Vaccination for SARS-CoV-2 in Hematological Patients

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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/μL) [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-1723 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, n | Vaccine type, dose/time of follow-up | Seropositive, %/titer | Neutralizing antibodies | T-cell response | Breakthrough infection after full vaccination |
|----------|-----------------|-------------------------|--------------------------------------|-----------------------|------------------------|-----------------|-----------------------------------------------|
| Maneikis 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: 2,135 (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 Anti body 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 | BNT162b or mRNA-1273, 2/med 23 d | 2 Seroconversion: 31/67 (46) | NS | NS | NS |
| Greenberg et al. [11] | Mixed | Prospective, 1445p | BNT162b 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 |
| Ollila 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$: 30/105 (29); active HM 22/88 (25); remission 31/63 (49); watchful waiting 10/15 (67) | 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 (45.6%); 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 | BNT162b or mRNA-1273, 2/4–8 wk | 2 Seroconversion: <9 months from anti-CD206/52 (11), >9 month 22/25 (88), other treatments: 8/9 (89), controls: <65 yr 15/4154 (100), >65 yr 43/47 (91.5%) | NS | NS | NS |
| Jurgens et al. [62] | NHL | Prospective, comparative, 67p | BNT162b or mRNA-1273, 2/11–70 d | 1 Seroconversion: CLL 12/21 (57 overall, 40 under therapy), NHL 57/25 (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 |
| 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 |
|----------|-----------------|--------------------------|------------------------------------|--------------------------|--------------------------|----------------|--------------------------------------------|
| Del Poeta et al. [30] | CLL | Prospective, 46p | BNT162b, 2/26 d | 4 | Seroconversion: 2/46 (46) | NS | NS | NS |
| Benjamini et al. [29] | CLL | Prospective, 37p | BNT162b, 2/2-3 wk | 2 | Seroconversion: 160/373 (33); treatment naïve 61; anti-CD20 previous 12 months 5%, over 12 months 35% | Consistent with IgG response | NS | 2/373 |
| Roeker et al. [83] | CLL | Prospective, 4p | BNT162b2 or mRNA-1273, 2/21 d | 2 | Seroconversion: 2/44 (52) | NS | NS | NS |
| HSCT and CART* | Le Bourgeois et al. [43] | Allogeneic HSCT | Prospective, 117p | NS | 97/117 (83). Less than 12 month from transplant 52, haploidentical 69, ongoing treatment 63, lymphocyte <1,000 cells/μL 64 | NS | 0/117 |
| Ram et al. [44]** | HSCT, CART | Prospective, 57p allo-HSCT, 14p CART | BNT162b, 2/7–14 d | 2 | Seroconversion: CART 47/77 (75), median titer 178 (range 0.4–250); CART 5/14 (36%); median titer 0.4 (range, 0.4–250) | 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 | 2 | Seroconversion: overall 79/130 (60)***: 27/45 (60) auto, 49/71 allo (69), 3/14 CART (21) | NS | NS |
| Gastinne et al. [47] | CART | Prospective, comparative, 23p | BNT162b, 2/21–99 d | 2 | Seroconversion: CART 6/20 (30), controls 25/25 (100) | NS | 0/23 |
| Redjoul et al. [19] | HSCT | Prospective, 88p allo HSCT | BNT162b, 2/24 d | 2 | Seroconversion: 69/88 (78) Surrogate title: >4160 AU/mL: 52/88 (59%) | NS | 0/88 |
| Yeshurun et al. [46] | HSCT | Prospective, 106p, allo HSCT | BNT162b, 2/4–6 wk | 2 | 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% (n = 43) of MM patients had a likely clinically significant response > 250 IU/mL, with an additional 22% (n = 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 |

**Note:** Table 1 (continued)
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| Study ID | Malignancy type | Study Design, participants | Vaccine type, dose/time of follow-up | Seropositivity, %/titer | Neutralizing antibodies (if applicable) | 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 MBP patients; 78.6 MM patients | NS | NS | NS |
| 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 12/15 (92.3%) patients; multifunctional responses in 12/15 (80%) patients | NS |

Notes: NS, not specified; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; HM, hematological malignancies; CLL, chronic lymphocytic leukemia; allo HSCT, allogeneic HSCT; 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-2S assay, measured as U/mL, cutoff 0.80 U/mL. 4 Meso Scale Discovery, Rockville, MD, USA, electrochemiluminescent assay, measured as BAU/mL, cutoff (0.73 BAU/mL) for anti-RBD IgG; (0.55 BAU/mL) for anti-S IgG concentrations. 5 KSL chemiluminescence immunoassays (CLIA), result is expressed by critical value index (COI), cutoff 1 COI. 6 Maglumi 2019 nCOV IgG chemiluminescence Anti-SARS CoV 2 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. 9 In studies evaluating HSCT 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 6 months after treatment (COVID-19 vaccines). Version 6.0, May 27, 2021 at https://www.ebmt.org/sites/default/files/2021-05/SARS-CoV2vaccines%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 (77%) was 56%; mRNA-1273 (47%) – 68%; Johnson & Johnson (6%) – 67%. $ B-cell depleting therapy: rituximab (n = 85), daratumumab (n = 9), obinutuzumab (n = 7), or bispecific CD3/CD20 antibodies (n = 12).

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

Due to this adverse event, some countries restrict these vaccines to the general population or based on age, though an overall total of 1,500 cases had been reported worldwide until July 31, 2021. [21]
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 ≥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. Lieder 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 unlikely 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 Stamper 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 latters 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.COV2.S 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 (~), 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 ~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 ≥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].
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