Review Article

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Immune Response to COVID-19 Vaccination in Hematologic Malignancies: A Mini-Review

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The outbreak of the COVID-19 infection has led to the rapidity of vaccine usage in recent years. Emerging data indicate that the efficacy of vaccination against COVID-19 was about 95% in the general population, though its impact is impaired in patients with hematologic malignancies. As such, we decided to research the publications in which the authors reported the impacts of COVID-19 vaccination in patients suffering from hematologic malignancies. We concluded that patients with hematologic malignancies have lower responses, antibody titers as well as an impaired humoral response following vaccination, notably in patients with chronic lymphocytic leukemia (CLL) and lymphoma. Furthermore, it seems that the status of treatment can significantly affect the responses to the COVID-19 vaccination.

Key Words: *COVID-19; Vaccination; Lymphoma; Neoplasms; Leukemia*

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has resulted in a meaningful rise in the death rate throughout the world.[1] The people infected with COVID-19 while at the same time suffering from other diseases such as cancer, especially hematologic malignancies (e.g., B-cell non-Hodgkin lymphoma [B-NHL]) have an increased risk for worse sequels including higher morbidity and subsequent hospitalization ($>80\%$) as well as higher mortality rate up to 30-40% (at least 2.5-fold compared to healthy subjects).[2,3]

Owing to the severity and importance of COVID-19 as well as the occurrence of new mutations of SARS-CoV-2, and to prevent its further prevalence, numerous vaccines associated with COVID-19 including the mRNA-based (Pfizer-BioNTech and Moderna), viral vector (e.g., AstraZeneca, Johnson and Johnson, and Sputnik), and inactivated pathogen (e.g., Sinopharm, and Sinovac) vaccines were urgently developed and distributed. The major goals of COVID-19 vaccination are to provoke protective and neutralizing SARS-CoV-2 antibody (Ab) production while being a safe and well-tolerated vaccine.[4,5] For example, the efficacy of the mRNA vaccine named Pfizer-BioNTech BNT162b2 in prophylaxis against SARS-CoV-2 was 95% in the phase II/III clinical study.[6]

According to studies, the rate of seroconversion (a positive anti-COVID Ab titer) is generally 50-60% in patients with hematologic malignancies.[7,8] Similar results have been achieved by administering influenza, hepatitis B, and recombinant zoster vaccines in lymphoma patients.[9] The reason for this is that this immunodeficiency is attributable to either the disease pathology or current cancer treatment.[10,11] Limited data have been published regarding the influence of COVID-19 vaccination in patients with cancer undergoing anticancer therapy as a result of exclusion from clinical trials.[12] In accordance with the investigations, older age, recent treatment with anti-CD20 monoclonal Abs (mAbs), Bruton's tyrosine kinase inhibitor (BTKi), chemotherapy, stem cell transplantation (SCT), and higher lactate dehydrogenase, are related to insufficient or delayed humoral response to COVID-19 vaccines such as BNT162b2 in patients with hematologic malignancies.[7,13] For example, induced-B-cell depletion and hypogammaglobulinemia via rituximab (as an anti-CD20 mAb) decrease anti-spike (anti-S) Ab responses to the COVID-19 vaccines, albeit obinutuzumab (another anti-CD20 mAb) cannot stimulate any Ab production.[14] This

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might leave these patients vulnerable to infection with SARS-CoV-2. Additionally, there are limited data on the role of cellular immunity (T-cell response) to COVID-19 vaccines in patients with hematologic malignancies. Accordingly, a study reported that T-cell response reduced as compared to healthy subjects by measuring blood interferon-gamma (IFN-γ) release assays (IGRA).[15] Based on a systematic review and meta-analysis of 44 clinical studies, humoral responses to first and second SARS-CoV-2 vaccination in patients with hematologic malignancies were 37-51% and 62-66%, respectively. Additionally, a rate of 40-75% for the cellular response was determined after the second dose.[16] According to the study conducted in the United Kingdom (UK), the rate of anti-S IgG titer was 18% for hematologic malignancies vs. 38% for solid tumors after a single dose of the BNT162b2 vaccine.[17] On the other hand, in another similar study in the UK, the humoral response was increased from 34% to 75% after a single and second dose of BNT162b2/ChAdOx1 (AstraZeneca) vaccine, respectively, in patients with chronic lymphocytic leukemia (CLL).[18]

The present mini-review aims to research the publications in which the authors reported the responses to COVID-19 vaccination in patients suffering from hematologic malignancies.

LEUKEMIA AND MYELODYSPLASTIC SYNDROME (MDS)

Acute myeloid leukemia (AML) results from uncontrolled clonal proliferation of myeloid precursor cells and is regarded as a heterogeneous disease with high prevalence in the older population.[19] In a related study, responses to the COVID-19 vaccinations were reported to be lower in AML patients who were on treatment although the Ab titers were improved in patients after completion of therapy.[20]

As an adverse event, Varicella-Zoster virus (VZV) reactivation was seen in two patients with acute lymphoblastic leukemia (ALL) cancer in lymphoid precursor cells, following vaccination with BNT162b2.[21] Allergic reactions might appear in some ALL patients treated with polyethylene glycol-asparaginase (PEG-ASNase) in response to PEG, as an allergen. Thus, since PEG is applied as a stabilizer in mRNA vaccines such as BNT162b2, it is important to make vaccination safe by following up with patients 30 minutes after vaccination as performed by Mark et al.[22]

CLL is defined as an immune dysregulation that is connected with hypogammaglobulinemia, abnormal cellular immunity, and immunosuppression-related treatments. It has been reported that immune responses might be weakened in CLL following vaccination, particularly in patients treated with BTKi.[23,24] In this regard, it was found that the BNT162b2 vaccine seems to be preferred in CLL patients, though treatments can reduce the effectiveness of vaccination.[25] In another study, it was concluded that a third boosting vaccine dosage is needed in patients with CLL due to the impaired serological response to the BNT162b2 vaccine.[26] In this respect, it was also stated that serological response to BNT162b2 vaccine is noticeably impaired in patients suffering from hematologic malignancies. Thus, these patients might be at high risk for intensive COVID-19 complications and death.[9] Furthermore, the humoral response is low after COVID-19 vaccination in patients with CLL/lymphomas, so timely vaccination is important for controlling the infection, especially during a treatment-free interval. In addition, Ab response to the widely used mRNA COVID-19 vaccines is weakened in persons who suffer from B-cell malignancies, both treatment-naïve and under treatment, as compared with a reference cohort.[27] In connection with the BNT162b2 vaccine, Benda et al.[28] stated that serological non-response could remarkably increase in patients with hematologic malignancies notably in lymphoma or CLL. For instance, systemic treatment caused a 14.2-fold elevation in the occurrence of non-response. In this study, although vaccination with BNT162b2 was demonstrated to be safe and well-tolerated in hemato-oncological patients, an inadequate Ab response was considerably linked to low levels of total immunoglobulin G (IgG), and low lymphocyte and natural killer (NK) cell count.

In a study by Mori et al.[20], it was reported that Ab titer is considerably lower in patients with myelodysplastic syndrome (MDS) during certain treatments followed by COVID-19 vaccination (BNT162b2 or Moderna mRNA-1273) as compared to healthy controls or patients with AML. MDS is generally recognized as a myeloid malignancy that usually occurs at an older age.[29] In a report by Candoni et al.[30], AML or MDS-contracted patients who were under treatment showed favorable seroconversion following the first 2 doses of the COVID-19 vaccine. More importantly, a large population of the selected patients experienced an alleviated seroconversion following the second dose of vaccination. However, it was observed that the third dose of vaccination can remarkably increase the Ab titers in these patients.

All in all, investigations showed that patients who suffer from lymphoid malignancies, especially those receiving anti-CD20 mAbs, have a minimal humoral response to mRNA COVID-19 vaccines in comparison to normal populations.[31]

LYMPHOMA AND MULTIPLE MYELOMA

Immune response to COVID vaccines has also been evaluated in lymphoma as cancer of the lymphatic system that develops from lymphocytes.[32] In a study by Della Pia et al.[3], humoral response (anti-S protein Abs) was assessed upon second COVID vaccination with COVID mRNA, and adenovirus vaccines in 137 lymphoma patients (e.g., CLL and small lymphocytic lymphoma (CLL/SLL), Burkitt's, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma and T-cell lymphomas (HL/TCL). The majority of vac-

cine-receiving patients (67.2%) generated anti-S Abs. However, anti-S Abs were merely detected in 14 of 27 patients (52%) who were treated with anti-CD20 mAb within 12 months before vaccination. This rate was measured at 72.2% in patients (26 of 36) who were given anti-CD20 mAb >12 months prior to vaccination. Furthermore, patients with HL/TCL showed a significant Ab response in comparison to other lymphomas. In this study, the Ab response to the vaccine in CLL/SLL patients was regarded as seronegative. Similar results with seropositivity of 51% in total, were obtained in another study by Gurion et al.[13] evaluating humoral response after two doses of BNT162b2 vaccine in 162 lymphoma patients. In this non-interventional cross-sectional study, the range of post-vaccination Ab response in patients receiving anti-CD20 treatment in the period of <45 days and >12 months (parallel to non-anti-CD20 treated patients) varied between 3% and 80%, respectively. Two cutaneous T-cell lymphoma (CTCL) cases with worsening conditions such as nodules and erythematous papules were reported after being vaccinated with a viral vector (adenovirus)-based COVID-19 vaccine (AstraZeneca), while these patients were in clinical remission. It could be probably due to overproduction and exhaustion of adenovirus-induced CD30-expressing $CD4^+/CD8^+$ T cells. $CD30^{hi}$ as a biomarker was observed in histologic samples, however, this issue might be irrelevant to the vaccine.[33] Besides, Brumfiel et al.[34] declared that this relapse also occurred after receiving the mRNA vaccine (Pfizer-BioNTech). Ariamanesh et al.[14] reported a seroconversion rate of 61.9% in patients with hematologic malignancies vs. 86.9% in other cancer patients through the Sinopharm inactivated vaccine (BBIBP-CorV). These results were in line with findings of a previous study by Agha et al.[35] that anti-S IgG Abs were detected in 23.1% of B-CLL patients vs. 61.1% in patients with other hematological malignancies including lymphomas upon administering two doses of COVID-19 mRNA vaccines. Additionally, a poor humoral response to two doses of BNT162b2 vaccines was obtained in patients with aggressive or indolent B-NHL receiving rituximab/obinutuzumab (R/Obi) compared to healthy controls.[11] Although in a recent study by Herishanu et al.[7], a few numbers of CLL patients (8/50) treated with a BTKi developed Abs upon BN2T162b2 vaccination with a seropositivity rate of 16% as opposed to 13.6% in the venetoclax ± anti-CD20 antibody-treated patients (3/22), high-titer IgGs were produced in CLL and other NHL patients with active BTKi monotherapy following COVID mRNA vaccine in another related work.[36] More importantly, in another study presented by Herishanu et al.[37], a quarter of patients (41/172) with CLL/SLL approximately responded to the third dose of vaccination (23.8%). However, the rate of Ab responses was lower in patients who received anti-CD20 therapy.

Vaccine-associated hypermetabolic lymphadenopathy (VAHL) concerning the proliferation of the B cell germinal-center (GC) is a common side effect following mRNA-based COVID-19 vaccines.[38] A study conducted by Cohen et al.[39] revealed that VAHL is related to a significant humoral response in lymphoma patients on [18F]FDG PET-CT after being vaccinated with two doses of BNT162b2 which was lower than in patients treated with anti-CD20 mAb before vaccination.

There are limited studies on the serological response to COVID-19 vaccination in multiple myeloma (MM) patients. MM is a cancer that involves plasma cells as antibody-producing cells. However, a rate of 76% humoral response was gained in patients with active MM (vs. 98% in the control group and 100% in smoldering myeloma patients) following the second BNT162b2 vaccine in Avivi and colleagues' work.[40] A similar result (70%) was acquired after the first SARS-CoV-2 vaccination in myeloma patients in another study.[41] Of note, according to a study, the lowest Ab titers following two doses of the BNT162b2 vaccines, pertained to CLL $<$ NHL $<$ MM, in comparison to chronic myeloid leukemia (CML) $>$ HL $>$ BCR-ABL-negative myeloproliferative neoplasms (MPN) with the highest titers, respectively.[9] In a systematic review containing 49 studies, the Ab response was measured at 64%, 96%, and 98% for hemato-oncological malignancies, solid tumors, and healthy subjects, respectively, after COVID vaccination. Amongst them, this rate was 50% for CLL, 58% for aggressive and 61% for indolent NHL, 76% for MM, 83% for MPN, and 91% for HL.[42]

Further, in >12 months from allogeneic (allo-HSCT) and autologous (ASCT) hematopoietic stem cell transplant, Ab response rate after full mRNA-based SARS-CoV-2 vaccination was 78% and 85%, respectively, in recipients with a history of hematologic malignancies.[43] Response to the COVID-19 vaccine in patients receiving chimeric antigen receptor T-cell (CAR-T) therapy has been investigated in a small number of studies. CAR-T therapy such as anti-CD19 CAR can cause B cell depletion and subsequent T cell reduction. The Ab response rate was determined to be 31% in these studies.[4,44] Table 1 summarizes the Ab response rate following SARS-CoV-2 vaccination applied for hematologic malignancies in certain studies.

CONCLUSION

Taken together, a <12 months' interval between SARS-CoV-2 vaccination and common therapy for hematologic malignancies (e.g., anti-CD20 mAbs, BTK inhibitors, and chemotherapy), low lymphocyte count, and active malignant disease, especially CLL, are considered predictors of a weak humoral response in patients with hematologic malignancies. These factors may put patients at risk of moderate to severe COVID-19 disease. Despite the safety of COVID-19 vaccines, safety and efficacy data are insufficient for hematologic malignancies as a consequence of the exclusion of patients with this type of disease from clinical trials. It could be recommended to organize an appropriate schedule for vaccination in these patients such as vaccine administration at least 6 or 9 months from the last cancer therapy, to delay therapy until completing vac-

Table 1. Antibody response rate following SARS-CoV-2 vaccination applied for hematologic malignancies in certain studies

Type of hematologic malignancy	Number of patients	Vaccine name	Type of vaccine	Response rate (%)	Dose	Ref.
Hematologic malignancies						
CLL NHL (aggressive and indolent) MM CML MPN MDS HL	315	BNT162b2	mRNA	• 74.6 (overall) • 47.0 (CLL) • 71.0&60.0 (aggressive and indolent NHL, respectively) • 76.0 (MM) • 91.0 (CML) • 84.0 (MPN) • 94.0 (MDS) • 94.0 (HL)	2	9
Hematologic malignancies						
MM CLL Lymphoma Waldenstrm macroglobulinaemia AML/MDS/MPN	259: including 123 hematological patients	BNT162b2	mRNA	• 71.4	2	28
Hematologic malignancies						
B-CLL Lymphomas MM Other myeloid malignancies	67	BNT162b2& mRNA-1273	mRNA	• 23.1 (CLL) • 52.4 (lymphomas) • 65.5 (MM) • 75.0 (other myeloid malignancies)	2	35
Hematologic malignancies	364: including 24 hematological patients	Sinopharm (BBIBP -CorV)	Inactivated	• 61.9	2	14
AML, MDS	69: (AML=46 and MDS=23)	BNT162b2& mRNA1273	mRNA	• 94.7 (AML) • 100 (MDS)	2	20
AML, MDS	46: (AML=36 and MDS=10)	Pfizer-BioNTech	mRNA	• 91.0 (30/33) following the second dose of vaccine • 96.0 (23/24) following the third dose of vaccine	2&3	30
CLL	167	BNT162b2	mRNA	• 39.5 (overall) • 79.2 (clinical remission after treatment) • 55.2 (treatment-naïve) • 16.0 and 13.6 (BTKi or venetoclax ±anti-CD20 mAb-treated)	2	7
CLL	70	BNT162b2	mRNA	• 58.5 (overall) • 87.0 (treatment-naïve) • 87.7 (sustained clinical remission) • 10.0 (anti-CD20-treated) • 52.0 (pathway inhibitor-treated)	2	26
CLL/SLL (failed standard 2-dose vaccination)	172	BNT162b2	mRNA	• 23.8	3	37
CLL or SLL	299	Pfizer-BioNTech BNT162b2 (n=154)& AstraZeneca/ Oxford ChAdOx1 (n=145)	mRNA & Viral vector (adeno-virus)	• from 34.0% to 75.0% following the first and second dose of vaccines, respectively	2	18

TABLE 1. Continued

Type of hematologic malignancy	Number of patients	Vaccine name	Type of vaccine	Response rate (%)	Dose	Ref.
Lymphoma						
Indolent lymphomas CLL/SLL Burkitt's DLBCL PMBCL MCL HL/TCL	137	Pfzer-BioNTech, Moderna, &Johnson &Johnson (1 person)	mRNA & Viral vector (adeno-virus)	• 67.2 (overall) • 52.0 (anti-CD20 mAb treatment within 12 months) • 72.2 (anti-CD20 mAb treatment >12 months) • 43.0 (CLL) • 88.0 (HL/TCL)	2	3
Lymphoma NHL (aggressive and indolent) HL	162	BNT162b2	mRNA	• 51.0 (overall) • From 3.0% (vaccinated within 45 days after anti-CD20 mAb treatment) to 80.0% (vaccinated >1 year after mAb treatment)	2	13
B-NHL (aggressive or indolent)	149	BNT162b2	mRNA	• 49.0	2	11
MM	93	Pfizer (n=48)& AstraZenec a (n=45)	mRNA& Viral vector	• 70.0	1	41
MM	171	BNT162b2	mRNA	• 76.0 (active MM) • 100 (SMM)	2	40

CLL: chronic lymphocytic leukemia, SLL: small lymphocytic leukemia, DLBCL: diffuse large B-cell lymphoma, PMBCL: primary mediastinal large B-cell lymphoma, MCL: mantle cell lymphoma, HL: hodgkin lymphoma, TCL: T-cell lymphomas, NHL: non-hodgkin lymphoma, MM: multiple myeloma, CML: chronic myeloid leukemia, MPN: myeloproliferative neoplasms, MDS: myelodysplastic syndrome, SMM: smoldering multiple myeloma, AML: acute myeloid leukemia, BTKi: Bruton's tyrosine kinase inhibitor.

cination programs, to be referred for revaccination, or to evaluate antibody titers after vaccination. However, there is a requirement to vaccinate these patients due to high morbidity and mortality. Certainly, further studies are necessary to support the role of cellular immune responses to the vaccine.

CONFLICT OF INTEREST STATEMENT

None declared.

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