-a 69. godina života, ukazuje na to da najveći broj bolesnika sa AML-om spada u grupu pacijenata sa nepovoljnim rizikom, nevezano od kliničkih i genetičkih parametara, što je u skladu sa ranijim studijama [25,26]. Ovoj tvrdnji doprinosi i podatak da na svakih pet godina starosti odnos hazarda za nepovoljniji ishod lečenja raste za 22% [29]. Brojni su faktori koji bi mogli da objasne lošiju prognozu kod starijih bolesnika sa AML-om. Na prvom mestu jeste lošiji *ECOG PS* uslovljen brojnim komorbi-

50% in younger patients, while being less than 10% in patients older than 60 years [4,10,24]. Numerous studies have shown that prognostic factors at diagnosis (cytogenetic-molecular status, age, initial leukocytosis, percentage of blasts, AML subtype, ECOG PS, HCT-CI) have an impact on the outcome of the disease [1,8,25-30]. Also, other significant predictors of outcome include the response to applied therapy and drug resistance [8,31].

Our group comprising 206 patients treated with intensive therapy was younger, with an average age of 50.3 years, compared to literature data [4,26], with a low ECOG PS and HCT-CI score. The majority of patients had AML NOS, 123 (59.7%), according to the WHO classification from 2016, and in this group, there was a predominance of patients with granulocytic differentiation (80/123, i.e., 65%), and the most common subtype was AML with maturation, which corresponds to literature data [5]. In our group of patients, EMD at diagnosis presented as: hepatosplenomegaly (29.8%), lymphadenopathy (21.6%), and gingival hypertrophy (10.3%), while CNS infiltration was confirmed in 46 (22.3%) patients, which is in keeping with recently published results [3].

Our patients achieved a high rate of CR (79.7%), while 32 (20.3%) patients had primary refractory disease, which corresponds to literature data [10,16]. Early or induced death occurred in 48 (23.3%) cases. In clinical studies, carried out over the last two decades, mortality associated with induction therapy has been reduced from 15-20% to less than 5% [32]. The most common cause of early death was sepsis 52.6%. In fact, infection is described as one of the most common causes of early death [33]. In our group, relapse occurred in 62 (67.4%) patients, which is more as compared to literature data [34,16]. Treatment with HSCT is the only method by which patients can be cured of AML, as shown by our results – there was a statically significant difference in survival between transplanted and non-transplanted patients [2,7,10,11].

In keeping with numerous other studies [25,26,31], univariate analysis highlighted the patient's age at diagnosis as a predictor of clinical outcome. Namely, the results of our study show that patients older than 60 years have a 50% higher risk of shorter OS, compared to younger patients. The fact that the median age of AML diagnosis is 69 years indicates that the greatest number of patients with AML belong to the group of patients with an unfavorable risk, regardless of clinical and genetic parameters, which is in accordance with earlier studies [25,26]. This premise is supported by the fact that for every five years of age, the hazard ratio for a less favorable treatment outcome increases by

ditetima koji su povezani sa godinama starosti [25]. S druge strane, ranije studije su pokazale veću učestalost lošijih citogenetskih markera u starijoj populaciji u odnosu na mlađu. Naime, u studiji u kojoj su poređeni pacijenti mlađi od 56 godina u odnosu na one starije od 75 godina, nepovoljne citogenetske aberacije su bile prisutne kod 51% starijih, odnosno u 35% mlađih bolesnika sa AML-om [29]. U skladu sa time, povoljne citogenetske mutacije u grupi starijih pacijenata činile su samo 4%, dok je u grupi mlađih pacijenata 17% bilo nosilac povoljne citogenetske aberacije [29]. Veće prisustvo povoljnih aberacija kao što su *CBF* AML ili *NPM1* kod mlađih bolesnika donekle odslikava i drugačiju prirodu AML-a u različitim starosnim populacijama. Sa starošću se smanjuje procenat povoljnih citogenetskih aberacija, a raste učestalost nepovoljnih, na prvom mestu kompleksnog i monozomalnog kariotipa, koji nose nepovoljniji rizik za *CR* i *OS* [30]. Takođe, u starijoj populaciji se češće sreće tzv. *multidrug resistance* fenotip: 57% u odnosu na 33% [30].

U našoj grupi obolelih od AML-a, klasifikacija rizika po *ELN*-u nije pokazala svoj prediktivni uticaj. Razlog za to može biti veličina našeg uzorka ili mogući uzrok može biti veoma mali udeo pacijenata sa povoljnim citogenetskim aberacijama u našoj ispitivanoj grupi, odnosno 27 (13,1%). Novi lekovi poput *FTL3* inhibitora, *GO* i *CPV-351*, pokazali su svoj povoljan uticaj na ishod kod bolesnika sa AML-om [35-37]. Navedena ciljna terapija polako menja prognostičke kategorije bolesnika. Naime, uvođenje *FLT3* inhibitora u terapiju AML-a je dovelo do toga da se AML sa *FLT3* mutacijom, koja je do tada bila u najvećoj meri hemorezistentna [34,25] i spadala u grupu nepovoljnih molekularnih aberacija, svrsta u intermedijarni stepen rizika u najnovijoj *ELN* klasifikaciji [7]. Napominjemo da su u našoj studiji bolesnici lečeni standardnim hemioterapijskim protokolima, bez ciljne terapije.

Pored prethodnog prisustva MDS-a, kao i MDS-povezanih citogenetskih abnormalnosti [5], *MRC* AML je povezana sa kompleksnim i monozomalnim kariotipom, kao i genskim mutacijama povezanim sa MDS-om, kao što su: *TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* [7]. U našoj grupi bolesnika sa *MRC* AML-om, u univarijantnoj analizi se pokazao nepovoljan uticaj na *DFS*. U studiji koja je poredila *MCR* AML bolesnike sa bolesnicima koji pripadaju podtipu *NOS* AML, prikazano je da su *MRC* AML bolesnici imali značajno nižu stopu *CR* [38]. Iako terapijske mogućnosti koje bi značajno produžile *OS* ovog podtipa AML-a, još uvek nisu istražene, terapija sa *CPX-351* pokazala je veću stopu petogodišnjeg *OS* u poređenju sa standardnom hemioterapijom [37].

22% [29]. Numerous factors could explain the poorer prognosis in elderly patients with AML, primarily poorer ECOG PS due to numerous comorbidities related to age [25]. On the other hand, previous studies have shown a higher frequency of unfavorable cytogenetic markers in the older population, as compared to the younger. Namely, in a study in which patients younger than 56 years were compared to those older than 75 years, unfavorable cytogenetic aberrations were present in 51% of older and 35% of younger patients with AML [29]. Accordingly, favorable cytogenetic mutations in the group of elderly patients accounted for only 4%, while in the group of younger patients, 17% were carriers of favorable cytogenetic aberrations [29]. The higher presence of favorable aberrations such as CBF AML or NPM1 in younger patients somewhat reflects the different nature of AML in different age populations. With age, the percentage of favorable cytogenetic aberrations decreases, and the frequency of unfavorable ones increases, primarily complex and monosomal karyotypes, which carry a less favorable risk for CR and OS [30]. Also, in the older population, the so-called multidrug resistance phenotype is found more frequently, 57% versus 33% [30].

In our group of AML patients, ELN risk classification did not show its predictive impact. The reason for this may be the size of our sample or a possible cause may be the very small proportion of patients with favorable cytogenetic aberrations in our study group, i.e. 27 (13.1%). New drugs such as FTL3 inhibitors, GO and CPV-351, have shown their beneficial effect on the outcome of patients with AML [35-37]. The aforementioned target therapy has been slowly changing the prognostic categories of patients. Namely, the introduction of FLT3 inhibitors in the treatment of AML led to the fact that AML with FLT3 mutation, which was previously mostly chemoresistant [34,25] and belonged to the group of unfavorable molecular aberrations, was classified as intermediate risk in the latest ELN classification [7]. It should be noted that, in our study, patients were treated with standard chemotherapy protocols, without targeted therapy.

In addition to the prior presence of MDS as well as MDS-associated cytogenetic abnormalities [5], MRC AML is associated with a complex and monosomal karyotype, as well as MDS-associated gene mutations such as the following: TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2 [7]. In our group of patients with MRC AML, univariate analysis showed an unfavorable influence on DFS. In a study comparing MCR AML patients with patients belonging to the AML NOS subtype, it was shown that MRC AML patients had a significantly lower CR rate [38]. Although

ZAKLJUČAK

U našoj studiji smo potvrdili da godine starosti predstavljaju nezavistan prognostički faktor ukupnog preživljavanja kod bolesnika sa AML-om. Takođe, rezultati našeg istraživanja ukazuju da *MRC* AML predstavlja nepovoljan prognostički parametar za *DFS*. Ukupno petogodišnje preživljavanje u analiziranoj grupi je bilo loše. S tim u vezi, uvođenjem novih terapijskih pristupa kao deo standardne terapije za lečenje AML-a, kao i uključivanje bolesnika u studije sa inovativnim lekovima, može doprineti poboljšanju ishoda bolesnika sa akutnom mijeloidnom leukemijom.

SPISAK SKRAĆENICA

AML – akutna mijelodna leukemija
OS – ukupno preživljavanje (engl. *overall survival*)
DFS – preživljavanje bez znakova bolesti (engl. *disease-free survival*)
ECOG PS – engl. *Eastern Cooperative Oncology Group performance status*
ELN – Evropska mreža za leukemiju (engl. *European LeukemiaNet*)
NOS – engl. *not otherwise specified*
MRC – engl. *myelodysplasia-related changes*
CNS – centralni nervni sistem
SZO – Svetska zdravstvena organizacija
RCA – rekurentne citogenetske abnormalnosti
t-AML – engl. *therapy-related AML*
ICC – engl. *International Consensus Classification*
MDS – mijelodisplačni sindrom
MRB – merljiva rezidualna bolest
PCR – engl. *polymerase chain reaction*
TMĆH – transplantacija matičnih ćelija hematopoeze
CR – kompletna remisija (engl. *complete remission*)
FLT3 – engl. *fms-related receptor tyrosine kinase 3*
FLT3-ITD – engl. *mutation an internal tandem duplication*
FLT3-TKD – engl. *tyrosine kinase domain*
NPM1 – engl. *nucleophosmin*
IDH1/IDH2 – izocitrat dehidrogenaze 1/2
GO – gemtuzumab ozogamicin
CPX-351 – lipozomalna formulacija daunorubicina i citarabina
BCL-2 – engl. *B cell lymphoma 2*
EMB – ekstramedularna bolest
LDH – laktat dehidrogenaza
CBF – engl. *core binding factor*
HCT-CI – engl. *hematopoietic cell transplantation-specific comorbidity index*
RB – refraktorna bolest

Sukob interesa: Nije prijavljen.

therapeutic options that would significantly prolong OS in this AML subtype have not yet been investigated, therapy with CPX-351 has shown a higher five-year OS rate, compared to standard chemotherapy [37].

CONCLUSION

In our study, we confirmed that age is an independent prognostic factor of overall survival in patients with AML. Also, the results of our study indicate that MRC AML represents an unfavorable prognostic parameter for DFS. Overall five-year survival in the analyzed group was poor. In this regard, the introduction of new therapeutic approaches as part of standard therapy for the treatment of AML, as well as the inclusion of patients in studies with innovative drugs, can contribute to improving the outcome of patients with acute myeloid leukemia.

ABBREVIATIONS AND ACRONYMS

AML – acute myeloid leukemia
OS – overall survival
DFS – disease-free survival
ECOG PS – Eastern Cooperative Oncology Group performance status
ELN – European LeukemiaNet
NOS – not otherwise specified
MRC – myelodysplasia-related changes
CNS – central nervous system
WHO – World Health Organization
RCA – AML with recurrent cytogenetic abnormalities
t-AML – therapy-related AML
ICC – International Consensus Classification
MDS – myelodysplastic syndrome
MRD – measurable residual disease
PCR – polymerase chain reaction
HSCT – hematopoietic stem cell transplantation
CR – complete remission
FLT3 – fms-related receptor tyrosine kinase 3
FLT3-ITD – mutation an internal tandem duplication
FLT3-TKD – tyrosine kinase domain
NPM1 – nucleophosmin
IDH1/IDH2 – isocitrate dehydrogenase 1/2
GO – gemtuzumab ozogamicin
CPX-351 – liposomal daunorubicin and cytarabine
BCL-2 – B cell lymphoma 2
EMD – extramedullary disease
LDH – lactate dehydrogenase
CBF – core binding factor
HCT-CI – hematopoietic cell transplantation-specific comorbidity index
RD – refractory disease

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