The Impact of Hematological Malignancy and Type of Therapy on COVID-19 Severity and Mortality

Hematologinių piktybinių navikų ir gydymo būdų įtaka COVID-19 sunkumui ir mirtingumui

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Summary

The COVID-19 is one of the most important recent events in the world. Its long asymptomatic incubation period, efficient airborne transmission and high infectivity have contributed to its rapid global spread. The spectrum of symptoms, mortality and morbidity varies widely. Chronic diseases are an important risk factor for the development of severe and fatal forms of COVID-19. Many studies have confirmed that malignant hematological diseases have the worst morbidity and mortality outcomes. Currently, the most effective way to fight infection is through vaccination. This has been effective and has had a dramatic effect on reducing serious illness and mortality rates in the general population, but the benefits of the vaccine have not been successfully replicated in patients with hematological malignancies. The COVID-19 pandemic poses several medical challenges that encourage researchers and clinicians to provide the best possible care for patients with hematological malignancies during this difficult period.

Keywords: Hematooncological Disorders, Chemotherapy, COVID-19.

Santrauka

COVID-19 yra vienas svarbiausių pastarojo meto įvykių. Ilga besimptomė inkubacinio laikotarpio trukmė, plitimas oru bei didelis užkrečiamumas padėjo ligai greitai išplisti visame pasaulyje. Patiriamų simptomų, mirtingumo ir sergamumo spektras labai skiriasi. Lėtinės ligos yra svarbus rizikos veiksnys susirgti sunkiomis ir mirtinomis COVID-19 formomis. Daugelis tyrimų patvirtino, kad piktybinės hematologinės ligos lemia blogiausius sergamumo ir mirtingumo padarinius. Šiuo metu efektyviausia kova su infekcija – vakcinacija. Ji buvo veiksminga ir turėjo didžiulį poveikį sunkių ligų ir mirtingumo rodiklių mažėjimui bendrojoje populiacijoje, tačiau vakcinos nauda nebuvo tokia sėkminga pacientams, sergantiems hematologiniais piktybiniais navikais. COVID-19 pandemija kelia daug medicininių iššūkių, kurie skatina mokslininkus ir gydytojus šiuo sunkiu laikotarpiu teikti kuo geresnę pagalbą pacientams, sergantiems hematologiniais piktybiniais navikais.

Raktažodžiai: hematoonkologinės ligos, chemoterapija, COVID-19.

Introduction

COVID-19 is a respiratory viral disease caused by the SARS-CoV-2 virus. It is one of the most significant event in recent time. Its long asymptomatic incubation period, effective airborne and fomites spread, and its highly contagious nature helped it spread quickly around the globe [1]. The range of experienced symptoms, mortality, and morbidity varies dramatically. Most of the patients experience a light course of the disease, many others experience severe and even fatal courses of disease.

Chronic diseases were identified as an important risk factor for getting affected by severe and fatal forms of COVID-19 [2]. Many studies had confirmed that compared to the general public, cancer patients are at a greater risk to develop severe or critical forms of COVID-19 [3, 4]. Furthermore, among cancer patients, hematological malignancies were found to result in the worst outcomes both in morbidity and mortality [2, 4, 5].

Throughout 2021, global-scale COVID-19 vaccination campaigns were launched worldwide. Even though the vaccination was found to be effective, and had a dramatic effect on decreasing severe disease and mortality rates in the general population [6, 7], the benefits of the vaccine were not successfully replicated in patients with hematological malignancies [8–10].

The COVID-19 pandemic brings about many medical challenges that prompt researchers and clinicians to provide the best possible care to patients that suffer from hematological malignancies in these difficult times. This literature review attempts to gather the most recent data on the effects of hematological malignancies, anti-cancer treatment regimens, and vaccines on COVID-19 mortality and morbidity.

Literature review

Hematological malignancies – patient characteristics, risk factors, and considerations in the context of COVID-19

One of the defining characteristics of COVID-19 is the variety of its clinical presentations, their severity, and their outcomes. Many factors seem to play a role in the pathophysiological developments that influence the severity and the outcomes of the disease. The presence of chronic diseases and cancer has a crucial role in the development of severe COVID-19 and a worse prognosis. Cancer was found to be an independent adverse factor on COVID-19 severity and threefold mortality compared to the general public [3, 4]. Exact percentages of COVID-19 caused mortality was different in various studies, but they all confirm that it is substantially higher than in the general population [4, 5, 11–13].

COVID-19 symptoms that are manifested in cancer patients do not differ substantially from the ones experienced in the general population. However, Zhang et al. had found that anemia and hypoproteinemia might be more pronounced in cancer patients. They highlight that these symptoms are of importance because of their impact on immunocompetence [11].

The disparity of COVID-19 outcomes is also common among patients of different types of cancer, as different types of malignancies lead to dramatically different outcomes of COVID-19. The current consensus is that patients with hematological malignancies are the most vulnerable subgroup among cancer patients, as multiple studies conclude that they are at a greater risk to experience a severe type of COVID-19, they are more likely to require critical care in the intensive care unit (ICU) and their mortality rates are the highest [3–5, 14–16]. Among hematological leukemias, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) were found to result in the direst outcomes, possibly because of the usually older age of the patients and the aggressive chemotherapeutic regimens that are required in that subgroup [3, 17]. Passamonti et al. had also found that AML is predictive of poor outcomes, but they had also mentioned non-Hodgkin lymphoma and plasma cell neoplasms as related to such outcomes [16] as shown in table 1. Pagano et al. had also mentioned lymphoproliferative disorders, in particular Non-Hodgkin's Lymphoma (NHL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM) to be associated with a high risk from COVID-19 [17]. Wang et al. had different results, as they had found that patients with a recent hematologic malignancies diagnosis had the largest odds to get infected with COVID-19 [18]. Several studies had found that the number of chronic myeloid leukemia (CML) patients infected with COVID-19 was low and that their prognoses were better. These results raised hypotheses about the possibility of tyrosine kinase inhibitors being efficacious against COVID-19 in some cases [3, 16]. The inconsistent results of the various studies point that a consensus about the most hazardous sub-types of hematological malignancies in the context of the COVID-19 disease is yet to be reached and that further research is needed for more conclusive results to be obtained as shown in table 1.

Several hypotheses were proposed to explain the effects of COVID-19 on the cohort of patients with hematological malignancies. Mehta et al. had proposed that patients with hematological malignancies might be more susceptible to the highly dangerous cytokine-storm syndrome, which in many cases leads to severe and fatal COVID-19. They hypothesize that the perturbations in myeloid and lymphocyte cell compartments may increase the susceptibility to such events [4]. He et al. had proposed that the increased mortality rate is attributable to bacterial co-infections, linking it to the enhanced vulnerability of patients with hematological malignancies to such pathogens due to the severe lack

Table 1. **Mortality rates in different hematological malignancies**

	Passamonti F. et al. (2020) [16]			Mehta V. et al. (2020) [4]		
Type of hematological malignancy	**TOTAL (N=536)**	**SURVIVORS (N=338)**	**NON-SURVIVORS (N=198)**	**TOTAL (N=50)**	**SURVIVORS (N=32)**	**NON- SURVIVORS (N=18)**
Myeloid neoplasms	175 (33%)	106 (31%)	69 (35%)	13 (26%)	8 (25%)	5 (28%)
Myeloproliferative neoplasms	83 (15%)	56 (17%)	27 (14%)	7 (14%)	5 (16%)	2 (11%)
Myelodysplastic syndromes	41 (8%)	21 (6%)	20 (10%)	5 (10%)	2 (6%)	3 (17%)
Acute myeloid leukaemias	51 (10%)	29 (9%)	22 (11%)	1 (2%)	1(3%)	0 (0%)
Acute lymphoblastic leukaemias	16 (3%)	13 (4%)	3 (2%)	4 (8%)	4 (13%)	0 (0%)
Hodgkin lymphoma	17 (3%)	14 (4%)	3 (2%)	5 (10%)	2 (6%)	3 (17%)
Non-Hodgkin lymphomas	222 (41%)	138 (41%)	84 (42%)	15 (30%)	10 (31%)	5 (28%)
Chronic lymphoproliferative neoplasms	69 (13%)	47 (14%)	22 (11%)	NA	NA	NA
Indolent lymphomas	54 (10%)	33 (10%)	21 (11%)	NA	NA	NA
Aggressive lymphomas	99 (18%)	58 (17%)	41 (21%)	NA	NA	NA
Plasma cell neoplasms	106 (20%)	67 (20%)	39 (20%)	13 (26%)	8 (25%)	5 (28%)

of granulocytes [15]. Wang et al. had also proposed a similar hypothesis about the mechanisms of immunodeficiency, mentioning the abundance of defective immature or dysfunctional neoplastic granulocytes in AML, and the lack of IgG immunoglobulins in CLL [18].

Wang et al. had found that patients with hematological malignancies undergo more chemotherapeutic treatments and are more likely to have more co-morbidities [1]. Even after adjusting to age, gender, and COVID-19 increasing co-morbidities, hematological malignancies were still found to be an especially adverse risk factor for COVID-19 infection [18]. Vijenthira et al. had contributed an important insight about the comparison between patients with solid and hematological cancers, stating that the mortality range of hospitalized solid cancer patients is within the range of 19–42%, which is comparable to the percentages observed in hematological malignancies patients [19].

Nadkarni et al. researched the admission and survival of hematological malignancies patients with COVID-19 in ICUs. They had concluded that the current mortality in that patient group is 60%, Garcia-Suarez et al. had found even lower mortality of 51% in an equivalent group of patients in Spain, this number is reaffirmed in the study of Ramasamy et al, that found mortality rates to be 50% [14]. Despite of high mortality rates and the scarcity of ICU beds, studies conclude that these patients should not be deferred from receiving life-saving care in the ICU [3, 13].

Hematological Cancers Treatment in the COVID-19 Era

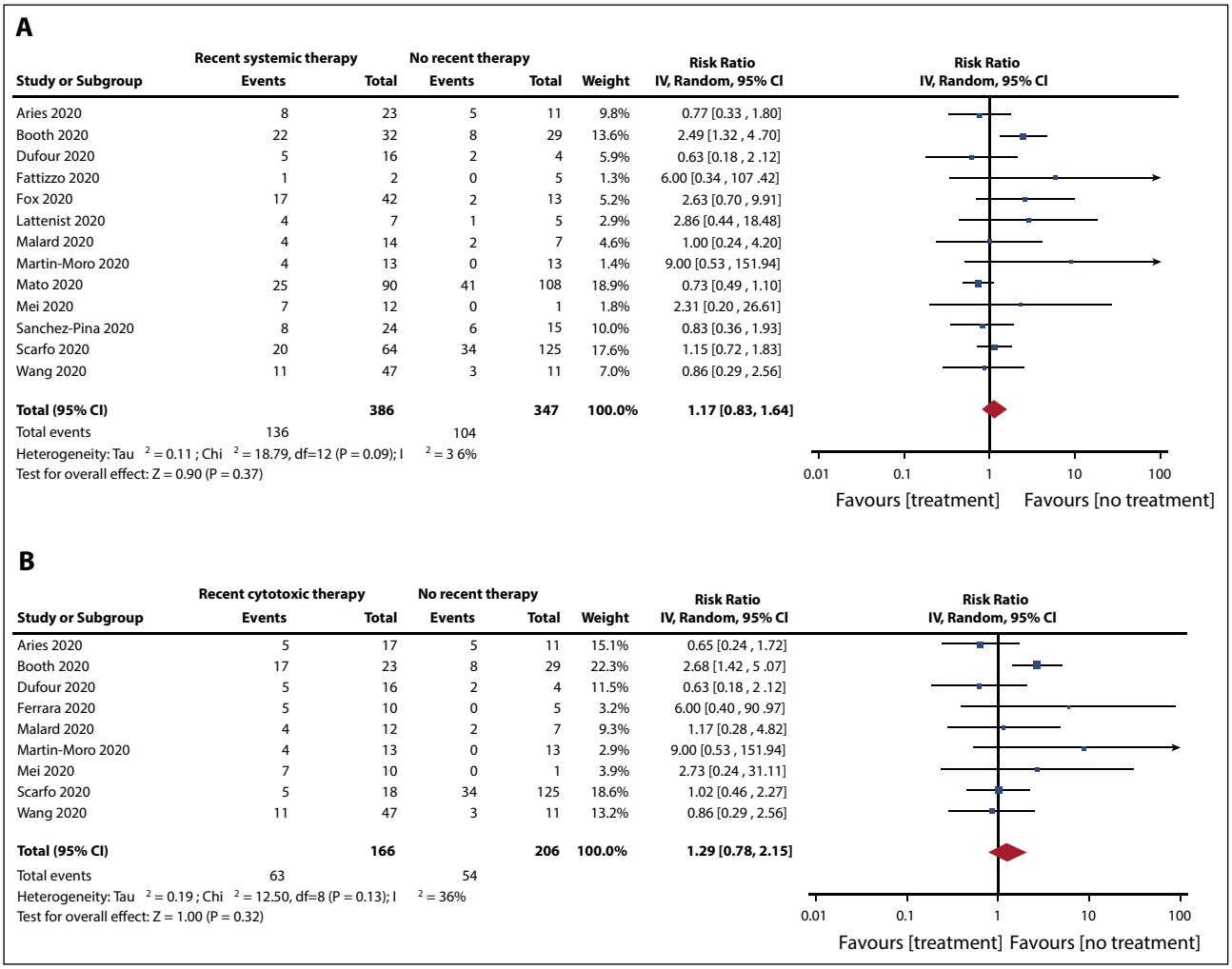
Treating hematological malignancies during the COVID-19 pandemic is very challenging. Weakened by the disease itself, the frail immune systems are further exhausted by immunocompromising anti-cancer treatments. Several studies explored the effects of various treatment modalities for hematological cancer on COVID-19 severity and mortality rates.

In a meta-analysis by Liu et al. on the effects of anti-cancer treatment, they had found that in contrast to the treatment of solid tumours, chemotherapy against hematological cancers within 3 months before COVID-19 diagnosis had resulted in higher mortality risk [20]. A study by Wu et al. had further confirmed these findings, as they have observed that cytotoxic therapy that was given in the span of 4 weeks before the initiation of COVID-19 symptoms resulted in increased mortality [21]. Their analysis had found that intensive chemotherapy is an independent adverse factor for worse outcomes. Fox et al. found similar results, finding higher numbers of severe illness and death in those treated with chemotherapy within 28 days before COVID-19 diagnosis. Interestingly, they found that the intensity of chemotherapy did not have any effect on disease severity and death [22].

Fox et al. state that although chemotherapy and other regimens raise understandable concerns, the initiation of life-saving chemotherapeutic therapies must not be deterred or delayed. A significant portion of hematological patients with recent and concurrent anti-cancer treatment survive the disease despite their challenging circumstances [22]. Vijenthira et al. in a systematic review and meta-analysis of 3 377 patients suggests that in patients who require urgent therapy for their hematologic malignancy, treatment can be delivered despite the risks of COVID-19 as it does not show statistically significant excess risk of death compared with no treatment (Figure 1) [19].

Wang et al. propose general ground-principles to approach hematological malignancies treatment during the COVID-19 pandemic: implementation of home-based admission of oral chemotherapy, when possible, simplification of regimens and reduction of visit time and frequency to the absolute minimum, consideration of the risk and benefits of the therapy, and deferral of non-emergency chemotherapy and medical procedures [1]. They also highlight the importance of the involvement of a multi-disciplinary

Figure 1. **Risk rations of death in patients. (A) On systemic anticancer therapy vs on no treatment. (B) On cytotoxic systemic anticancer therapy vs on no treatment [19]**



team of hematologists, infectious diseases experts, and other relevant experts and the tailoring of an individualized patient-focused treatment plant [23].

Hematological stem cell transplantation in COVID-19 times

Hematological stem cell transplantation (HSCT) is an important therapy in the inventory of the hematologist. This procedure is crucial in the treatment of otherwise untreatable hematologic malignancies. However, the procedure itself, and the immunosuppression that is associated with it pose great challenges in the face of the COVID-19 pandemic [24]. Several studies had reported on high mortality rates in patients after HSCT that had developed COVID-19. In the study of Passamonti et al., 35% and 33% of patients after allogenic and use autologous HSCT respectively had died after they had developed COVID-19 [16]. In a study by Piñana et al, death occurred in 17% of allogeneic HSCT recipients and 18% of autologous HSCT recipients [25]. High mortality rates were also found in the study by Sharma et al., which had reported a 68% survival in allogeneic HSCT recipients and 67% in autologous HSCT recipients [24]. These results suggest that the recipients of both alloHSCT and auto-HSCT are at a similarly great risk of death if infected with SARS-COV-2 [24]. Altuntas et al. found that mechanical ventilation, ICU admission, and case fatality rates were all the same between recipients of allogeneic and autologous HSCT [26]. Furthermore, they had found that there was no significant difference in the occurrence of severe and critical disease between hematological cancer patients that had received HSCT and those that did not [26]. Interestingly, the results of the study by Piñana et al. had found a lower mortality rate in recipients of HSCT compared to non-HSCT patients [25]. These results were likely skewed by the fact that the cohort of HSCT receiving patients are younger than the general population of patients with hematological malignancies [25].

Along with old age, other risk factors for higher mortality included male sex, HSCT within the last 12 months [24, 27, 28]. As in immunocompetent patients, comorbidities such as diabetes mellitus, chronic renal disorders, heart failure were adverse prognostic factors in HSCT patients [28]. Shah et al. had also found that having more than 2 comorbidities, an active malignancy and an active relapsed disease were especially significant risk factors for adverse outcomes [29]. Moreover, they had found that patients with lymphoma were at a greater risk than multiple

myeloma patients within the autologous HSCT group. It is important to note that in all mentioned studies, the cut-off for higher mortality rate was 50 years and more in the studies of Sharma et al. and Sahu et al., and 40 and more in the study by Varma et al. [24, 27, 28]. This cut-off suggests that patients treated by HSCT experience adverse results at a younger age compared to non-HSCT receiving hematological malignancy patients. Male sex was found to be a significant predictor of morbidity, Sharma et al had found that the risk of death in males was four times greater than in women and that the mortality difference between the groups increases in older patients [24]. Sahu et al. had found that active immunosuppression, prolonged immunosuppression, previous graft versus host disease (GVHD), had increased the susceptibility of post-HSCT patients to contract SARS-CoV-2 [28]. Patients that had received HSCT 2 years ago and more, which are off immunosuppressive therapy, without GVHD present with a similar risk rate as the general population. Interestingly, cyclophosphamide therapy after HSCT had resulted in a milder form of COVID-19 [28].

Despite the inherent risk of HSCT therapy during the COVID-19 pandemic, the current consensus is to proceed with HSCT procedures. It is of notice that clinical judgment and the differentiation of urgent and non-urgent cases are advised. Algwaiz et al. mention acute leukemias, high-risk myelodysplastic syndrome, certain refractory bone marrow failure syndromes, and autologous HCTs (if being performed for curative intent) for high-risk myelomas, Hodgkin lymphoma, large B-cell lymphomas as examples of cases that should not be deferred [30]. Adherence to strict infection prevention measures, careful patient selection, increased screening, and the usage of protective equipment reduces the risk involved in HSCT administration despite of the challenging setting of COVID-19 [31, 32].

Hematological Cancer and Response to Vaccines

Vaccines against COVID-19 are currently the most accepted and efficacious measure against the disease. The effect of the vaccines on patients with hematological malignancies was questionable from the start, as patients with hematological malignancies were not included in any of the various COVID-19 vaccine trials [33, 34]. Several studies were conducted in order to fill that important gap and assess the effect of the vaccine on cancer patients in general, and patients with hematological malignancies patients specifically. Although the vaccines were found to be safe, with adverse reactions similar or diminished compared to the general population [9, 10], the bottom line of the studies was unanimous – the response of patients with hematological malignancies to the vaccine is weak as shown in figure 2 and figure 3. These results are not surprising, as previous studies of immunological responses to

Figure 2. **Association of anti-SARS-CoV-2 spike IgG with vaccine types and cancer types [36]**

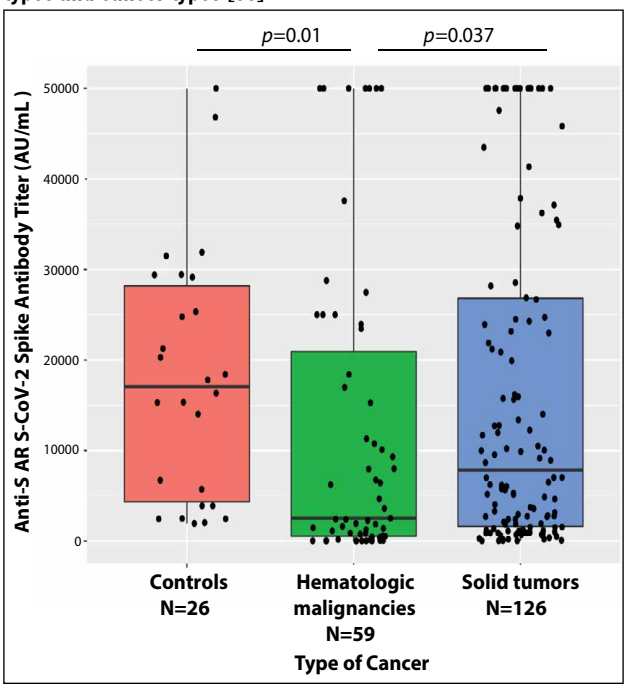
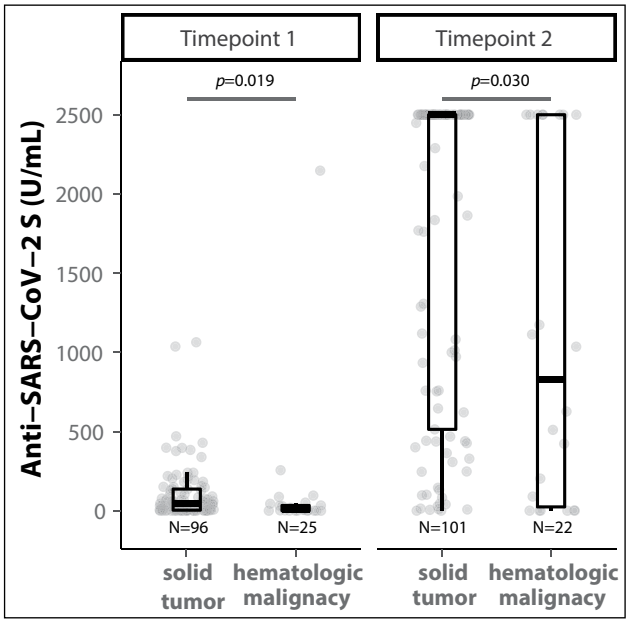


Figure 3. **Differences in anti-SARS-CoV-2 S (anti-S) IgG titers following partial and complete vaccination, stratified by type of cancer [37]**



Time point 1 – post first vaccination dose and at time point 2 – post second vaccination dose.

other vaccines, such as those against *Streptococcus pneumoniae* and Influenza virus, in this patient group, showed similar results [8, 33]. Both malignancy-induced immune dysregulation and therapy-related immunosuppression are thought to play a role in the relatively weak response to vaccination [8].

Several studies had compared the difference of seroconversion in patients with solid and hematological malignancies. While the specific percentages differed, all studies had found that seroconversion rates in hematological

patients were significantly lower. Monin et al. had found seroconversion rates of 38% in the solid cancer group vs. 18% in the hematological cancer group 3 weeks after a single dose vaccination [35]. Thakkar et al. [36] had found similar tendencies after full completion of the vaccine regimen, patients with solid tumours presented with seroconversion of 98 % compared to 85 % in the hematological group, Addeo et al. found even a more significant discrepancy between the group, of 98% compared to 77% [37]. These results show the dramatic effect of a fully completed vaccine schedule, but also confirm that even after the completion of the vaccinations, many patients remain with insufficient seroconversion results. Iacono et al. compared the seroconversion in old patients, presenting a significant difference of 40% in hematological cancers patients vs 96.75% conversion rate in solid cancers [38].

Discrepancies between seroconversion rates of various hematological malignancies were found. In contrast to acute leukemia; MDS, CML, BCR-ABL negative myeloproliferative neoplasm (MPN), and Hodgkin lymphoma patients showed a preserved serologic capacity [33]. CLL and multiple myeloma patients were found to have especially low seroconversion rates. Tzarfati et al. have found MM patients to acquire seroconversion levels of 56% and 76%, after the first and second doses, respectively [33]. A study done by Maneikis et al had added, that the treatment and disease-related reduction of immunoglobulins are difficult to separate because of the wide variety of therapies used in different stages of treatment [10]. The overall result complies with the findings of Tzarfati et al., as they also showed blunted antibody response [33].

Ongoing anti-cancer treatment is an important factor influencing seroconversion and the development of a humoral response. In a study about the effects of vaccination on MM patients Bird et al. have stated therapy of any type is detrimental to antibody development [39]. Ongoing treatment in other types of malignancy with other anti-cancer therapeutics had shown similar effects. In a study by Herishanu et al., the seropositivity in treatment-naive patients was 55.2% compared to 16% in treated patients [8]. Tzarfati et al. had also researched the effects of different treatment modalities [33]. Most of the treatments appeared to have a negative influence on the serological tests. Of note, patients treated with immunomodulatory drugs (IMIDs), proteasome inhibitors (PIs), BCR-ABL tyrosine-kinase inhibitors (TKIs), and non-anti-CD20 monoclonal antibody (MoAb) had higher positive anti-COVID-19 serological test percentages. Of note, the combination of several of these treatments, PI/IMID/MoAb combination had resulted in the reduction of seropositivity [33].

Other anti-cancer treatments were found to have worse outcomes, as patients treated BTKI, BCL-2 blocker (Venetoclax), Janus kinase 2 (JAK2) inhibitor (Ruxolitinib) and anti-CD-20 MoAb had constantly presented with poorer anti-COVID-19 serological results [8, 10, 33].

Tzarfati et al. had found that treatment with Ruxolitinib had especially detrimental effects on the development of protective antibodies [33]. However, they also mention the possible beneficiary effects of Ruxolitinib, although this result was not being observed in a randomized controlled trial, some patients experienced a clinical improvement and a reduction in hyperinflammatory states. Maneikis et al had found results that increase the probability of a therapeutic effect of Ruxolitinib, as that they found that myelofibrosis patients infected with SARS-COV-2 that had discontinued the treatment showed increased mortality [10, 33]. These preliminary observations prompt further research on the possibilities that Ruxolitinib might have.

Maneikis and Tran had also noted Hydroxycarbomide as detrimental to seropositivity, Maneikis, however, added that the age of the receiving patients could be a confounding factor, as children that are were treated with Hydroxycarbomide against sickle-cell disease didn't differ from children that were not treated with it in their response to vaccines against pneumococcus [9, 10].

Daratumumab, an anti-CD38 MM treatment was also found to evoke immunosuppression, Pimpinelli et al. found a reduced response in a patient treated with Daratumumab to COVID-19 vaccines (50%) compared to the response in the Daratumumab-naive patients (93%) [40]. Van Oekelen et al. have further confirmed these results and found poor seroconversion results after 2 doses of Pfizer BioNTech (BNT162b2/mRNA-1273) vaccines [41]. An important observation in the work of Tran et al., is that these results differ from the response of the patients being treated with Daratumumab to pneumococcus and influenza and that further investigation about the differences in the immune responses to mRNA vaccines vs traditional types of vaccines [9].

It is accepted that humoral protection is a crucial component in the protection against COVID-19 and that the poor seroconversion rates observed in hematological malignancies patients are alarming. However, it is plausible that seronegative patients still may benefit from the vaccine by the workings of the cellular immune response. Trials have shown the development of specific CD4+ and CD8+ T-cell immune response [33]. The extent of the protective value of the vaccine is especially important in the face of the findings of Maneikis et al, which reported several breakthrough infections in hematological malignancies patients, 3 of which were fatal [10]. It is of note that one of the patients in their study was with reasonable antibody response. In contrast to these findings, in a study conducted by Iacono et al., no vaccinated cancer patients had been infected with COVID-19 [38].

Herishanu et al. have found a few characteristics which were associated with a better response to the vaccination, and a mounting of higher antibody counts [8]. Patients that were younger than 65, female, those with favourable disease-related factors and early disease stage, and a lack of active treatment. Maneikis et al found that patients that had finished treatment with systemic chemotherapy, HSCT, and TKI 6 months or more before getting vaccinated had plausible seroconversion rates [10]. In contrast to these treatment modalities, treatment with anti-CD20 antibodies within 12 months before the vaccination resulted in a poor immune response [8, 10].

As for now, the benefit of the vaccine in immunocompromised patients is not clear. Although both the American Association of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) have endorsed the vaccination of cancer patients, further studies are needed in order to understand the role of the involvement of the cellular response to the vaccine, the real protective value of seropositivity in patients with hematological malignancies, and the overall protective role the vaccines might have in hematological malignancy patients and in immunocompromised patients in general [38].

Conclusion

Since the outbreak of the COVID-19 pandemic, many studies investigated the effect of hematooncological diseases on the outcomes of COVID disease, tried differentiating between sub-types and find the most hazardous one. All studies confirm that patients with hematooncological malignancy are more at risk than general public. Treatment of said patients with chemotherapy or HSCT are more dangerous than ever with added risk of COVID infection, but it shouldn't intervene with lifesaving therapies.

Vaccines against COVID-19 are currently the most accepted and efficacious measure against the disease. The benefit of the vaccine in immunocompromised patients is not clear because many studies have found that seroconversion rates in hematooncological patients were significantly low, though it depends on type of malignancy and the type of treatment patient received. Further studies are needed in terms of patient treatment, infection control or vaccination of said group.

Straipsnis recenzuotas
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