KLINIČKE KARAKTERISTIKE KOVID-19 INFEKCIJE I EFIKASNOST VAKCINACIJE KOD BOLESNIKA SA HEMATOLOŠKIM MALIGNITETIMA

PREGLEDNI RAD

REVIEW ARTICLE

CLINICAL CHARACTERISTICS OF COVID-19 AND THE EFFICACY OF VACCINATION IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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SAŽETAK

Pacijenti sa hematološkim malignitetima imaju povećan rizik od teških formi KOVID-19 infekcije i veću smrtnost, u poređenju sa pacijentima sa KOVID-19 infekcijom u opštoj populaciji, zbog imunosupresije izazvane samom hematološkom bolešću i/ili onkološkom terapijom, često uznapredovalog životnog doba, ali i niskog nivoa serokonverzije nakon vakcinacije. Oni takođe imaju povećan rizik i od zaražavanja, zbog potrebe za čestim dolascima u zdravstvene ustanove i visoke izloženosti drugim bolesnicima. Rezultati publikovanih studija naglašavaju važnost strategija prevencije KOVID-19 infekcije kod ovih bolesnika, zasnovanih na merama kontrole infekcije i fizičkog distanciranja, kao i na pravovremenoj vakcinaciji. Faktori rizika, koji su se pokazali ključnim za razvoj teških oblika bolesti, jesu: starosno doba, prisustvo komorbiditeta, prisustvo maligniteta, progresivna bolest, kao i vrsta onkološke terapije koju je pacijent dobijao. Stoga, bolesnici sa hematološkim malignitetima predstavljaju prioritetnu grupu pacijenata za vakcinaciju, koja je preporučena od strane svih međunarodnih stručnih udruženja. Imajući u vidu da su ovi bolesnici pod rizikom da ne razviju adekvatan imunološki odgovor na vakcinu, postoje dileme oko optimalnog vremenskog perioda kada treba primeniti vakcinu, u kojoj dozi, i kakav je kapacitet razvoja imunološkog odgovora na vakcine kod pojedinih hematoloških maligniteta. Studije su pokazale da je, i pored slabijeg imunološkog odgovora na vakcinu, smrtnost vakcinisanih pacijenata kod hematoloških maligniteta značajno manja, u odnosu na nevakcinisane bolesnike.

U ovom članku urađen je pregled relevantnih studija, u kojima su analizirane karakteristike, morbiditet i mortalitet pacijenata sa hematološkim malignitetima i infekcijom KOVID-19, kao i uloga i efikasnost vakcinacije kod ovih pacijenata.

Ključne reči: KOVID-19, hematološki maligniteti, vakcina

ABSTRACT

Patients with hematologic malignancies are at increased risk of severe forms of COVID-19 and have higher mortality, compared to patients with COVID-19 in the general population. The reasons for this include immunosuppression caused by the underlying hematologic disease and/or anticancer therapy received by these patients, advanced age, but also low levels of seroconversion after vaccination. These patients are also at a higher risk of getting infected because of frequent visits to health care facilities and high exposure to other patients. Results from published studies highlight the importance of prevention strategies in these patients, based on infection control measures and physical distancing, but also on well-timed vaccination. Risk factors which have proven to be crucial for severe forms of COVID-19 are age, the presence of comorbidities, malignancy type, progressive disease, and the type of oncologic therapy that these patients receive. Therefore, patients with hematologic malignancies represent a priority group for vaccination, which is recommended by all international professional associations. Considering that these patients are at risk of not developing an adequate immune response to the vaccine, the issues of determining the optimal time period for receiving the vaccine, the optimal dose, and the capacity of developing an immune response to the vaccine in specific groups of patients with hematologic malignancies, are questions that remain unresolved. Studies have shown that, despite the weak immune response to the vaccine, the mortality of vaccinated patients with hematologic malignancies is significantly lower than the mortality of unvaccinated patients.

This article provides a review of relevant studies which analyze the characteristics, morbidity and mortality of patients with hematologic malignancies and COVID-19 and the role of vaccination in these patients.

Key words: COVID-19, hematologic malignancies, vaccine

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UVOD

KOVID-19 je infektivna bolest izazvana virusom SARS-KoV-2, koja prvenstveno pogađa respiratorni sistem, uz mogućnost pojave sistemske bolesti. Virus SARS-KoV-2 je prvi put izolovan u gradu Vuhanu, decembra 2019. godine, a zbog brzog širenja infekcije na svetskom nivou, proglašena je pandemija, marta 2020. godine [1]. Do decembra 2021. godine, u svetu je zabeleženo 263 miliona slučajeva zaražavanja i 5,22 miliona smrtnih slučajeva [2]. Zbog sve većih posledica KOVID-19 oboljenja, lekari se susreću sa dodatnim izazovima u zbrinjavanju i lečenju pacijenata sa hematološkim malignitetima (HM). Incidencija KOVID-19 infekcije kod pacijenata sa hematološkim malignitietima je između 1 i 3,9% [3]. Pacijenti sa hematološkim malignitetima imaju povećan rizik od morbiditeta i mortaliteta od infekcije KOVID-19 zbog imunosupresije uzrokovane samim prisustvom maligniteta i/ili primenom onkološke terapije; zatim zbog potrebe za čestim dolascima u zdravstvene ustanove gde imaju visoku izloženost infekciji; kao i zbog uznapredovalog životnog doba, ali i slabijeg imunološkog odgovora nakon vakcinacije. Procena rizika od KOVID-19 infekcije kod hematoloških pacijenata je od velikog značaja za poboljšanje lečenja ovih pacijenata.

STOPA MORTALITETA KOD PACIJENATA SA HEMATOLOŠKIM MALIGNITETIMA I KOVID-19 INFEKCIJOM

Najveće multicentrične studije, koje su analizirale pacijente sa hematološkim malignitetima i KOVID-19 infekcijom, pokazuju da stopa mortaliteta varira između 31% i 50% [4,5,6,7]. Ovi rezultati pokazuju znatno veću stopu mortaliteta kod pacijenata sa hematološkim malignitetima, u poređenju sa ukupnom populacijom, kod koje je stopa mortaliteta procenjena na između 0,1% i 9,4% [8], dok kod pacijenata sa svim malignitetima ova stopa iznosi 13% [9]. U većinu ovih studija bili su uključeni hospitalizovani pacijenti. Na primer, u najvećoj ovakvoj studiji, Studiji Evropskog hematološkog udruženja (engl. European Hematology Association Survey - EPICOVIDEHA), koja je analizirala 3.801 pacijenta sa KOVID-19 infekcijom i hematološkim malgnitetima, 73,1% pacijenata je bilo hospitalizovano [7]. Stopa mortaliteta u ovoj studiji iznosila je 31,2%. U svojoj multicentričnoj studiji, Vijentira i saradnici su prijavili stopu mortaliteta od 34%, sa 77% hospitalizovanih pacijenata [4]. Da bi se utvrdila stopa mortaliteta svih pacijenata sa hematološkim malignitetima i KOVID-19 infekcijom (uključujući i nehospitalizovane pacijente), važno je da studije neselektivno prikupe podatke u populaciji pacijenata.

INTRODUCTION

Coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, is primarily a respiratory disease, with possible systemic effects. First identified in Wuhan City, in December 2019, in the ensuing months the disease spread worldwide and was declared a pandemic by the World Health Organization (WHO), in March 2020 [1]. As of December 2021, there had been a total of 263 million cases and 5.22 million deaths worldwide [2]. With the growing impact of COVID-19, physicians face additional challenges when it comes to the management and treatment of patients with hematologic malignancies (HM). The incidence of COVID-19 infection in patients with HM ranges between 1 and 3.9% [3]. Patients with hematologic malignancies are considered to be at increased risk of morbidity and mortality from COVID-19, due to immunosuppression caused by the underlying disease and/or anticancer treatment that these patients receive; due to frequent visits to health care facilities and high exposure to other patients; due to advanced age; and finally, due to low levels of seroconversion after vaccination. It is of great importance to estimate the risks related to COVID-19 in hematologic patients, in order to inform and improve clinical decision-making.

MORTALITY RATE IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES AND COVID-19

The largest multicenter studies analyzing patients with hematologic malignancies and COVID-19 reported a mortality rate ranging from 31% to 50% [4–7]. These results show a substantially higher mortality rate in patients with hematologic malignancies, as compared to the overall population, for which the mortality rate is estimated to be between 0.1% and 9.4% [8], and patients with all cancers, whose mortality rate is estimated at 13% [9]. The majority of patients included in these studies were hospitalized patients. For example, in the largest study analyzing patients with hematologic malignancies and COVID-19, carried out by the European Hematology Association (European Hematology Association Survey - EPICOVIDEHA), which included 3,801 HM patients with COVID-19, 73.1% of patients were hospitalized [7]. The mortality rate in this study was 31.2%. In their multicenter study, Vijenthira et al. reported a mortality rate of 34%, with 77% hospitalized patients [4]. In order to determine the mortality rate among all patients with hematologic malignancies and COVID-19, it is important for studies to collect data on an unselected population of patients.

Yigenoglu et al, from Turkey, are considered to be the closest in estimating the true population mortality

Smatra se da su Jinegoglu i saradnici, iz Turske, najbliži u proceni pravog rizika od smrtnosti kod pacijenata sa hematološkim malignitetima zaraženih SARS-KoV-2 virusom. Korišćenjem podataka zasnovanih na populaciji iz baze podataka Ministarstva zdravlja Turske (188.897 laboratorijski potvrđenih pacijenata sa KOVID-19 infekcijom, uključujući 740 pacijenata sa hematološkim malignitetima), procenjeno je da je rizik od smrti pacijenata sa hematološkim malignitetima i infekcijom KOVID-19, 13,8% [10]. Rizik od smrti u opštoj populaciji ove studije iznosio je 7%. Procena rizika od 13,8% kod pacijenata sa hematološkim malignitetima, koju su pokazali Jinegoglu i saradnici, takođe je uporediva sa procenjenim rizikom od smrti od 13% kod pacijenata sa svim malignitetima [9].

Prema Vijentiri i autorima, stopa mortaliteta hospitalizovanih pacijenata sa hematološkim malignitetima i KOVID-19 infekcijom iznosila je 39%, što je znatno više od stope smrtnosti kod hospitalizovanih pacijenata bez maligniteta (17,1%) [11]. U drugom talasu (oktobar – decembar 2020.), zabeležena je značajno niža stopa mortaliteta kod pacijenata sa hematološkim malignitetima i KOVID-19 infekcijom (24%), u poređenju sa prvim talasom (mart – maj 2020.) (40%) [7]. Povoljniji klinički ishod u drugom talasu najverovatnije je posledica boljeg poznavanja kliničkog toka bolesti, boljih zaštitnih mera za pacijente sa hematološkim malignitetima, većeg broja asimptomatskih/blagih slučajeva otkrivenih skrining brisevima, kao i samog napretka u lečenju pacijenata sa KOVID-19 infekcijom.

STOPE MORBIDITETA I MORTALITETA PACIJENATA SA POJEDINIM HEMATOLOŠKIM MALIGNITETIMA

U svojoj multicentričnoj studiji, koja je uključila 3.801 pacijenta, Pagano i saradnici su prijavili veći broj slučajeva KOVID-19 infekcije kod pacijenata sa limfoproliferativnim poremećajima, posebno kod pacijenata sa Nehočkinovim limfomom (1.084 pacijenta, 28,5%) i multiplim mijelomom (684 pacijenta, 18%), što su potvrdili prethodni izveštaji [12,13], a zabeležen je i veliki broj slučajeva KOVID-19 infekcije kod pacijenata sa akutnom mijeloidnom leukemijom (AML) (497 pacijenata, 12,5%), koja se smatra retkim malignitetom [7].

Kada su u pitanju stope mortaliteta kod određenih hematoloških maligniteta, brojne studije su pokazale da pacijenti sa mijelodisplastičnim sindromom (MDS) i AML-om imaju najveću stopu mortaliteta, koja se kreće u rasponu od 42% do 53%, za MDS, odnosno 40% do 44%, za AML (Grafikon 1) [5,7,6,14]. Vijentira i saradnici su imali slične rezultate. Pacijenti sa MDS-om su imali najveću stopu mortaliteta (53%); slede pacijenti sa akutnim leukemijama (41%); potom pacijenti sa mijeloproliferativnim neoplazmama, uključujući hroničnu mijeloidnu

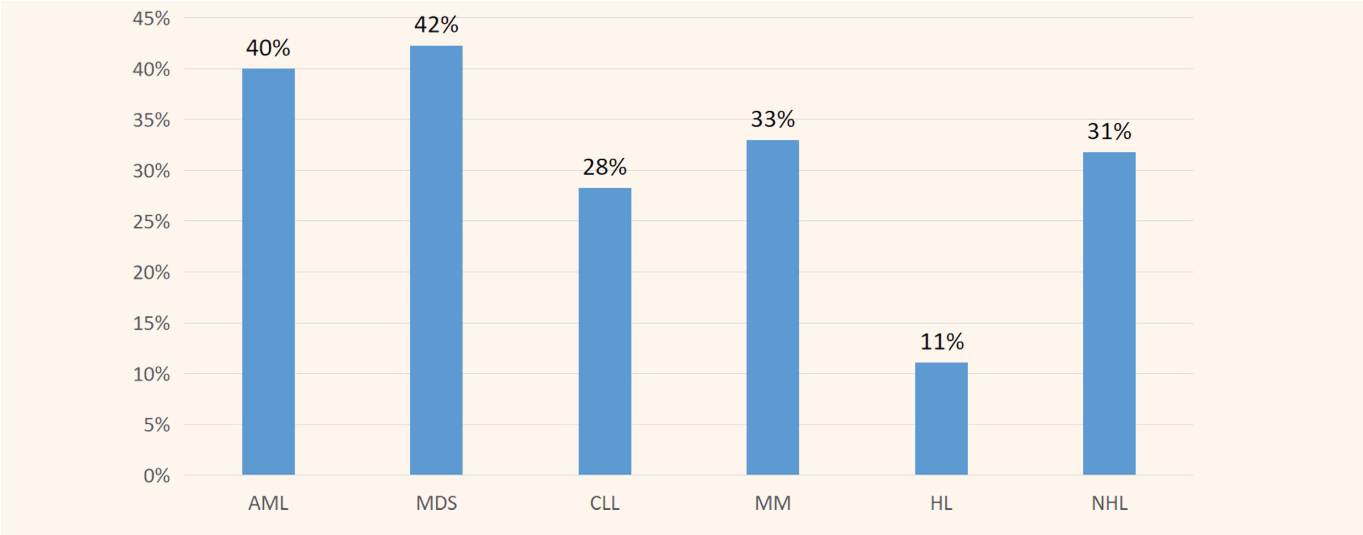
risk for patients with hematologic malignancies infected with COVID-19. Based on population-based data from the countrywide Ministry of Health database (188.897 laboratory confirmed COVID-19 patients, including 740 patients with hematologic malignancies), the mortality risk for patients with HM and COVID-19 was estimated to be 13.8% [10]. The risk of death in the control population of this study was 7%. The risk estimate of 13.8%, reported by Yigenoglu et al., is also comparable to the estimated risk of death of 13% in patients with all cancers [9].

According to Vijenthira et al., the mortality rate for hospitalized patients with HM and COVID-19 was 39%, which is substantially higher than in hospitalized patients without malignancy (17.1%) [11]. A significantly lower mortality rate in patients with HM and COVID-19 was observed in the second wave of the pandemic (October – December 2020) (24%), as compared to the first wave of COVID-19 (March – May 2020) (40%) [7]. The improved clinical outcome in the second wave is most likely due to better knowledge of the clinical course of the disease, better protective measures for HM patients, a larger number of asymptomatic/mild cases detected by screening swabs, and improved treatment for COVID-19.

MORBIDITY AND MORTALITY RATES IN PATIENTS WITH SPECIFIC HEMATOLOGIC MALIGNANCIES

In their multicenter study involving 3,801 patients, Pagano et al. reported a larger number of COVID-19 cases among patients with lymphoproliferative disorders, particularly in non-Hodgkin lymphoma patients (1,084 patients, 28.5%) and multiple myeloma patients (684 patients, 18%), which had also been confirmed by previous reports [12,13], but they also found a large number of COVID-19 cases among patients with acute myeloid leukemia (AML) (497 patients, 12.5%), which is considered a rare malignancy [7].

When it comes to mortality rates from specific hematologic malignancies, multiple studies have shown that patients with myelodysplastic syndrome (MDS) and AML have the highest mortality rates, ranging from 42% – 53%, for MDS, to 40% – 44%, for AML (Figure 1) [5,7,6,14]. Vijenthira et al. observed similar results, with patients with acquired bone marrow failure syndromes (MDS, aplastic anemia) having the highest mortality rate (53%); followed by patients with acute leukemias (41%); patients with myeloproliferative neoplasms, including chronic myeloid leukemia, polycythemia vera, essential thrombocytosis, myelofibrosis (34%); patients with plasma cell dyscrasias, such as multiple myeloma, amyloidosis, smoldering



* AML – akutna mijeloidna leukemija; MDS – mijelodisplastični sindromi; *CLL* – hronična limfatična leukemija (engl. *chronic lymphatic leukemia*); HL – Hočkinov limfom; NHL – Nehočkinov limfom

Grafikon 1. Stopa mortaliteta pacijenata sa specifičnim hematološkim malignitetima prema Paganu i saradnicima.

*AML – acute myeloid leukemia; MDS – myelodysplastic syndromes; CLL – chronic lymphoid leukemia; HL – Hodgkin lymphoma; NHL – non-Hodgkin lymphoma

Figure 1. Mortality rate of patients with specific hematologic malignancies according to Pagano et al.

leukemiju, policitemiju veru, esencijalnu trombocitozu, mijelofibrozu (34%); zatim pacijenti sa diskrazijama plazmocita, kao što su multipli mijelom, amiloidoza, tinjajući mijelom, monoklonalna gamopatija neutvrđenog značaja (33%); i na kraju pacijenti sa limfomima (32%) i hroničnim limfocitnim leukemijama (31%) [4]. Pagano i saradnici su naveli niz razloga za ovu pojavu. Pre svega, pacijenti sa AML-om/MDS-om su često stariji od 65 godina. Kao što će kasnije biti pomenuto, starosno doba je u značajnoj korelaciji sa mortalitetom. Nadalje, ovi pacijenti su takođe imunosuprimirani, zbog osnovne bolesti i onkološke terapije. Takođe, odlaganje lečenja često nije moguće kod ovih pacijenata, zbog hitne potrebe za započinjanjem aktivne terapije [7]. Ovaj aspekt je posebno važan, s obzirom na to da je uočen niži mortalitet kod pacijenata koji su odložili lečenje AML-a [15]. Pagano i saradnici su takođe primetili da je, kod pacijenata sa visokorizičnim MDS-om, lečenje demetilirajućim agensima povezano sa posebno visokom stopom mortaliteta, što govori o značaju ovih agenasa u smislu njihove potencijalne povezanosti sa visokim mortalitetom pacijenata obolelih od AML-a/MDS-a i KOVID-19 infekcije [7].

FAKTORI RIZIKA ZA TEŽI OBLIK BOLESTI I POVEĆANI MORTALITET KOD PACIJENATA SA HEMATOLOŠKIM MALIGNITETIMA I KOVID-19 INFEKCIJOM

Kao i u opštoj populaciji, starosno doba i prisustvo komorbiditeta su u visokoj korelaciji sa mortalitetom pacijenata sa hematološkim malignitetima i KOVID-19 infekcijom [4,7,16]. U svojoj multicentričnoj studiji, koja je analizirala rezultate preko 3,000 pacijenata, Vijentira

myeloma, monoclonal gammopathy of undetermined significance (33%); and finally patients with lymphomas (32%) and chronic lymphocytic leukemia (31%) [4]. Pagano et al. listed a number of reasons for this occurrence. Firstly, patients with AML/MDS are often over the age of 65, and, as will be mentioned later, advanced age highly correlates with mortality. Furthermore, these patients are also severely immunocompromised, due to the underlying disease and treatments received. Also, treatment delay is often not possible in these patients, due to the urgent need for starting active treatment [7]. This aspect is particularly important, considering that lower mortality was observed in patients who delayed AML treatment [15]. Pagano et al. also observed that, in high-risk MDS patients, treatment with demethylating agents was associated with a particularly high mortality rate, which highlights the role of these agents as being potentially associated with high mortality in AML/MDS patients with COVID-19 [7].

RISK FACTORS RELATED TO SEVERITY AND INCREASED MORTALITY IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES AND COVID-19

As in the general population, increasing age and the presence of comorbidities are highly correlated with mortality in patients with hematologic malignancies and COVID-19 [4,7,16]. In their multicenter study, which analyzed the outcomes of over 3,000 patients, Vijenthira et al. observed that patients aged ≥ 60 had a significantly higher risk of dying (47%) than those aged <60 (25%) and <18 (4%) [4]. Why increasing age

i saradnici su primetili da pacijenti stariji od 60 godina imaju značajno veći rizik od umiranja (47%), u odnosu na pacijente mlađe od 60 godina (25%) i mlađe od 18 godina (4%) [4]. Još uvek nije utvrđeno zašto je starosno doba usko povezano sa smrtnošću od KOVID-19 infekcije. Teorije uključuju mogućnost da su mlađe osobe manje sklone hiperinflamatornom imunološkom odgovoru, u poređenju sa starijim osobama, kao i mogućnost da su od značaja razlike u distribuciji enzima koji konvertuje angiotenzin 2, a koji može uticati na ulazak virusa i naknadnu upalu, hipoksiju i povredu tkiva [17]. Progresivna bolest, tip maligniteta i vrsta terapije takođe su povezani sa višim stopama mortaliteta [6]. Pacijenti koji su primali terapiju monoklonskim antitelima su imali značajno veći rizik od smrtnog ishoda (HR 2,02), u odnosu na one koji nisu primali ovu terapiju, dok su oni koji su primali konvencionalnu hemioterapiju imali 50% veću verovatnoću da umru od KOVID-19 infekcije. Nasuprot tome, pokazana je značajno niža stopa mortaliteta (53%) kod pacijenata koji su primali hipometilirajuće agense [4].

Rezultati pokazuju da je rizik od smrtnog ishoda heterogen i da se ne može predvideti isključivo na osnovu pojedinih faktora rizika, kao što su starost pacijenta i težina osnovne bolesti. Tako, na primer, neki stariji pacijenti sa lošom prognozom u vreme dijagnoze KOVID-19 infekcije nisu razvili tešku bolest i oporavili su se, dok je 13% pacijenata mlađih od 40 godina sa prognozom dužom od 12 meseci imalo loš ishod [10,12].

U zaključku, pacijenti sa hematološkim malignitetima i KOVID-19 infekcijom imaju visok rizik za razvoj teške formi bolesti i veću smrtnost, u poređenju sa pacijentima sa KOVID-19 infekcijom u opštoj populaciji. Starosno doba, broj komorbiditeta, vrsta maligniteta, progresivna bolest, kao i vrsta onkološke terapije koju je pacijent dobijao su ključni faktori rizika za težinu oboljenja. Rezultati ovih studija potvrđuju vulnerabilnost hematoloških pacijenata sa KOVID-19 infekcijom i naglašavaju važnost prevencije kod pacijenata sa hematološkim malignitetima. Strategije prevencije zasnovane na dokazima, kao što su vakcinacija, mere kontrole infekcije, kao i fizičko distanciranje i saveti o fizičkoj zaštiti od virusa, posebno su bitne za pacijente sa hematološkim malignitetima, kao i za jedinice zdravstvene zaštite u kojima se oni zbrinjavaju.

EFIKASNOST SARS-KOV-2 VAKCINE KOD BOLESNIKA SA HEMATOLOŠKIM MALIGNITETIMA

Pored primene preventivnih mera u cilju sprečavanja širenja infekcije, vakcinacija predstavlja glavnu strategiju u borbi protiv infekcije izazvane SARS-KoV-2 virusom. Cilj vakcine je da se stvori humoralni i celularni

is closely linked to COVID-19 mortality has as yet not been determined. Theories include the possibility that younger individuals are less prone to hyperinflammatory immune response, as compared to older people, as well as the possibility of the significance of the differences in angiotensin-converting enzyme 2 distribution, which may limit viral entry and subsequent inflammation, hypoxia, and tissue injury [17]. Progressive disease, type of malignancy, and type of antineoplastic treatment, as described earlier, have also been linked to higher mortality rates [6]. Patients receiving monoclonal antibody-based therapy had a significantly greater (HR 2.02) risk of death, as compared to those not receiving active antineoplastic treatment, while those receiving active conventional chemotherapy were 50% more likely to die from COVID-19. By contrast, there was significantly lower mortality (53%) among patients receiving hypomethylating agents [4].

Results have shown that the risk of mortality is heterogeneous and cannot be predicted solely on the basis of individual risk factors, such as patient age and the severity of the underlying disease. For example, some elderly patients, with a poor prognosis at the time of diagnosis of COVID-19, did not develop severe disease and they recovered, while 13% of patients younger than 40, with a prognosis of more than 12 months of survival, had a poor outcome [10,12].

In conclusion, patients with hematologic malignancies and COVID-19 are at increased risk from severe disease and mortality, as compared to COVID-19 patients in the general population. Increasing age, the number of comorbidities, type of malignancy, progressive disease and the type of antineoplastic treatment received are key risk factors for disease severity. The results observed in these studies confirm the frailty of hematologic patients with COVID-19 and highlight the importance of preventing COVID-19 among patients with hematologic malignancy. Evidence-based prevention strategies such as vaccination, infection-control measures, physical distancing, and appropriate shielding advice should be emphasized for hematology patients and the units in which they receive their care.

EFFICACY OF THE SARS-COV-2 VACCINE IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

In addition to other preventive measures, vaccination against the SARS-CoV-2 virus is the main strategy in the fight against COVID-19. Vaccines aim to induce humoral and cell-mediated immunity against the receptor-binding domain of the spike protein and other viral epitopes of the SARS-CoV-2 virus, which bind to the receptor of the host. To date, there have been

Tabela 1. Tipovi vakcina protiv SARS-KoV-2 virusa koji se koriste u većem delu sveta

Table 1. Types of vaccines against SARS-CoV-2 used in most countries of the world

	Tip vakcine / Vaccine type	Proizvođač / Manufacturer
mRNA1273	iRNK / *mRNA*	*MODERNA* (SAD / *USA*)
BNT162b2	iRNK / *mRNA*	*Pfizer-BioNtech* (SAD / *USA*)
Ad 26.COV2.5	Virusni vektor / *Viral vector*	*Johnson & Johnson* (SAD / *USA*)
ChAdOx1 nCoV-19	Virusni vektor / *Viral vector*	*Oxford-AstraZeneca* (Velika Britanija / *UK*)
BBIBP-CorV	Inaktivisani virus / *Inactivated virus*	*Sinopharm* (Kina / *China*)
CoronaVac	Inaktivisani virus / *Inactivated virus*	*Sinovac* (Kina / *China*)
Covishield	Virusni vektor / *Viral vector*	*Oxford-AstraZeneca* (Indija / *India*)
Covaxin	Inaktivisani virus / *Inactivated virus*	*Bharat-Biotech* (Indija / *India*)
Gam-COVID-Vac	Virusni vektor / *Viral vector*	*Sputnik V* (Rusija / *Russia*)*

* Nije odobrena od strane SZO; iRNK – informaciona RNK

* Not approved by the WHO; mRNA – messenger RNA

odgovor protiv vezujućeg regiona S proteina i drugih epitopa SARS-KoV-2 virusa koji se vezuju za receptor domaćina. Za sada, postoje 4 vrste pristupa pravljenju SARS-KoV-2 vakcine. Prvi pristup koristi tehnologiju izolovanja virusne DNK ili informacione RNK (iRNK) (engl. mRNA); drugi pristup koristi omotače drugih virusa kao vektor za prenos proteina SARS-KoV-2; treći pristup je mrtva vakcina; dok četvrti pristup podrazumeva ubacivanje proteinske subjedinice antigena virusa [18]. Trenutno je dostupno više tipova vakcina, dok se u budućnosti očekuje odobrenje još nekoliko vrsta vakcina različitih proizvođača. Svetska zdravstvena organizacija (SZO) je do sada odobrila 8 vakcina različitih proizvođača [19]. Vakcine koje se koriste u najvećem delu sveta su prikazane u Tabeli 1.

Za većinu vakcina se preporučuje primena dve doze u razmaku od 3 do 12 nedelja, jedino se Ad26.COV2.S vakcina daje u pojedinačnoj dozi. Od nedavno, američki Centar za kontrolu i prevenciju bolesti preporučuje i primenu treće doze vakcine kod imunokompromitovanih bolesnika (odnosno druge doze Ad26.COV2.S vakcine) [20].

Efikasnost vakcine se ogleda u stvaranju dovoljnog titra antitela i stvaranju T ćelijskog odgovora koji štiti od KOVID-19 oboljenja [21,22]. U randomizovanim kliničkim studijama, pokazana je efikasnost vakcine od 72% – 95% u zaštiti od blage i srednje teške forme, i efikasnost od čak 86% – 100% u zaštiti od teške forme KOVID-19 bolesti, u opštoj populaciji [23].

Najveća efikasnost se postiže nakon primene dve doze kod mRNA1273 vakcine (94,1%) i BNT162b2 vakcine (94,6%) [22,24]. Najmanja efikasnost je pokazana nakon primene dve doze BBIBP-CorV vakcine (78,1%) [25]. Ovi podaci su dobijeni ispitivanjima na opštoj populaciji i u ove studije nisu bili uključeni pacijenti sa malignitetima.

4 approaches to developing SARS-CoV-2 vaccines. The first approach uses the technology of isolating the DNA or messenger RNA (mRNA) of the virus; the second approach uses envelopes of other viruses as vectors for SARS-CoV-2 protein transfer; the third approach is an inactive vaccine; while the fourth approach involves the insertion of protein subunits of the virus antigen [18]. Several vaccines are currently available, while several more from different manufacturers are expected to be approved in the future. So far, the World Health Organization (WHO) has approved 8 vaccines from different manufacturers [19]. Details about the vaccines are shown in Table 1.

For almost all vaccines, two doses administered 3 – 12 weeks apart are recommended, while, only for the Ad26.COV2.S vaccine, just one dose is required. Recently, a third dose (i.e., a second dose for the Ad26.COV2.S vaccine) has been recommended for immunocompromised patients by the Centers for Disease Control and Prevention [20].

The efficacy of the vaccine is reflected in the development of a sufficient antibody titer and the development of a T cell response that protects against COVID-19 [21,22]. In randomized clinical studies, vaccination has been shown to be 72% – 95% effective in protecting against mild to moderate COVID-19, and as much as 86% – 100% effective in protecting against severe COVID-19, in the general population [23].

Highest efficacy is achieved after the administration of two doses of the mRNA1273 vaccine (94.1%) and the BNT162b2 (94.6%) vaccine [22,24]. The lowest efficacy was observed after the administration of two doses of the BBIBP-CorV vaccine (78.1%) [25]. These data are based on studies in the general population; patients with malignancies were not included.

Poznato je da pacijenti sa hematološkim malignitetima predstavljaju posebno osetljivu grupu, zbog neadekvatnog humoralnog i celularnog imuniteta, pa tako predstavljaju prioritetnu grupu pacijenata za vakcinaciju. Kod hematoloških bolesnika, vakcinacija protiv virusa SARS-KoV-2 je preporučena od strane nekoliko međunarodnih stručnih udruženja [26–28]. Vakcinacija se preporučuje kod pacijenata sa kontrolisanim hematološkim malignitetom (kompletna ili parcijalna remisija bolesti), zatim nakon 3 meseca od transplantacije matičnih ćelija koštane srži, kao i kod pacijenata koji su prethodno preležali infekciju SARS-KoV-2 virusom. Kod pacijenta sa loše kontrolisanim hematološkim malignitetom ili kod pacijenta koji su u toku lečenja hemioterapijom, neophodno je napraviti individualnu procenu potrebe za vakcinacijom [23].

Do sada je objavljen mali broj publikacija koje su ispitivale imunološki odgovor hematoloških pacijenata nakon primenjene vakcine. Preliminarni rezultati su pokazali da se samo kod 18% – 25% pacijenata sa hematološkim malignitetima registruje serokonverzija nakon primene prve doze BNT162b2 vakcine, a nakon primenjene druge doze, kod 46,7% pacijenata. S druge strane, ako se ispituje granična (engl. cut-off) vrednost titra antitela koja može efikasno da neutralizuje virus SARS-KoV-2, broj hematoloških pacijenata koji postiže imunološki odgovor je ispod 2% [29–31]. Slab imunološki odgovor kod pacijenata sa hematološkim malignitetima je posledica aktivnosti maligne bolesti i primenjene imunohemioterapije, koja posebno pogađa populaciju B limfocita, ali i transplantacije matičnih ćelija hematopoeze, koja dovodi do slabljenja humoralnog i ćelijskog odgovora [32].

Malard i sardanici su pokazali da su faktori koji utiču na seropozitivnost nakon primene druge doze BNT162b2 vakcine kod hematoloških pacijenata: muški pol, primena antitela na B ćelijske antigene u prethodnih 12 meseci, kao i niske vrednosti CD19+ B ćelija. Međutim, mali broj pacijenata kod kojih nije postignuta serokonverzija je imao adekvatan T ćelijski odgovor na SARS-KoV-2 virus, što pokazuje da je kod pacijenata koji nemaju adekvatan humoralni odgovor moguće postići neku zaštitu protiv KOVID-19 infekcije [31].

Nedavno je objavljena studija koja je procenjivala imunološki odgovor na BBIBP-CorV vakcinu kod pacijenata sa malignitetima. Najlošiji rezultat serokonverzije (61,9%) su imali pacijenti sa hematološkim malignitetima [33].

Studija, koja je istraživala smrtnost hematoloških pacijenata nakon vakcinacije, uključila je 113 bolesnika koji su bili vakcinisani jednom ili dvema dozama vakcine, u trenutku istraživanja [34]. Većina ispitanika su bili muškarci (61,1%) i pacijenti stariji od 50 godina

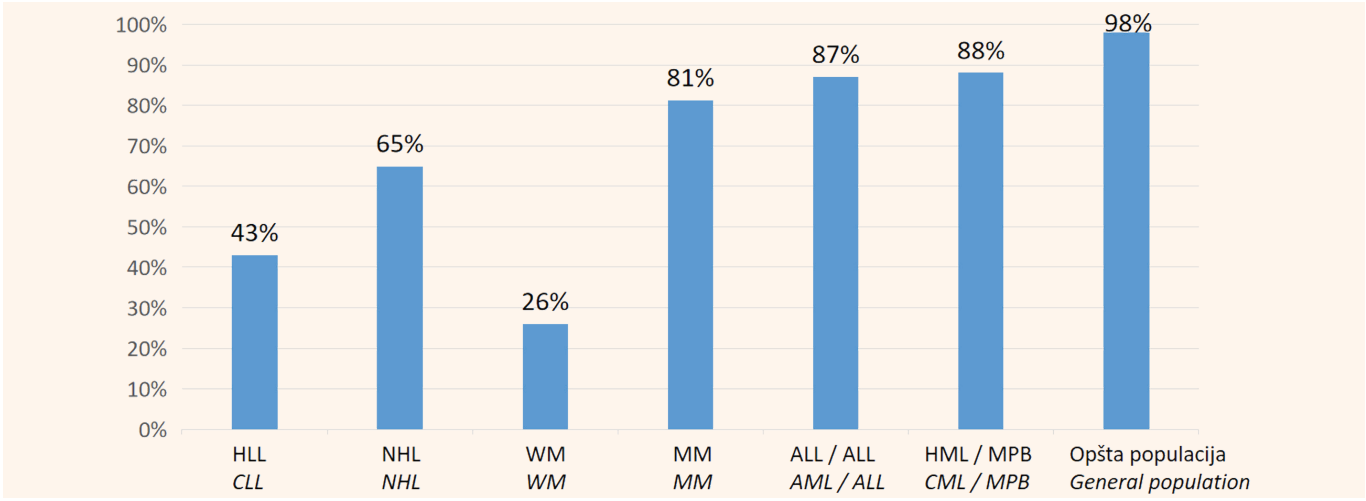
It is known that patients with hematologic malignancies represent a particularly sensitive group, due to inadequate humoral and cellular immunity, and thus represent a priority group for vaccination. Vaccination against SARS-CoV-2 in hematological patients has been recommended by several scientific associations [26–28]. Vaccination is recommended for patients with controlled hematologic malignancies (complete or partial remission of the disease), also, 3 months after bone marrow stem cell transplantation, as well as in patients who had previously been infected with the SARS-CoV-2 virus. For patients with poorly controlled hematologic malignancies or patients undergoing chemotherapy, it is necessary to make an individual assessment of the need for vaccination [23].

To date, there has been a small number of publications examining the immune response of hematological patients after vaccine administration. Preliminary results have shown that only 18% – 25% of patients with hematologic malignancies registered seroconversion after the first dose of the BNT162b2 vaccine, while seroconversion was registered in 46.7% patients after the second dose. If the cut-off value of the antibody titer that can effectively neutralize the SARS-CoV-2 virus is examined, the number of hematological patients who achieve immune response is below 2% [29–31]. The reasons why patients with hematologic malignancies may have a weak immune response are connected to the activity of the malignant disease and the applied immunochemotherapy, which especially affects the B lymphocyte population, but also to the transplantation of hematopoietic cells, which leads to the weakening of the humoral and cellular response [32].

Mallard et al. showed that the factors affecting seropositivity after the administration of the second dose of the BNT162b2 vaccine in hematological patients were the male sex, anti-B cell-targeted treatment in the previous 12 months, and a low CD19 + B cell count. However, a small number of patients without seroconversion had an adequate T cell response to SARS-CoV-2, indicating that, in patients without an adequate humoral response, some protection against the COVID-19 infection may be achieved [31].

A study evaluating the immune response to the BBIBP-CorV vaccine, in patients with malignancy, was recently published, with patients with hematologic malignancies having the worst seroconversion score (61.9%) [33].

A study investigating the mortality of hematological patients after vaccination included 113 patients vaccinated with one or two doses of the vaccine at the time of the study [34]. The majority of patients were men (61.1%) and patients older than 50 years (85.5%).



* HLL – hronična limfocitna leukemija; NHL – Nehočkinov limfom; *WM – Waldenstrom* makroglobulinemija; MM – multipli mijelom; ALL/AML – akutna limfoblastna/mijeloidna leukemija; HML/MPB – hronična mijeloidna leukemija/mijeloproliferativne bolesti

*CLL – chronic lymphocytic leukemia; NHL – non-Hodgkin lymphoma; WM – Waldestrom macroglobulinemia; MM – multiple myeloma; ALL/AML – acute myeloid/lymphoid leukemia; CML/MPD – chronic myeloid leukemia/myeloproliferative disease

Slika 2. Procenat pacijenata sa različitim hematološkim malignitetima kod kojih je postignuta serokonverzija

Figure 2. Seroconversion in various hematologic malignancies

(85,5%). Više od 80% bolesnika je imalo dijagnozu limfoproliferativnog oboljenja. Sedamdeset i osam pacijenata (68,1%) je bilo na aktivnom lečenju, ili je prošlo manje od 3 meseca od poslednjeg ciklusa hemioterapije u trenutku postavljanja dijagnoze infekcije uzrokovane SARS-KoV-2 virusom. Većina pacijenata je primila iRNK vakcinu (BNT162b2, *n* = 79 (69,9%), mRNA1273, *n* = 20 (17,7%)), dok je preostalih 14 (12,4%) dobilo vektorsku vakcinu (ChAdOx1 nCoV-19, *n* = 10), ili inaktiviranu vakcinu (CoronaVac, *n* = 4). Srednje vreme između poslednje doze vakcine i dijagnoze KOVID-19 infekcije bilo je 64 dana. Serokonverzija je analizirana kod 40 pacijenata koji su vakcinisani sa dve doze vakcine, i samo kod 13 pacijenata je postignuta serokonverzija (kod 8 pacijenata optimalna vrednost titra, a kod 5 pacijenata slab imunološki odgovor), dok 27 pacijenata nije postiglo imunološki odgovor. Mortalitet kod vakcinisanih pacijenata u navedenoj studiji je bio 12,4%, što je značajno manje u odnosu na mortalitet nevakcinisanih hematoloških pacijenata [34]. Serokonverzija kod različitih hematoloških maligniteta je prikazana u Grafikonu 2 [35–38].

EFIKASNOST SARS-KOV-2 VAKCINE KOD BOLESNIKA SA POJEDINIM HEMATOLOŠKIM MALIGNITETIMA

Hronična limfocitna leukemija (HLL)

Herižanu i saradnici su ispitivali serokonverziju nakon primene druge doze BNT162b2 vakcine, kod pacijenata sa HLL-om. U studiju je uključeno 167 pacijenata. Medijana starosti je bila 71 godina, a 67,1% pacijenata su bili muškarci. Serokonverzija je bila registrovana kod

More than 80% of patients were diagnosed with lymphoproliferative disease. Seventy-eight patients (68.1%) were on active treatment or less than three months had passed since their last chemotherapy at the time of diagnosis of the COVID-19 infection. Most of the patients received the mRNA vaccine (BNT162b2, *n* = 79 (69.9%), mRNA1273, *n* = 20 (17.7%)), while the remaining 14 (12.4%) received the vector vaccine (ChAdOx1 nCoV-19, *n* = 10) or the inactivated vaccine (CoronaVac, *n* = 4). The median time between the latest dose of the vaccine and the diagnosis of COVID-19 infection was 64 days. Seroconversion was analyzed in 40 patients vaccinated with two doses of the vaccine. Seroconversion was achieved in only 13 patients (optimal titer value in 8 patients and weak immune response in 5 patients), while 27 patients did not achieve an immune response. The mortality in vaccinated patients in this study was 12.4%, which is significantly lower than the mortality of unvaccinated hematological patients [34]. Seroconversion in various hematologic malignancies is shown in Figure 2 [35–38].

SARS-COV-2 VACCINE EFFICACY IN SPECIAL POPULATIONS WITH HEMATOLOGIC MALIGNANCIES

Chronic lymphocytic leukemia (CLL)

Herishanu et al. examined seroconversion after the administration of the second dose of the BNT162b2 vaccine in patients with CLL. The study included 167 patients; the median age was 71 years and 67.1% of the patients were men. Seroconversion was registered in only 66 patients (39.5%). The variables associated with

samo 66 pacijenata (39,5%). Parametri koji su bili povezani sa stvaranjem imunološkog odgovora su: ženski pol, pacijenti mlađi od 65 godina, rani stadijum bolesti (Binet A), pacijenti koji nisu na aktivnoj terapiji i/ili nisu primali anti-CD20 antitela unazad 12 meseci, normalan nivo ukupnih imunoglobulina [39].

Pacijenti koji su aktivno lečeni inhibitorom Brutonove tirozin-kinaze i anti-CD20 antitelima su imali značajno lošiji imunološki odgovor nakon primene dve doze iRNK vakcine [40]. Da bi se rekonstituisali B limfociti, potrebno je da prođe 9 – 12 meseci od primene anti-CD20 antitela [41].

Kod pacijenata koji su bili na aktivnoj terapiji BCL-2 inhibitorom, u jednoj studiji nije došlo do serokonverzije nakon vakcinacije [42], a u drugoj su samo 2 od 5 pacijenata imala minimalan serološki odgovor na vakcinaciju [39].

Multipli mijelom (MM)

Terpos i saradnici su poredili koncentraciju neutrališućih antitela na virus SARS-KoV-2, dvadeset drugog dana nakon primene prve doze BNT162b2 vakcine, kod 48 pacijenata sa multiplim mijelomom (medijana starosti je bila 83 godine), u odnosu na kontrolnu grupu. Od 48 pacijenata sa MM-om, 35 pacijenata je bilo na hemioterapiji, 4 pacijenta je bilo u remisiji bolesti, a 9 pacijenata je imalo dijagnozu tinjajućeg mijeloma. Pacijenti sa MM-om su imali značajno manji titar neutrališućih antitela u odnosu na kontrolnu grupu (20,6% naspram 32,5%; $p < 0,01$). Titar iznad 30% je imalo 55% ispitanika u kontrolnoj grupi, dok je tu vrednost postigla samo jedna četvrtina pacijenata sa MM-om. Pacijenti koji su postigli odgovarajući titar antitela su bili u remisiji bolesti i imali normalnu vrednost ukupnih imunoglobulina, dok je 8 pacijenata koji nisu napravili serokonverziju imalo imunoparezu [30]. Druga studija istih autora je poredila vrednosti titra neutrališućih antitela kod pacijenata sa plazmaćelijskim malignitetom, pedesetog dana od primanja BNT162b2 vakcine i 7 nedelja nakon primene prve doze ChAdOx1nCoV-19 vakcine, u odnosu na kontrolnu grupu [43]. Pacijenti sa MM-om su imali značajno manji titar u odnosu na kontrolnu grupu. Parametri koji su se pokazali značajnim za neadekvatni imunološki odgovor jesu limfopenija, primena anti-CD38 antitela i muški pol. Slično tome, Van Ekelen i saradnici su utvrdili da su faktori koji negativno utiču na serokonverziju kod pacijenata sa MM-om limfopenija gradus 3, primena anti-CD38 terapije, kao i primena više od tri terapijske linije [38].

Mijeloproliferativne neoplazme

Studija, koja je ispitivala imunološki odgovor u mijeloproliferativnim bolestima, uključila je 42 pacijenta (10 pacijenata sa dijagnozom mijelofibroze, 15 pacijenata

the generation of an immune response were the following: the female sex, patients younger than 65 years, early-stage disease (Binet A), patients not on active therapy and/or not receiving anti-CD20 antibodies for 12 months, normal total immunoglobulin levels [39].

Patients actively treated with Bruton's tyrosine kinase inhibitor and anti-CD20 antibodies had a significantly poorer immune response, after receiving two doses of an mRNA vaccine [40]. It is believed that it takes 9 – 12 months, following the administration of anti-CD20 antibodies, for the reconstitution of B lymphocytes [41].

In patients on active BCL-2 inhibitor therapy, seroconversion did not occur after vaccination in one study [42], and in another study, only two patients out of five had some serological response to vaccination [39].

Multiple myeloma (MM)

Terpos et al. analyzed the concentration of neutralizing antibodies to SARS-CoV-2 on day 22 after the first dose of the BNT162b2 vaccine, in 48 patients (median age 83 years) with multiple myeloma, as compared to controls. Of the 48 patients with MM, 35 patients were on chemotherapy, 4 patients were in remission, and 9 patients were diagnosed with smoldering myeloma. Patients with MM had a significantly lower titer of neutralizing antibodies, compared to the control group (20.6% vs. 32.5%; $p < 0.01$). A total of 55% of subjects in the control group had a titer above 30%, while only one quarter of the patients with MM achieved this value. Patients who achieved the appropriate antibody titer were in remission of the disease and had a total value of immunoglobulins in the reference range, while the 8 patients in whom seroconversion was not registered had immunoparesis [30]. Another study, by the same authors, compared the titer values of neutralizing antibodies on the 50th day of the BNT162b2 vaccine and 7 weeks after the administration of the first dose of the ChAdOx1 nCoV-19 vaccine, in patients with plasma cell malignancy, as compared to the control group. It was shown that patients with MM had significantly lower titers, as compared to the control group, while the prognostic parameters that proved most significant in case of inadequate immune response were lymphopenia, use of anti-CD38 agents and the male sex [43]. Van Oekelen et al. demonstrated that the factors negatively affecting seroconversion in patients with MM were the following: grade 3 lymphopenia, application of anti-CD38 therapy, and the application of more than 3 treatment lines in patients [38].

Myeloproliferative diseases

A study examining the immune response in myeloproliferative diseases included 42 patients (10 patients

sa dijagnozom policitemije vere (PV) i 17 pacijenata sa dijagnozom esencijalne trombocitemije (ET)). Svi pacijenti su bili na aktivnom lečenju. Dvadeset devet pacijenata je bilo na hidroksikarbamidu, 8 bolesnika je lečeno ruksolitinibom, tri pacijenta su bila na anagrelidu, dok su dva bolesnika bila na terapiji interferonom-alfa. Pacijenti sa mijelofibrozom su imali značajno lošiju serokonverziju u odnosu na pacijente sa PV-om i ET-om (60% naspram 93,8%) [44]. Smatra se da je jedan od razloga za to primena ruksolitiniba [37,42].

Nehočkinovi limfomi (NHL)

Studija koja je procenjivala imunološki odgovor nakon druge doze iRNK vakcine kod pacijenata sa NHL-om je uključila 147 pacijenata. Agresivni tip limfoma je imalo 47% pacijenata, dok je ostatak bolesnika imao dijagnozu indolentnog limfoma. Na aktivnom lečenju je bilo 37% pacijenata sa režimom primene anti-CD20 antitela (rituksimab ili obinutuzumab). Kod 44% pacijenata je prošlo više od 6 meseci od primene anti-CD20 antitela, dok kod 19% pacijenata terapija nije primenjivana. Najlošiji imunološki odgovor je registrovan kod pacijenata na aktivnom lečenju (7,7% pacijenata je postiglo serokonverziju), a najbolji odgovor kod pacijenata koji nisu prethodno lečeni (89% pacijenata je postiglo serokonverziju). Limfopenija i primena anti-CD20 antitela su bili nezavisni prognostički parametri za razvoj lošeg imunološkog odgovora [45].

ZAKLJUČAK

Interpretacija imunološkog odgovora na vakcinu kod bolesnika sa hematološkim malignitetima je kompleksna, jer se moraju uzeti u obzir starosno doba, tip vakcine, osnovna bolest, primenjena terapija, kao i vreme proteklo od poslednje terapije do vakcinacije.

Ukratko, iRNK vakcine se preporučuju kod ovih pacijenata zbog sigurnosnog profila, ali efikasnost vakcine se mora posmatrati kroz imunokompromitovanost i smanjenu imunogenost vakcina kod ovih pacijenata. S jedne strane, ovi pacijenti su pod visokim rizikom da razviju težak oblik KOVID-19 bolesti, a sa druge strane su u riziku da ne razviju adekvatan imunološki odgovor na vakcinu, usled već spomenutih razloga imunosupresije. Stoga, postoje nepoznanice oko toga koji je optimalni vremenski period kada treba primeniti vakcinu; u kojoj dozi je treba dati; kao i kakav je kapacitet razvoja imunološkog odgovora na vakcine kod pojedinih grupa pacijenata sa hematološkim malignitetima. Studije su pokazale da je, i pored slabijeg imunološkog odgovora na vakcinu, smrtnost vakcinisanih pacijenata sa hematološkim malignitetima značajno manja u odnosu na nevakcinisane bolesnike. Poslednji podaci iz registra Radne grupe za infektivne bolesti Evropske

diagnosed with myelofibrosis, 15 patients diagnosed with polycythemia vera (PV), and 17 patients diagnosed with essential thrombocythemia (ET)). All patients were on active treatment – 29 patients were on hydroxycarbamide, 8 patients were on ruxolitinib, three on anagrelide, while two patients were on interferon-alpha therapy. Patients with myelofibrosis had a significantly lower seroconversion rate, as compared with patients with PV and ET (60% vs. 93.8%) [44]. It is believed that one of the reasons why patients with myelofibrosis have a poorer immune response to vaccines is the use of ruxolitinib [37,42].

Non-Hodgkin Lymphoma (NHL)

A study evaluating the immune response after the second dose of an mRNA vaccine in patients with NHL included 147 patients. Of these patients, 47% had an aggressive type of lymphoma, while the rest were diagnosed with indolent lymphoma. A total of 37% of patients were on active treatment with the anti-CD20 antibody regimen (rituximab or obinutuzumab). In 44% of patients, more than 6 months had passed after anti-CD20 antibody administration, and 19% of patients did not receive therapy. The worst immune response was registered in patients on active treatment (7.7% of patients achieved seroconversion), while the best response was registered in patients who had not previously been treated (89% of patients achieved seroconversion). A multivariate analysis showed that lymphopenia and the use of anti-CD20 antibodies were associated with a poorer serological response [45].

CONCLUSION

Interpretation of immune response to vaccination in patients with hematologic malignancies is complex. Age, type of vaccine, underlying disease, applied therapy, and the time elapsed from the last therapy to vaccination must be taken into account.

In summary, mRNA vaccines are recommended in these patients because of the safety profile, but immunosuppression and reduced vaccine immunogenicity must be considered. On the one hand, these patients are at high risk of developing severe forms of COVID-19, but, on the other, they are also at risk of not developing an adequate immune response to the vaccine, due to the already mentioned reasons of immunosuppression. Therefore, the following remains unknown: what is the optimal time for vaccine administration; which dose should be applied; and what is the capacity of developing an immune response to vaccines in certain groups of patients with hematologic malignancy. A small number of studies have shown that, despite a weaker immune response to the vaccine, the mortality of vaccinated patients with hematologic malignancies

hematološke asocijacije ukazuju na značajno smanjenje mortaliteta kod bolesnika sa hematološkim malignitetima nakon vakcinacije. Naime, mortalitet kod bolesnika obolelih od KOVID-19 sa hematološkim malignitetima je smanjen sa 31%, u prevakcinalnom periodu, na 12.4%, u postvakcinalnom periodu. Neophodno je sprovesti kliničke studije o efikasnosti drugih tipova vakcina, ali i uvesti treću dozu vakcine kod ovih pacijenata, radi unapređenja preporuka o vakcinaciji kod ovih pacijenata i poboljšanja imunološkog odgovora.

Sukob interesa: Nije prijavljen.

is significantly lower, as compared to unvaccinated patients. The latest data from the register of the Working Group on Infectious Diseases of the European Hematological Association indicate a significant reduction in mortality in patients with hematologic malignancies after vaccination. Mortality in COVID-19 patients with hematologic malignancies decreased from 31%, in the pre-vaccination period, to 12.4%, in the post-vaccination period. However, it is necessary to conduct clinical studies on the effectiveness of other types of vaccines, but also to administer a third dose to these patients, in order to improve vaccination recommendations in these patients and improve immune response.

Conflict of interest: None declared.

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