SAŽETAK

Uvod: Bolesnici sa hematološkim malignitetima, kao što su akutna mijeloidna leukemija i akutna limfoblastna leukemija (AML/ALL), mijelodisplastični sindrom (MDS) i oni koji su podvrgnuti alogenej transplantaciji matičnih ćelija (aloTMĆ) su pod najvećim rizikom od nastanka invazivnih gljivičnih infekcija (engl. invasive fungal infections – IFI). Najčešći među uzročnicima su Candida spp. i Aspergillus spp. Među strategijama za prevenciju nastanka invazivnih gljivičnih infekcija je blagovremena i adekvatna primena antifungi̇čne profilakse koju preporučuje NCCN (National Comprehensive Cancer Network).

Cilj: Cilj istraživanja bila je analiza pojave IFI infekcija kod ovih pacijenata, kao i analiza uticaja i značaja pravovremene antifungi̇čne profilakse za njihovo nastajanje.

Materijal i metode: U retrospektivnoj studiji, ispitivano je 42 bolesnika, pro- sečne starosti 35 godina, koji su bili u programu aloTMĆ-a, u periodu od 2017. do 2019. godine, i kod kojih je primenjivana antifungi̇čna profilaksa na Klinici za hematologiju, Univerzitetskog kliničkog centra Srbije (UKCS). Na osnovu informacija dobijenih iz istorija bolesti, formirane su baze podataka. Statistička analiza podataka obuhvatala je metode deskriptivne i analitičke statistike i urađena je u SPSS programu.

Rezultati: Klinički manifestnu infekciju u vidu oralne kandidijaze imalo je 19 (45,2%) bolesnika, dok se plućna aspergiluloza razvila kod svega 3 (7,1%) bolesnika. Statistički značajna povezanost postojala je između klinički manifestne aspergiluloze (7,1%) i prisustva antigena (Galactomannan) kod ovih bolesnika (p < 0,001). Utvrđena je i statistički značajna povezanost između klinički manifestne aspergiluloze i slabosti kalema: 2 (66,6%) naspram 1 (33,3%), (p = 0,016).

Zaključak: Primena adekvatne antifungi̇čne profilakse značajno smanjuje incidenciju pojave IFI kod bolesnika u programu aloTMĆ-a, i na taj način doprinosi smanjenju morbiditeta i mortaliteta.

Ključne reči: antifungi̇čna profilaksa, invazivne gljivične infekcije, aspergiluloza, antigen

ABSTRACT:

Introduction: Patients with hematologic malignancies, such as acute myeloid leukemia and acute lymphoblastic leukemia (AML/ALL), myelodysplastic syndrome (MDS), and those undergoing allogeneic stem cell transplantation (allogeneic SCT) are at the highest risk of invasive fungal infections (IFI). The most common causative agents are Candida spp. and Aspergillus spp. Among the strategies for preventing IFIs is the adequate implementation of antifungal prophylaxis recommended by the NCCN (National Comprehensive Cancer Network).

Aim: The aim of the study was to analyze the occurrence of IFIs in these patients, as well as to analyze the impact and importance of timely antifungal prophylaxis with regards to the development of these infections.

Materials and methods: The retrospective study included 42 patients, of the average age of 35 years, who underwent the allo-SCT program, between 2017 to 2019, and received antifungal prophylaxis at the Clinic for Hematology of the Clinical Center of Serbia (CCS). Based on information obtained from medical histories, databases were formed. Statistical analysis included descriptive statistical methods that were performed in the SPSS program.

Results: Nineteen (45.2%) patients presented with the clinical manifestation of oral candidiasis. Invasive pulmonary aspergillosis developed in only 3 (7.1%) patients. There was a statistically significant association between clinically manifest aspergillosis (7.1%) and the presence of antigens (Galactomannan) in these patients (p <0.001). There was also a statistically significant association between clinically manifest aspergillosis and graft weakness: 2 (66.6%) vs. 1 (33.3%), (p = 0.016).

Conclusion: The use of adequate antifungal prophylaxis significantly reduces the incidence of IFIs in patients undergoing the allo-SCT program, and this contributes to the reduction of morbidity and mortality.

Key words: antifungal prophylaxis, invasive fungal infections, aspergillosis, antigen
UVOD

S pojavom poboljšanih hemioterapijskih režima, mogućnosti alogene transplantacije matičnih ĉelija (alo-TMĆ), i novih bioloških ciljanih terapija, ishod mnogih ozbiljnih hematoloških oboljenja se stalno poboljšava [1]. Međutim, invazivne gljivične infekcije (engl. invasive fungal infections – IFI) su i dalje vodeći infektivni uzrok morbiditeta i mortaliteta kod bolesnika sa hematološkim malignitetima [8].

Bolesnici sa hematološkim malignitetima, kao što su akutna mijeloidna leukemija i akutna limfoblastna leukemija (AML/ALL), mijelodisplastični sindrom (MDS) i oni koji su podvrgnuti alogenoj transplantaciji matičnih ĉelija hematopoze (aloTMĆ) su u najvećem riziku od nastanka IFI infekcija [9], pri čemu je incidencija najviša kod akutne mijeloidne leukemije (AML) [10]. Imajući ovo u vidu, gljivične infekcije i dalje ostaju izazov kod ovih, tzv. „riziĉnih” bolesnika. Pored toga, nastanku gljivičnih infekcija dodatno doprinosi neprimenjena antiguļiViĉ-na profilaksa širokog spektra dejstva. [2,3,4]. Invazivne gljivične infekcije (IFI) su infekcije visoke incidencije, ugrožavajuće su po život pacijenta, i zahtevaju ulaganje znaĉajnih finansijskih sredstava kod bolesnika na programu alogene transplantacije matičnih ĉelija (aloTMĆ) [7]. Najĉešći meĊu patogenim uzroĉnicima infekcije su Candida spp. i Aspergillus spp. Infekcije izazvane ovim vrstama, posebno, Aspergillus spp., još uvek su u porastu u ovoj populaciji bolesnika, i znaĉajan su uzrok morbiditeta i mortaliteta, posebno u kontekstu produžene neutropenije i imunosupresivnog leĉenja [5,7].

Prevencija i leĉenje invazivnih gljiviĉnih infekcija kod bolesnika u programu alo-TMĆ-a predstavlja veliki izazov. Stoga su u protekle dve decenije uĉinjeni veliĉi napori kako bi se pronašla adekvatna strategija za spreĉavanje nastanka teških IFI infekcija u ovoj populaciji bolesnika. MeĊu strategijama za poboljšanje ishoda da je blagovremen i adekvatna primena antigljiViĉne profilakse [6]. Trenutno postoji nekoliko antiguļiViĉnih lekova koje preporuĉuje Nacionalna sveobuhvatna mreţa protiv raka za profilaksu IFI (National Comprehensive Cancer Network – NCCN). Tu spadaju: flukonazol, itraconazol, vorikonazol, posaconazol i mikafungin [6]. Dostupnost ovih novih triazola (vorikonazol, posaconazol), karakteristiĉkih za širi spektar, u poslednje vreme, promenila je ulogu antiguļiViĉne profilakse. Primena posaconazola i mikafungina znaĉajno je poboljšala efikasnost antiguļiViĉne profilakse u ovoj populaciji bolesnika [11,12,13].

Cilj ovog istraživanja bila je analiza pojave manifes-tnih gljiviĉnih infekcija kod bolesnika u programu alogene transplantacije matičnih ĉelija hematopoze, kao i analiza uticaja i znaĉaja pravovremene antiguļiViĉne profilakse za njihovo nastajanje.

INTRODUCTION

With the emergence of improved chemotherapeutic regimens, and the possibility of allogenic stem cell transplantation (allo-SCT), as well as with new biologic targeted therapies, the outcome for many serious hematological diseases is constantly improving [1]. However, invasive fungal infections (IFI) remain the leading infective cause of morbidity and mortality in patients with hematological malignancies [8].

Patients with hematological malignancies, such as acute myeloid leukemia and acute lymphoblastic leukemia (AML/ALL), patients with myelodysplastic syndrome (MDS), as well as patients who undergo allogenic hematopoietic stem-cell transplantation (allo-HSCT), are at the highest risk of developing IFI infections [9], with the incidence of these infections being the highest in acute myeloid leukemia (AML) [10]. Bearing this in mind, fungal infections remain a challenge in these, so called, “risky” patients. Additionally, the lack of the application of prophylactic antifungal broad-spectrum therapy contributes to the development of fungal infections [2,3,4]. Invasive fungal infections (IFI) are infections of high incidence, they endanger the patient’s life, and they require the investment of significant financial resources in patients who are in the program of allogenic stem-cell transplantation (allo-SCT) [7]. The most common pathogens causing infection are Candida spp. and Aspergillus spp. Infections caused by these species of pathogens, especially, Aspergillus spp., are still on the rise in this population of patients, and they are a significant cause of morbidity and mortality, especially in the context of prolonged neutropenia and immunosuppressive treatment [5,7].

The prevention and treatment of fungal infections in patients who are in the allo-SCT program is a great challenge. This is why, in the previous two decades, great efforts have been made to find the appropriate strategy for preventing the development of severe IFIs in this population of patients. Timely and adequate application of antifungal prophylaxis is among the strategies for outcome improvement [6]. Currently, there are several antifungal drugs recommended by the National Comprehensive Cancer Network (NCCN) for IFI prophylaxis, namely: fluconazole, itraconazole, voriconazole, posaconazole, and micafungin [6]. The accessibility of these new triazoles (voriconazole, posaconazole), characteristic of the broad spectrum, has lately changed the role of antifungal prophylaxis. The application of posaconazole and micafungin has significantly improved the efficacy of antifungal prophylaxis in this population of patients [11,12,13].

The aim of this study was to analyze the occurrence of manifest fungal infections in patients included in
the program of allogenic hemopoietic stem-cell transplantation, as well as to analyze the impact and importance of timely antifungal prophylaxis in relation to the development of these infections.

METHODS

The research was carried out as a retrospective observational cohort study, based on the database of the Clinic for Hematology of the Clinical Center of Serbia, during October and November 2019. The study included 42 patients, who had undergone the program of allogenic stem-cell transplantation between 2017 to 2019. The patients were diagnosed with one of the following: Hodgkin lymphoma (HL), Non-Hodgkin lymphoma (NHL), acute leukemia (AML/ALL), chronic lymphocytic leukemia (CLL), and myelodysplastic syndrome (MDS), in the period between 2003 and 2019.

The data on the demographic characteristics (age, sex), data on the diagnosis, which were acquired for the purpose of the study from pathohistological and immunohistochemical analyses of biopsy samples, as well as data on the allogenic transplantation that had been carried out, were obtained from patient medical records (medical histories). The medical records were also the source of the following information: data on the intensity of the applied conditioning regimen (Reduced-Intensity Conditioning – RIC; Myeloablative Conditioning – MAC), data on the presence/absence of specific antibodies to Candida spp and Aspergillus spp. (IgM, IgG), which were obtained on the basis of serological testing (ELISA), data on the presence/absence of antigens specific to Candida spp and Aspergillus spp. (Candida mannan test and galactomannan test), as well as data on clinically manifest infection in patients, in the form of candidiasis or aspergillosis. Oral candidiasis was diagnosed by the inspection of the buccal mucosa and cultivation of the sample that was taken with a sterile swab from the buccal mucosa and the tongue, while the diagnosis of pulmonary aspergillosis was established based on serological (galactomannan test) and radiological (X-ray, CT scan) analyses and tests.

All patients received antifungal prophylaxis: micafungin 50 mg intravenously, for a total of 15 days, beginning with the first day of preforming the conditioning regimen, upon which they received posaconazole in a dose of a 5 ml suspension, three times a day until D+100 (day 100 as of the day of allogeneic hemopoietic stem cell transplantation).

Statistical processing included the forming of a database, with grouping and tabular presentation of the results by tested patient characteristics. Statistical analysis of the collected data included descriptive and analytical statistical methods and it was performed in the
**REZULTATI**

Tokom navedenog dvogodišnjeg perioda, na Odeljenju transplantacije koštane srži Klinike za hematologiju Kliničkog centra Srbije, koje postoji od 2017. godine, u program alogene transplantacije bilo je uključeno ukupno 42 bolesnika.

U Tabeli 1 prikazane su demografske i kliničke karakteristike bolesnika.

Studijom je obuhvaćeno 42 bolesnika kod kojih je postavljeno sledećih šest dijagnoza: 19% HL, 4,8% NHL, 33,3% AML, 35,7% ALL, 2,4% HLL, i 4,8% MDS. U ispitivanoj grupi, muškaraca je bilo 21 (50%), a isto toliko i žena. Prosечна starost iznosila je 35 ± 12,02 godina. Najmlađi bolesnik je imao 14, a najstariji 56 godina, u vreme postavljanja dijagnoze. Kod 12 bolesnika (28,6%) primenjen je RIC kondicioni režim aloTMĆ-a dok je kod 30 (71,4%) primenjen MAC kondicioni režim.

U Tabeli 2 prikazani su podaci o prisustvu specifičnih IgG i IgM antitela i antigena za *Candida spp.* i *Aspergillus spp.*

### Tabela 1. Demografske i kliničke karakteristike bolesnika

| Varijabla / Variable | Broj / Number | Procenat / Percentage |
|-----------------------|---------------|------------------------|
| Muškarci / Men        | 21            | 50%                    |
| Žene / Women          | 21            | 50%                    |
| Starost / Age         | 35 ± 12.02    |                        |

### Tabela 2. Prisustvo specifičnih IgG i IgM antitela i antigena za *Candida spp.* i *Aspergillus spp.*

| Varijabla / Variable | Broj / Number | Procenat / Percentage |
|-----------------------|---------------|------------------------|
| Pozitivna antitela na Candida-u / Positive antibodies to Candida | 29 | 69% |
| Pozitivna antitela na Aspergillus / Positive antibodies to *Aspergillus* | 21 | 50% |
| Pozitivan Candida manan / Positive *Candida* manan | 1 | 2.4% |
| Pozitivan galaktomannan / Positive galaktomannan | 4 | 9.5% |

Legend: HL (Hockinov limfom); NHL (Nehočkinov limfom); AML (akutna mijeloidna leuke-mija); ALL (akutna mijeloblastna leuke-mija); HLL (horonična limfocitna leuke-mija); MDS (mije-lodiskastični sindrom); MAC (mijeloblastivni kondicioni režim, engl. myeloablative conditioning); RIC (kondicioni režim redukovanog intenziteta, engl. reduced-intensity conditioning).

**RESULTS**

During the abovementioned two-year period, at the Department for Bone Marrow Transplant of the CCS Clinic for Hematology, which was established in 2017, a total of 42 patients were included in the program of allogeneic transplantation.

Table 1 shows the demographic and clinical characteristics of the patients.

The study included 42 patients in whom the following six diagnoses were established: 19% HL, 4,8% NHL, 33,3% AML, 35,7% ALL, 2,4% CLL, and 4,8% MDS. In the analyzed group, there were 21 men (50%), and the same number of women. The average age was 35 ± 12.02 years. The youngest patient was 14, while the oldest one was 56 years old, at the time of diagnosis. The RIC conditioning regimen of allo-SCT was carried out in 12 patients (28,6%), while the MAC conditioning regimen was applied in 30 patients (71,4%).

Table 2 shows the data on the presence of specific IgG and IgM antibodies and antigens to *Candida spp.* and *Aspergillus spp.*

In 29 patients (69%) the presence of antibodies to *Candida spp.* was registered, while in 13 patients (31%) the antibody test was negative. The positive antibody test for *Aspergillus spp.* was registered in 50% of the patients. The *Candida spp.* mannan test was positive in one patient (2.4%), while the positive galactomannan test was registered in 4 patients (9.5%).
Kod 29 bolesnika (69%) zabeleženo je prisustvo antitela na Candida spp. dok su kod 13 pacijenata (31%) antitela bila negativna. Pozitivna antitela na Aspergillus spp. su zabeležena kod 50% bolesnika. Pozitivan Candida spp. manan test je zabeležen kod 1 bolesnika (2,4%) dok je pozitivan galakтоманан test zabeležen kod 4 bolesnika (9,5%). Klinički manifestnu infekciju, u vidu oralne kandidijaze, imalo je 19 bolesnika (45,2%), dok se plućna aspergiloloza razvila kod svega 3 bolesnika (7,1%).

Ispitivano je da li postoji statistički značajna povezanost između klinički manifestne infekcije (oralna kandidijaza/plućna aspergiloloza) i jačine primjenjenog kondicioniranog režima, međutim statistički značajna povezanost nije nađena (p = 0,327 MAC, p = 0,256 RIC), odnosno nije bilo statistički značajne razlike u ispoljavanju manifestne gljivične infekcije između bolesnika koji su primali MAC i onih koji su primali RIC kondicioni režim. Takođe, nije bilo statistički značajne povezanosti između klinički manifestne infekcije i dijagnoze bolesnika (p = 0,580).

Od troje bolesnika (7,1%) koji su imali klinički manifastnu plućnu aspergilolozu, svo troje je imalo i pozitivan galaktomanan test (100%), što se pokazalo kao statistički značajno (p < 0,001). Takođe, utvrđena je statistički značajna povezanost između klinički manifestne plućne aspergiloloze i slabosti kalem: 2 (66,6%) naspram 1 (33,3%), (p = 0,016).

Procjenjena mediana preživljanja bolesnika nakon aloTMC-a, a bila je 56 meseci.

**DISKUSIJA**

Invazivne gljivične infekcije (IFI) jesu značajan uzrok morbidity i mortaliteta kod bolesnika u programu alogene transplantacije matičnih celija (aloTMC). U literaturi postoje brojni podaci o učestalosti IFI infekcija, značaju primarne antigliivične profilakse i njenom uticaju na smanjenje pojave gljivičnih infekcija, kod bolesnika koji su u programu aloTMC-a.

 Prospektivna studija, u kojoj je bilo uključeno 23 centra za transplantaciju u Sjedinjenim Američkim Državama, analizirala je epidemiologiju i faktore rizika kod IFI infekcija i dala podatke da je invazivna aspergiloloza bila najčešća infekcija, dok su invazivna kandidijaza i ne-Aspergillus plesnima izazvane infekcije bile ređe [14]. Takođe, multicentrična prospektivna studija iz Brazila dala je rezultate da su IFI infekcije otkrivene kod 9,2% slučajeva, nakon aloTMC-a [15]. U ovom istraživanju, učestalosti invazivne aspergiloloze i kandidijaze su bile slične, dok je u prospektivnom istraživanju iz Italije, aspergiloloza bila prva po učestalosti (81,1%), dok je kandidijaza bila znatno manje zastupljena (11%).

Na osnovu rezultata brojnih studija, primena mikafungina, posaconazole, i ostalih antigliivičnih lekova, kao antigliivične profilakse, jeste sveopšte prihvaćena

Clinically manifest infection, in the form of oral candidiasis, was present in 19 patients (45.2%), while pulmonary aspergillosis developed in only 3 patients (7.1%).

The existence of a statistically significant connection between clinically manifest infection (oral candidiasis/pulmonary aspergillosis) and the intensity of the applied conditioning regimen was analyzed, however, a statistically significant connection was not found (p = 0.327 MAC, p = 0.256 RIC), i.e., there was no statistically significant difference in the expression of manifest fungal infection between patients on the MAC and the ones on the RIC regimen. Also, there was no statistically significant connection between clinically manifest infection and the diagnosis of the patients (p = 0.580).

Of the three patients (7.1%) who developed clinically manifest pulmonary aspergillosis, all three tested positive on the galactomannan test (100%), which proved statistically significant (p < 0.001). Also, a statistically significant connection between clinically manifest pulmonary aspergillosis and graft weakness was established: 2 (66.6%) vs. 1 (33.3%), (p = 0.016).

The approximated median length of patient survival after allo-SCT was 56 months.

**DISCUSSION**

Invasive fungal infections (IFI) are a significant cause of morbidity and mortality in patients submitted to the program of allogeneic stem-cell transplantation (allo-SCT). There are numerous data in literature on the frequency of IFI infections, the significance of primary antifungal prophylaxis, and its influence on the reduction of the occurrence of fungal infections, in patients submitted to the program of allo-SCT.

A prospective study, which included 23 transplantation centers in the United States of America, analyzed the epidemiology and risk factors in IFIs and provided data confirming invasive aspergillosis to be the most frequent infection, while invasive candidiasis and non-Aspergillus spp. related invasive fungal infections were less frequent [14]. Also, results of a multicentric prospective study from Brazil concluded that IFIs were found in 9.2% of cases, after allo-SCT [15]. In this study, the frequency of the occurrence of aspergillosis and the frequency of occurrence of candidiasis were similar, while, in a prospective study from Italy, aspergillosis was the most common infection (81.1%), while candidiasis was far less frequent (11%).

Based on the results of numerous studies, the application of micafungin, posaconazole, and other antifungal drugs as antifungal prophylaxis, is generally accepted for the prevention of IFIs in patients submitted to the allo-SCT program. This is why analyzing the effect of antifungal prophylaxis remains a challenge and the subject of many studies [17,18,19].
ZAKLJUČAK
Ovo istraživanje je pokazalo da se invazivne glji-
vične infekcije javljaju i kod pacijenata u programu aloTMČ-a, a
Cakić J. et al.

CONCLUSION
This study has shown that, while invasive fungal
infections occur also in patients in the program of al-
lo-SCT, who are treated with antifungal prophylaxis,
aloTMČ-a, koji su na tretmanu antigihićne profilakse, ali se ove infekcije javljaju kod značajno manjeg broja ovakvih pacijenata. Rezultati ove studije pokazali su da je uvodenje dvojne kombinovane antigihićne profilakse (mikafungin i posaconazol) imalo za posledicu da incidencija IFI infekcija kod bolesnika u programu aloTMČ-a bude začajno manja.

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