# UČESTALOST I TERAPIJA RELAPSA NAKON ALOGENE TRANSPLANTACIJE MATIČNIH ĆELIJA HEMATOPOEZE

ORIGINALNI RAD

ORIGINAL ARTICLE

# INCIDENCE AND THERAPY OF RELAPSE AFTER ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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## SAŽETAK

**Uvod/Cilj:** Relaps osnovne bolesti nakon alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH) je jedna od najtežih i najćešćih posttransplantacijskih komplikacija i predstavlja vodeći uzrok neuspeha terapije i smrti pacijenata. Cilj rada jeste procena učestalosti i tipa relapsa, u odnosu na vreme javljanja; analiza uticaja kondicionih režima na pojavu relapsa; pregled terapijskih mogućnosti nakon pojave relapsa; kao i procena prognoze pacijenata koji ispolje relaps.

**Metode:** U retrospektivnu kohortnu studiju uključeno je 58 pacijenata kojima je izvršena alo-TMĆH. Pre transplantacije, sprovedena je terapija kondicionim režimom redukovanog intenziteta *(RIC)* ili mijeloablativnim režimom *(MAC)*. Dijagnoza relapsa je postavljana analizom mijelograma, analizom citogenetike, analizom minimalne rezidualne bolesti, analizom ćelijskog himerizma, kao i analizom imunohematološkog himerizma antigena krvno grupnih sistema. Formirana je baza podataka po ispitivanim obeležjima bolesnika. Preživljavanje bolesnika analizirano je Kaplan-Majerovom metodom i upoređivano uz pomoć *log-rank* testa.

**Rezultati:** Češće je upotrebljavan *MAC* (43 pacijenta) u odnosu na *RIC* (15 pacijenata), kao kondicioni režim. Nakon transplantacije, relaps je imalo 18 (34%) od 53 pacijenta. Izbor kondicionog režima nije imao uticaja na javljanje relapsa, ali su pacijenti na *RIC* režimu duže živeli (38,5 ± 7 meseci) u odnosu na pacijente na *MAC* režimu (27,8 ± 3,5 meseci). Međutim, razlika u preživljavanju nije imala statistički značaj ($p = 0,318$). Prosečno vreme preživljavanja pacijenata koji su imali relaps iznosilo je 26 ± 5 meseci, dok je kod pacijenata koji nisu imali relaps iznosilo 41 ± 4 meseca.

**Zaključak:** Pacijenti koji su primili slabije kondicione režime *(RIC)* imali su duže vreme preživljavanja, bez povećanja stope relapsa. U budućnosti treba razmotriti uključivanje pacijenata starijih od 60 godina, kao kandidata za transplantaciju, kao i moguću primenu profilaktičke terapije, radi preveniranja relapsa kod visokorizičnih pacijenata.

**Ključne reči:** kondicioni režim redukovanog intenziteta, mijeloablativni kondicioni režim, preživljavanje

## ABSTRACT

**Introduction/Aim:** Disease relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the most common and most severe post transplantation complications and represents the leading cause of treatment failure and patient death. The aim of this study is to assess the frequency and types of relapse, in relation to the time of occurrence; analyze the influence of conditioning regimens on relapse occurrence; review the therapeutic options after the occurrence of relapse; assess the prognosis in patients with relapse.

**Methods:** This retrospective cohort study included 58 patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). Pre-transplantation therapy was performed with a reduced-intensity conditioning regimen (RIC) or a myeloablative regimen (MAC). The diagnosis of relapse was made through myelogram analysis, analysis of cytogenetics, analysis of minimal residual disease (MRD), analysis of cellular chimerism, and analysis of immunohematological chimerism of blood group antigens. A database was formed in relation to the examined patient characteristics. Patient survival was analyzed using the Kaplan-Meier method and the log-rang test.

**Results:** MAC (43 patients) was used more frequently than RIC (15 patients), as a conditioning regimen. After transplantation, 18 (34%) out of 53 patients had a relapse. The choice of regimen did not affect the occurrence of relapse, but patients on the RIC regimen lived longer (38.5 ± 7 months) as compared to patients on the MAC regimen (27.8 ± 3.5 months). However, the difference in survival was without statistical significance ($p = 0.318$). The median survival time of patients who relapsed was 26 ± 5 months, while patients without disease relapse had a median survival time of 41 ± 4 months.

**Conclusion:** Patients who received reduced-intensity regimens (RIC) had a longer survival time, without an increase in the relapse rate. In future, consideration should be given to the inclusion of patients older than 60 years, as candidates for transplantation, as well as to the possible use of prophylactic therapy aimed at preventing relapse in high-risk patients.

**Keywords:** reduced intensity conditioning, myeloablative conditioning, survival

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## UVOD

Alogena transplantacija matičnih ćelija hematopoeze (alo-TMĆH) predstavlja zamenu i repopulaciju hematopoeznog tkiva primaoca hematopoeznim tkivom druge osobe, koja može da bude u srodstvu sa primaocem ili se pronalazi pretragom registra davalaca. Alogena transplantacija ima za cilj da bude kurativna metoda lečenja hematoloških maligniteta, a koristi se kod pacijenata kod kojih su male šanse da se postigne kontrola njihove bolesti manje intenzivnim metodama lečenja. Transplantacija uglavnom predstavlja poslednju terapijsku mogućnost.

Moguće komplikacije nakon transplantacije su: odbacivanje kalema, bolest kalema protiv domaćina (engl. *graft versus host disease – GvHD*), slabost kalema, kao i relaps osnovne bolesti.

Relaps predstavlja povratak osnovne bolesti, koju je pacijent imao pre transplantacije, nakon što je terapijom postignuta kompletna remisija bolesti. Podaci ukazuju na to da se relaps može očekivati kod 40 – 45% primalaca *HLA* (engl. *human leukocyte antigen*) identičnih matičnih ćelija, odnosno kod približno 35% primalaca matičnih ćelija od nesrodnih donora. Relaps je moguće dijagnostikovati *PCR* (engl. *polymerase chain reaction*) analizom, upotrebom protočne citometrije ili analizom aspirata koštane srži [1,2].

Relaps može da se javi rano nakon transplantacije, ako je inicijalni kondicioni režim bio nedovoljan, ako dođe do slabljenja imunološkog sistema ili ako bolest ima imunološki beg preko klonalne selekcije imunorezistentnih progenitora. Ređe može da dođe do pojave *de novo* leukemije u donorskim ćelijama, što daje sliku relapsa po tipu leukemije donora [1].

Relapsi se najčešće javljaju kod pacijenata sa akutnim leukemijama ili mijelodisplastičnim sindromom i može se očekivati da će se polovina relapsa desiti u prvih šest meseci. U zavisnosti od vremena javljanja relapsa, on može biti rani (unutar prvih 100 dana), intermedijarni (unutar prvih 200 dana) i kasni (nakon 200 dana). Za pojedine dijagnoze, relaps unutar prvih šest meseci je povezan sa medijanom preživljavanja od šest meseci, a samo 5% pacijenata živi duže od jedne godine [1].

Terapija relapsa predstavlja veliki izazov i uključuje različite vidove hemioterapije, biološku ciljanu terapiju, radioterapiju, donorsku infuziju limfocita, i sekundarnu transplantaciju.

Infuzija donorskih limfocita (engl. *donor lymphocyte infusion – DLI*) predstavlja vid adaptivne imunoterapije, koja se koristi nakon transplantacije matičnih ćelija hematopoeze, radi moduliranja antitumorskog efekta grafta (engl. *graft versus tumor effect - GvT*), kao i da bi se povećala verovatnoća postizanja engraftmen-

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the replacement and repopulation of the hematopoietic tissue of the recipient with the hematopoietic tissue of another person, who may be related to the recipient or is found through a search in the donor registry. Allogeneic transplantation aims at being a curative method of treating hematological malignancies and it is used in patients in whom the chance of controlling their disease with less invasive treatment methods is small. Transplantation is usually the last therapeutic option.

Possible complications upon transplantation are as follows: rejection of the graft, graft versus host disease (GvHD), graft failure, as well as relapse of the underlying disease.

Relapse is the recurrence of the underlying disease, which the patient had suffered from prior to transplantation, after complete remission of the disease had been achieved with therapy. Data indicates that relapse may be expected in 40 – 45% of recipients of HLA (human leukocyte antigen) identical stem cells, as well as in approximately 35% of stem cells originating from unrelated donors. Relapse can be diagnosed with PCR (polymerase chain reaction) analysis, use of flow cytometry, or bone marrow aspirate evaluation [1,2].

Relapse can occur early after transplantation, if the initial conditioning regimen was insufficient, if the immune system weakens, or if the disease undergoes immune escape through clonal selection of immune-resistant progenitors. Less frequently, *de novo* leukemia may develop in the donor cells, which presents as relapse in the form of donor derived leukemia [1].

Relapses most frequently occur in patients with acute leukemia or myelodysplastic syndrome, and it can be expected that half of all relapses will occur within the first six months. Depending on the time when relapse occurs, it can be categorized as early (within the first 100 days), intermediate (within the first 200 days) and late (after 200 days). For certain prognoses, relapse within the first six months is linked to a median survival of six months, with only 5% of cases surviving for more than a year [1].

Therapy of relapse is a great challenge and entails the application of different forms of chemotherapy, as well as targeted biological therapy, radiation therapy, donor lymphocyte infusion, and secondary transplantation.

Donor lymphocyte infusion (DLI) is a form of adaptive immunotherapy which is used after hematopoietic stem cell transplantation, in order to modulate the graft versus tumor effect (GvT), as well as to increase the probability of achieving the engraftment of donor

ta donorskih ćelija. Efekat kalema protiv ćelija tumora, odnosno reakcija grafta protiv leukemije (engl. *graft versus leukemia – GvL*) je od posebnog značaja kod pacijenata kojima se javio relaps osnovne bolesti [3,4,5].

Cilj ovog rada jeste da se, na osnovu podataka iz medicinske dokumentacije Klinike za hematologiju Univerzitetskog kliničkog centra Srbije (UKCS), izvrši procena učestalosti i tipa relapsa osnovne bolesti; sprovede analiza uticaja kondicionih režima na javljanje relapsa; analiziraju različite terapijske mogućnosti i njihov efekat; te analizira prognoza pacijenata, a radi mogućnosti eventualne profilaktičke primene terapije, koja bi prevenirala pojavu relapsa nakon alogene transplantacije matičnih ćelija hematopoeze.

## MATERIJALI I METODE

U retrospektivnu kohortnu studiju je uključeno 58 bolesnika sa Klinike za hematologiju UKCS-a, kojima je izvršena alo-TMĆH. Uključeni su bolesnici sa sledećim dijagnozama: Hočkinov limfom (HL), Nehočkinov limfom (NHL), akutna limfoblastna leukemija (ALL), akutna mijeloblastna leukemija (AML), te mijelodisplastični/mijeloproliferativni sindrom (MDS/MPN), koje su postavljene u skladu sa klasifikacijom hematoloških bolesti Svetske zdravstvene organizacije (SZO), iz 2016. godine [6].

Kao kondicioni režimi, korišćeni su samo oni na bazi hemioterapeutika, bez zračenja pre alogene transplantacije matičnih ćelija hematopoeze. Kondicioni režimi se po svojoj jačini mogu podeliti na mijeloablativne režime (engl. *myeloablative conditioning – MAC*), koji dovode do potpunog opustošenja koštane srži, i režime smanjenog intenziteta (engl. *reduced intensity conditioning – RIC*), koji ne dovode do opustošenja koštane srži bolesnika.

Prevencija *GvHD*-a je sprovedena primenom imunosupresivne terapije u sklopu kondicioniranja anti-T limfocitnim globulinom uz ciklosporin A, u dozi od 3 mg/kg TM, od d-1 do d+180, uz primenu *Seattle* protokola za srodne alogene transplantacije, koji podrazumeva primenu metotreksata, u dozi od 15 mg/m$^2$ na d+1 i 10mg/m$^2$ na d+3 i d+6, dok kod nesrodnih zahteva primenu i na d+11, u dozi od 10mg/m$^2$.

Za prevenciju bakterijskih infekcija je korišćena terapija hinolonima, u dozi 500 mg *per os,* i trimetoprim-sulfametaksazolom, u dozi 2 x 400 mg *per os,* do d+90, radi zaštite od *T. Gondi* i *P. Jirovecii.* Antivirusna prevencija se sastojala od aciklovira, u dozi od 3 x 400 mg *per os*. Zaštita od gljivičnih infekcija se sprovodila mikafunginom, u dozi od 50 mg i.v., dve nedelje od d-0 do engraftmenta, a potom posakonazolom, do d+90.

Za dan engraftmenta, uziman je dan u kome je broj neutrofila bio iznad 1 x 10$^9$/l i broj trombocita iznad 20

cells. The effect of graft versus tumor cells, i.e., graft versus leukemia (GvL) is of special significance in patients in whom relapse of the underlying disease occurs [3,4,5].

The purpose of this study is to use the data from the medical records of the Clinic for Hematology of the University Clinical Center of Serbia (UCCS) in order to: assess the incidence and type of relapse of the underlying disease; analyze the effect of conditioning regimens on the incidence of relapse; analyze the different treatment options and their effect; as well as analyze patient prognosis, all for the purpose of possible prophylactic application of therapy that would prevent relapse after allogeneic hematopoietic stem cell transplantation.

## MATERIALS AND METHODS

A total of 58 patients from the Clinic for Hematology of the UCCS, who had undergone allo-HSCT, were included in this cohort study. The patients with the following diagnoses were included: Hodgkin's lymphoma (HL), Non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), and myelodysplastic/myeloproliferative syndrome (MDS/MPN), which were all established in keeping with the Classification of Tumors of Hematopoietic and Lymphoid Tissues of the World Health Organization (WHO), from 2016 [6].

As conditioning regimens, only those based on chemotherapeutic drugs were used, without the application of radiation therapy prior to allogeneic hematopoietic stem cell transplantation. The conditioning regimens can be categorized, according to their intensity as: myeloablative conditioning (MAC) regimens, which lead to the complete ablation of the bone marrow, and reduced intensity regimens (reduced intensity conditioning – RIC), which do not cause bone marrow ablation in the patient.

GvHD prevention was carried out through the application of immunosuppressive therapy within the conditioning regimen with anti-T lymphocyte globulin and cyclosporine A, at the dose of 3 mg/kg BM, from d-1 to d+180, with the application of the Seattle protocol for related allogeneic transplantations, which entails the use of the following: methotrexate, at the dose of 15 mg/m$^2$ on d+1, and 10mg/m$^2$ on d+3 and d+6, while in unrelated transplantations, it requires to be also used on d+11, at the dose of 10mg/m$^2$.

For the prevention of bacterial infections, the therapy consisted of quinolones, at a dose of 500 mg *per os,* and trimethoprim-sulfamethoxazole, at a dose of 2 x 400 mg *per os,* until d+90, as protection against *T. Gondi* and *P. Jirovecii.* Antiviral prevention consisted of acyclovir, at a dose of 3 x 400 mg *per os*. Protection against fungal infections was carried out with micafungin, at a

x $10^9$/l u tri uzastopna dana, a bez transfuzije trombocita. Ćelijski himerizam se proveravao na, d+30, d+90, d+180 i d+360, pomoću *PCR* metode.

Dijagnoza relapsa se postavljala analizom mijelograma, analizom minimalne rezidualne bolesti (engl. *minimal residual disease – MRD*), na osnovu nalaza protočne citometrije ćelija koštane srži i periferne krvi, analizom ćelijskog himerizma *PCR* tehnikom, kao i analizom imunohematološkog himerizma antigena krvno-grupnih sistema.

## STATISTIČKA OBRADA

Inicijalno je formirana baza podataka grupisanjem i tabeliranjem rezultata po ispitivanim obeležjima bolesnika. Deskriptivni statistički parametri izraženi su kroz medijanu, modus i raspodele relativnih frekvencija. Ukupno preživljavanje bolesnika je obuhvatalo period od momenta dijagnoze do smrtnog ishoda ili zaključno sa decembrom 2020. godine, kod živih bolesnika. Preživljavanje bolesnika, u odnosu na lečenje, analizirano je Kaplan-Majerovom metodom i upoređivano *log-rank (Mantel–Cox)* testom. Za statističku obradu podataka je korišćen softver *SPSS 23.0 for Windows (IBM Chicago, Illinois, USA)*.

## REZULTATI

Demografske i kliničke karakteristike naših pacijenata predstavljene su u Tabeli 1.

Najveći broj davalaca su bili članovi familije pacijenata, 27 srodnih (46,5%) i 8 haploidentičnih (13,8%)

**Tabela 1.** Demografske karakteristike i kliničke karakteristike bolesnika

**Table 1.** Patient demographic and clinical characteristics

| | | |
|---|---|---|
| Broj pacijenata / *Number of patients* | | 58 |
| Prosečna starost / *Average age* | | 38.4 ± 11.03 |
| Pol / *Gender* | Muški / *Male* | 33 (56.9%) |
| | Ženski / *Female* | 25 (43.1%) |
| Dijagnoza / *Diagnosis* | ALL | 18 (31%) |
| | AML | 26 (44.8%) |
| | HLL | 1 (1.7%) |
| | HL | 8 (13.8%) |
| | MDS | 1 (1.7%) |
| | MDS/MPN | 2 (3.4%) |
| | NHL | 2 (3.4%) |

ALL – akutna limfoblastna leukemija; AML – akutna mijeloblastna leukemija; HLL – hronična limfocitna leukemija; HL – Hočkinov limfom; MDS/MPN – mijelodisplastični sindrom/mijeloproliferativna neoplazma; NHL – Nehočkinov limfom

*ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia; HL – Hodgkin's lymphoma; MDS/MPN – myelodysplastic/myeloproliferative neoplasms; NHL – Non-Hodgkin's lymphoma*

dose of 50 mg IV, for two weeks, from d-0 until engraftment, and after that with posaconazole, until d+90.

The day when the neutrophil count was above 1 x $10^9$/l and the platelet count was 20 x $10^9$/l for the third consecutive day, without platelet transfusion, was considered to be the day of engraftment. Patients were tested for cellular chimerism on the following days: d+30, d+90, d+180, and d+360, with the PCR method.

Diagnosis of relapse was established with myelogram analysis, with the analysis of minimal residual disease (MRD), on the basis of the findings of flow cytometry of the bone marrow cells and peripheral blood cells, with PCR analysis of cellular chimerism, as well as with the analysis of immunohematological chimerism of blood group antigens.

## STATISTICAL ANALYSIS

Initially, a database was formed by grouping and tabulating results according to the patient characteristics being investigated. Descriptive statistical parameters are expressed as the median, mode, and relative frequency distribution. The overall patient survival covered the period from the moment of diagnosis until the lethal outcome, or until the end of December 2020, in living patients. Patient survival, in relation to treatment, was analyzed with the Kaplan-Meier method and compared with the use of the log-rank (Mantel–Cox) test. The SPSS 23.0 for Windows software (IBM Chicago, Illinois, USA) was used for statistical data processing.

## RESULTS

The demographic and clinical characteristics of our patients are presented in Table 1.

The greatest number of the donors were patients' family members, 27 related (46.5%) and 8 haploidentical (13.8%) donors, while 23 (39.6%) patients received stem cells from unrelated donors, found through the search of the registry.

Of the 58 patients included in the study, transplantation was performed in 53 patients, while five patients died in the early induction period. MAC was the most commonly applied induction regimen – in 43 (74.1%) patients, while the RIC regimen was administered to five (25.8%) patients. Chimerism on d+30 was achieved in 45 patients, while it was not achieved in eight patients. Complete remission of the disease was achieved in 47 patients. Relapse upon transplantation occurred in 18 (34%) patients out of 53 (Table 2).

The average time elapsing before the occurrence of relapse was 275 days. The greatest number – nine (50%) patients, had late relapse, four (22.2%) patients had intermediate relapse, while five (27.7%) patients had early relapse (Figure 1). A total of 25 patients died, from

donora, dok su 23 (39,6%) pacijenta dobila matične ćelije od nesrodnih davaoca, koji su nađeni pretragom registra.

Od 58 pacijenata uključenih u rad, kod 53 je izvršena transplantacija, dok je pet umrlo u ranom indukcionom periodu. *MAC* je bio najčešće korišćeni indukcioni režim – kod 43 (74,1%) pacijenta, dok je *RIC* primilo 15 (25,8%) pacijenata. Himerizam na d+30 je postignut kod 45 pacijenata, a nije postignut kod osam pacijenata. Kompletna remisija bolesti postignuta je kod 47 pacijenata. Relaps nakon transplantacije je imalo 18 (34%) od 53 pacijenta (Tabela 2).

Prosečno vreme nakon kojeg se ralaps javio je bilo 275 dana. Najveći broj – devet (50%) pacijenata, imalo je kasni relaps; četiri (22,2%) pacijenta su imala intermedijarni relaps, a 5 (27,7%) pacijenata je imalo rani relaps (Grafikon 1). Ukupno 25 pacijenata je preminulo, od početka praćenja do kraja decembra 2020. godine,.

Prosečno vreme preživljavanja od momenta postavljanja dijagnoze je iznosilo 96,8 ± 16,4 meseci, a prosečno vreme preživljavanja od momenta transplantacije je bilo 34 ± 3,6 meseci. Medijana preživljavanja od momenta dijagnoze je iznosila 20 meseci, a od momenta transplantacije, devet meseci.

Ženski pacijenti, koji su praćeni od momenta dijagnoze, u proseku su živeli duže (111 ± 26 meseci), u odnosu na muške pacijente (58 ± 9 meseci). Prosečno posttransplantacijsko preživljavanje je bilo bolje kod žena (40 ± 5 meseci) nego kod muškaraca (25 ± 4 meseca). Izbor kondicionog režima nije imao uticaja na dužinu preživljavanja pacijenata – *RIC*: 38,5 ± 7 meseci, a *MAC*: 27,8 ± 3,5 meseci. Iako je duže preživljavanje bilo prisutno kod pacijenata koji su primili *RIC* a ne *MAC*,

**Tabela 2.** Izbor kondicionog režima, himerizam nakon alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH), distribucija u odnosu na postizanje kompletne remisije i u odnosu na relaps osnovne bolesti

**Table 2.** Use of the conditioning regimen, chimerism after allogenic hematopoietic stem cell transplantation (allo-HSCT), distribution in relation to the achievement of complete remission and in relation to the relapse of the underlying disease

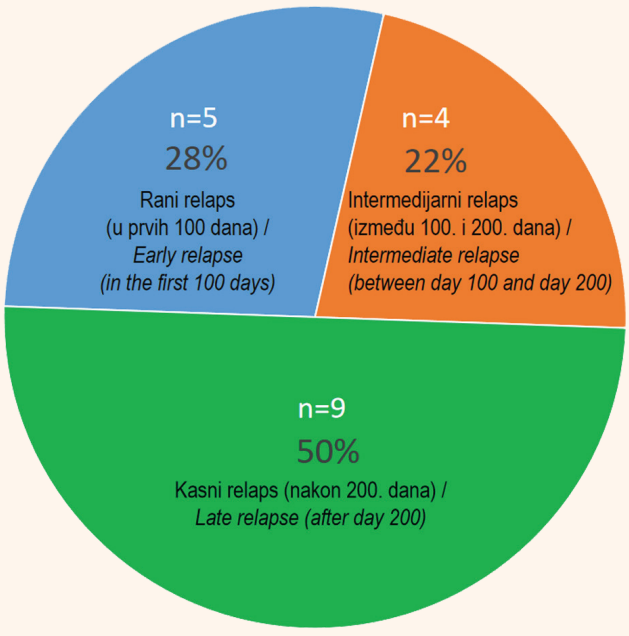
| | | n (%) |
|---|---|---|
| Kondicioni režim / *Conditioning regimen* | RIC / *RIC* | 15 (25.9%) |
| | MAC / *MAC* | 43 (74.1%) |
| Himerizam na d+30 / *Chimerism at d+30* | DA / *YES* | 45 (77.6%) |
| | NE / *NO* | 8 (13.8%) |
| Kompletna remisija / *Complete remission* | DA / *YES* | 6 (10.3%) |
| | NE / *NO* | 47 (81%) |
| Relaps / *Relapse* | DA / *YES* | 18 (34%) |
| | NE / *NO* | 35 (60.3%) |

*RIC* – kondicioni režim redukovanog intenziteta (engl. *reduced intensity conditioning*) / *RIC - reduced intensity conditioning*

*MAC* – mijeloablativni kondicioni režim (engl. *myeloablative conditioning*) / *MAC – myeloablative conditioning*

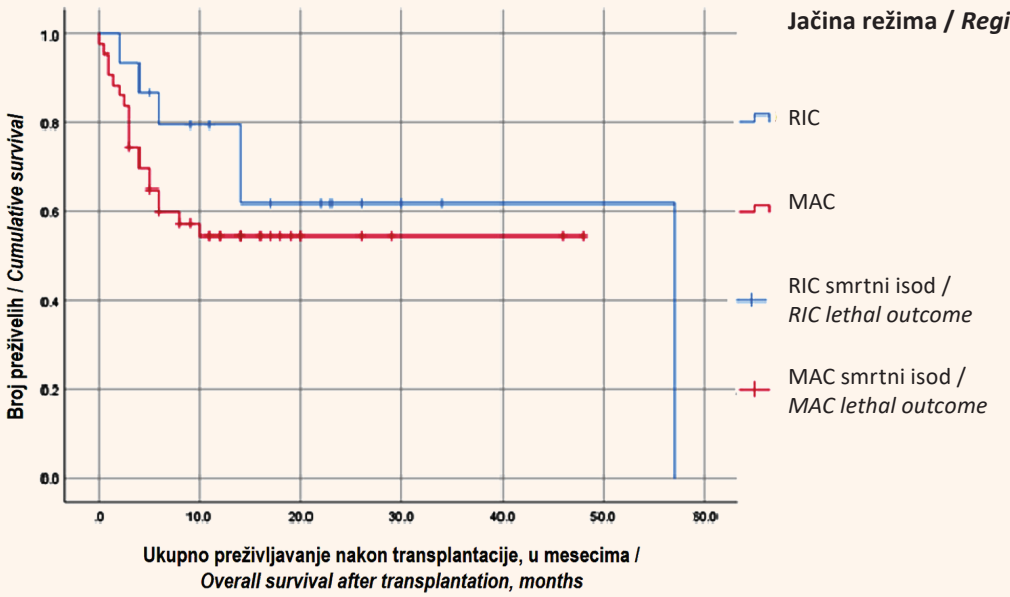
the beginning of patient monitoring until the end of December 2020.

The average time of survival, from the moment when diagnosis was established, was 96.8 ± 16.4 months, while the average time of survival, from the moment of transplantation, was 34 ± 3.6 months. Median survival, from the moment of diagnosis, was 20 months, and from the moment of transplantation, it was nine months.




**Grafikon 1.** Vreme javljanja relapsa

**Figure 1.** Time to relapse



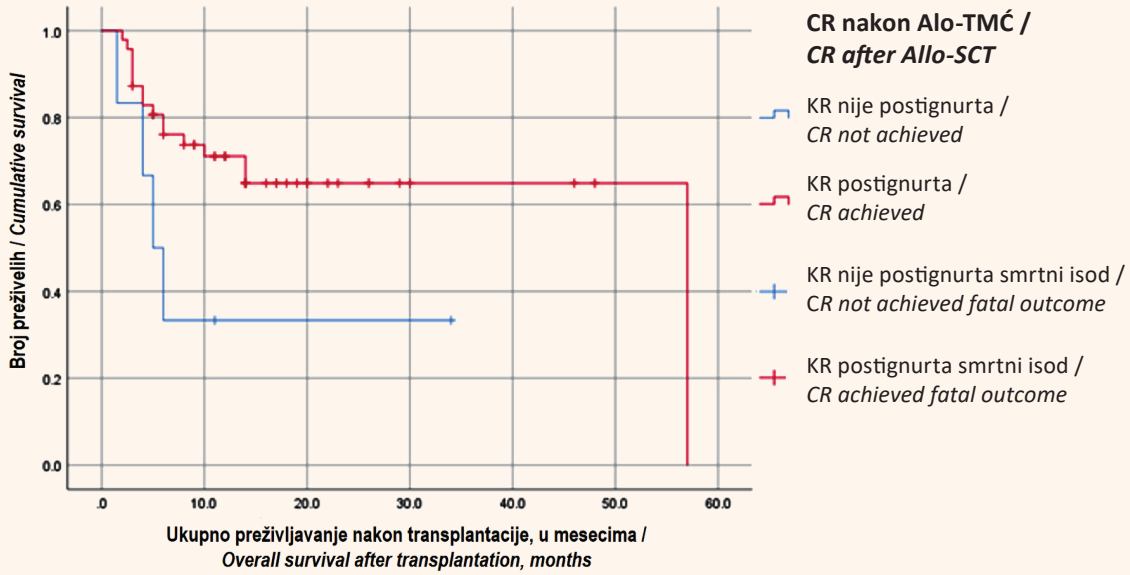

**Grafikon 2.** Preživljavanje nakon alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH), u odnosu na kondicioni režim

**Figure 2.** Survival after allogenic hematopoietic stem cell transplantation (allo-HSCT), depending on the conditioning regimen applied

dobijeni podaci nisu bili statistički značajni ($p = 0,318$), (Grafikon 2).

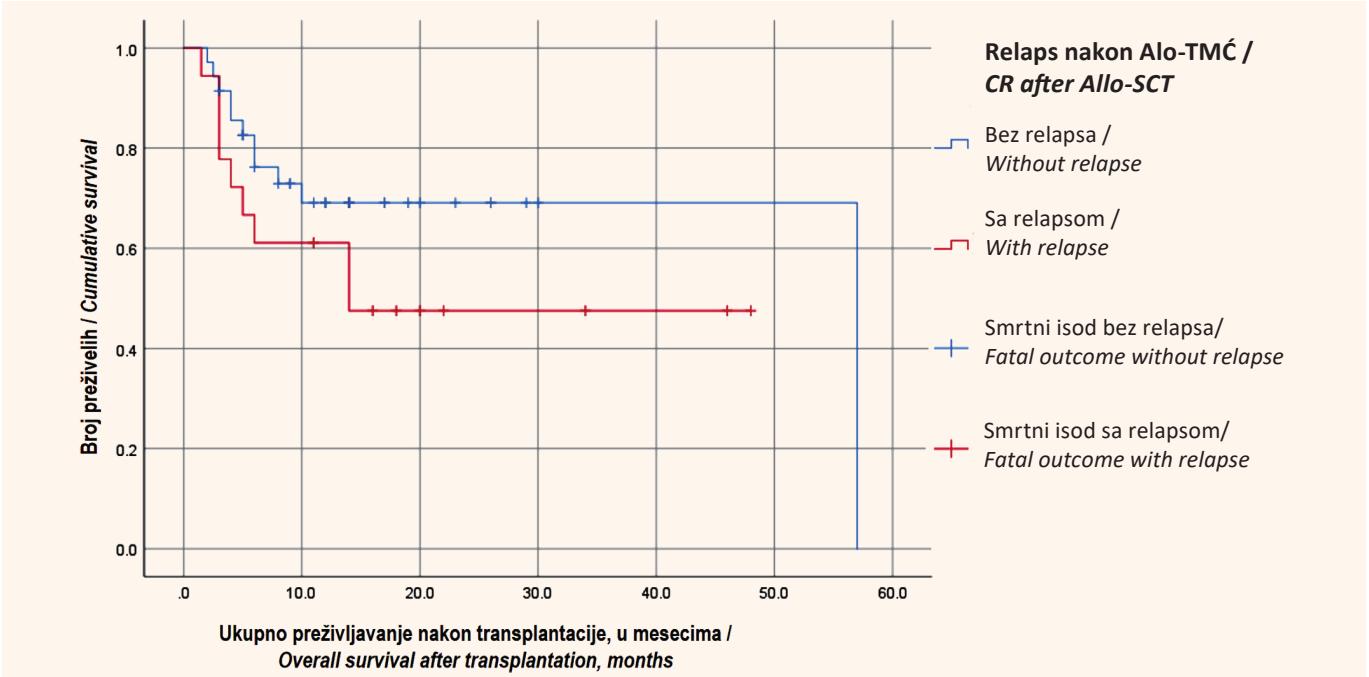
Pacijenti koji su postigli kompletnu remisiju nakon prve transplantacije živeli su duže nego pacijenti koji to nisu postigli (39 ± 4 meseca u poređenju sa 14 ± 6 meseci), ali uočena razlika nije bila od statističkog značaja ($p = 0,055$), (Grafikon 3). Prosečno vreme preživljavanja pacijenata koji su imali relaps, iznosilo je 26 ± 5 meseci, dok je kod pacijenata koji nisu imali relaps bilo 41 ± 4 meseci. Medijana preživljavanja pacijenata koji su imali relaps, iznosila je 14 meseci, odnosno 57 meseci kod pacijenata bez relapsa ($p = 0,180$), (Grafikon 4).

Female patients, who were followed-up from the moment of diagnosis, lived longer on average (111 ± 26 months), in relation to male patients (58 ± 9 months). Average posttransplantation survival was better in women (40 ± 5 months) than in men (25 ± 4 months). The choice of conditioning regimen had no influence on the length of patient survival – RIC: 38.5 ± 7 months, and MAC: 27.8 ± 3.5 months. Although longer survival was present in patients who received RIC and not MAC, the data obtained were not statistically significant ($p = 0.318$), (Figure 2).




**Grafikon 3.** Preživljavanje nakon alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH), u zavisnosti od postizanja kompletne remisije

**Figure 3.** Survival after allogenic hematopoietic stem cell transplantation (allo-HSCT), with and without the achievement of complete remission




**Grafikon 4.** Preživljavanje nakon alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH), u zavisnosti od pojave relapsa bolesti

**Figure 4.** Survival after allogenic hematopoietic stem cell transplantation (allo--HSCT), with and without relapse of the disease

## DISKUSIJA

Usled razvoja novih terapijskih modaliteta, usavršavanja bioloških terapija, primene novih generacija lekova, kao i primene novih tehnologija, kao što je *CAR-T* (engl. *chimeric antigen receptor T-cell*) ćelijska terapija, preživljavanje i prognoza hematoloških bolesnika pokazuje konstantni trend poboljšanja. Drastičan porast hematoloških maligniteta, porast leukemija za 26% i NHL-a za 45%, 2016. u odnosu na 2006. godinu, kao i razvoj boljih kondicionih i imunosupresivnih režima, doveli su do toga da je broj alogenih transplantacija u znatnom porastu. Evropska grupa za krv i transplantaciju koštane srži (engl. *European Group for Blood and Marrow Transplantation – EBMT*) navodi da je u poslednjih 20 godina, broj alogenih transplantacija matičnih ćelija hematopoeze, izvedenih na godišnjem nivou, porastao za 360% [5,7,8].

Naš rad je obuhvatio 58 adultnih pacijenata koji su imali alogenu transplantaciju matičnih ćelija hematopoeze. Akutne leukemije (AML i ALL) su bile najčešće dijagnoze pacijenata kod kojih je izvedena alo-TMĆH (75%), dok su, prema *EBMT*-u, akutne leukemije uzrok 54,5% svih alogenih transplantacija matičnih ćelija hematopoeze. Drugu najveću učestalost imao je HL, sa 13,8%. NHL je činio 5,1%, dok *EBMT* navodi podatak od 9,1% za ovu dijagnozu. MDS/MPN su bili zastupljeni sa 5,1%, dok za njih *EBMT* navodi udeo od 15,6%. Nijedan pacijent sa dijagnozom koja nije pripadala grupi malignih hemopatija nije imao alogenu transplantaciju matičnih ćelija hematopoeze [6,8].

The patients who achieved complete remission after the first transplantation lived longer than the patients who did not (39 ± 4 months, as compared to 4 ± 6 months), however, the noted difference was not statistically significant (p = 0.055), (Figure 3). The average time of the survival of patients who had relapse was 26 ± 5 months, while in patients without relapse it was 41 ± 4 months. The median survival of patients who had relapse was 14 months, and it was 57 months in patients who did not experience relapse ($p = 0.180$), (Figure 4).

## DISCUSSION

Due to the development of new therapeutic modalities, the improvement of biological therapies, the application of new generation medications, as well as the application of new technologies, such as CAR-T (chimeric antigen receptor T-cell) therapy, survival and prognosis of hematological patients has shown a constant improvement trend. A drastic increase in hematological malignancies, the increase in the incidence of leukemias by 26% and NHL by 45% (in 2016 as compared to 2006), as well as the development of better conditioning and immunosuppressive regimens, have led to a significant increase in the number of allogeneic transplantations. The European Group for Blood and Marrow Transplantation (EBMT) states that the number of allogeneic hematopoietic stem cell transplantations performed annually has risen by 360% in the past 20 years [5,7,8].

Razvojem manje intenzivnih kondicionih režima, alo-TMĆH je postala terapijska mogućnost mnogih pacijenata, koji bi ranije bili isključeni iz razmatranja, zbog godina (>50) i zbog komorbiditeta. To je dovelo do toga da se, u SAD, procentualni udeo starijih od 60 godina koji se leče transplantacijom, poveća sa 4% na 25%, u periodu od 2000. do 2015. godine. U našem radu, starost pacijenata se kretala između 18 i 58 godina, a prosečna starost je iznosila 38 godina [9].

Većina (74%) naših pacijenata je primila mijeloablativni režim (*MAC*), dok je 26% pacijenata primilo *RIC*. Preovlađujući udeo *MAC* režima je u skladu sa trendovima izbora kondicionog režima koje navode Dsouza i Girkoca [9,10].

Javljanje relapsa umnogome zavisi od dijagnoze i od izbora kondicionog režima. Relaps se najčešće javljao kod pacijenata sa ALL-om, gde je od 18 pacijenata, osam imalo relaps. To čini 44,4% svih relapsa u našem radu. Pacijenti sa AML-om su sledili nakon pacijenata sa ALL-om – od 26 pacijenata, sedam je imalo relaps, i činili su 38,8% svih relapsa. Akutne leukemije su zajedno činile 75% svih dijagnoza u našem radu, te 82,8% svih relapsa.

Jedna trećina pacijenata na *RIC* režimu, odnosno pet od 15 pacijenata, imalo je relaps, a u grupi pacijenata na *MAC* režimu, relaps je imalo 13 (30,2%) od 43 pacijenta. Očekivano, veću verovatnoću relapsa su imali pacijenti kod kojih je korišćen *RIC* režim. Ovu razliku je moguće objasniti samim karakteristikama režima. Takođe, starost pacijenata i njihovi *HCT-CI* (engl. *hematopoietic cell transplantation-specific comorbidity index*), *EBMT* i *ECOG PS* (engl. *Eastern Cooperative Oncology Group Performance Status Scale*) skorovi imaju uticaja na ishod transplantacije. Dobijeni podaci su u skladu sa podacima koje u svom radu navode Martino i saradnici (23% za *MAC* i 39% za *RIC*), kao i Ringden i saradnici (42% ± 3% za *RIC* i 29% ± 3% za *MAC*), dok Luger i saradnici navode relativni rizik za relaps nakon *RIC*-a od 1,32 u odnosu na *MAC* [11–15].

Pacijenti koji su primali *RIC* režim su imali duže preživljavanje u odnosu na pacijente koji su primali *MAC* režim, ali razlika u preživljavanju u našoj studiji nije imala statistički značaj – *RIC* 38,5 ± 7 meseci; *MAC* 27,8 ± 3,5 meseci ($p = 0,318$). Skot i saradnici, tokom perioda praćenja od 18 meseci, nisu ustanovili statistički značajne razlike u ukupnom preživljavanju (engl. *overall survival - OS*) između *MAC* i *RIC* režima. Slični podaci, koji su takođe u skladu sa našim, dobijeni su dužim periodom praćena pacijenata – studija Ćiftćilera i saradnika je obuhvatila period od tri godine, a studija Martina i saradnika je obuhvatila period od sedam godina, što bliže odgovara našem ispitivanju. Ni ove studije ne navode statistički značajne razlike u ukupnom preživljavanju između pacijenata na *MAC* i *RIC* režimu [13,16,17].

Our study included 58 adult patients who had received allo-HSCT. Acute leukemias (AML and ALL) were the most frequent diagnoses in patients who had allo-HSCT (75%), while, according to the EBMT, acute leukemias are the cause of 54.5% of all allogeneic hematopoietic stem cell transplantations. The second highest was the incidence of HL, with 13.8%. NHL made up 5.1%, while EBMT states a percentage of 9.1% for NHL. In our study, MDS/MPN were present with 5.1%, while EBMT reports a percentage of 15.6%. None of the patients diagnosed with a disease outside the group of malignant hemopathies received allogeneic hematopoietic stem cell transplantation [6,8].

With the development of less intensive conditioning regimens, allo-HSCT has become a therapeutic option for many patients who would earlier have been excluded from consideration, due to their age (>50) and their comorbidities. In USA, this led to the rise in the percentage of patients older than 60 being treated with transplantation, from 4% to 25%, in the period between 2000 and 2015. In our study, the patient age ranged from 18 to 58 years, while the average age was 38 years [9].

Most (74%) of our patients received the myeloablative conditioning regimen (MAC), while 26% of patients received RIC. The predominant proportion of the MAC regimen is in keeping with the trends of selecting the conditioning regimens, as stated by D'Souza and Gyurkocza [9,10].

The occurrence of relapse greatly depends on the diagnosis and the selection of the conditioning regimen. Relapse occurred most frequently in patients with ALL, wherein out of 18 patients, 8 had relapse. This makes up 44,4% of all relapses in our study. Patients with AML followed after patients with ALL; of 26 patients, seven had a relapse, and they made up 38.8% of all relapses. Acute leukemias jointly made up 75% of all diagnoses in our study and 82.8% of all relapses.

One third of the patients on the RIC regimen, i.e., five out of 15 patients, had a relapse, while in the group of patients on the MAC regimen, relapse occurred in 13 (30.2%) out of 43 patients. As expected, a higher probability of relapse was noted in patients who were on the RIC regimen. This difference can be explained with the characteristics of the regimens themselves. Also, the age of the patients, as well as their HCT-CI (hematopoietic cell transplantation-specific comorbidity index), EBMT, and ECOG PS (Eastern Cooperative Oncology Group Performance Status Scale) scores affect the outcome of transplantation. The data obtained is consistent with the data reported by Martino et al. (23% for MAC and 39% for RIC), and Ringdén et al. (42% ± 3% for RIC and 29% ± 3% for MAC), while Luger et al.

Vreme javljanja relapsa ima značajan uticaj na ishod same transplantacije, kao i na preživljavanje pacijenata. Postoje različita mišljenja kako klasifikovati relapse po vremenu javljanja. Pojedini autori postavljaju šest meseci kao granicu za rani, a sve preko toga pripada kasnom relapsu. *Seattle* grupa navodi tri tipa: rani – u prvih 100 dana, intermedijarni – između 100. i 200. dana, i kasni – nakon 200. dana. S obzirom da smo mi koristili *Seattle* protokol za prevenciju *GvHD*-a, podelili smo pacijente koji su imali relaps, prema kriterijumima ove grupe autora. *Seattle* grupa u svom radu navodi da je, od 1.111 pacijenata, 307 (27,6%) bolesnika imalo relaps, od kojih je 111 (36,1%) imalo relaps unutar prvih 100 dana, intermedijarni relaps je imalo 73 (23,7%) pacijenata, a kasni relaps je konstatovan kod 123 (40%) bolesnika. U našem radu, 18 (34%) pacijenata je imalo relaps. Pet (27,7%) pacijenata je imalo rani relaps, odnosno relaps unutar prvih 100 dana, srednji relaps, odnosno relaps između 100. i 200. dana su imala četiri (22,2%) pacijenta, a kasni, nakon 200 dana, imalo je devet (50%) pacijenata. Naši podaci su slični podacima koji su dobijeni u studiji *Seattle* grupe, i pored toga što se radi o malom uzorku [1,18].

Terapija relapsa predstavlja veliki problem, pogotovo kod pacijenata koji boluju od AML-a i MDS-a, gde je verovatnoća relapsa velika, a sam relaps se javlja rano nakon transplantacije i povezan je sa lošijom prognozom. Ovaj kompleksni problem zahteva primenu širokog spektra lekova i različitih procedura. Od lekova se najčešće koriste različiti citostatici, imunosupresivi i imunomodulatori, a u novije vreme ciljana biološka terapija dobija na značaju. Nekim pacijentima je nakon relapsa potrebno dati *DLI* terapiju, ćelijski 'bust' (engl. *CD34+ stem cell boost*) ili čak izvršiti sekundarnu alogenu transplantaciju matičnih ćelija hematopoeze.

Na osnovu podataka o 2.815 pacijenata dobijenih iz baze *EBMT*-a, *Šmid* i saradnici u svom radu navode da je u lečenju najčešće korišćena samo umerena hemioterapija (33,5%); intenzivna hemioterapija korišćena je kod 17,9% slučajeva; hemioterapija praćena sa *DLI* terapijom je primenjena kod 18,3% pacijenata; hemioterapija praćena sekundarnom alogenom transplantacijom matičnih ćelija hematopoeze je primenjena kod 7,6% bolesnika; *DLI* terapija bez hemioterapije je korišćena u 15,2% slučajeva, dok je sekundarna alo-TMĆH bez prethodne hemioterapije primenjena kod 7,6% pacijenata. U našem radu, samo hemioterapiju kao jedini način lečenja relapsa, primilo je sedam od 18 pacijenata (38,8%), s tim što je jedan od pacijenata primio i biološku terapiju nivolumabom. *DLI* terapiju, kojoj je prethodila hemioterapija, primilo je četiri (22,2%) pacijenta, od toga je jedan pacijent lečen kombinacijom *COP* protokola i biološke terapije blinatumomabom.

reported a relative relapse risk after RIC of 1.32 in relation to MAC [11–15].

Patients on the RIC regimen had a longer survival, in relation to patients who were on the MAC regimen, however, the difference in survival in our study was not statistically significant – RIC: 38.5 ± 7 months; MAC: 27.8 ± 3.5 months ($p = 0.318$). During the follow-up period of 18 months, Scott et al. did not determine statistically significant differences in the overall survival (OS) between the MAC and the RIC regimen. Similar data, which was also in accordance with our results, were obtained over a longer follow-up period – the study by Çiftçiler et al. covered a period of three years, while the study by Martin et al. covered a period of seven years, which more closely matches our study. These studies also did not report statistically significant differences in the overall survival between patents on the MAC and those on the RIC regimen [13,16,17].

Time of relapse occurrence has significant impact on the outcome of the transplantation itself, as well as on patient survival. There are different opinions on how relapses should be classified by the time of their occurrence. Some authors set six months as the cutoff point for early relapse, categorizing everything after that as late relapse. The Seattle group categorizes three types of relapse: early relapse – in the first 100 days, intermediate relapse – between day 100 and day 200, and late relapse – after day 200. Since we used the Seattle protocol for preventing GvHD, we categorized patients with relapse according to the criteria defined by this group of authors. In their study, the Seattle group reports that out of 1,111 patients, 307 (27.6%) patients had a relapse, of whom 111 (36.1%) had a relapse within the first 100 dana, intermediate relapse was experienced by 73 (23.7%) patients, while late relapse occurred in 123 (40%) patients. In our study, 18 (34%) patients had a relapse. Five (27.7%) patients had an early relapse, i.e., relapse within the first 100 days, intermediate, i.e., relapse between day 100 and day 200 occurred in four (22.2%) patients, while late relapse, after 200 days, occurred in nine (50%) patients. Our data are similar to the data obtained in the Seattle group study, even though our sample size was small [1,18].

Relapse treatment is a great problem, especially in patients suffering from AML and MDS, where probability of relapse is high, and relapse itself occurs early after transplantation and is connected to a poor prognosis. This complex problem requires the application of a wide spectrum of drugs and different procedures. The drugs most frequently used are different cytostatic drugs, immunosuppressants, and immunomodulators, and lately, targeted biological therapy is becoming more and more significant. After relapse, some pa-

Sekundarnu alo-TMĆH, sa prethodnom hemioterapijom, dobilo je pet (27,7%) pacijenata, od toga je jedan pacijent dobio samo biološku terapiju blinatumomabom, pre transplantacije. Sekundarnom transplantacijom, bez prethodne primene hemioterapije, lečena su dva (11,1%) pacijenta, s tim što je jedan pacijent primio i terapiju antitimocitnim globulinom. Od ukupno sedam sekundarnih transplantacija, kod četiri pacijenta je postojala potreba za dodatnom terapijom u vidu *DLI* terapije, a kod jednog bolesnika su bile potrebne *DLI* i 'bust' terapija.

Od ukupno 18 pacijenata sa relapsom, 9 (50%) bolesnika je primilo *DLI* terapiju. Ovo se znatno razlikuje od studije Šmida i saradnika, koji navode da je 33,5% pacijenata primilo *DLI* terapiju, te od studije koju su sproveli Čurea i saradnici, u kojoj se navodi da je samo 13,7% pacijenata primilo *DLI* terapiju. Razlike u terapijskim modalitetima i njihovim zastupljenostima mogu se pripisati strukturi pacijenata, kao i ukupnom broju pacijenata koji su bili uključeni u istraživanje. I *Šmid* i *Čurea* su analizirali samo pacijente sa AML-om, dok je naša studija imali širi spektar dijagnoza [19,20].

## ZAKLJUČAK

Podaci dobijeni u našem radu, koji se tiču trendova u izboru kondicionog režima, stope relapsa nakon transplantacije, ukupnog preživljavanja nakon relapsa, kao i primene terapije nakon relapsa, u skladu su sa podacima različitih svetskih centara. Pacijenti koji su primili slabije kondicione režime su imali bolje vreme preživljavanja, ali bez prisustva statističke značajnosti, kao i bez povećanja stope relapsa. Naš centar još uvek nije počeo sa značajnim udelom transplantacija kod pacijenata starijih od 60 godina. U budućnosti treba početi sa inkluzijom starijih pacijenata i nastaviti rad na daljem smanjenju stope relapsa, pogotovo kod pacijenata sa akutnim leukemijama. Treba razmotriti ciljanu profilaktičku primenu terapije kod pacijenata sa ALL-om i AML-om, radi preveniranja relapsa.

## SPISAK SKRAĆENICA

alo-TMĆH – alogena transplantacija matičnih ćelija hematopoeze
*MAC* – mijeloablativni kondicioni režim (engl. *myeloablative conditioning*)
*RIC* – kondicioni režim redukovanog intenziteta (engl. *reduced intensity conditioning*)
*MRD* – minimalna rezidualna bolest (engl. *minimal residual disease*)
*GvHD* – bolest kalema protiv domaćina (engl. *graft versus host disease*)
*HLA* – sistem leukocitnih antigena (engl. *human leukocyte antigen*)
*PCR* – reakcija lančanog umnožavanja (engl. *polymerase chain reaction*)
*DLI* – infuzija donorskih limfocita (engl. *donor lymphocyte infusion*)
*GvT* – antitumorski efekat grafta (engl. *graft versus tumor effect*)
*GvL* – reakcija grafta protiv leukemije (engl. *graft versus leukemia effect*)
ALL – akutna limfoblastna leukemija

tients need to be given DLI, CD34+ stem cell boost, or may even need to receive secondary allogeneic hematopoietic stem cell transplantation.

Based on data related to 2,815 patients, obtained from the EBMT database, Schmid et al. reported that only moderate chemotherapy was used most frequently in treatment (33.5%); intensive chemotherapy was used in 17.9% of cases; chemotherapy followed by DLI was applied in 18.3% of patients; chemotherapy followed by secondary allogeneic hematopoietic stem cell transplantation was applied in 7.6% of patients; DLI without chemotherapy was given to 15.2% of patients, while secondary allo-HSCT without previous chemotherapy was applied in 7.6% cases. In our study, only chemotherapy as the sole method of relapse treatment was administered to seven (38.8%) out of 18 patients, with one of these patients also receiving biological therapy (nivolumab). DLI preceded by chemotherapy was given to four (22.2%) patients, of whom one patient was treated with a combination of COP protocol and biological therapy (blinatumomab). Secondary allo-HSCT with previous chemotherapy was administered to five (27.7%) patients, of whom one patient received only biological therapy (blinatumomab) prior to the transplantation. Two (11.1%) patients were treated with secondary transplantation without previous chemotherapy, with one of the patients receiving antithymocyte globulin therapy as well. Of the seven secondary transplantations in total, in four patients, additional therapy in the form of DLI was needed, and in one patient, DLI and boost therapy were needed.

Out of the 18 patients with relapse, nine (50%) of them received DLI. This significantly differs from the study by Schmid et al., where 33.5% patients received DLI, as well as the study by Ciurea et al., where only 13.7% of patients were reported to have received DLI. The differences in therapeutic modalities and their prevalence can be attributed to the patient structure, as well as to the total number of patients included in the study. Both Schmid and Ciurea analyzed only patients with AML, while our study covered a broader spectrum of diagnoses [19,20].

## CONCLUSION

The data from our study, which relate to trends in the choice of the conditioning regimen, the relapse rate upon transplantation, the overall survival upon relapse, as well as to the application of therapy upon relapse, are in keeping with data from different centers in the world. Patients who received reduced intensity conditioning regimens had a better length of survival, however without statistical significance, as well with-

AML – akutna mijeloblastna leukemija
HL – Hočkinov limfom
NHL – Nehočkinov limfom
MDS – mijelodisplastični sindrom
MPN – mijeloproliferativni sindrom
d – dan transplantacije
SZO – Svetska zdravstvena organizacija
iv – intravenski
SAD – Sjedinjene Američke Države
*CAR-T* – himera antigen receptor T-ćelija (engl. *chimeric antigen receptor T-cell*)
*EBMT* – Evropska grupa za krv i transplantaciju koštane srži (engl. *European Group for Blood and Marrow Transplantation*)
*OS* – ukupno preživljavanje (engl. *overall survival*)
*HCT-CI* – indeks komorbiditeta pri transplantaciji hematopoeznih ćelija (engl. *hematopoietic cell transplantation-specific comorbidity index*)
*ECOG PS* – procena opšteg telesnog stanja pacijenta Istočne kooperativne grupe za onkologiju (engl. *Eastern Cooperative Oncology Group Performance Status Scale*)

## IZJAVA ZAHVALNOSTI

Ovim putem zahvalnost upućujem svojoj mentorki, prof. dr Mileni Todorović-Balint i doc. dr Ireni Đunić, zbog nesebične pomoći pri celokupnoj izradi rada. Bez njihovih konstruktivnih saveta i kritika pisanje ovog rada ne bi bilo moguće. Zahvalnost upućujem i svojim kolegama Nikoli Peuliću i Stefanu Stankoviću, na pomoći pri izradi i sastavljanju baze podataka, kao i prof. dr Dejani Stanisavljević, za pomoć pri statističkoj obradi podataka.

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out an increase in the relapse rate. As yet, our center has not introduced a significant ratio of patients above the age of 60 years in transplantation procedures. In the future, inclusion of older patients should be initiated, and efforts should be made to further reduce relapse rates, especially in patients with acute leukemias. Targeted prophylactic application of therapy should be considered in patients with ALL and AML, for the purpose of preventing relapse.

## LIST OF ABBREVIATIONS AND ACRONYMS

allo-HSCT – allogeneic hematopoietic stem cell transplantation
MAC – myeloablative conditioning
RIC – reduced intensity conditioning
MRD –minimal residual disease
GvHD – graft versus host disease
HLA – human leukocyte antigen
PCR – polymerase chain reaction
DLI – donor lymphocyte infusion
GvT – graft versus tumor effect
GvL – graft versus leukemia effect
ALL – acute lymphoblastic leukemia
AML – acute myeloblastic leukemia
HL – Hodgkin's lymphoma
NHL – Non-Hodgkin's lymphoma
MDS – myelodysplastic syndrome
MPN – myeloproliferative syndrome
d – day of transplantation
WHO – World Health Organization
IV – intravenous
USA – United States of America
CAR-T – chimeric antigen receptor T-cell
EBMT – European Group for Blood and Marrow Transplantation
OS – overall survival
HCT-CI – hematopoietic cell transplantation-specific comorbidity index
ECOG PS – Eastern Cooperative Oncology Group Performance Status Scale

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