

KLINIČKE KARAKTERISTIKE I ISHOD LEČENJA KOD BOLESNIKA SA AKUTNOM LIMFOBLASTNOM LEUKEMIJOM

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CLINICAL CHARACTERISTICS AND THE TREATMENT OUTCOME IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Ivana Damnjanović¹, Marijana Virijejić^{2,3}, Nada Suvajdžić Vuković^{2,3}

¹ Opšta bolnica Valjevo, Valjevo, Srbija

² Klinika za hematologiju, Univerzitetski klinički centar Srbije, Beograd, Srbija

³ Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

¹ General Hospital Valjevo, Valjevo, Serbia

² Clinic for Hematology, University Clinical Center of Serbia, Belgrade, Serbia

³ Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SAŽETAK

Uvod: Akutna limfoblastna leukemija (ALL) predstavlja malignu transformaciju i proliferaciju progenitorskih limfoidnih ćelija. Na ishod bolesti značajno utiču citogenetsko-molekularne karakteristike, broj leukocita, procenat blasta u krvi i koštanoj srži, zahvaćenost centralnog nervnog sistema (CNS), i modalitet primenjene terapije.

Cilj: Utvrditi kliničke, imunofenotipske i citogenetske osobine bolesnika sa ALL-om i odrediti stopu postizanja remisije, zastupljenost rezistentnih oblika, stopu relapsa, i ukupno preživljavanje (UP) (engl. *overall survival* – OS) bolesnika sa ALL-om; utvrditi prognostičke faktore preživljavanja bolesnika.

Materijali i metode: Retrospektivna studija sprovedena je na 74 bolesnika a obuhvatila je petogodišnji period, od novembra 2013. do oktobra 2018. godine. Analiziran je uticaj pola, starosti, imunološkog podtipa akutne limfoblastne leukemije, broja leukocita, procenta blasta u krvi i koštanoj srži, i citogenetsko-molekularnih karakteristika na preživljavanje bolesnika sa ALL-om.

Rezultati: Istraživanje je obuhvatilo 56 (75,0%) bolesnika sa B-ćelijskom ALL i 18 (25,0%) pacijenata sa T-ćelijskom ALL, prosečne starosti 49,5 godina (opseg: 20 - 77). Kompletne remisije je postignuta kod 54 (72,9%) bolesnika, 40 (71,4%) pacijenata sa B-ćelijskom ALL i 14 (77,7%) pacijenata sa T-ćelijskom ALL. Refraktarnost na indukciju terapiju potvrđena je kod 7 (9,4%) bolesnika sa ALL-om, 5 (8,9%) pacijenata sa B-ćelijskom ALL i 2 (11,1%) pacijenata sa T-ćelijskom ALL. Smrtnost u indukciji zabeležena je kod 13 (17,5%) bolesnika, 8 (14,2%) pacijenata sa B-ćelijskom ALL i 5 (27,7%) pacijenata sa T-ćelijskom ALL. Relaps je imalo 25 (46,3%) bolesnika, 20 (47,5%) pacijenata sa B-ćelijskom ALL i 5 (33,3%) pacijenata sa T-ćelijskom ALL. Univarijantnom analizom utvrđeno je da su sledeći parametri statistički značajno uticali na kraće ukupno preživljavanje: starost ≥ 50 godina ($p < 0,001$), primena COP hemioterapije ($p < 0,001$), netransplantirani bolesnici ($p = 0,011$) i infiltracija CNS-a ($p < 0,001$).

Zaključak: Na preživljavanje bolesnika sa ALL-om značajno utiču starost, modalitet primenjene terapije i zahvaćenost CNS-a.

Ključne reči: akutna limfoblastna leukemija, preživljavanje, prognostički faktori

ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is the malignant transformation and proliferation of lymphoid progenitor cells. The disease outcome is significantly influenced by cytogenetic and molecular characteristics, leukocyte levels, the percentage of blood and bone marrow blasts, infiltration of the CNS, and the modality of the applied therapy.

Aim: Determining clinical, immunophenotypic, and cytogenetic characteristics of patients with ALL; ascertaining remission rates, the presence of resistant forms, the rates of relapse and overall survival (OS); determining prognostic factors for patient survival.

Materials and methods: This five-year retrospective study included 74 patients. The study covered the period from November 2013 to October 2018. The influence of sex, age, immune subtype of ALL, leukocyte levels, percent of blood and bone marrow blasts, and cytotoxic-molecular characteristics on survival were analyzed.

Results: A total of 56 (75.0%) patients had B-cell ALL, while 18 (25.0%) patients had T-cell ALL. The average age was 49.5 years (20 - 77). Complete remission was achieved in 54 (72.9%) patients, 40 (71.4%) B-cell ALL patients and 14 (77.7%) T-cell ALL patients. Refractory leukemia was confirmed in 7 (9.4%) ALL patients, 5 (8.9%) B-cell ALL patients and 2 (11.1%) T-cell ALL patients. Mortality during induction was observed in 13 (17.56%) patients, 8 (14.2%) B-cell ALL patients and 5 (27.7%) T-cell ALL patients. Relapse occurred in 25 (46.3%) patients, 20 (47.5%) B-cell ALL patients and 5 (33.3%) T-cell ALL patients. Univariate analysis showed that an unfavorable outcome was associated with age ≥ 50 years ($p < 0.001$), COP chemotherapy ($p < 0.001$), non-transplant patients ($p = 0.011$), and infiltration of the CNS ($p < 0.001$).

Conclusion: Survival in ALL patients is significantly affected by patient age, modality of applied therapy, and infiltration of the CNS by disease.

Key words: acute lymphoblastic leukemia, survival, prognostic factors

Autor za korespondenciju:

Ivana Damnjanović

Opšta bolnica Valjevo, Valjevo, Srbija

Milenka Stojkovića 2, 14 000 Valjevo, Srbija

Elektronska adresa: idamnjanovic60@gmail.com

Corresponding author:

Ivana Damnjanović

General Hospital Valjevo, Valjevo, Serbia

2 Milenka Stojkovića Street, 14 000 Valjevo, Serbia

E-mail: idamnjanovic60@gmail.com

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UVOD

Akutna limfoblastna leukemija (ALL) je heterogeno oboljenje koje karakteriše maligna transformacija i proliferacija progenitorskih limfoidnih ćelija u koštanoj srži, perifernoj krvi i drugim tkivima [1].

Incidencija akutne limfoblastne leukemije u Evropi iznosi 1,28/100.000 godišnje, sa značajnim varijacijama u odnosu na starosno doba [1]. Najveći procenat obolelih, gotovo 80,0%, registruje se u pedijatrijskoj populaciji, sa stopom preživljavanja od 90,0%, dok adultna populacija ima znatno lošiju prognozu [2].

Prema imunološkoj klasifikaciji, akutne limfoblastne leukemije se dele na B-ćelijsku ALL i T-ćelijsku ALL. U okviru B-ćelijskog tipa akutne limfoblastne leukemije, razlikuju se četiri podtipa: pro B-ALL, *common* B-ALL, pre B-ALL i nezreli B-ALL podtip. T-ćelijski podtipovi akutne limfoblastne leukemije su klasifikovani kao: pro T-ALL, pre T-ALL, kortikalna T-ALL i zrela T-ALL [3].

Najznačajniji prognostički faktor u akutnoj limfoblastnoj leukemiji jesu citogenetske abnormalnosti hromozoma. Postojanje numeričkih hromozomskih aberacija (tetraploidija, hipodiploidija, pseudodiploidija) predstavlja loš prognostički faktor, a procenat preživljavanja kod ovih osoba iznosi 25,0%. Kod osoba sa ALL-om, najbolje proučavana i ujedno najpoznatija strukturna hromozomska aberacija je translokacija t(9;22) (Filadelfija hromozom). Ova aberacija može se uočiti kod 20,0% - 30,0% odraslih bolesnika sa ALL-om. Pored t(9;22), loš prognostički faktor predstavljaju i translokacije na pozicijama t(8;14) i t(4;11) [4]. Osim citogenetskih abnormalnosti, na prognozu kod akutne limfoblastne leukemije utiču i pol (veći broj relapsa kod muškog pola), starosno doba (lošija prognoza kod odraslih nakon šezdesete godine), vreme neophodno za postizanje kompletne remisije (KR), broj leukocita ($>30 \times 10^9$ za B-ALL tip i $>100 \times 10^9$ za T-ALL tip), kao i zahvaćenost centralnog nervnog sistema (CNS) [1,5]. Prisustvo nezrelih prekursorskih T i B ćelija takođe se povezuje sa lošijom prognozom, pa se postojanje B ćelija, koje na svojoj površini ekspimiraju CD19, CD22 i CD79a, kao i T ćelija, koje ne ekspimiraju CD1a, CD8 i CD5, smatra lošim prognostičkim faktorom [6].

Iako se nakon inicijalne hemioterapije (HT) remisija postiže kod gotovo 90,0% bolesnika, stopa izlečenja je samo 40,0% - 50,0%, zbog relapsa. Konvencionalni hemioterapijski režimi koji se primenjuju kod bolesnika sa relapsom ili refraktarnim oblikom B-ćelijske ALL povezuju se sa stopom preživljavanja od 31,0% do 44,0%, ukoliko se primene u ranoj fazi relapsa, odnosno sa stopom preživljavanja od 18,0% - 25,0%, ukoliko se prime ne u kasnijoj fazi i kao druga linija izbora [7].

Transplantacija matičnih ćelija hematopoeze (TMČH) pokazala se veoma efikasnom u lečenju visoko

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by

the malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, peripheral blood, and other tissues [1].

The incidence of ALL in Europe is 1.28 per 100.000 individuals annually, with significant variations in relation to age [1]. The highest percentage of individuals affected by this disease, almost 80.0%, is registered in the pediatric population, whose survival rate is 90.0%, while the adult population has a significantly poorer prognosis [2].

According to immunological classification, there are two types of acute lymphoblastic leukemia: B-cell ALL and T-cell ALL. There are four subtypes within the B-cell type of ALL: pro B-ALL, common B-ALL, pre B-ALL, and immature B-ALL. The subtypes of T-cell ALL are classified as: pro T-ALL, pre T-ALL, cortical T-ALL, and mature T-ALL [3].

The most significant prognostic factor in acute lymphoblastic leukemia is the existence of cytogenetic chromosomal abnormalities. Numeric chromosomal aberrations (tertraploidy, hypodiploidy, and pseudodiploidy) represent a poor prognostic factor, and the survival rate in these individuals is 25.0%. In persons with ALL, the most analyzed and best known structural chromosomal aberration is translocation t(9;22) (Philadelphia chromosome). This aberration is apparent in 20.0% - 30.0% of adult patients suffering from ALL. In addition to t(9;22), translocations t(8;14) and t(4;11) are also poor prognostic factors [4]. Besides cytogenetic abnormalities, the prognosis in acute lymphoblastic leukemia is also affected by sex (greater number of relapses in the male sex), age (poorer prognosis in adults older than 60 years), time necessary for achieving complete remission (CR), leukocyte count ($>30 \times 10^9$ for B-cell ALL and $>100 \times 10^9$ for T-cell ALL), and central nervous system (CNS) involvement [1,5]. The presence of immature precursor T and B cells is also linked to a poor prognosis, which is why the presence of B cells which manifest CD19, CD22 and CD79a on their surface, as well as the presence of T cells which do not manifest CD1a, CD8 and CD5, are believed to be poor prognostic factors [6].

Although remission is achieved in almost 90.0% of the patients, after initial chemotherapy (CT), the cure rate is only 40.0% - 50.0%, due to relapse. Conventional chemotherapy regimens applied in patients with relapse or with the refractory form of B-cell ALL are linked to the survival rate of 31% to 44%, if administered in the early stage of relapse, and with a survival rate of 18.0% - 25.0%, if administered at a later stage of relapse or as a *second-line CT treatment option* [7].

rizičnih bolesnika sa ALL-om. Petogodišnje preživljavanje kod bolesnika kod kojih se ne registruje minimalna rezidualna bolest (MRB) nakon transplantacije je 75,0%, dok je kod bolesnika sa pozitivnom MRB procenat preživljavanja 33,0% [8].

Ciljevi ovog rada bili su da se utvrde kliničke, imunofenotipske i citogenetske osobine bolesnika sa ALL-om, te da se odrede stope postizanja kompletne remisije, zastupljenost rezistentnih oblika, stope relapsa, i ukupno preživljavanje (engl. *overall survival* – OS) bolesnika sa ALL-om. Takođe je cilj bio i da se utvrde prognostički faktor koji utiču na preživljavanje bolesnika sa ALL-om.

MATERIJALI I METODE

Ispitivanu grupu sačinjavalo je 74 bolesnika sa ALL-om; 56 (75,0%) pacijenata sa B-ćelijskom ALL i 18 (25,0%) pacijenata sa T-ćelijskom ALL. Studija je retrospektivna i obuhvata petogodišnji period praćenja bolesnika, od novembra 2013. godine do oktobra 2018. godine. Dijagnoza bolesti je postavljena na osnovu: kliničke slike, nalaza u perifernoj krvi i koštanoj srži, prema preporukama Svetske zdravstvene organizacije (SZO) [9,10]. Kod bolesnika je praćen uticaj određenih parametara na preživljavanje, a to su: pol, starost, imunološki podtip akutne limfoblastne leukemije, broj leukocita, procenat blasta u perifernoj krvi i koštanoj srži, citogenetsko-molekularne karakteristike. Grupa rizika za akutnu limfoblastnu leukemiju je određivana prema modelu grupe rizika GMALL (*German Multicenter Study Group for Adult ALL*) i obuhvatala je standardni, visoki i veoma visoki stepen rizika [11].

Hematološka dijagnostika je podrazumevala:

1. **Morfološku i citohemijsku analizu razmaza koštane srži**
Razmazi koštane srži su prvo bojeni *May-Grünwald-Giemsa* metodom, a potom su vršena specifična citohemijska bojenja (PAS, POX, SB, ANAE). Citohemijsko bojenje omogućava da se odredi linijska pripadnost blasta. Istovremeno se određuju celularnost, prisutnost, brojnost i stepen zrelosti pojedinih ćelija hematopoeze, kao i njihove morfološke osobine [9,10].
2. **Imunofenotipizaciju protočnom citometrijom**
Uzorci ispitanika su prikupljeni i obrađivani prema standardnim preporukama i protokolima, metodom direktne višekolorne imunofluorescencije [12].
3. **Klasičnu citogenetsku analizu metodom HG traka**
Kariotip bolesnika, u momentu postavljanja dijagnoze, utvrđivan je tehnikom HG traka i analiziran je prema Internacionalnom sistemu za humanu citogenetsku nomenklaturu [13].

Hematopoietic stem cell transplantation (HSCT) has proven to be very efficient in the treatment of high-risk patients suffering from ALL. Five-year survival in patients in whom minimal residual disease (MRD) after transplantation is not registered is 75.0%, while the survival rate in patients with a positive MRD status is 33.0% [8].

The aims of this study were to determine clinical, immunophenotypic, and cytogenetic characteristics of ALL patients, as well as to ascertain complete remission rates, the presence of resistant forms, the rates of relapse, and overall survival (OS) in ALL patients. Also, the aim was to determine prognostic factors affecting ALL patient survival.

MATERIALS AND METHODS

The analyzed group included 74 ALL patients; 56 (75.0%) patients with B-cell ALL and 18 (25.0%) patients with T-cell ALL. The study is retrospective, and it encompasses a five-year period of patient follow-up, from November 2013 to October 2018. The diagnosis of the disease was established based on clinical presentation and on peripheral blood and bone marrow findings, in keeping with World Health Organization (WHO) recommendations [9,10]. The following specific parameters were monitored in patients: sex, age, immunological subtype of acute lymphoblastic leukemia, leukocyte count, percentage of blasts in peripheral blood and bone marrow, molecular cytogenetic characteristics. The group of risk factors for acute lymphoblastic leukemia was determined according to the GMALL (*German Multicenter Study Group for Adult ALL*) risk factor group model and it included standard, high and very high level of risk [11].

Hematological diagnostics included:

1. **Morphological and cytochemical analysis of the bone marrow smear**
Bone marrow smears were first dyed with the application of the May-Grünwald-Giemsa method, after which specific cytochemical staining techniques were applied (PAS, POX, SB, ANAE). Cytochemical staining makes it possible to determine the lineage of the blasts. At the same time, the cellularity, presence, number, and the maturation stage of individual hematopoietic cells, as well as their morphological characteristics were determined [9,10].
2. **Immunophenotypization by means of flow cytometry**
The samples of the test subjects were collected and processed according to the standard recommendations and protocols, with the application of the method of direct multicolor immunofluorescence [12].
3. **Classical cytogenetic analysis with the application of the method of HG strips**
The patient's karyotype, at the time of establishing diagnosis, was determined with the use of the G

4. Molekularno - genetska istraživanja

U okviru molekularno-genetskih istraživanja vršene su sledeće procedure: izolacija mononuklearnih ćelija iz aspirata koštane srži, izolacija RNK iz mononuklearnih ćelija, reverzna transkripcija (RT), standardizovani RT-PCR (*polymerase chain reaction*) protokol za detekciju BCR-ABL fuzionih transkripta.

Terapija bolesnika sa ALL-om

Bolesnici sa ALL-om lečeni su hemioterapijskim protokolima: Hyper-CVAD i COP. Hyper-CVAD protokol sastoji se od neparne i parne kure i primenjivan je kod bolesnika koji su imali ≤ 65 godina, ECOG (*Eastern Cooperative Oncology Group*) ≤ 2 i HCT-CI (*hematopoietic cell transplantation-comorbidity index*) ≤ 3 . Neparna kura obuhvata primenu: ciklofosfamida, 300 mg/m² i.v., D1-3; mesne, 600 mg/m² i.v., D1-3; doxorubicina, 50 mg/m² i.v., D4; vinkristina, 2 mg i.v., D4 i D11; deksametazona, 40 mg i.v., D1-4 i D11-14. Sastav parne kure čine: metotreksat (MTX), 200 mg/m² i 800 mg/m² i.v., D1 tokom 22 h, i visoke doze citozara (Ara-C) 3 g/m²/12 h, D2 i D3. Terapija održavanja u trajanju od dve godine podrazumeva primenu: 6-merkaptopurina *per os*, 3x50 mg dnevno; MTX-a, i.m., 20 mg/m² jednom nedeljno; prednizona, 200 mg dnevno, D1-5 u mesecu; vinkristina, 2 mg i.v., jednom mesečno. Bolesnici sa ALL-om su primali profilaktičnu terapiju za centralni nervni sistem. COP protokol je primenjivan kod bolesnika koji su imali ECOG >2 , HCT-CI >3 , >65 godina, u sastavu: ciklofosfamid amp, 750 mg/m² i.v., D1; onkovin, 2 mg i.v., D1; i prednizon tbl, 100 mg p.o., D1-5. Alogena transplantacija matičnih ćelija hematopoeze (TMČH) je sprovedena kod bolesnika sa ALL-om koji su imali visoki i veoma visoki stepen rizika. Kompletne remisije (KR) podrazumeva $\leq 5,0\%$ blasta u koštanoj srži, dok se pod refraktarnom bolešću podrazumeva nepostizanje kompletne remisije, nakon primenjena dva ciklusa hemioterapije. Ukupno preživljavanje (engl. *overall survival* - OS) je definisano kao vreme od dijagnoze do smrti ili datuma poslednjeg praćenja. Preživljavanje bez znakova bolesti (engl. *disease-free survival* - DFS) je definisano kao vreme od postizanja kompletne remisije do recidiva ili smrti. Rana smrt (engl. *early death* - ED) je definisana kao smrt u roku od 28 dana od otpočinjanja indukcione hemioterapije.

U statističkoj obradi podataka korišćene su metode deskriptivne statistike. Za ispitivanje razlike učestalosti, korišćeni su hi-kvadrat test, odnosno Fišerov test tačne verovatnoće. Za analizu dužine preživljavanja korišćena je Kaplan-Majerova metoda, a log-rank test je primenjen za poređenje preživljavanja među ispitivanim grupama. Za identifikaciju faktora rizika korišćen je univarijantni Koksov proporcionalni regresioni model. Svi statistički testovi su posmatrani

banding technique and analyzed in keeping with the International System for Human Cytogenetic Nomenclature [13].

4. Molecular - genetic study

The following procedures were performed within molecular genetic studies: isolation of mononuclear cells from bone marrow aspirate, isolation of RNA from mononuclear cells, reverse transcription (RT), standardized RT-PCR (*polymerase chain reaction*) protocol for the detection of BCR-ABL fusion transcripts.

Treatment of ALL patients

ALL patients were treated with the Hyper-CVAD and COP chemotherapy protocols. The Hyper-CVAD protocol consists of even and odd treatment courses applied in patients aged ≤ 65 years, who had an ECOG (Eastern Cooperative Oncology Group) ≤ 2 and an HCT-CI (hematopoietic cell transplantation-comorbidity index) ≤ 3 . The odd course of treatment includes the application of the following: cyclophosphamide, 300 mg/m² IV, D1-3; mesna, 600 mg/m² IV, D1-3; doxorubicin, 50 mg/m² IV, D4; vincristine, 2 mg IV, D4 and D11; dexamethasone, IV 40 mg, D1-4 and D11-14. The composition of the even course of treatment is the following: methotrexate (MTX), 200 mg/m² and 800 mg/m² IV, D1 for 22h; and high doses of cytosar (Ara-C) 3 g/m²/12 h, D2 and D3. The maintenance therapy over a period of two years included the application of: 6-mercaptopurine *per os*, 3x50 mg per day; MTX, IM 20 mg/m², once a week; prednisone, 200 mg a day, D1-5 in the month; vincristine, 2 mg IV, once a month. Patients with ALL received CNS prophylaxis. The COP protocol was applied in patients who had ECOG >2 , HCT-CI >3 , >65 years, and consisted of the following: cyclophosphamide amp, 750 mg/m² IV, D1; oncovin, 2 mg IV, D1; and prednisone tbl, 100 mg p.o., D1-5. Allogeneic hematopoietic stem cell transplantation (HSCT) was carried out in ALL patients who had a high or very high level of risk. Complete remission (CR) means $\leq 5.0\%$ of blasts in the bone marrow, while failing to achieve full remission after two cycles of chemotherapy is considered to be refractory disease. Overall survival (OS) is defined as the time from diagnosis until death or the last follow-up date. Disease-free survival (DFS) is defined as the time from achieving complete remission until relapse or death. Early death (ED) is defined as death within 28 days of starting induction chemotherapy.

In the statistical processing of data, methods of descriptive statistics were applied. For analyzing the difference in frequency, the Chi-square test, i.e., the Fisher's exact test was applied. For the analysis of the length of survival, the Kaplan-Meier method was used, while the log-rank test was applied for comparing survival amongst the test groups. The univariate Cox proportional hazards

na nivou značajnosti nulte hipoteze od $p < 0,05$. Statistička analiza je urađena na računaru primenom licenciranog statističkog paketa SPSS 15.0.

REZULTATI

Istraživanje je obuhvatilo 74 bolesnika sa ALL-om, od kojih je 75,0% imalo B-ćelijsku ALL, a 25% T-ćelijsku ALL. Kliničko laboratorijske karakteristike bolesnika prikazane su u Tabeli 1.

Najviše bolesnika, 33 (47,1%) je imalo normalan kariotip, dok je t(9;22) bila prisutna kod 15 (23,5%) bolesnika. Druge hromozomske aberacije bile su prisutne kod 20 (29,4%) bolesnika. PCR analizom utvrđeno je prisustvo BCR-ABL rearanžmana kod 22 (29,7%) bolesnika; 50 (67,5%) bolesnika nije imalo pozitivan PCR na BCR-ABL; dok za 2 bolesnika (2,7%) nisu postojali podaci.

regression model was used for identifying risk factors. All statistical tests were observed at the null-hypothesis significance level of $p < 0.05$. Statistical analysis was performed on a PC with the application of a licensed SPSS 15.0 statistical package.

RESULTS

The study included 74 patients with ALL, of whom 75% suffered from B-cell ALL, while 25.0% were affected with T-cell ALL. The clinical and laboratory characteristics of the patients are presented in Table 1.

Most of the patients, 33 (47,1%) had a normal karyotype, while t(9;22) was present in 15 (23.5%) patients. Other chromosomal aberrations were present in 20 (29.4%) patients. PCR analysis determined the presence of BCR-ABL rearrangement in 22 (29.7%) patients; 50

Tabela 1. Kliničko-laboratorijske karakteristike

Table 1. Clinical and laboratory characteristics

Karakteristika / Characteristic	Vrednosti / Values
Pol, n (%) / Gender, n (%)	74 (100.0%)
Muški / Male	35 (47.3%)
Ženski / Female	39 (52.7%)
Starost, $x \pm sd$ / Age, $x \pm sd$, med (min-max)	47.2 $\pm$ 16.4 49.5 (20 - 77)
CNS infiltracija, n (%) / CNS infiltration, n (%)	
Da / Yes	24 (38.1%)
Ne / No	39 (61.9%)
Imunofenotip, n (%) / Immunophenotype, n (%)	
B-ALL / B-ALL	56 (75.0%)
Pro B-ALL / Pro B-ALL	3 (3.7%)
Common B-ALL / Common B-ALL	37 (66.7%)
Pre B-ALL / Pre B-ALL	16 (29.6%)
T-ALL / T-ALL	18 (25.0%)
Pro T-ALL / Pro T-ALL	9 (50.0%)
Pre T-ALL / Pre T-ALL	6 (33.3%)
Kortikalna T-ALL / Cortical T-ALL	3 (16.7%)
B-ALL / B-ALL	
Le $\geq 30 \times 10^9/L$ / Le $\geq 30 \times 10^9/L$	13 (24.5%)
Le $< 30 \times 10^9/L$ / Le $< 30 \times 10^9/L$	40 (75.5%)
T-ALL / T-ALL	
Le $\geq 100 \times 10^9/L$ / Le $\geq 100 \times 10^9/L$	16 (88.9%)
Le $< 100 \times 10^9/L$ / Le $< 100 \times 10^9/L$	2 (11.1%)
% blasta u perifernoj krvi, med (min-max) / % of blasts in peripheral blood, med (min-max)	46.5 (0 - 94)
% blasta u koštanoj srži / % of blasts in bone marrow	
$< 50\%$	9.0%
$\geq 50\%$	62.0%

Standardni stepen rizika postojao je kod 20 (26,0%) bolesnika, visoki rizik kod 31 (45,2%) pacijenta, a veoma visoki rizik kod 22 (28,8%) bolesnika.

Najveći broj bolesnika sa B-ćelijskom ALL (75,5%) je imao broj leukocita manji od $30 \times 10^9/L$, a njih 24,5% je imalo broj leukocita veći od $30 \times 10^9/L$. Među bolesnicima sa T-ćelijskom ALL, 88,9% je imalo broj leukocita veći od $100 \times 10^9/L$, a svega 11,1% bolesnika je imalo broj leukocita manji od $100 \times 10^9/L$.

Najveći broj bolesnika sa ALL-om, 63 (85,1%) je lečen HT-om, po protokolu *Hyper-CVAD*, dok je 11 (14,9%) bolesnika lečeno po *COP* protokolu. Transplantacija matičnih ćelija hematopoeze je sprovedena kod 17 (27,4%) bolesnika, dok 41 bolesnik (70,7%) nije bio podvrgnut transplantaciji.

Kod 54 (72,9%) bolesnika postignuta je KR i to kod 40 (71,4%) pacijenata sa B-ćelijskom ALL i 14 (77,7%) bolesnika sa T-ćelijskom ALL. Refraktarnost na indukcionu terapiju potvrđena je kod 7 (9,4%) bolesnika sa ALL-om, od kojih je 5 (8,9%) bilo sa B-ćelijskom ALL i 2 (11,1%) sa T-ćelijskom ALL. Smrtnost u indukciji zabeležena je kod 13 (17,56%) bolesnika, među kojima je bilo 8 (14,2%) pacijenata sa B-ćelijskom ALL i 5 (27,7%) pacijenata sa T-ćelijskom ALL. Relaps je imalo 25 (46,3%) bolesnika, odnosno 20 (47,5%) pacijenata sa B-ćelijskom ALL i 5 (33,3%) pacijenata sa T-ćelijskom ALL. Ni za jedan od analiziranih parametara nije utvrđena statistički značajna razlika između bolesnika sa B-ćelijskom ALL i onih sa T-ćelijskom ALL.

Medijana preživljavanja bolesnika sa ALL-om bila je 8 meseci, dok je petogodišnje preživljavanje registrovano kod 23,2% ispitanika (Grafikon 1). Medijana preživljavanja bez znakova bolesti bila je 12 (1 - 72) meseci. Analiza ukupnog preživljavanja prema tipu leukemije pokazala je da je medijana preživljavanja bolesnika

(67,5%) patients did not have a positive PCR result for BCR-ABL, while there was no data for 2 (2,7%) patients.

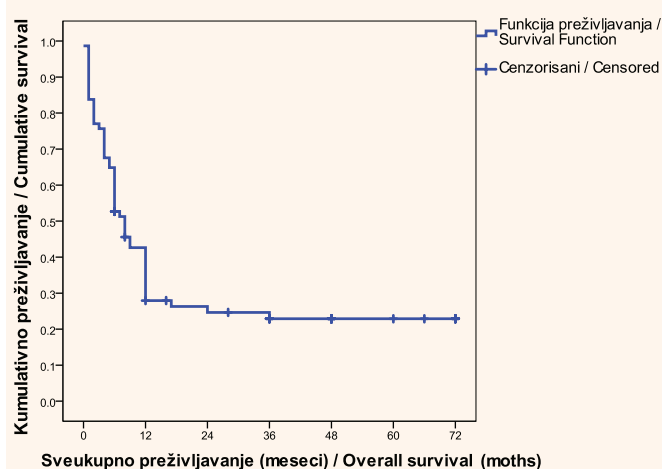
The standard risk level was present in 20 (26,0%) patients; high risk was registered in 31 (45,2%) patients, while a very high risk was found in 22 (28,8%) patients.

A majority of the patients with B-cell ALL (75,5%) had a leukocyte count lower than $30 \times 10^9/L$, while 24,5% had a leukocyte count above $30 \times 10^9/L$. Amongst the patients with T-cell ALL, 88,9% had a leukocyte count above $100 \times 10^9/L$, and only 11,1% patients had a leukocyte count lower than $100 \times 10^9/L$.

The greatest number of patients with ALL, 63 (85,1%) of them, were treated with CT in keeping with the *Hyper-CVAD* protocol, while 11 (14,9%) patients were treated with the *COP* protocol. Hematopoietic stem cell transplantation was carried out in 17 (27,4%) patients, while 41 (70,7%) patients did not undergo transplantation.

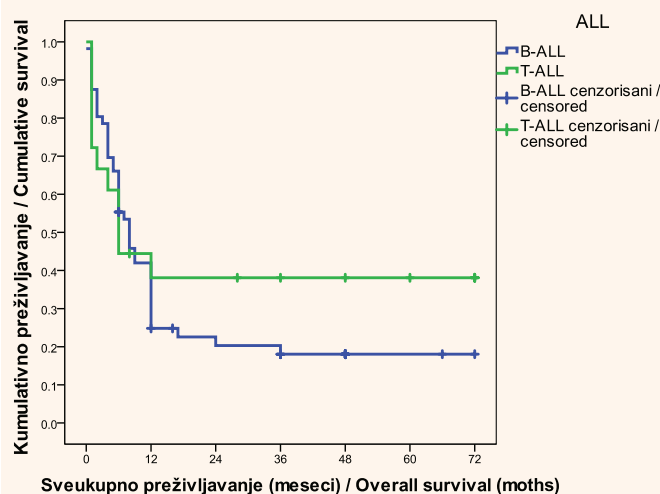
In 54 (72,9%) patients, CR was achieved in 40 (71,4%) patients with B-cell ALL and 14 (77,7%) patients with T-cell ALL. Refractoriness to induction therapy was confirmed in 7 (9,4%) ALL patients, of whom 5 (8,9%) patients suffered from B-cell ALL, and 2 (11,1%) patients had T-ALL. Mortality in induction was registered in 13 (17,56%) patients, of whom 8 (14,2%) patients had B-cell ALL and 5 (27,7%) patients had T-cell ALL. Relapse occurred in 25 (46,3%) patients, i.e., 20 (47,5%) patients with B-cell ALL and 5 (33,3%) with T-cell ALL. Statistically significant difference between patients with B-cell ALL and those with T-cell ALL was not found for any of the analyzed parameters.

The median survival of ALL patients was 8 months, while five-year survival was registered in 23,2% subjects (Graph 1). Median survival without signs of disease was 12 (1 - 72) months. The analysis of overall survival, according to the type of leukemia, showed



Grafikon 1. Kaplan-Majerova kriva preživljavanja bolesnika sa ALL

Graph 1. Overall survival of All patients by Kaplan-Meier method



Grafikon 2. Kaplan-Majerova kriva preživljavanja prema imunološkom tipu ALL

Graph 2. Overall survival of All patients according to immune type ALL by Kaplan-Meier method

Tabela 2. Prediktorni faktori za loše ukupno preživljavanje kod bolesnika sa ALL-om

Prediktor OS / Predictor of OS	HR	95% CI HR	p
Starost ≥ 55 godina / Age ≥ 55	3.32	1.91 - 5.79	<0.001
HT (Hyper-CVAD/COP) / CP (Hyper-CVAD/COP)	3.19	1.61 - 6.30	<0.001
TMČH (da/ne) / HSCT (yes/no)	0.38	0.18 - 0.80	0.011
CNS infiltracija / CNS infiltration	3.25	1.75 - 6.02	<0.001

Spisak skraćenica: OS – Ukupno preživljavanje (engl. *overall survival*); R – Odnos hazarda (engl. *hazard ratio*); CI – Interval poverenja (engl. *confidence interval*); HT – Hemioterapijski protokol; TMČH – Transplantacija matične ćelije hematopoeze; CNS – centralni nervni sistem

sa B-ćelijskom ALL bila 8 meseci, dok je kod pacijenata sa T-ćelijskom ALL iznosila 6 meseci. Nije uočena statistički značajna razlika u vremenu preživljavanja između obolelih od B i T leukemije ($p = 0,372$) (Grafikon 2).

Koksovom regresijom (univarijantnom) analizom utvrđeno je da su sledeći parametri statistički značajno uticali na loše ukupno preživljavanje: starost ≥ 50 godina ($p < 0,001$), primena COP HT protokola ($p < 0,001$), netransplantirani bolesnici ($p = 0,011$) i infiltracija CNS-a ($p < 0,001$) (Tabela 2).

Zbog nepovoljnog odnosa ishoda i potencijalnih prediktora, multivarijantna analiza nije sprovedena.

DISKUSIJA

Akutna limfoblastna leukemija predstavlja maligno oboljenje koje se sa znatno lošijom prognozom javlja u odrasloj dobi u odnosu na pedijatrijsku populaciju [2]. Na ishod bolesti, pored uzrasta, utiču i brojni faktori među kojima su najznačajnije citogenetske molekularne promene.

Naše istraživanje obuhvatilo je 74 bolesnika, među kojima je procenat žena (52,7%) bio nešto veći u odnosu na ispitanike muškog pola (47,3%). Prema literaturnim podacima, među obolelim od akutne limfoblastne leukemije dominiraju osobe muškog pola [14,15].

U našoj studijskoj grupi najviše je bilo bolesnika sa B-ćelijskom ALL koji su imali *common* B-ALL imunološki podtip - 37 (66,7%). Rezultati prethodnih studija pokazuju da je B-ALL tip znatno češći od T-ALL tipa i da je zastupljen kod 88,0% bolesnika sa akutnom limfoblastnom leukemijom, dok je T-ALL tip prisutan kod 12,0% bolesnika sa ALL-om [16].

PCR analizom potvrđena je BCR-ABL pozitivnost kod 22 (29,7%) bolesnika, od kojih su 4 (18,2%) imala normalan kariotip, dok je kod 18 (81,8%) bolesnika registrovana t(9;22). Prisustvo Filadelfija hromozoma kod bolesnika sa ALL-om smatra se lošim prognostičkim faktorom i povezuje se sa kraćom kompletnom

Table 2. Predictors of overall survival in patients with ALL

List of abbreviations: OS – Overall survival; HR – Hazard ratio; CI – Confidence interval; CP – Chemotherapy protocol; HSCT – Hematopoietic stem cell transplantation; CNS – Central nervous system

that median survival in patients with B-cell ALL was 8 months, while it was 6 months in patients with T-cell ALL. Statistically significant difference in the survival time between B-cell and T-cell leukemia patients was not registered ($p = 0.372$) (Graph 2).

With the aid of the univariate Cox regression analysis, it was established that the following parameters had a statistically significant impact on poor overall survival: age ≥ 50 years ($p < 0.001$), application of the COP chemotherapy protocol ($p < 0.001$), non-transplant patients ($p = 0.011$), and CNS infiltration ($p < 0.001$) (Table 2).

Due to the unfavorable relationship between the outcome and the potential predictors, multivariate analysis was not performed.

DISCUSSION

Acute lymphoblastic leukemia is a malignant disease which occurs with a significantly poorer prognosis in adult age than in the pediatric population [2]. In addition to age, numerous factors, amongst which the most important are cytogenetic molecular changes, affect the outcome of the disease.

Our study included 74 patients, amongst whom the percentage of women (52.7%) was somewhat higher as compared to male subjects (47.3%). According to the data from literature, amongst ALL patients, male individuals are prevalent [14,15].

In our test group, most of the patients had B-cell ALL; the *common* B-ALL immunological subtype - 37 (66.7%). The results of previous studies indicate that B-cell ALL is much more frequent than T-cell ALL and that it is present in 88.0% ALL patients, while T-cell ALL is present in 12.0% of ALL patients [16].

PCR analysis confirmed BCR-ABL positivity in 22 (29.7%) patients, of whom 4 (18.2%) had a normal karyotype, while in 18 (81.8%) patients t(9;22) was registered. The presence of the Philadelphia chromosome in ALL patients is considered to be a poor prognostic

remisijom, većom refraktarnošću na primenjivanu terapiju i lošim ukupnim preživljavanjem. Rezultati drugih istraživanja pokazuju da se Filadelfija hromozom kod osoba sa ALL-om javlja sa učestalošću od 20% - 30% u adultnoj populaciji, dok je u pedijatrijskoj populaciji učestalost manja i iznosi 5,0% [17].

Broj leukocita predstavlja važan prognostički faktor u akutnoj limfoblastnoj leukemiji. U našem istraživanju, 13 bolesnika (24,5%) sa B-ćelijskom ALL je imalo broj leukocita veći od $30 \times 10^9/L$, dok je 16 (88,9%) bolesnika sa T-ćelijskom ALL imalo broj leukocita veći od $100 \times 10^9/L$. Smatra se da broj leukocita veći od $30 \times 10^9/L$ kod B-ALL tipa, kao i broj leukocita veći od $100 \times 10^9/L$ kod T-ALL tipa predstavlja loš prognostički faktor. Ovo potvrđuje i istraživanje Roua i saradnika, koje je pokazalo da broj leukocita veći od $30 \times 10^9/L$ predstavlja nepovoljan prognostički faktor [18].

Najveći procenat naših bolesnika, 63 (85,1%), lečen je pomoću HT-a, po protokolu *Hyper-CVAD*. Bolesnici koji su bili stariji od 65 godina i koji su imali *ECOG* >2 i *HCT-CI* >3 lečeni su po *COP* protokolu (11 bolesnika - 14,9%). Rezultati prethodno sprovedenih studija pokazuju da se dobar odgovor na primenu *Hyper-CVAD* protokola registruje u 92,0% slučajeva, sa petogodišnjom stopom preživljavanja koja iznosi 32,0% [19].

KR je postignuta kod 54 bolesnika (72,9%), 40 (71,4%) sa B-ćelijskom ALL i 14 (77,7%) sa T-ćelijskom ALL. Smrtnost u indukciji je zabeležena kod 13 (17,5%) bolesnika, među kojima je bilo 8 (14,2%) pacijenata sa B-ćelijskom ALL i 5 (27,7%) pacijenata sa T-ćelijskom ALL. Relaps je imalo 25 (46,3%) bolesnika, odnosno 20 (47,5%) pacijenata sa B-ćelijskom ALL i 5 (33,3%) pacijenata sa T-ćelijskom ALL. Refraktarnost na indukcionu terapiju potvrđena je kod 7 (9,4%) bolesnika sa ALL-om, od kojih je 5 (8,9%) bilo sa B-ćelijskom ALL, a 2 (11,1%) sa T-ćelijskom ALL. Rezultati prethodnih istraživanja pokazuju da se refraktarnost sreće kod 10,0% bolesnika [17], dok se rana smrtnost kreće od 5,0% do 10,0%, a u pedijatrijskoj populaciji je znatno niža i iznosi 1,0% [20]. TMČH je sprovedena kod 17 bolesnika (27,4%) sa visokim i veoma visokim stepenom rizika.

S obzirom na to da se ALL retko registruje u adultnoj populaciji, postoji malo podataka koji pokazuju stope preživljavanja bolesnika sa ALL-om. Sprovedeno istraživanje je pokazalo da je medijana ukupnog preživljavanja ispitanika sa ALL-om bila 8 meseci, sa nešto dužim preživljavanjem kod osoba sa B-ćelijskom ALL, što se nije pokazalo kao statistički značajna razlika u odnosu na bolesnike sa T-ćelijskom ALL. Petogodišnje preživljavanje u ovom istraživanju bilo je 23,2%. U našem istraživanju, medijana preživljavanja bez znakova bolesti bila je 12 meseci. Stopa petogodišnjeg preživljavanja, u odnosu na naše rezultate,

factor and is connected with shorter complete remission, grater refractoriness to the applied therapy, and poor overall survival. The results of other studies show that the Philadelphia chromosome occurs in 20% - 30% of the ALL adult patient population, while in the pediatric population, the frequency of its occurrence is lesser, amounting to 5.0% [17].

The leukocyte count is an important prognostic factor in acute lymphoblastic leukemia. In our study, 13 (24.5%) patients with B-cell ALL had a leukocyte count above $30 \times 10^9/L$, while 16 (88.9%) patients with T-cell ALL had a leukocyte count above $100 \times 10^9/L$. It is considered that a leukocyte count above $30 \times 10^9/L$ in B-cell ALL, as well as a leukocyte count above $100 \times 10^9/L$ in T-cell ALL, represents a poor prognostic factor. This is confirmed by a study by Rowe et al., showing that a leukocyte count above $30 \times 10^9/L$ presents an unfavorable prognostic factor [18].

The highest percentage of our patients, 63 (85.1%), was treated with CT, according to the *Hyper-CVAD* protocol. Patients older than 65 years with an *ECOG* >2 and an *HCT-CI* >3 were treated with the *COP* protocol (11 patients - 14.9%). The results of previous studies show that a good response to the application of the *Hyper-CVAD* protocol was registered in 92.0% of the cases, with a 5-year survival rate of 32.0% [19].

CR was achieved in 54 (72.9%) patients, 40 (71.4%) patients with B-cell ALL and 14 (77.7%) patients with T-cell ALL. Mortality in induction was registered in 13 (17.5%) patients, among whom there were 8 (14.2%) patients with B-cell ALL and 5 (27.7%) patients with T-cell ALL. Relapse occurred in 25 (46.3%) patients, i.e., 20 (47.5%) patients with B-cell ALL and 5 (33.3%) patients with T-cell ALL. Refractoriness to induction therapy was confirmed in 7 (9.4%) ALL patients, of whom 5 (8.9%) had B-cell ALL, and 2 (11.1%) had T-cell ALL. The results from previous studies show that refractoriness is found in 10.0% of patients [17], while the early death rate ranges from 5.0% to 10.0%, while in the pediatric population it is significantly lower, amounting to 1.0% [20]. HSCT was carried out in 17 (27.4%) patients with a high and very high level of risk.

Bearing in mind that ALL is rarely registered in the adult population, there is little data indicating the survival rates of ALL patients. The study that was carried out demonstrated that the median overall survival of ALL subjects was 8 months, with somewhat longer survival in individuals with B-cell ALL, which did not prove to be as a statistically significant difference as compared to patients with T-cell ALL. Five-year survival in this study was 23.2%. In our study, median survival without signs of illness was 12 months. As compared to the results from our study, the rate of five-year survival

bila je viša u američkim (35,5%) i nemačkim (43,4%) studijskim grupama [21].

Univarijantnom analizom je utvrđeno da, osim uzrasta, loš prognostički faktor predstavljaju i modalitet primenjene terapije i zahvaćenost CNS-a. Ove rezultate potvrđuju i druga istraživanja koja pokazuju da se starije životno doba povezuje sa lošijom prognozom kao i da se stope preživljavanja značajno smanjuju sa povećanjem godina starosti [21]. Bolesnici starosti između 15 i 24 godine imaju 10,0% veću stopu petogodišnjeg preživljavanja u odnosu na bolesnike starijeg doba između 25 i 39 godina [5]. U radu Lazarusa i saradnika pokazana je statistički značajna razlika u ukupnom preživljavanju kod bolesnika koji su pri dijagnozi bolesti imali zahvaćenost CNS-a [22].

ZAKLJUČAK

Naše istraživanje je pokazalo loše preživljavanje bolesnika sa ALL-om, na koje značajno utiču starost, modalitet primenjene terapije i zahvaćenost CNS-a. Uvođenje preciznije molekularne dijagnostike, praćenje minimalne rezidualne bolesti i primena ciljne terapije može doprineti boljem preživljavanju ovih bolesnika, što poslednja istraživanja i potvrđuju.

Sukob interesa: Nije prijavljen.

was higher in American (35.5%) and German (43.4%) test groups [21].

Univariate analysis established that, in addition to age, the modality of applied therapy and CNS involvement were poor prognostic factors. These results have been confirmed by other studies demonstrating that older age is linked to a poorer prognosis, as well as that survival rates significantly decrease with increased age [21]. Patients aged between 15 and 24 years have a 10.0% higher rate of five-year survival as compared to patients aged between 25 and 39 years [5]. In a study by Lazarus et al., a statistically significant difference in overall survival was established in patients who had CNS involvement at diagnosis [22].

CONCLUSION

Our study has shown poor survival of ALL patients, which is significantly affected by age, the modality of administered therapy, and the involvement of the CNS. Introducing more precise molecular diagnostics, monitoring minimal residual disease, and the application of targeted therapy may contribute to a better survival of these patients, which has been confirmed by the latest research.

Conflict of interest: None declared.

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