Vaccination for SARS-CoV-2 in Hematological Patients

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Keywords

Vaccinations · Severe acute respiratory syndrome coronavirus 2 · Hematological malignancies · Coronavirus disease 2019

Abstract

Patients with specific hematological malignancies (HM) are at increased risk for severe disease and death from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In healthy subjects, vaccination against SARS-CoV-2 has been demonstrated to be highly effective in disease prevention; however, immunocompromised patients were largely excluded from vaccine randomized controlled trials. In this review, we overview available non-randomized studies addressing effectiveness and safety of several coronavirus disease 2019 (COVID-19) vaccines in patients with HM. Overall, COVID-19 vaccines are safe in patients with HM, with adverse events similar to those in the general population. Though serology testing is not recommended as a test to evaluate vaccine effectiveness, a correlation between higher antibody levels and protection against infection has been reported. Studies evaluating humoral response to COVID-19 vaccine in HM patients demonstrate low immunogenicity, mainly in patients with lymphoproliferative disorders, as well as with certain drugs, including mainly anti-CD20 antibodies, Bruton tyrosine kinase inhibitors, and also ruxolitinib

and venetoclax. Seropositivity rates of patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia following mRNA vaccination reach 40%–50%. T-cell responses to vaccination are also impaired among these patients. Better humoral response rates are reported in multiple myeloma patients and hematopoietic stem-cell transplant, reaching ~75%–80%, but not in patients following chimeric antigen receptor T-cell therapy. Patients with chronic myeloid leukemia and myeloproliferative diseases have high response rate to vaccination. Third mRNA vaccine dose is currently recommended to all HM patients. Alternative approaches for vaccination and prevention in patients unable to mount an immune response following full vaccination are provided in the review.

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Introduction

Patients with hematological malignancies (HM) have an increased risk for coronavirus disease 2019 (COVID-19) infection compared to the general population, with odds ratios of ~12 for leukemia patients and ~8 for non-Hodgkin lymphoma (NHL) patients [1]. Moreover, in these patients COVID-19 disease severity is increased, leading to hospitalizations and mortality. In addition, severe acute respiratory syndrome coronavirus 2 (SARS-

CoV-2) infection may also cause delays in chemotherapy, contributing to the poor outcome [1, 2]. In healthy subjects, SARS-CoV-2 mRNA vaccines have demonstrated robust immune response and clinical efficacy in clinical trials, as well as considerable effectiveness in real life in the general population [3]. However, patients with HM were largely excluded from clinical vaccine trials or were poorly represented, and demonstrated relatively poor immunogenicity to these vaccines [2, 4]. Immunogenicity varies depending on type of malignancy and therapy. Little is known about clinical effectiveness in HM patients. In this review, we aim to evaluate the available literature on immunogenicity and clinical effectiveness of different vaccines for various HMs, their safety, and the available strategies to improve immunogenicity in this population.

Approved Vaccines for HM Individuals

Vaccines based on live attenuated virus or replicating viral vectors (as vesicular stomatitis virus) are contraindicated for immunocompromised patients. None of these are currently approved for use [5, 6].

Immune Response to Vaccines in HM

Patients with HM have diminished immune response to vaccines in general [7] (Table 1). Reduced immunogenicity to SARS-CoV-2 vaccines have been suggested in HM as well, with several factors associated with this reduced response. In general, active immunosuppressive treatment is associated with lower anti-SARS-CoV-2 neutralizing antibody levels when tested compared to untreated patients [4]. Improved antibody response is demonstrated while vaccinated at least 6 months after the end of chemotherapy or hematopoietic stem-cell transplantation (HSCT), excluding anti-CD 20, for which antibody response improves significantly only at least 12 months after the end of therapy [4]. Other factors associated with blunted humoral response in HM patients in general include age [4, 8], male gender [9], CD19 + B cells levels ($<120/\mu\text{L}$) [9], and type of treatment, with Bruton tyrosine kinase inhibitors, ruxolitinib, venetoclax, and anti-CD20 antibody therapies associated with most diminished response. In addition, waning antibody titers have been demonstrated in HM patients 4–6 months after vaccination, though most patients maintained detectable levels [10]. In regards to type of mRNA vaccine, several studies in immunocompromised patients demonstrated

better antibody response with higher titers among patients receiving mRNA-1273 versus BNT162b2 vaccine [11–13].

Most studies evaluated humoral immune response; however, T-cell response has also a role in protecting against COVID-19 and has been demonstrated to confer improved survival in HM patients [14]. Few data are available regarding T-cell response to COVID-19 vaccine in HM patients. Malard et al. [9] demonstrated T-cell response in 53% (36/68) of mixed HM population in response to two BNT162b2 doses, and also found that this was achieved among 17 patients with no humoral response, suggesting some protective effect in these patients. Current treatment was associated with the absence of T-cell response in this study. Mairhofer et al. [15] reported either a CD4+ or a CD8+ T-cell response in 76% (34/35) patients with HM, and a 58% (26/45) antibody response in the same group. Notably, none of the patients treated with anti-CD20 achieved a “triple” response, of both antibodies, CD4+ and CD8+.

The response after one dose of mRNA vaccine is poor, leaving most patients practically unprotected. Hence, for HM patients, it is not recommended to prolong the interval between vaccine doses, rather consider adding further booster doses in order to increase immunogenicity [16, 17]. In this review, we will not consider vaccine efficacy after one dose, rather use the term “vaccination” as referring to at least two mRNA vaccine doses.

In general, it is not recommended to perform serological tests in order to determine whether the patient is protected [18]. Nevertheless, antibody levels are often used both in research and in clinical practice, and a correlation between higher antibody levels and neutralization of virus has been shown, though not in all studies [19, 20]. We cannot provide any recommendation regarding use of serology to guide vaccination schedule in this review, and local guidelines on vaccination schedule should be followed.

Safety of COVID-19 Vaccines in HM Patients

As of September 2021, 392 million doses of BNT162b2 and over 54 million doses of mRNA-1273 were administered in European countries [21]. Safety of mRNA vaccines has been demonstrated to be similar in patients with HM compared to healthy individuals [16]. The most common adverse events among HM patients are sore arm and muscle aches [12]. Regarding the Oxford-AstraZeneca and Janssen/Johnson & Johnson vaccines, safety has

Table 1. Data on immune response to vaccine among HM patients

Study ID	Malignancy type	Design, participants, <i>n</i>	Vaccine type, dose/time of follow-up	Seropositive, %/titer	Neutralizing antibodies	T-cell response	Breakthrough infection after full vaccination
Mixed HM population							
Manekis et al. [4]	Mixed	Prospective comparative, 885p entire cohort, 315p matched	BNT162b, 2/7–21 d	¹ HM: med 6961 (IQR 1,292–20,672), control: 21,395 (14,831–33,553)	NS	NS	9/885 (6 severe, 3 deaths)
Malard et al. [9]	Mixed	Prospective, comparative, 195p HM, 30p controls	BNT162b, 2/14 d	¹ Antibody levels significantly lower for HM versus controls	Positive ichroma COVID-19 nAB (Boditech): HM 91/196 (47%), controls 87%	Positive ELISpot assay – 363/68 (53%)	NS
Agha et al. [8]	Mixed	Prospective, 67p	BNT162b2 or mRNA-1273, 2/med 23 d	² Seroconversion: 31/67 (46)	NS	NS	NS
Greenberg et al. [11]	Mixed	Prospective, 1445p	BNT162b2 or mRNA-1273, 2/14 d	³ Seroconversion overall: 1,088/1,445 (75); B-cell malignancies – 44%–79% seropositivity, AML 91, ALL 88, CML 97	NS	NS	3/160 (all non-detectable antibodies), one death
Olilia et al. [59]	Mixed	Retrospective, 160p	BNT162b or mRNA-1273 2 doses, Johnson & Johnson (J&J) 1 dose/med 8 wk from 1st dose	¹ Seroconversion overall: 63/160 (39); B-cell depleting therapy ² : 30/105 (29); active HM 22/88 (25); remission 31/63 (49); watchful waiting 10/15 (67)	NS	NS	NS
Re et al. [60]	Mixed	Retrospective, 102p	BNT162b or mRNA-1273, 2/6–8 wk from 1st vaccine	Seroconversion overall: 63/102 (62); anti-CD20 last 12 months 1/17 (6)	NS	NS	NS
Lymphoproliferative – lymphoma, CLL							
Lim et al. [35]	NHL, HD	Prospective comparative, 119p	BNT162b or ChAdOx1, 2/2–4 wk	⁴ On treatment: med 2.5 (95 CI 1.1–5.8), not on treatment: 141.8 (75.6–266) control BNT162b2: 2,339 (1,923–2,844), ChAdOx1: 199 (140–282)	NS	NS	NS
Perry et al. [26]	NHL, HD	Prospective, comparative, 149p	BNT162b, 2/2–3 wk	³ Seroconversion – HM: 73/149 (49), control: 64/65 (98.5) HM mean 440±1,124, control mean: 1,332±1,111	NS	NS	1/149
Gurion et al. [25]	NHL, HD	Prospective, 162p	BNT162b, 2/4±2 wk	¹ Seroconversion: 83/162 (51)	NS	NS	NS
Ghione et al. [61]	NHL, HD	Prospective, comparative, 86p	BNT162b2 or mRNA-1273, 2/4–8 wk	⁵ Seroconversion: <9 months from anti-CD20 6/52 (11), >9 month 22/25 (88), other treatments: 8/9 (89), controls: <65 yr 154/154 (100), >65 yr 43/47 (91.5%)	NS	NS	NS
Jurgens et al. [62]	NHL	Prospective, comparative, 67p	BNT162b2 or mRNA-1273, 2/11–70 d	¹ Seroconversion: CLL 12/21 (57 overall, 40 under therapy), NHL 25/42 (60 overall, 21 under therapy), HD 4/4 (100); zero response 6 months rituximab	NS	NS	NS
Herishanu et al. [28]	CLL	Prospective, comparative, 167p	BNT162b, 2/2–3 wk	³ Seroconversion: CLL 66/167 (39.5), Clinical remission 79, treatment naïve 55, under treatment 16. BTK-i 16, venetoclax 13	NS	NS	0/167

Table 1 (continued)

Study ID	Malignancy type	Design, participants, <i>n</i>	Vaccine type, dose/time of follow-up	Seropositive, %/titer	Neutralizing antibodies	T-cell response	Breakthrough infection after full vaccination
Del Poeta et al. [30]	CLL	Prospective, 46p	BNT162b, 2/26 d	⁶ Seroconversion: 21/46 (46)	NS	NS	NS
Benjaminini et al. [29]	CLL	Prospective, 373p	BNT162b, 2/2–3 wk	¹ Seroconversion: 160/373 (43); treatment naïve 61; anti-CD20 previous 12 months–5%, over 12 months–35%	Consistent with IgG response	NS	2/373
Roeker et al. [63]	CLL	Prospective, 44p	BNT162b2 or mRNA-1273, 2/21 d	⁷ Seroconversion: 23/44 (52)	NS	NS	NS
HSCt and CART*							
Le Bourgeois et al. [43]	Allogeneic HSCt	Prospective, 117p	BNT162b, 2/4 wk	³ Seroconversion: 97/117 (83). Less than 12 month from transplant 52, haploidentical 69, ongoing treatment 63, lymphocyte <1,000 cells/μL 64	NS	NS	0/117
Ram et al. [44]**	HSCt, CART	Prospective, 57p allo-HSCt, 14p CART	BNT162b, 2/7–14 d	³ Seroconversion: HSCt 47/57 (75), median titer 178 (range 0.4–250); CART 5/14 (36%), median titer 0.4 (range, 0.4–250)	NS	Positive ELISpot assay – CART 6/12 (50%), allo HSCt 7/37 (19%)	NS
Dhakal et al. [45]	HSCt, CART	Prospective, 130p: 45p auto HSCt, 71p allo HSCt, 14p CART	BNT162b or mRNA-1273 2 doses, J&J 1 dose/±2 wk	⁸ Seroconversion: overall 79/130 (60)**; 27/45 (60) auto, 49/71 allo (69), 3/14 CART (21)	NS	NS	NS
Gastinne et al. [47]	CART	Prospective, comparative, 23p	BNT162b, 2/21–99 d	³ Seroconversion: CART 6/20 (30), controls 25/25 (100)	NS	NS	0/23
Redjoul et al. [19]	HSCt	Prospective, 88p allo HSCt	BNT162b, 2/28 d	¹ Seroconversion: 69/88 (78)	Surrogate titre >4160 AU/mL: 52/88 (59%)	NS	0/88
Yeshurun et al. [46]	HSCt	Prospective, 106p, allo HSCt	BNT162b, 2/4–6 wk	¹ Seroconversion: 91/106 (86)	NS	NS	NS
MM							
Stampfer et al. [36]	MM	Prospective, 96 patients with active MM and 7 with smoldering disease and 31 healthy subjects	mRNA-1273 and BNT162b2/2–3 wk	Seroconversion: 2/3 of patients	45% (<i>n</i> = 43) of MM patients had a likely clinically significant response > 250 IU/mL with an additional 22% (<i>n</i> = 21) having a partial response	NS	One patient vaccinated with mRNA-1273 was diagnosed with severe COVID-19 10 wk following his second vaccination
Van Oekelen et al. [37]	MM	Prospective, 320 patients and 67 healthy subjects	mRNA-1273 and BNT162b2/10 d	Seroconversion: 68 (219/320)	NS	NS	7 cases after 1 dose and 3 cases after 2 doses
MPD							
Harrington et al. [41]	MPD	Prospective, 21 patients with MPD	Immune response after first dose of BNT162b2 mRNA	Seroconversion: 76.1 (16)	85.7% (18)	Memory T-cell response in 80% (16) of patients, with a CD4+ T-cell response in 75% (15) and a CD8+ T-cell response in 35% (7)	NS

Table 1 (continued)

Study ID	Malignancy type	Design, participants, n	Vaccine type, dose/time of follow-up	Seropositive, %/titer	Neutralizing antibodies	T-cell response	Breakthrough infection after full vaccination
Pimpinelli et al. [42]	MPD	Prospective, 50 patients (20 chronic myeloid leukemias and 30 myeloproliferative neoplasms) + 42 MM	5 wk response after BNT162b2 mRNA	Seroconversion: 88 MPD patients; 78.6 MM patients	NS	NS	NS
CML							
Harrington et al. [41]	CML	Prospective, 16 patients with CML	Humoral and cellular response after 21 days from the first injection of BNT162b2 mRNA	Seroconversion: (87.5) 14/16 CML patients	(100%) 14/14 of CML patients that underwent seroconversion	T-cell response in 14/15 (93.3%) patients; polyfunctional responses in 12/15 (80%) patients	NS

NS, not specified; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; HM, hematological malignancies; CLL, chronic lymphocytic leukemia; allo HCT, allogeneic HCT; CART, chimeric antigen T-cell receptor; MPD, myeloproliferative disease; CML, chronic myeloid leukemia. ¹ Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle assay, measured as AU/mL, cutoff 50 AU/mL. ² Beckman Coulter SARS-CoV-2 platform, measured as extinction coefficient, cutoff ≥ 1.00 . ³ Elecsys Anti-SARS-CoV-2 assay, measured as U/mL, cutoff 0.80 U/mL. ⁴ Meso Scale Discovery, Rockville, MD, USA, electrochemiluminescent assay, measured as BAU/mL, cutoff for anti-RBD IgG 0.73 BAU/mL; for anti-SIgG concentrations 0.55 BAU/mL. ⁵ KSL chemiluminescence immunoassays (CLIA), results expressed by critical value index (CVI), cutoff 1.0. ⁶ Maglumi 2019nCoV IgG chemoluminescence immunoassay, measured as AU/mL, cutoff 1.1 AU/mL. ⁷ Liaison SARS-CoV-2 S1/S2 IgG assay, measured as AU/mL, cutoff 15 AU/mL. ⁸ Enzyme immunoassay (EUROIMMUN), measured as AU/mL, cutoff 1.1 AU/mL. * In studies evaluating HCT patients, vaccines were administered at least 3 months after transplant, according to EBMT recommendations. For CAT-T, at 3 months, unless B-cell aplasia, in which vaccine is recommended at six months after treatment (COVID-19 vaccines, Version 6.0, May 27, 2021; at <https://www.ebmt.org/sites/default/files/2021-05/COVID%20vaccines%20version%206.0%20-%202021-05-28.pdf>). ** Exclusion criteria were grade 3 or 4 acute GVHD, treatment for acute or chronic GVHD with ≥ 0.5 mg/kg of prednisone, rituximab within the previous 6 months, mesenchymal cells within 1 month, hematologic relapse, maintenance therapy (excluding tyrosine kinase inhibitors), previous infection with SARS-CoV-2 or recent exposure to a SARS-CoV-2 infected person, or known allergy to vaccine components. *** Overall response with BNT162b2 vaccine (77p) was 56%; mRNA-1273 (47p) – 68%; Johnson & Johnson (6p) – 67%. ⁴ B-cell depleting therapy: rituximab (n = 85), daratumumab (n = 9), obinutuzumab (n = 7), or bispecific CD3/CD20 antibodies (n = 12).

become a concern due to reports on vaccine-induced immune thrombocytopenia and thrombosis (also termed “thrombosis with thrombocytopenia syndrome”) [22]. Due to this adverse event, some countries restrict these vaccines to the general population or based on age, though an overall total of 1,503 cases had been reported worldwide until July 31, 2021 [21].

Immunogenicity of COVID-19 Vaccines in Specific HM

As HM and their therapy are highly heterogeneous, so is the immune response to vaccines. In the following sections, we will review immune response and adverse events for several types of HM, and overview current recommendations for vaccination.

Lymphoproliferative Disorders – Chronic Lymphocytic Leukemia, Lymphoma, and Anti-CD20 Therapy

Patients with NHL and chronic lymphocytic leukemia (CLL) experience poor prognosis of COVID-19, with 30-day mortality reaching ~35% in unvaccinated patients [23, 24]. Seropositivity rates following 2 doses of BNT162b2 among lymphoma patients are reported at ~50% [25–27], and among CLL patients at ~40%–45% [27–30]. Several predictors of seronegativity are described in the literature. These include the type of lymphoma – aggressive NHL (63% seronegativity) versus indolent NHL (54%) versus Hodgkin disease, with low rates of seronegativity (10%) in the latter [25]. Active therapy (considered until at least 6 months since discontinuation) is also associated with decreased antibody response and titers [26], depending on type and timing of therapy. Seropositivity rates for patients treated with anti-CD20 in the last 12 months are in most studies 0%–10% [4, 26, 28, 29]. These rates reach 25%–35% after over 12 months [26, 29], with one study even showing 68% response [31]. Median time from anti-CD20 to seropositivity was demonstrated in one study to be 36 months in indolent NHL and 20 months in aggressive NHL [26]. Gurion et al. [25] reported zero seroconversion among 28 patients treated with obinutuzumab, compared to 38% with rituximab.

Other predictors of negative response included older age (>80 year [25], >60 [29]), low lymphocyte counts ($<0.9\text{--}1.2 \times 10^3/\mu\text{L}$) [25, 26], hypogammaglobulinemia (below 630 g/L) [25, 28], male gender [28], IgM <40 mg/

dL, and IgA<80 mg/dL [29]. Benjamini et al. [29] suggested a model to predict immune response to vaccine among CLL patients, including recent anti-CD20 treatment, age<70 year, treatment naïve status, and normal IGG, IGA, IGM, and hemoglobin levels.

Few data are available regarding response to vaccines other than mRNA based, neutralizing antibody or T-cell responses, and seropositivity under therapies other than anti-CD20. Gavriatopoulou et al. [32] demonstrated neutralizing antibody response $\geq 50\%$ (cutoff of clinically relevant inhibition) in 3% of 58 patients with NHL, Waldenstrom macroglobulinemia or CLL, compared to 24% response among controls, after one dose of either BNT162b2 or ChAdOx1 (AZD1222) vaccine. Terpos et al. [33] tested these values after BNT162b2 second dose, and found 44% among 132 patients with CLL/lymphoma, compared to 95% in 214 controls. Only 7 patients on active treatment developed adequate levels of neutralizing antibodies. Liebers et al. [31] tested T-cell response to 2 mRNA vaccine doses among anti-CD20 treated lymphoma patients and found 58% response, compared to 71% in controls. Response rates were higher among patients who seroconverted and were not associated with time elapsed since the last anti-CD20 dose. Other studies also demonstrated lower, but existing T-cell responses among seronegative lymphoma patients [34], suggesting a possible benefit of vaccination even in seronegative patients.

Lim et al. [35] demonstrated significantly reduced antibody titers for patients with various types of lymphoma compared to healthy controls, after 2 doses of either ChAdOx1 or BNT162b2. No significant difference was demonstrated between the two vaccines, though the small sample size was small (119 patients). Among patients on active treatment, 61% (20/33) did not seroconvert after 2 vaccine doses. In this study, patients with Hodgkin disease or aggressive B-cell NHL not on active treatment presented robust antibody responses, in contrast to patients with indolent B-cell NHL, who had reduced antibody levels [35].

Seropositivity under active BTK inhibitors therapy following 2 doses of mRNA vaccine is reported between 0% and 18% [4, 28, 29]. Previous therapy is also associated with only 37% response. Treatment with ibrutinib was found to be significantly associated with no antibody response among CLL patients in a large series [29]. Venetoclax-including regimens were also associated with low response of 0%–24% seropositivity. Few data on ruxolitinib also demonstrated the absence of antibody response [4, 28].

Overall, patients with lymphoproliferative disease treated with either anti-CD-20, BTK-I, or BCL-2i are un-

likely to produce adequate antibody response to mRNA vaccine and are probably not protected against SARS-CoV-2 infection even after 2 vaccine doses. Healthcare workers who treat these patients should emphasize the importance of non-pharmacological protective measures for these patients (mainly social distancing, masks, and hand hygiene). Household members of these patients should be encouraged to vaccinate. Some have suggested weighing the risk/benefit ratio of anti-CD20 therapy in patients receiving anti-CD20 as maintenance therapy.

Immune Response to SARS-CoV-2 Vaccines in Multiple Myeloma

Antibody responses to the two mRNA vaccines against SARS-CoV-2, mRNA-1273, and BNT162b2 were assessed in an observational study by Stampfer et al. [36] in 103 patients with multiple myeloma (MM) compared to age-matched healthy subjects. Interestingly, MM patients with age >65 years; low absolute lymphocytes count; reduced levels of uninvolved IgG, IgA, IgM, or sFLC lambda; elevated creatinine levels (>1.3 mg/dL); and current treatment with steroids had a lower antibody response. As expected, the more advanced the disease, the poorer the response to COVID-19 mRNA vaccination. Unfortunately, due to the heterogeneous MM treatments administered to the patients, no specific treatment could have been correlated with antibody response. More than half of MM patients in this cohort failed to fully respond to COVID-19 vaccination and the use of mRNA-1273 resulted in higher anti-spike antibody levels than BNT162b2 in this population. Van Oekelen et al. [37] reported higher response rates to 2 doses of mRNA vaccine in myeloma patients, with 68% (219/320) response, though 60 patients had COVID-19 prior to vaccination. Antibody levels achieved were significantly lower compared to healthy controls, and lower among patients treated with anti-CD38 or anti-BCMA. Unsatisfactory immune response was also observed in MM patients vaccinated with ChAdOx1 (AZD1222) vaccine [38]. Aleman et al. [39] demonstrated variable cellular immune response to 2 doses of mRNA vaccine among MM patients that correlated with humoral response. Seropositive MM patients had similar CD4+ and CD8+ responses as healthy controls; however, low response rates (35% for CD4+ and 28% for CD8+) were demonstrated among seronegative patients. The latter were more likely to be patients receiving anti-CD38 and anti-BCMA [39]. Variable immune responses among MM patients may be explained

by the heterogeneity of patients – rates of hypogammaglobulinemia, disease severity, and type of therapy. Currently, the CDC recommends a booster third dose of mRNA vaccine in MM patients [5]. Of note, a fatal systemic capillary leak syndrome has been documented in a patient with MM after vaccination with the double-stranded DNA-Ad26.COVS vaccine [40].

Immune Response to SARS-CoV-2 Vaccines in Myeloproliferative Disease

A recent study by Harrington et al. [41] correlated similar immunological response after a single dose of BNT162b2 to the general population in patients with myeloproliferative disease. In an Italian cohort of myeloproliferative disease patients, BNT162b2 full vaccination resulted in efficient protection after 5 weeks, except for patients with myelofibrosis, and with previous anti-CD38-based therapy [42].

Immune Response to SARS-CoV-2 Vaccines in Chronic Myeloid Leukemia

In contrast to patients with solid tumor or lymphoid HM, a good immunogenicity to a single dose of the BNT162b2 vaccine has been noticed. Both T-cell and polyfunctional responses were produced, thus creating the bases for a sustained protection after the second dose and the possible boosting third dose [41].

HSCT and Chimeric Antigen Receptor T-Cell Therapy

Immune Response to Vaccine

Depending on time from transplant, patients following HSCT have considerable antibody responses, relative to other HM. Vaccination at least 3 months after transplantation resulted in 75%–83% seroconversion among patients after allogeneic HSCT [19, 43, 44]. Le Bourgeois et al. [43] reported that 62% of allogeneic HSCT recipients reached the highest IgG titer of the relevant assay. Factors associated with lower antibody response rates in studies included time from transplantation (6–12 months cutoffs); haploidentical donor; acute or chronic graft-versus-host disease (GVHD); current or within 3 months of vaccine of systemic immunosuppressive treatment; and total lymphocyte count ($<1,000$ cells/ μL) [19, 43, 45, 46].

Antibody response in patients after chimeric antigen receptor T-cell (CART) infusion is reported to be 21%–36% [44, 45, 47]. Among a population of allogeneic HSCT and CART patients, longer time from transplant, female sex, and higher CD19 + cells were associated with improved immune response to BNT162b2 vaccine in one study [44].

T-cell response to BNT162B2 was evaluated by Ram et al. [44], demonstrating positive response in 50% CART patients evaluated (6/12) and 19% (7/37) after allogeneic HSCT. Either serology or T-cell response (evaluated by ELISpot test) was positive in 57% after CART infusion and 75% after allogeneic HSCT. The latter finding of high rates of T-cell response in HSCT patients is further supported by a recent study demonstrating over 80% of T-cell response after 2 mRNA vaccine doses, with high rates of polyfunctional T-cell response, assumed to provide more effective antiviral effect [48]. Though adequate antibody response is achieved in most HSCT patients, T-cell dysfunction expected in these patients may compromise overall immune response to vaccine, and further studies should explore T-cell immunity in these patients.

Safety in HSCT

Ram et al. [44] reported no grade 3 or 4 non-hematologic adverse events among 57 allogeneic HSCT recipients receiving 2 BNT162b2 doses; however, 4 patients (5%) developed grade 3 or 4 thrombocytopenia ($n = 3$) or neutropenia ($n = 1$) in this cohort, one impending secondary rejection event was considered to be possibly related to vaccine; and 3 cases of GVHD exacerbation were reported in this study after each vaccine dose ($\sim$), all easily controlled. Yeshurun et al. [46] also reported worsening of GVHD symptoms following vaccination in 7% of patients. Ali et al. [49] reported new chronic GVHD in $\sim 10\%$ and worsening chronic GVHD in 3.5% of 113 allogeneic HSCT recipients who received at least one mRNA vaccine dose. Grade 3–4 thrombocytopenia ($n = 4$) or neutropenia ($n = 4$) were also reported.

Specific Society Recommendations

According to EBMT recommendations, any non-live-attenuated vaccine can be used; however, vaccines that showed a $\geq 90\%$ response in phase 3 trials are preferable, due to the expected relatively low response in HSCT/CART. Recommended timing of vaccination in case the transmission rate in the community is high, is 3 months after HSCT, otherwise – 6 months. Patients receiving their COVID-19 vaccine prior to transplantation should be revaccinated. EBMT recommendation is to prioritize

the COVID-19 vaccine over the regular vaccinations program. Current recommendation is to administer this vaccine alone and to avoid other vaccines within 14 days of administration. EBMT suggests possible criteria to postpone the vaccine, including GVHD grade III–IV, anti-CD20 past 6 months, CART with B-cell aplasia within 6 months of infusion, recent ATG, or alemtuzumab [50].

Vaccine-Induced Immune Thrombocytopenia and Thrombosis

Along with the unprecedented worldwide administration of anti-SARS-CoV-2 vaccines, new side effects, previously not reported in clinical trials, have emerged. The ChAdOx1 nCoV-19 adenoviral vector vaccine has been associated with vaccine-induced immune thrombocytopenia and thrombosis, a clinical syndrome characterized by thrombosis at unusual sites, thrombocytopenia, elevated D-dimer levels, high-titer antibodies to platelet factor 4, and reduced fibrinogen levels in young patients (mainly age <60 years) and with high mortality [51, 52].

Timing of Vaccination

The recommendation of the American Society of Hematology regarding vaccinating persons who are less likely to respond to the vaccine is to weigh the decision on a case-by-case basis. It is recommended to consider both the incidence of SARS-CoV-2 infection in the community, type of vaccine available, and patient characteristics (underlying disease and level of immunosuppression). Recommended timing of vaccination is either 2–4 weeks prior to cancer therapy, or 6 months after the end of cancer therapy. However, if community transmission is high, it is reasonable to administer the vaccine earlier, even if it is expected to provide lower protection rates [53]. The European society of hematology recommends an interval of 3–6 months in analogy to other vaccinations [54].

Third mRNA Dose

In August 2021, the US Food and Drug Administration (FDA) authorized the third mRNA vaccine dose of both BNT162b2 and mRNA-1273 for immunocompromised patients. These include individuals on active chemotherapy, HSCT, and immunosuppressive therapy (e.g., anti CD20, other biologic agents, antimetabolites, alkylating agents, prednisone ≥ 20 mg daily). Several studies in kidney transplant recipients demonstrated improved humoral and cellular immunogenicity one month following a third mRNA vaccine dose, supporting FDA's decision [55]. In light of these findings, the Advisory Committee on Immunization Practices also recommends

an additional dose of either mRNA vaccine (BNT162b2 for persons aged ≥ 12 years or mRNA 1273 for persons aged ≥ 18 years) at least 28 days after an initial 2-dose regimen for patients who are moderately to severely immunocompromised. Both FDA and CDC do not recommend testing serologic or cellular response for the decision on an additional vaccine dose, due to lack of data to support this practice. Additional third vaccine dose is recommended by the CDC for immunocompromised individuals regardless of prior SARS-CoV-2 infection. It is also recommended to administer the third vaccine dose at least 90 days after passive antibody therapy (monoclonal antibodies or convalescent plasma) [5, 56]. Initial reports in HM show good response rates, with one study reporting seroconversion of over half of HM patients seronegative prior to the third dose. Anti-CD20 and BTK-I therapy were associated with lower rates of seroconversion and lower titer [10]. Fourth mRNA vaccine dose has been already administered in solid organ transplant recipients, showing good response for those with previous antibody response, and limited response among those who were seronegative after the third dose [57].

Conclusions

Patients with HM present diminished immune response to current vaccination strategies for COVID-19, as detailed above. Strategies to improve immunogenicity should be considered, which include the following:

1. Timing of vaccine – responses to vaccines were improved when administered later after HSCT or anti-CD20. Delays in vaccination schedule may be considered at times of low community transmission of the virus, however, not during local outbreaks.
2. Booster doses – third mRNA vaccine dose is currently approved by the FDA for immunocompromised patients.
3. Heterologous vaccination – Maneikis et al. [4] demonstrated poor response to the second BNT162b2 dose in patients responding poorly to the first dose of the same vaccine. In solid organ transplant recipients, a third homologous or heterologous vaccination resulted in a modest response, with 25% of patients who were seronegative after two doses, mounting an immune response after a third dose [55].

For patients with no antibody response to vaccines, pre-exposure monoclonal antibodies, administered routinely as prophylaxis at times of outbreaks, should be considered [58].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors contributed to the planning of this review and writing of the manuscript. All authors reviewed and approved the final version.

Funding Sources

None.

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