SARS-CoV-2 Vaccination IgG Antibody Responses in Patients with Hematologic Malignancies in a Myeloid Enriched Cohort: A Single Center Observation

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Abstract

Objective. Patients diagnosed with hematologic malignancies are at increased risk for severe SARS-CoV-2 infection. We evaluated the serological IgG response following two doses of the SARS-CoV-2 vaccine in patients with hematologic malignancies. Methods. Patients treated at UT Southwestern Medical Center with a diagnosis of a myeloid or lymphoid neoplasm were included. SARS-CoV-2 vaccination response was defined as a positive quantifiable spike IgG antibody titer. Results. Sixty patients were included in the study and 60% were diagnosed with a myeloid neoplasm. The majority (85%) of the patients with a myeloid malignancy and 50% of the patients with a lymphoid malignancy mounted a serological response after receiving two doses of the vaccine. Conclusion. Vaccination should be offered irrespective of ongoing treatment or active disease. Findings require validation in a larger cohort of patients.

Key Words: SARS-CoV-2 Vaccination • Hematologic Malignancy • Antibody Response.

Introduction

Patients with a hematologic malignancy are at increased risk for severe SARS-CoV-2 infection due to their immunocompromised status and as a result of receiving immunosuppressive treatments. Depending on the underlying disease, mortality rates have been reported as high as 30–40% (1, 2). While the BNT162b2 (Pfizer/BioNTech) and the mRNA-1273 (Moderna) COVID-19 vaccines both have been shown in large phase 3 clinical trials to be more than 90% effective at preventing lab-confirmed COVID-19 illness and severe infections, data on vaccine efficacy and safety in immunocompromised patients remain scarce (3, 4). In order to generate optimal protective immunity following vaccination, intact host immunity is needed. The American Society of Hematology and American Society of Transplant and Cellular Therapy COVID-19 vaccine guidelines indicate that certain immunocompromised patient populations could have an attenuated response to the SARS-CoV-2 vaccine. However, most pivotal SARS-CoV-2 vaccination trials required patients to be off immune suppression for a certain period to be eligible, and patients with hematologic malignancies were therefore often excluded.

In this study, we aimed to evaluate the serological response of Pfizer/BioNTech and Moderna vaccination after administration of two doses in patients with hematologic malignancies.

Methods

Patient Population

This retrospective observational study was approved by the institutional review board of the University of Texas Southwestern Medical Center.
(Dallas, TX, USA). Patients diagnosed with a myeloid or lymphoid malignancy that had a quantitative SARS-CoV-2 IgG spike antibody measured between December 2020 and November 2021 after receiving two doses of the Moderna or Pfizer/BioNTech SARS-CoV-2 vaccine were included in the study. Inhouse testing for a quantitative IgG antibody titer detection was performed for the majority (N=40) of the patients in accordance with the manufacturer’s package insert (AdviseDX SARS-CoV-2 IgG II/ SARS-CoV-2 IgG II Quant assay, Abbott Alinity i platform, Abbott Laboratories, Chicago, IL, USA) (5). Briefly, SARS-CoV-2 antigen-coated microparticles bind to the IgG antibodies that attach to the virus’s spike protein. Subsequently, an anti-human IgG conjugate is added and the degree of chemiluminescence is measured, reflecting the quantity of IgG present. The remaining patients had send-out testing performed either using an immunoassay that uses a recombinant protein that represents the nucleocapsid virus antigen (Roche Elecsys® anti-SARS-CoV2 reagent assay, Roche Diagnostics, Indianapolis, IN, USA (N=16)) or an assay that selects the receptor-binding domain of the S1 spike antigen to detect neutralizing IgG antigens (Atellica® IM SARS-CoV-2 IgG (COV2G) Siemens Healthcare Diagnostics, Terrytown, NY, USA (N=4)). Vaccine response was defined as having a positive quantifiable spike IgG antibody titer per the laboratory reference range.

**Ethics Statement**

**Statistical Analysis**

Categorical variables were compared using Fisher’s exact test and summarized as count with percentage. Continuous variables were compared using the Wilcoxon signed-rank test and summarized as median with interquartile range. P-value <0.05 was considered statistically significant. Statistical analyses were performed in R Version 4.2.2 (2022-10-31), (RStudio, Inc., Boston, MA).

**Results**

A total of 60 patients were included in the study. Patients had a median age of 72 year at time of first vaccination, and the large majority were non-Hispanic (88%) and were white (83%). Baseline patient and disease characteristics are shown in Table 1. Twenty patients (33%) received a complete vaccination series with the mRNA-1273 (Moderna) COVID-19 vaccine and 67% received the BNT162b2 (Pfizer/BioNTech) vaccine. Sixty percent of the patients were diagnosed with a myeloid neoplasm including acute myeloid leukemia (AML) (15%), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML) or clonal cytopenia or undetermined significance (CCUS) (23%), a myeloproliferative neoplasm (MPN) (15%) or chronic myeloid leukemia (CML) (7%). The remaining patients were diagnosed with chronic lymphocytic leukemia (17%), lymphoma (10%) or other (N=5).

At the time of first vaccine administration, 41 (68%) of patients were on active therapy or were treated within the past 12 months, and 41 (68%) of patients had active disease. The median number of days between administration of the first and second vaccine was 22 days (range 17-32) and 54 (range 26-277) days between second vaccine and IgG SARS-CoV-2 spike antibody collection.

Most patients (73%) mounted a serological response with quantifiable IgG SARS-CoV-2 spike antibodies after receiving two doses of the vaccine; 85% of the patients with a myeloid disease vs. 50% with a lymphoid malignancy (P=0.01). All patients (100%) with MDS, CMML, CCUS or CML showed a positive serological immune response, followed by 78% of the AML patients (Figure 1). Five of the nine patients diagnosed with MPN developed a positive spike antibody, including none of the two polycythemia vera patients. Additionally, one patient with AML secondary to JAK2 mutated MPN remained seronegative after vaccination. Forty percent (N=4) of the CLL patients mounted a positive response. Among the responders and the non-responders, 64% and 81% were on active therapy respectively (P=0.35), and 63% compared to 70% had active disease, respectively (P=0.55).
All (100%) patients who had received hypomethylating agent (HMA) therapy (N=4) or a tyrosine kinase receptor inhibitor (N=4) at the time of vaccination or within the past 12 months resulted with a positive IgG SARS-CoV-2 seroconversion, vs. 38% of the patients receiving a Bruton’s tyrosine kinase (BTK) inhibitor (ibrutinib (N=2), acalabrutinib (N=1)), 50% of the patients who had received rituximab and 57% of the patients on ruxolitinib mounted an IgG SARS-CoV-2 response. While two of the patients treated with rituximab that had a positive response were off the rituximab for more than 5 months, another patient who was off therapy for 5+ months did not. Out of the four patients receiving venetoclax-based combination therapy, 50% mounted a response; 2/3 AML patients and 0/1 CLL patient. The CLL patient has had several lines of therapy, including B-cell depleting therapy, but none within the past 12 months.

Five patients with a documented positive IgG response and one patient without positive IgG antibody response developed COVID-19 infection.
after two vaccinations (median 317 days), two patients had COVID-19 infection prior to the first dose of vaccination, both patients had IgG titers >10,000. No differences in response rates were seen between patients vaccinated with the BNT162b2 (Pfizer/BioNTech) and the mRNA-1273 (Moderna) vaccine. No statistical differences were observed in complete blood counts between responders and non-responders.

Discussion

In this retrospective single center observational study, we evaluated the IgG SARS-CoV-2 antibody response post two doses of SARS-CoV-2 vaccination in patients diagnosed with a hematologic malignancy. We observed a positive IgG antibody response in 73% of the patients, with a lower response rate in patients diagnosed with a lymphoid malignancy (50%) compared to patients diagnosed with a myeloid malignancy (85%). This observation is similar to what has been previously described in B-cell lymphoid malignancies (6), which given that they often have profound impaired humoral and cellular immune function is not surprising.

As published by several others, CLL is found to be associated with attenuated SARS-CoV-2 IgG response with CLL seroconversion rates ranging from 47-64% (7-9). A large multicenter international study that included 198 CLL patients with a symptomatic COVID-19 infection showed a high case fatality rate of 33% for all patients, and 37% for hospitalized patients (6, 10). This association is likely exacerbated by B-cell depleting therapy, such as anti-CD20 monoclonal antibodies and BTK-inhibitors, which further limits the protective response. Thakkar et al. studied IgG SARS-CoV-2 antibody response in patients with cancer (N=200) that had received full dosing of COVID-19 vaccine. While they found a seroconversion rate of 85% in hematologic malignancies, lowest positive response rates were associated with targeted CD20 therapy, BCL-2 inhibitors and BTK inhibitors (11). Others reported a cohort of 167 CLL patients with none of the 22 patients
who had received anti-CD20 therapy within the past 12 months mounted a positive response (9), and Rotterdam et al. showed therapies including rituximab and BTK inhibitors to be significantly correlated with negative seroconversion rates (12). Although we observed a positive response rate of 50% among the patients that had received rituximab, rituximab was discontinued at least 5 months prior to first vaccination date in three of the four patients, which may potentially have mitigated the effect.

While most studies have been focused on lymphoid malignancies, a limited number of studies have been published for myeloid diseases, in particular in the context of different treatment agents. One of the first published studies on COVID-19 in the setting of myeloid neoplasms, reported comparable antibody titers in patients with AML and MDS vs. healthy controls. However, when they compared titers obtained in AML patients in complete remission on maintenance therapy to patients in remission on treatment-free observation, they noted IgG levels to be lower in the treatment group. Most of these patients received an HMA. A similar observation was done for MDS patients on treatment showing lower titers compared to healthy controls (13). More recently, several other reports came out showing the antibody response rates were favorable in AML and MDS with seropositive rates ~90% both after treatment with HMA with or without venetoclax, although the latter remains controversial and most studies were performed using small cohorts (13, 14). Here we report seven patients treated with HMA, of which two received a combination with venetoclax, all with a positive antibody titer.

Other myeloid diseases associated with lower response rates were primary myelofibrosis and patients treated with ruxolitinib, whereas CML showed seroconversion in almost all cases, even in the setting of TKI treatment (12, 13). It may be debatable whether the disease or treatment predisposes to a low seroconversion rate. In a study that included 20 primary myelofibrosis patients (JAK2+ (N=15)), ten patients received ruxolitinib and the other 10 received hydroxyurea or supportive therapy with no significant differences seen between both groups in positive seroconversion rate or IgG spike levels (15). Interestingly, Rotterdam et al. reported one patient with JAK2+ CML patient on ruxolitinib who mounted a negative response (N=1/101), as did our patient with secondary AML with a history of JAK2 MPN on ruxolitinib therapy.

Limitations of Study

This study has several limitations including the small sample size and the large heterogeneity in hematologic disease subtypes and treatment regimens, which could perhaps result in statistical bias and low statistical power. Due to the different assays that we used to measure qualitative IgG COVID-19 SARS-CoV-2 antibody response, each with a different laboratory normal reference range and upper limit of detection level, qualitative IgG spike cannot be correlated with reported disease variables. Findings require validation in a larger, prospective and multi-institutional cohort of patients.

Conclusion

In this study we demonstrated that the majority of patients with a hematologic neoplasm mount a positive response following SARS-CoV-2 vaccination, suggesting that vaccination should be offered irrespective of ongoing treatment or active disease. This study further helps to identify higher-risk patients for negative seroconversion, including patients with CLL or MPN, and patients receiving anti-CD20 therapies, BTK-inhibitors or JAK2+ inhibitors.

What Is Already Known on This Topic:

Patients with a hematologic malignancy are at increased risk for severe SARS-CoV-2 infection and data on SARS-CoV-2 vaccination efficacy and safety in immunocompromised patients remain scarce. Particularly, chronic lymphocytic leukemia has been associated with attenuated SARS-CoV-2 IgG response, whereas patients diagnosed with a myeloid malignancy often show high seroconversion rates comparable to the healthy population.
What This Study Adds:
We demonstrated that the majority of patients with a hematological neoplasm mount a reasonable response following SARS-CoV-2 vaccination, suggesting that vaccination should be offered irrespective of ongoing treatment or active disease. Our findings help to identify higher-risk patients for negative seroconversion.

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Conflict of Interest: Y.F.M. has received honoraria/consulting fees from BluePrint Medicines, GERON, OncLive and MD Education. Y.F.M. participated in advisory boards and received honoraria from Sierra Oncology, Stemline Therapeutics, Blueprint Medicines, Morphosys, Taiho Oncology and Novartis. Y.F.M. received travel reimbursement from Blueprint Medicines and Morphosys. F.T.A. has provided consultancy services to Kite Pharma, Bristol Myers Squibb (BMS) and Rafael Pharma and served on the advisory boards of Pharmacyclics LLC, ADC Therapeutics and Cellectar Biosciences. G.K. has provided consultancy to Cellectar Biosciences and BMS. P.A.P. has served on the advisory boards of Servier and BMS Celgene and is currently employed by Servier. None of these relationships are related to this work.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

References
