UČESTALOST I ZNAČAJ RAZVOJA FEBRILNE NEUTROPENIJE KOD BOLESNIKA SA HEMATOLOŠKIM MALIGNITETIMA LEČENIH U USLOVIMA DNEVNE BOLNICE TERCIJARNE USTANOVE

ORIGINALNI RAD

ORIGINAL ARTICLE

FREQUENCY AND SIGNIFICANCE OF THE DEVELOPMENT OF FEBRILE NEUTROPENIA IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES TREATED IN THE DAY-CARE UNIT OF A TERTIARY INSTITUTION

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SAŽETAK

Uvod: Neutropenija uzrokovana primenom hemioterapije (HT) često se komplikuje pojavom febrilne neutropenije (FN), koja je povezana sa razvojem infekcija, redukcijom doze leka/odlaganjem hemioterapije, narušenim kvalitetom života i povećanim troškovima lečenja.

Cilj rada: Cilj rada je ispitivanje povezanosti faktora rizika za razvoj febrilne neutropenije i značaja primene granulocitnog faktora stimulacije rasta kolonija (*G-CSF*) kod bolesnika sa hematološkim malignitetima.

Materijali i metode: Obuhvaćeno je 90 bolesnika sa dijagnozom limfoma, multiplog mijeloma (MM) i mijelodisplaznog sindroma (MDS) lečenih u Dnevnoj bolnici Klinike za hematologiju Univerzitetskog kliničkog centra Srbije (UKCS), u periodu od januara do juna 2024.

Rezultati: Obuhvaćeno je 90 bolesnika sa sledećim dijagnozama: limfomi 70 (77,8%) pacijenata, MM 12 (13,3%) pacijenata, MDS 8 (8,9%) pacijenata, od čega 42,2% (38/90) muškog a 57,8% (52/90) ženskog pola. FN je zabeležena kod 22 (24,4%) bolesnika, dok 68 (75,6%) pacijenata nije razvilo febrilnu neutropeniju. Distribucija FN prema tipu limfoma je bila: 57,9% kod agresivnih, 31,6% kod indolentnih i 10,5% kod Hočkinovog limfoma. Uočena je povezanost febrilne neutropenije sa većom učestalošću viših kliničkih stadijuma bolesti, i za stadijum III i IV je iznosila 70%. Kod pacijenata sa FN-om je bilo značajno učestalije prisustvo velike (engl. *bulky*) tumorske mase (54,5% naspram 25%; $p = 0,010$). Pacijenti sa FN-om su imali statistički značajno veći broj primenjenih hemioterapijskih linija ($p = 0,020$), hemioterapijskih ciklusa ($p = 0,027$), ciklusa imunoterapije ($p = 0,025$), kao i veću učestalost infekcija (59,1% naspram 27,9%; $p = 0,008$), češću primenu antibiotika (95,5% naspram 33,8%; $p = 0,004$) i *G-CSF*-a (54,5% naspram 11,8%; $p < 0,001$), te veći broj primenjenih ampula *G-CSF*-a (5,0 naspram 1,0; $p < 0,001$). Dokazana je značajna razlika u višim vrednostima CRP-a kod bolesnika sa febrilnom neutropenijom (7,2% naspram 3,3%; $p = 0,012$).

Zaključak: Naša studija je pokazala da su na razvoj febrilne neutropenije uticali veći broj terapijskih linija i ciklusa imunohemioterapije, klinički stadijum bolesti, *bulky* tumorska masa i stepen agresivnosti limfoma.

Kjučne reči: febrilna neutropenija, *G-CSF*, hematološki maligniteti, dnevna bolnica

ABSTRACT

Introduction: Chemotherapy-induced neutropenia is often complicated by the development of febrile neutropenia (FN) which is associated with infections, dose reductions/delay of chemotherapy, quality of life deterioration, and increased treatment costs.

Study aim: The study aims to research the association between risk factors for FN and the significance of applying *G-CSF* in patients with hematological malignancies.

Materials and methods: We evaluated 90 patients with lymphoma, multiple myeloma (MM), and myelodysplastic syndrome (MDS) treated at the Day-care Unit of the University Clinical Center of Serbia (UCCS) Clinic for Hematology, between January and June 2024.

Results: The study included 90 patients with the following diagnoses: 70 (77.8%) patients with lymphomas, 12 (13.3%) patients with MM, and 8 (8.9%) patients with MDS, of whom 42.2% (38/90) male and 57.8% (52/90) female. FN was observed in 22 (24.4%) patients, while 68 (75.6%) patients did not develop FN. The distribution of FN by lymphoma type was as follows: 57.9% in aggressive lymphomas, 31.6% in indolent lymphomas, and 10.5% in Hodgkin's lymphoma. FN was associated with a higher incidence of advanced clinical stages of disease, with 70% in stages III and IV. Patients with FN had significantly higher rates of bulky tumor mass (54.5% vs. 25%; $p = 0.010$), more lines of chemotherapy ($p = 0.020$), more cycles of chemotherapy ($p = 0.027$), more immunotherapy cycles ($p = 0.025$), as well as more infections (59.1% vs. 27.9%; $p = 0.008$), antibiotic use (95.5% vs. 33.8%; $p = 0.004$), and G-CSF administration (54.5% vs. 11.8%; $p < 0.001$), with more G-CSF ampoules used (5.0 vs. 1.0; $p < 0.001$). Higher CRP levels were also significantly associated with FN (7.2% vs. 3.3%; $p = 0.012$).

Conclusion: Our study has shown that the number of lines of therapy, the number of immunochemotherapy cycles, the clinical stage, the presence of bulky tumor mass, and the aggressiveness of the lymphoma affected FN development.

Keywords: febrile neutropenia, G-CSF, hematological malignancies, day-care unit

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Primljeno • *Received*: July 29, 2024; **Revidirano • *Revised*:** September 4, 2024; **Prihvaćeno • *Accepted*:** September 13, 2024; ***Online first*:** September 25, 2024

DOI: 10.5937/smclk5-52460

UVOD

Neutropenija uzrokovana primenom hemioterapije (HT) predstavlja jedan od najčešćih neželjenih efekata lečenja i često se komplikuje febrilnom neutropenijom (FN). Neutropenija se javlja kod skoro petine hematoloških bolesnika, izuzev bolesnika kod kojih je sprovedena transplantacija matičnih ćelija hematopoeze gde se ova incidencija kreće u rasponu od 70% do 100%, za razliku od drugih onkoloških bolesnika kod kojih se kreće od 5% do 10%. Toksično dejstvo hemioterapije na hematopoetski sistem predstavlja ograničavajući faktor u adekvatnom doziranju leka. Komplikacije neutropenije uzrokovane mijelosupresivnim efektom hemioerapije igraju veliku ulogu u porastu morbiditeta i mortaliteta kod onkoloških bolesnika. Pojava febrilne neutropenije povezana je sa razvojem životno ugrožavajućih infekcija, odlaganjem hemioterapije, narušenim kvalitetom života i povećanim troškovima lečenja, što sve zajedno utiče na konačni ishod lečenja [1,2].

Upravo zbog toga je od velikog značaja identifikovanje faktora rizika koji dovode do febrilne neutropenije, u toku, kao i pre započinjanja specifičnog hematološkog lečenja. Najznačajni faktor jeste tip hemioterapije, mada do sada nije ustanovljen standardni bodovni (engl. *scoring*) sistem za poređenje agresivnosti različitih hemioterapeutika [3]. Drugi po redu najznačajniji faktor jeste osnovna bolest, iako se ovaj podatak u istraživanjima retko navodi zbog toga što neki od hematoloških maligniteta, za razliku od solidnih tumora, sami po sebi uključuju neutropeniju [4]. U literaturi se kao faktori rizika za pojavu febrilne neutropenije navode i površina tela, infiltracija koštane srži, godine starosti pri postavljanju dijagnoze, inicijalni ili broj monocita i limfocita nakon prvog ciklusa, kao i nivo hemoglobina [5–8].

U literaturi je opisana podela na faktore rizika koji su u vezi sa samim bolesnikom i faktore rizika koji su specifični za vrstu terapije. U prvu grupu spadaju prethodno podvrgavanje hemioterapijskom lečenju, inicijalna neutropenija, infiltracija koštane srži osnovnom bolešću, klinički stadijum bolesti, prisustvo komorbiditeta, lošiji *ECOG* performans status (engl. *Eastern Cooperative Oncology Group – ECOG performance status*), prethodno prisustvo infekcija, godine starosti, kao i tip maligniteta, uz napomenu da su bolesnici sa hematološkim malignitetima u povećanom riziku za razvoj neutropenije u odnosu na bolesnike sa solidnim tumorima, kako zbog same prirode osnovne bolesti tako i zbog intenziteta terapije. Faktori rizika specifični za vrstu terapije se mogu objasniti činjenicom da su neki lekovi mijelotoksičniji od drugih. Takođe, dokazano je da se neutropenije češće beleže u prvim ciklusima terapije.

INTRODUCTION

Chemotherapy-induced neutropenia is one of the most common side effects of treatment and is often complicated by febrile neutropenia (FN). Neutropenia occurs in almost a fifth of hematological patients, except for patients who undergo hematopoietic stem cell transplantation, among whom this incidence ranges from 70% to 100%, in contrast to other oncology patients, where it ranges from 5% to 10%. The toxic effect of chemotherapy on the hematopoietic system is a limiting factor in adequate drug dosing. Complications of neutropenia caused by the myelosuppressive effect of chemotherapy play a major role in the increase in morbidity and mortality in cancer patients. The occurrence of febrile neutropenia is associated with the development of life-threatening infections, chemotherapy treatment delay, impaired quality of life, and increased treatment costs, all of which affect the treatment outcome [1,2].

That is exactly why it is very important to identify the risk factors leading to febrile neutropenia, during and before starting specific hematological treatment. The most important factor is the type of chemotherapy, although so far, no standard scoring system has been established for comparing the aggressiveness of different chemotherapeutics [3]. The second most important factor is the underlying disease, although this information is rarely mentioned in research because some of the hematological malignancies, in contrast to solid tumors, inherently include neutropenia [4]. Body surface area, bone marrow infiltration, age at diagnosis, the initial or the number of monocytes and lymphocytes after the first cycle, as well as the hemoglobin level, are mentioned in literature as risk factors for the occurrence of febrile neutropenia [5–8].

In literature, risk factors are categorized as those associated with the patients themselves and those that are particular to the type of therapy. The first group of risk factors includes previous chemotherapy treatment, initial neutropenia, bone marrow infiltration due to the underlying disease, clinical stage of the disease, presence of comorbidities, a poorer ECOG (Eastern Cooperative Oncology Group) performance status, previous infections, age, as well as the type of malignancy, noting that patients with hematological malignancies are at increased risk of developing neutropenia, as compared to patients with solid tumors, both due to the very nature of the underlying disease and the intensity of the therapy. Risk factors particular to the type of therapy can be explained by the fact that some drugs are more myelotoxic than others. Also, it has been proven that neutropenia is more often found in the initial therapy cycles.

Stepen i razvoj neutropenije direktno utiču na rizik od nastajanja infekcije. Po težini, neutropenija se najčešće deli na četiri stepena. Stepen neutropenije gradusa 1 predstavlja *ANC* (engl. *absolute neutrophil count*) ≥ 1,5 i < 2,0 x 10^9/l, gradus 2 je kada je *ANC* ≥ 1,0 i < 1,5 x 10^9/l, gradus 3 je kada je *ANC* ≥ 0,5 i < 1,00 x 10^9/l, dok je gradus 4 vrednost *ANC*-a < 0,5 x 10^9/l. FN predstavlja stanje u kojem su *ANC* ≤ 0,5 x 10^9/l i telesna temperatura ≥ 38,3°C. Poznato je da u inflamatornom odgovoru upravo neutrofilni granulociti igraju bitnu ulogu celularnog imuniteta kao deo nespecifične zaštite organizma. Njihov broj je kompromitovan delom zbog citotoksičnog efekta terapije, a delom zbog same prirode osnovne bolesti. Upravo zbog toga, simptomi i znaci infekcije kod ovih bolesnika često budu prikriveni, a jedina manifestacija može biti povišena telesna temperatura. Preko 50% bolesnika sa febrilnom neutropenijom će ispoljiti septički sindrom, 20% – 30% ovih pacijenata će razviti težak oblik sepse, a 5% – 10% će imati septički šok. U tom slučaju, neophodna je hospitalizacija i primena intenzivne antibiotske terapije intravenskim antibioticima širokog spektra, s obzirom na stepen imunokompromitovanosti ovakvih bolesnika. Najčešće su infekcije digestivnog trakta, pluća i kože. Najčešći uzročnici su gram negativne bakterije *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, kao i aerobne, gram pozitivne koke *Staphylococcus, Streptococcus species* i *Enterococcus*, ali ne treba zanemariti ni često prisustvo gljivičnih infekcija [3]. Društvo za infektivne bolesti Amerike (engl. *Infectious Diseases Society of America – IDSA*) je publikovala smernice za lečenje febrilne neutropenije. Za većinu bolesnika intravenska primena antibiotika u bolničkim uslovima predstavlja standard lečenja. Antibiotsku terapiju treba birati vodeći računa o interakcijama antibiotika sa drugim lekovima i parametrima bubrežne i jetrene funkcije u zavisnosti od farmakokinetike leka [9].

Faktori stimulacije rasta kolonija (engl. *colony-stimulating factors* – CSFs) hematopoeze smanjuju trajanje i težinu stepena neutropenije i njenih komplikacija, omogućavajući brži oporavak parametara krvne slike i raniji nastavak primene započete hemioterapije [10].

CILJ RADA

Cilj rada je ispitivanje povezanosti faktora rizika za razvoj febrilne neutropenije i značaja primene granulocitnog faktora stimulacije rasta kolonija (engl. *granulocyte colony stimulating factor – G-CSF*) kod hematoloških bolesnika lečenih u Dnevnoj bolnici Klinike za hematologiju Univerzitetskog kliničkog centra Srbije.

The degree and development of neutropenia directly affect the risk of infection. Neutropenia is usually categorized into four grades, according to its severity. Grade 1 neutropenia is when the absolute neutrophil count (ANC) is ≥ 1.5 and < 2.0 x 10^9/l, grade 2 is when ANC is ≥ 1.0 and < 1.5 x 10^9/l, grade 3 is when ANC is ≥ 0.5 and < 1.00 x 10^9/l, while grade 4 is when the ANC value is < 0.5 x 10^9/l. Febrile neutropenia is a condition wherein ANC is ≤ 0.5 x 10^9/l and the body temperature is ≥ 38.3°C. It is known that in inflammatory response, it is neutrophil granulocytes that play an important role in cellular immunity as part of non-specific defense of the body. Their number is compromised partly due to the cytotoxic effect of the therapy, and partly due to the very nature of the underlying disease. Precisely because of this, the symptoms and signs of infection in these patients are often hidden, and the only manifestation may be elevated body temperature. Over 50% of patients with febrile neutropenia will develop septic syndrome, 20% – 30% will develop a severe form of sepsis, and 5% – 10% will have septic shock. In that event, hospitalization and the application of intensive antibiotic therapy with broad-spectrum intravenous antibiotics are necessary, given the degree of immunocompromise of such patients. The most common are infections of the digestive tract, lungs, and skin. The most common causative agents are gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, as well as aerobic, gram-positive cocci *Staphylococcus*, *Streptococcus species*, and *Enterococcus*. However, the frequent presence of fungal infections should not be ignored either [3]. The Infectious Diseases Society of America (IDSA) has published guidelines for the treatment of febrile neutropenia. For most patients, intravenous administration of antibiotics in a hospital setting is the treatment standard. Antibiotic therapy should be chosen taking into account the interactions of antibiotics with other drugs, as well as the parameters of kidney and liver function, depending on the pharmacokinetics of the drug [9].

Colony-stimulating factors (CSFs) of hematopoiesis reduce the duration and severity of the degree of neutropenia and its complications, enabling faster recovery of blood parameters and earlier continuation of chemotherapy [10].

STUDY AIM

The study aims to examine the association between risk factors for the development of febrile neutropenia and the significance of applying granulocyte colony-stimulating factor (G-CSF) in hematological patients treated at the Day Hospital of the Hematology Clinic of the University Clinical Center of Serbia.

MATERIJALI I METODE

Istraživanje je urađeno kao retrospektivna studija. Demografske karakteristike bolesnika obuhvatile su godine starosti pri dijagnozi, pol, tip hematološkog malignitеta, klinički stadijum bolesti, *ECOG* performans status, infiltraciju koštane srži, prisustvo *bulky* tumorske mase, komorbiditete, prethodno prisustvo infekcije, kao i inicijalne osnovne laboratorijske parametre. Dijagnoze su postavljene prema aktuelnim vodičima za datu bolest. Uzorkom je obuhvaćeno 90 bolesnika sa dijagnozom limfoma, multiplog mijeloma (MM) i mijelodsiplaznog sindroma (MDS), lečenih u Dnevnoj bolnici Klinike za hematologiju Univerzitetskog kliničkog centra Srbije, u periodu od januara do juna 2024.

Za deskripciju numeričkih podataka, u zavisnosti od normalnosti distribucije podataka, korišćeni su aritmetička sredina ± standardna devijacija ili medijana (opseg: min – max), dok su kategorijalni podaci prikazani kao učestalosti, odnosno broj ispitanika (procenat). Za testiranje značajnosti razlike između ispitivanih grupa pacijenata korišćen je t-test, Men-Vitnijev test i Hi-kvadratni test. Posmatrani klinički i laboratorijski parametri koji su se izdvojili kao statistički značajni na nivou $p < 0,01$ uključeni su u model višestruke regresione analize u cilju procene prediktora razvoja febrilne neutropenije. Kriterijum za statističku značajnost je bio $p < 0,05$ a softverski program *SPSS Statistics 22* (*SPSS Inc., Chicago, IL, USA*) je korišćen za statističku obradu podataka. Rezultati su prezentovani tekstualno i tabelarno.

REZULTATI

Studijom je obuhvaćeno 90 bolesnika prosečne starosti 60,0 ± 12,1 godina. Medijana starosnog doba je iznosila 63 godine (opseg: 23 – 77). Distribucija prema dijagnozi je bila sledeća: 70 (77,8%) pacijenata sa dijagnozom limfoma, 12 (13,3%) bolesnika sa dijagnozom multiplog mijeloma i 8 (8,9%) pacijenata sa dijagnozom mijelodisplaznog sindroma. Bolesnici muškog pola su činili 42,2% (38/90) a ženskog 57,8% (52/90). Medijana praćenja iznosila je 13,5 meseci (0 – 120). Smrtni ishod je nastupio kod četiri bolesnika (4,4%).

FN je zabeležena kod 22 (24,4%) bolesnika, dok 68 (75,6%) pacijenata nije razvilo febrilnu neutropeniju. U grupi bolesnika koji su imali febrilnu neutropeniju, učestalost muškog pola je iznosila 59,1% (naspram 42,2% ženskog pola; $p = 0,065$). Učestalost dijagnoza se nije značajno razlikovala u odnosu na prisustvo febrilne neutropenije ($p = 0,525$), te je u grupi pacijenata sa febrilnom neutropenijom, 86,4% njih imalo dijagnostikovan limfom, 9,1% je imalo MM a 4,5% njih MDS. Distribucija febrilne neutropenije prema tipu limfoma je bila: 57,9% kod agresivnih, 31,6% kod indolentnih i 10,5% kod Hočkinovog limfoma.

MATERIALS AND METHODS

This is a retrospective study. Patient demographic characteristics included the following: age at diagnosis, gender, type of hematological malignancy, clinical stage of disease, the *ECOG* performance status, bone marrow infiltration, presence of bulky tumor mass, comorbidities, previous presence of infection, as well as initial basic laboratory parameters. Diagnoses were established according to current guidelines for the given disease. The sample included 90 patients diagnosed with lymphoma, multiple myeloma (MM), or myelodysplastic syndrome (MDS), treated at the Day-care Unit of the University Clinical Center of Serbia (UCCS) Clinic for Hematology, between January and June 2024.

For the description of numerical data, depending on the normality of the data distribution, the arithmetic mean ± standard deviation or the median (range: min-max) was used, while categorical data were presented as frequencies, the number of respondents (percentage). The t-test, the Mann-Whitney test, and the Chi-square test were used to test the significance of the difference among the examined groups of patients. Observed clinical and laboratory parameters that were statistically significant at the $p < 0.01$ level were included in the multiple regression analysis model to assess predictors of the development of febrile neutropenia. The criterion for statistical significance was $p < 0.05$ and the SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software was used for statistical data processing. The results are presented in textual and tabular form.

RESULTS

The study included 90 patients aged 60.0 ± 12.1 years. The median age was 63 years (range: 23 – 77). The distribution according to diagnosis was as follows: 70 (77.8%) patients with lymphoma, 12 (13.3%) patients with multiple myeloma, and 8 (8.9%) patients with myelodysplastic syndrome. Male patients accounted for 42.2% (38/90) while female patients accounted for 57.8% (52/90). Median follow-up was 13.5 months (0 – 120). Death occurred in four patients (4.4%).

FN was recorded in 22 (24.4%) patients, while 68 (75.6%) patients did not develop febrile neutropenia. In the group of patients with febrile neutropenia, the frequency of male patients was 59.1% (versus 42.2% female; $p = 0.065$). The frequency of diagnoses did not differ significantly in relation to the presence of febrile neutropenia ($p = 0.525$) – in the group of patients with febrile neutropenia, 86.4% were diagnosed with lymphoma, 9.1% had MM and 4.5% MDS. The distribution of febrile neutropenia according to the type of lymphoma was as follows: 57.9% in the aggressive type, 31.6% in the indolent type, and 10.5% in Hodgkin's lymphoma.

Od ukupnog broja bolesnika, bolest kategorizovanu kao klinički stadijum (KS) I imalo je 9 (10%) bolesnika, KS II je imalo 22 (24,4%) bolesnika, KS III je bio prisutan kod 28 (31,1%) pacijenata, dok je KS IV imalo 22 (24,4%) bolesnika, i nije potvrđena značajna razlika između pacijenata sa i bez febrilne neutropenije (p = 0,191). Uočena je povezanost febrilne neutropenije sa većom učestalošću viših kliničkih stadijuma bolesti, i za stadijume III i IV učestalost je iznosila 70,0%.

Kod pacijenata sa febrilnom neutropenijom je bilo značajno učestalije prisustvo *bulky* tumorske mase (> 7 cm) i ustanovljeno je kod 54,5% ovih bolesnika, u odnosu na pacijente bez febrilne neutropenije, kod kojih je potvrđeno u 25% slučajeva (p = 0,010). Infiltra-

Of the total number of patients, in 9 (10%) subjects the disease was categorized as clinical stage (CS) I, 22 (24.4%) patients had CS II, 28 (31.1%) patients had CS III, while 22 (24.4%) patients had CS IV, while no significant difference was found between patients with and without febrile neutropenia (p = 0.191). An association of febrile neutropenia with a higher frequency of more advanced clinical stages of the disease was observed, and for stages III and IV the frequency was 70.0%.

In patients with febrile neutropenia, the presence of a bulky tumor mass (> 7 cm) was significantly more frequent and was found in 54.5% of these patients, compared to patients without febrile neutropenia, in whom it was confirmed in 25% of cases (p = 0.010).

Tabela 1. Opšti podaci

Table 1. General data

Varijable / Variables	**n (%)**
Starost / ***Age***	
Medijana (opseg) / *Median (range)*	63 (23 – 77)
Pol / ***Gender***	
M / *M*	38 (42.2%)
Ž / *F*	52 (57.8%)
Dijagnoza / ***Diagnosis***	
Limfom / *Lymphoma*	70 (77.8%)/3 HL/67 NHL
Multipli mijelom / *Multiple Myeloma*	12 (13.3%)
Mijelodisplazni sindrom / *Myelodysplastic syndrome*	8 (8.9%)
Klinički **stadijum**/ ***Clinical stage***	
I	9 (10%)
II	22 (24.4%)
III	28 (31.1%)
IV	22 (24.4%)
Bulky* TU masa > 7 cm** / ***Bulky TU mass > 7cm	29 (32.2%)
Infiltracija koštane srži / ***Bone marrow infiltration***	36 (40%)
Labora*torijski* parametri, medijana (opseg) / ***Laboratory parameters, median (range)***	
Hb g/l / *Hb g/*	118 (47 – 172)
MCV fl / *MCV fl*	92 (74 – 112)
Le x10e9/l / *WBC x10e9/l*	5.5 (1.9 – 233)
Tr x10e9/l / *PLT x10e9/*	206.5 (10 – 520)
ANC x10e9/l / *ANC x10e9/l*	3.2 (0.7 – 13.7)
AMC x10e9/l / *AMC x10e9/*	0.42 (0 – 12.2)
CRP mg/l / *CRP mg/l*	3.85 (0.1 – 116)
ECOG / ***ECOG***	
0	60 (66.7%)
1	21 (23.3%)
2	7 (7.8%)
3	2 (2.2%)
Smrtni ishod / ***Fatal outcome***	4 (4.4%)
Dužina praćenja u mesecima / ***Follow-up (months)***	
Medijana (opseg) / *Median (range)*	13.5 (0 – 120)
FN / ***FN***	
ima/nema / *yes/no*	22 (24.4%)/86 (75.6%)

Tabela 2. Sociodemografski i klinički parametri prema prisustvu febrilne neutropenije

Table 2. Sociodemographic and clinical parameters according to the presence of febrile neutropenia

	Febrilna neutropenija / *Febrile neutropenia*		
	Ne / *No*	**Da / *Yes***	***p***
Ukupan broj (%) / *Total number (%)*	**68 (75.6%)**	**22 (24.4%)**	
Pol / *Gender*			
Muški / *Male*	25 (36.8%%)	13 (59.1%)	0.065
Ženski / *Female*	43 (63.2%)	9 (40.9%)	
Starost (godine), medijana (opseg) / *Age (years), median (range)*	63.0 (23 – 77)	63.0 (31 – 74)	0.408
Dijagnoza / *Diagnosis*			
Limfom / *Lymphoma*	51 (75.0%)	19 (86.4%)	
MM / *MM*	10 (14.7%)	2 (9.1%)	0.525
MDS / *MDS*	7 (10.3%)	1 (4.5%)	
Klinički stadijum / *Clinical stage*			
1	8 (13.1%)	1 (5.0%)	
2	17 (27.9%)	5 (25.0%)	0.191
3	23 (37.7%)	5 (25.0%)	
4	13 (21.3%)	9 (45.0%)	
Bulky TU masa > 7 cm / *Bulky tumor mass > 7 cm*	17 (25.0%)	12 (54.5%)	**0.010**
Infiltracija koštane srži / *Bone marrow infiltration*	26 (38.2%)	10 (45.5%)	0.548
ECOG / *ECOG*			
0	48 (70.6%)	12 (54.5%)	
1	14 (20.6%)	7 (31.8%)	/
2	4 (5.9%)	3 (13.6%)	
3	2 (2.9%)	0 (0.0%)	
Prethodne infekcije / *Previous infections*	6 (8.8%)	5 (22.7%)	0.084
Broj primenjenih hemioterapijskih linija / *Number of administered lines of therapy*	1 (1 – 4)	2 (1 – 6)	**0.020**
Broj hemioterapijskih ciklusa / *Number of chemotherapy cycles*	6 (1 – 25)	6 (4 – 30)	**0.027**
Broj ciklusa imunoterapije / *Number of immunotherapy cycles*	5 (0 – 18)	6 (0 – 25)	**0.022**
≥ 10 ciklusa hemioterapije / ≥ *10 chemotherapy cycles*	12 (17.6%)	9 (40.9%)	**0.025**
≥ 3 hemioterapijske linije / ≥ *3 lines of chemotherapy*	7 (10.3%)	8 (36.4%)	**0.004**
Infekcije tokom lečenja / *Infections during treatment*	19 (27.9%)	13 (59.1%)	**0.008**
Primena antibiotika / *Application of antibiotics*	23 (33.8%)	21 (95.5%)	**0.004**
Primena G-CSF-a / *Application of G-CSF*	8 (11.8%)	12 (54.5%)	**< 0.001**
Broj ampula G-CSF-a / *Number of G-CSF ampoules*	1 (0 – 20)	5 (1 – 28)	**< 0.001**
Komorbiditeti / *Comorbidities*	53 (77.9%)	19 (86.4%)	0.391
KOVID-19 infekcija / *COVID-19 infection*	7 (10.3%)	3 (13.6%)	0.665
Dužina praćenja (meseci) / *Length of follow-up (months)*	13.5 (0 – 120)	14 (6 – 113)	0.735
Smrtni ishod / *Fatal outcome*	2 (2.9%)	2 (9.1%)	0.224

Numerički podaci, u zavisnosti od normalnosti raspodele podataka, prikazani su kao aritmetička sredina ± standardna devijacija ili medijana (min-maks), a kategorijalni podaci su prikazani kao broj pacijenata i procenat, n (%); statistički značajna razlika je prikazana podebljanim slovima.
Legenda: MM – multipli mijelom; MDS – mijelodisplazni sindrom, G-CSF – engl. *granulocyte colony-stimulating factor*

Numerical data, depending on the normality of data distribution, are presented as the arithmetic mean ± standard deviation or as the median (min-max), and categorical data are presented as the number of patients and percentage, n (%); statistically significant difference is given in bold letters.
Legend: MM – multiple myeloma; MDS – myelodysplastic syndrome, G-CSF – granulocyte colony-stimulating factor

cija koštane srži nije pokazala značajnu razliku u odnosu na razvoj febrilne neutropenije (p = 0,548), kao ni u odnosu na *ECOG* performans status. U našem uzorku, distribucija bolesnika prema *ECOG* performans statusu je bila sledeća: *ECOG* 0 je imalo 60 (66,7%) bolesnika, *ECOG* 1 je ustanovljen kod 21 (23,3%) pacijenta, *ECOG* 2 je bio prisutan kod 7 (7,8%) pacijenata, dok je dva (2,2%) bolesnika imalo ECOG 3 (Tabela 1).

Pacijenti sa febrilnom neutropenijom su imali statistički značajno veći broj primenjenih hemioterapijskih linija (p = 0,020), hemioterapijskih ciklusa (p = 0,027) i ciklusa imunoterapije (p = 0,025). Pacijenti kod kojih se razvila FN su značajno učestalije imali primenjenih ≥ 3 hemioterapijskih linija (36,4% naspram 10,3%; p = 0,004) kao i primenjenih ≥ 10 ciklusa hemioterapije (40,9% naspram 17,6%; p = 0,025) ili imunoterapije (IT), (31,6% naspram 11,3%; p = 0,042). Takođe, kod pacijenata sa febrilnom neutropenijom je bila značajno veća učestalost infekcije tokom lečenja (59,1% naspram 27,9%; p = 0,008), kao i primena antibiotika (95,5% naspram 33,8%; p = 0,004), primena *G-CSF*-a (54,5% naspram 11,8%; p < 0,001), te broj primenjenih ampula *G-CSF*-a (5,0 naspram 1,0; p < 0,001). Posmatrani klinički parametri koji se nisu razlikovali između pacijenata sa i bez febrilne neutropenije su: komorbiditeti (p = 0,391), KOVID-19 infekcija (p = 0,665), dužina praćenja (p = 0,735) i smrtni ishod (p = 0,224), (Tabela 2).

Među pacijentima koji su razvili FN, stepen neutropenije gradusa 1 je uočen kod jednog (4,5%) bolesnika, gradus 2 je utvrđen kod četiri (18,2%) bolesnika, gradus 3 kod 10 (45,5%) pacijenata, a gradus 4 kod 7 (31,8%) bolesnika.

Bone marrow infiltration did not show a significant difference in relation to the development of febrile neutropenia (p = 0.548), nor in relation to the ECOG performance status. In our sample, the distribution of patients according to the ECOG performance status was as follows: ECOG 0 was present in 60 (66.7%) patients, ECOG 1 was established in 21 (23.3%) patients, ECOG 2 was present in 7 (7.8%) patients, while two (2.2%) patients had ECOG 3 (Table 1).

Patients with febrile neutropenia had a statistically significantly higher number of applied lines of chemotherapy (p = 0.020), chemotherapy cycles (p = 0.027), and immunotherapy cycles (p = 0.025). Patients who developed FN significantly more often had ≥ 3 lines of chemotherapy administered (36.4% vs. 10.3%; p = 0.004), as well as ≥ 10 chemotherapy cycles (40.9% vs. 17.6%; p = 0.025) or immunotherapy (IT) cycles administered, (31.6% vs. 11.3%; p = 0.042). Also, in patients with febrile neutropenia, there was a significantly higher frequency of infection during treatment (59.1% vs. 27.9%; p = 0.008), as well as a significantly higher frequency of antibiotics use (95.5% vs. 33.8%; p = 0.004), a significantly higher frequency of G-CSF administration (54.5% vs. 11.8%; p < 0.001), and a significantly higher number of administered ampoules of G-CSF (5.0 vs. 1.0; p < 0.001). The clinical parameters that were observed not to differ between patients with and without febrile neutropenia were as follows: comorbidities (p = 0.391), COVID-19 infection (p = 0.665), length of follow-up (p = 0.735), and the fatal outcome (p = 0.224), (Table 2).

Tabela 3. Laboratorijski parametri prema prisustvu febrilne neutropenije

Table 3. Laboratory parameters according to the presence of febrile neutropenia

	Febrilna neutropenija / *Febrile neutropenia*		
	Ne / *No*	**Da / *Yes***	***p***
Ukupan broj (%) / *Total number (%)*	**68 (75.6%)**	**22 (24.4%)**	
Hb (g/l)	117.4 ± 24.3	112.9 ± 23.7	0.449
MCV (fl)	92.0 ± 7.6	89.8 ± 6.6	0.237
WBC (x10e9/l)	5.5 (2.2 – 233.0)	5.8 (1.9 – 116.0)	0.602
PLT (x10e9/l)	206.5 (10.0 – 520.0)	199.0 (51.0 – 503.0)	0.981
ANC (x10e9/l)	3.1 (0.7 – 12.4)	3.7 (0.8 – 13.7)	0.430
AMC (x10e9/l)	0.4 (0.0 – 12.2)	0.5 (0.0 – 1.1)	0.960
CRP (mg/l)	3.3 (0.1 – 116.0)	7.2 (0.1 – 116.0)	**0.012**

Numerički podaci, u zavisnosti od normalnosti raspodele podataka, prikazani su kao aritmetička sredina ± standardna devijacija ili medijana (min-maks) a kategorijalni podaci su predstavljeni kao broj pacijenata i procenat, *n* (%).
Hb – hemoglobin, MCV – engl. *mean corpuscular volume*, Le – leukociti, Tr – trombociti, *ANC*– *engl. absolute neutrophil count, AMC* – engl. *absolute monocyte count, CRP* – C reaktivni protein

Numerical data, depending on the normality of data distribution, are presented as the arithmetic mean ± standard deviation or as the median (min-max), and categorical data are presented as the number of patients and percentage, n (%).
Hb – hemoglobin, MCV– mean corpuscular volume, WBC – white blood cell count, PLT –platelet count, ANC– absolute neutrophil count, AMC – absolute monocyte count, CRP – C reactive protein

Tabela 4. Multivarijantna logistička regresija u predikciji razvoja febrilne neutropenije kod bolesnika sa hematološkim malignitetima

Table 4. Multivariate logistic regression in predicting the development of febrile neutropenia in patients with hematological malignancies

Nezavisne varijable / *Independent variables*	**Multivarijantna logistička regresija / *Multivariate logistic regression***		
	B	***p***	**OS (95% CI)**
Bulky TU masa > 7 cm / *Bulky tumor mass > 7 cm*	0.588	0.419	1.8 (0.4 – 7.5)
≥ 3 hemioterapijskih linija / ≥ *3 lines of chemotherapy*	0.917	0.310	2.5 (0.4 – 14.71)
Infekcije tokom lečenja / *Infections during treatment*	-3.547	0.055	0.03 (0.001 – 1.1)
Primena antibiotika / *Application of antibiotics*	4.551	**< 0.001**	94.7 (8.1 – 1109.7)
Primena **G-CSF**-a / *Application of G-CSF*	2.901	0.102	18.2 (0.6 – 591.1)
Broj ampula *G-CSF*-a / *Number of G-CSF ampoules*	0.154	**0.028**	1.2 (1.0 – 1.3)

B – koeficijent, OR – odnos šansi (engl. odds ratio), CI – interval poverenja (engl. confidence interval), podebljano – statistički značajni prediktori

B – coefficient, OR – odds ratio, CI – confidence interval, bold – statistically significant predictors

Između pacijenata sa i bez febrilne neutropenije upoređivani su i laboratorijski parametri i jedino su vrednosti C-reaktivnog proteina (CRP) pokazale značajnu razliku sa većim vrednostima kod bolesnika kod kojih se razvila FN (7,2% naspram 3,3%; $p = 0,012$). Ostali parametri: hemoglobin (Hb), ($p = 0,449$), *MCV* (engl. *mean corpuscular volume*), ($p = 0,237$), leukociti (Le), ($p = 0,602$), trombociti (Tr), ($p = 0,981$), *ANC* (engl. *absolute neutrophil count*), ($p = 0,430$) i *AMC* (engl. *absolute monocyte count*), ($p = 0,960$), nisu se značajno razlikovali u odnosu na razvoj febrilne neutropenije (Tabela 3).

Svi prediktori koji su univarijantnom analizom imali statističku značajnost na nivou od 0,01 uključeni su u model multivarijantne regresione analize sa zavisnom varijablom – razvoj febrilne neutropenije. Model sadrži šest prediktora i statistički je značajan ($p < 0,001$). Kao značajni prediktori razvoja febrilne neutropenije izdvojili su se primena antibiotika ($B = 4,551$; $p < 0,001$) i broj primenjenih ampula *G-CSF*-a ($B = 0,154$; $p = 0,028$), (Tabela 4).

DISKUSIJA

U našoj studiji je dokazana statistički značajna razlika u pojavi febrilne neutropenije kod bolesnika koji su prethodno primali hemioterapiju, što je u skladu sa dostupnim literaturnim podacima. Dodatak monoklonskih antitela hemioterapijskim protokolima povećava rizik od pojave febrilne neutropenije [11,12]. Dokazali smo da je pojava febrilne neutropenije bila češća i kod bolesnika kod kojih je primenjeno nekoliko terapijskih linija: ≥3 terapijske linije (36,4% naspram 10,3%; $p = 0,004$), ali i kod onih kod kojih je primenjen veći broj ciklusa istog citostatika: ≥ 10 ciklusa hemioterapije (40,9% naspram 17,6%; $p = 0,025$), uključujući i imunoterapiju (31,6% naspram 11,3%; $p = 0,042$).

Kada je reč o distribuciji febrilne neutropenije prema tipu limfoma, u rezultatima naše studije se može

Among the patients who developed FN, grade 1 neutropenia was observed in one (4.5%) patient, grade 2 was found in four (18.2%) patients, grade 3 in 10 (45.5%) patients, and grade 4 in 7 (31.8%) patients.

Laboratory parameters were also compared between patients with and without febrile neutropenia and only C-reactive protein (CRP) levels showed a significant difference, with higher values in patients who developed FN (7.2% vs. 3.3%; $p = 0.012$). Other parameters, namely: hemoglobin (Hb), ($p = 0.449$), mean corpuscular volume (MCV), ($p = 0.237$), white blood cell count (WBC), ($p = 0.602$), platelet count (PLT), ($p = 0.981$), absolute neutrophil count (ANC), ($p = 0.430$), and absolute monocyte count (AMC), ($p = 0.960$), did not differ significantly in relation to the development of febrile neutropenia (Table 3).

All predictors with statistical significance at the level of 0.01 in the univariate analysis were included in the multivariate regression analysis model with the development of febrile neutropenia as the dependent variable. The model contains six predictors and is statistically significant ($p < 0.001$). The use of antibiotics ($B = 4.551$; $p < 0.001$) and the number of administered ampoules of G-CSF ($B = 0.154$; $p = 0.028$) were distinctly significant predictors of the development of febrile neutropenia (Table 4).

DISCUSSION

Our study demonstrated a statistically significant difference in the occurrence of febrile neutropenia in patients who had previously received chemotherapy, which is in keeping with available literature data. The addition of monoclonal antibodies to chemotherapy protocols increases the risk of febrile neutropenia [11,12]. We have proven that the occurrence of febrile neutropenia was more frequent in patients who received several lines of therapy: ≥3 lines of therapy

videti najmanja učestalost kod Hočkinovog limfoma. Ovakvi rezultati se mogu objasniti činjenicom da se u našem uzorku mogu naći samo bolesnici koji su tretirani *ABVD* protokolom (doksorubicin, bleomicin, vinblastin i dakarbazin), te shodno tome, a u skladu sa *NCCN* (engl. *National Comprehensive Cancer Network*) preporukama, nije primenjivan *G-CSF* zbog opisane pulmološke toksičnosti bleomicina u ovakvoj kombinaciji kod bolesnika starosti < 40 godina [13]. U svom radu iz 2024. godine, Islas-Munjoz i saradnici su objavili podatke da je FN najčešća upravo kod bolesnika sa Hočkinovim limfom i kod bolesnika sa akutnom limfoblastnom leukemijom (ALL), odnosno akutnom mijeloidnom leukemijom (AML) [14]. S obzirom da je naš uzorak mali i da ne obuhvata bolesnike sa akutnim leukemijama, ove podatke ne možemo u potpunosti korelirati.

U literaturi je opisan prediktivni model razvoja neutropenije, redukcije doze leka i odlaganja primene terapije, zasnovan na hematološkim parametrima krvne slike tokom prvog ciklusa hemioterapije. Model procenjuje rizik od potrebe za redukcijom doze usled mijelosupresije i rangira bolesnike u grupe sa srednjim i visokim rizikom od nastanka neutropenije u narednim ciklusima lečenja. Shodno tome, ova podela omogućava pravovremenu primenu *G-CSF*-a, prevenciju febrilne neutropenije i sledstvenu adekvatnu dozu hemioterapije, bez potrebe za redukcijom. Dokazano je da kod bolesnika sa najvišim stepenom neutropenije češće dolazi do razvoja febrilne neutropenije [15,16]. U našoj studiji, treći i četvrti stepen neutropenije u grupi onih koji su razvili febrilnu neutropeniju, uočen je kod više od dve trećine bolesnika.

Dokazali smo češću pojavu febrilne neutropenije kod bolesnika sa prethodnim infekcijama, bolesnika sa uznapredovalim kliničkim stadijumom bolesti i onih koji su imali *bulky* tumorsku masu, što je opisano i u dostupnoj literaturi [6].

Interesantno je da je u našem uzorku kod bolesnika sa povoljnijim *ECOG* performans statusom (0 i 1) češće dolazilo do razvoja febrilne neutropenije, što nije u saglasnosti sa objavljenim studijama [17]. Ovo se može objasniti time što bolesnici lošijeg performans statusa zahtevaju lečenje u bolničkim uslovima na matičnim odeljenjima, zbog pratećih komplikacija, dok pokretni bolesnici mogu primati terapiju i u uslovima dnevne bolnice.

Teški i produženi oblici neutropenije dokazano su povezani, u mnogim istraživanjima, sa češćom pojavom infektivnog sindroma [14] što je potvrđeno i u našoj studiji: bolesnici sa febrilnom neutropenijom su imali češće infekcije (59,1% naspram 27,9%; $p = 0{,}008$), kao i češću primenu antibiotika (95,5% naspram 33,3%; $p < 0{,}001$). Literaturni podaci ukazuju da se kod hema-

(36.4% vs. 10.3%; $p = 0.004$), but also in those who received a higher number of cycles of the same cytostatic drug: ≥ 10 cycles of chemotherapy (40.9% vs. 17.6%; $p = 0.025$), including immunotherapy (31.6% vs. 11.3%; $p = 0.042$).

Regarding the distribution of febrile neutropenia according to the type of lymphoma, the results of our study show the lowest frequency in Hodgkin's lymphoma. Such results can be explained by the fact that our sample comprised only patients treated with the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine). Because of this, and per the National Comprehensive Cancer Network (NCCN) recommendations, G-CSF was not applied due to the described pulmonary toxicity of bleomycin in this combination in patients aged < 40 years [13]. In their study from 2024, Islas-Muñoz et al. reported that FN is, indeed, most common in patients with Hodgkin's lymphoma and those with acute lymphoblastic leukemia (ALL)/acute myeloid leukemia (AML) [14]. Since our sample is small and does not include patients with acute leukemias, we cannot fully correlate these data.

The literature describes a predictive model of the development of neutropenia, drug dose reduction, and treatment delay, based on blood count hematological parameters during the first cycle of chemotherapy. The model estimates the risk of the need for dose reduction due to myelosuppression and ranks patients into groups with a medium and high risk of developing neutropenia in subsequent treatment cycles. Consequently, this patient categorization allows timely administration of G-CSF, prevention of febrile neutropenia, and the administration of an appropriate chemotherapy dose, without the need for reduction. It has been proven that patients with the highest degree of neutropenia often develop febrile neutropenia [15,16]. In our study, in the group of patients who developed febrile neutropenia, grade III and grade IV neutropenia was observed in more than two-thirds of the subjects.

We have proven the more frequent occurrence of febrile neutropenia in patients with previous infections, patients with an advanced clinical stage of the disease, and those who had a bulky tumor mass, which has also been reported in the available literature [6].

Interestingly, in our sample, patients with a more favorable ECOG performance status (0 and 1) developed febrile neutropenia more often, which is not in agreement with published studies [17]. This can be explained by the fact that patients with a poorer performance status require treatment in specialized hospital wards, due to accompanying complications, while ambulatory patients can receive therapy in day-care settings.

toloških bolesnika beleže duži periodi neutropenije, kao i neutropenije većeg stepena, te shodno tome i veći mortalitet u odnosu na bolesnike sa tumorima solidnih organa [18]. Ovi podaci naglašavaju potrebu za blagovremenim intenzivnim praćenjem i lečenjem hematoloških bolesnika sa teškim oblicima neutropenije u bolničkim uslovima. Takođe, naglašava se potreba za primenom *G-CSF*-a kod ovakvih bolesnika, u cilju bržeg oporavka.

Već pomenuti faktori rizika za razvoj febrilne neutropenije, kao što su uzrast, performans status, mijelosupresivni efekat terapije, odnosno izbor hemioterapeutika, stepen neutropenije, te pad vrednosti drugih parametara krvne slike, ključni su u blagovremenom prepoznavanju potrebe za primenom *G-CSF*-a. Neki od ovih faktora su uvršćeni u *ASCO CSF* preporuke (engl. *American Society of Clinical Oncology – ASCO CSF guidelines*) za profilaktičku primenu faktora stimulacije rasta kolonija [17]. U našoj studiji smo dokazali da je primena *G-CSF*-a bila češća kod onih pacijenata kod kojih je došlo do razvoja febrilne neutropenije (54,5% naspram 11,8%; $p < 0,001$), kao i da je kod njih primenjen veći broj ampula *G-CSF*-a (5,0 naspram 1,0; $p < 0,001$), što je u skladu sa do sada objavljenim podacima.

Kod četiri bolesnika je zabeležen letalni ishod zbog pratećih komorbiditeta, što je svakako nedovoljan uzorak za poređenje sa dostupnim podacima iz literature.

Ograničenja naše studije su sledeća: retrospektivni tip studije, uključivanje pacijenata samo jednog odeljenja, odnosno mali broj ispitanika, teritorijalna pripadnost određenog broja bolesnika drugim zdravstvenim centrima i samim tim nedostupnost podataka o primeni *G-CSF*-a u tim centrima, primena terapijskih protokola u skladu sa individualnom kliničkom praksom, kao i sekundarna primena G-CSF-a u ovoj grupi bolesnika. Ipak, prednost prikupljanja podataka u dnevnoj bolnici tercijarne ustanove je bilo prisustvo heterogene grupe bolesnika sa najvećim spektrom hematoloških dijagnoza, te će buduća istraživanja sa većim uzorkom nesumnjivo doprineti dobijanju statistički značajnijih podataka.

ZAKLJUČAK

Naša studija je pokazala da je na razvoj febrilne neutropenije uticao veći broj primenjenih terapijskih linija i ciklusa imunohemioterapije, klinički stadijum bolesti, prisustvo *bulky* tumorske mase prilikom uspostavljanja dijagnoze, kao i stepen agresivnosti tipa limfoma. Česte infekcije kod ovih bolesnika i veća potreba za primenom *G-CSF*-a i antibiotika naglašavaju potrebu za daljim istraživanjima u ovom polju, u cilju poboljšanja kvaliteta lečenja. Takođe, potrebno je usmeriti pažnju u pravcu preciznije identifikacije faktora rizika koji do-

Severe and prolonged forms of neutropenia have been proven to be associated, in many studies, with a more frequent occurrence of an infective syndrome [14], which was also confirmed in our study: patients with febrile neutropenia had more frequent infections (59.1% vs. 27.9%; $p = 0.008$), as well as a more frequent use of antibiotics (95.5% vs. 33.3%; $p < 0.001$). Literature data indicate that hematological patients experience longer periods of neutropenia, as well as a higher degree of neutropenia, and consequently higher mortality, compared to patients with solid-organ tumors [18]. These data emphasize the need for timely intensive monitoring and treatment of hematological patients with severe forms of neutropenia in the hospital setting. Also, the need for the application of G-CSF in such patients is emphasized, in order to achieve faster recovery in patients.

The aforementioned risk factors for the development of febrile neutropenia, such as age, performance status, the myelosuppressive effect of treatment, i.e. the choice of chemotherapeutic agents, the degree of neutropenia, and the drop in other parameters in the blood count, are key in timely recognition of the need for G-CSF administration. Some of these factors are included in the American Society of Clinical Oncology (ASCO) CSF guidelines for the prophylactic use of the colony-stimulating factor [17]. In our study, we have proven that the use of G-CSF was more frequent in those patients who developed febrile neutropenia (54.5% vs. 11.8%; $p < 0.001$) and that they were given a higher number of ampoules of G-CSF (5.0 vs. 1.0; $p < 0.001$), which is consistent with previously published data.

The fatal outcome was recorded in four patients, due to accompanying comorbidities, which is certainly not a sufficient sample for comparison with available data from literature.

The limitations of our study are as follows: retrospective type of study, the inclusion of patients from only one hospital department, i.e., a small number of respondents, the territorial affiliation of a certain number of patients to other health centers, and therefore the unavailability of data on the use of G-CSF in those centers, the application of therapeutic regimens in keeping with individual clinical practice, as well as the secondary application of G-CSF in this group of patients. However, the advantage of collecting data in a day hospital belonging to a tertiary institution was the presence of a heterogeneous group of patients with a very wide spectrum of hematological diagnoses. Therefore, future research on a larger sample will undoubtedly contribute to the obtaining of more statistically significant data.

vode do febrilne neutropenije, kako bi se sprovela pravovremena profilaksa i postigao veći uspeh u lečenju bolesnika sa hematološkim malignitetima.

Sukob interesa: Nije prijavljen.

CONCLUSION

Our study showed that the development of febrile neutropenia was influenced by the number of applied lines of therapy and the number of cycles of immunochemotherapy, the clinical stage of the disease, the presence of a bulky tumor mass at the time of diagnosis, as well as the degree of aggressiveness of the specific lymphoma type. Frequently occurring infections in these patients, as well as the greater need for the use of G-CSF and antibiotics, emphasize the need for further research in this field, in order to improve the quality of treatment. Also, it is necessary to focus attention on more precise identification of risk factors that lead to febrile neutropenia, so as to implement timely prophylaxis and achieve greater success in the treatment of patients with hematological malignancies.

Conflict of interest: None declared

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