Humoral Responses After SARS-CoV-2 mRNA Vaccination and Breakthrough Infection in Cancer Patients

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Abstract

Objective: To evaluate the magnitude of humoral response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines in patients with cancer receiving active therapies.

Patients and Methods: Patients 18 years or older in whom SARS-CoV-2 spike antibody (anti-S Ab) levels were measured after 2 doses of SARS-CoV-2 mRNA vaccines were included. Patients with prior coronavirus disease 2019 (COVID-19) infection or receiving other immunosuppressive therapy were excluded.

Results: Among 201 patients who met the criteria, 61 were immunocompetent, 91 had a hematologic malignancy, and 49 had a solid malignancy while receiving treatments associated with cytopenia, including chemotherapy or cyclin-dependent kinase 4 and 6 inhibitors. A significantly greater proportion of immunocompetent patients (96.7% [59 of 61]) had anti-S Ab titers of 500 U/mL or greater compared to patients with hematologic (7.7% [7 of 91]) and solid (55.1% [27 of 49]) malignancy (P<.001). Despite 2 doses of SARS-CoV-2 mRNA vaccines, 52.7% of patients with hematologic malignancy (48 of 91) and 8.2% of those with solid malignancy (4 of 49) receiving cytopenic therapy had no seroconversion (spike antibody titers <0.8 U/mL). Two patients subsequently had development of breakthrough COVID-19 infection after full vaccination.

Conclusion: A substantial proportion of patients with hematologic and solid malignancies receiving chemotherapies and CDK4/6i had poor humoral responses after SARS-CoV-2 mRNA vaccination. Our study adds to a growing body of literature suggesting that immunosuppressed patients have a suboptimal humoral response to COVID-19 vaccination. Our study also underscores the importance of assessing antibody response after COVID-19 vaccines in these vulnerable patients.

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PATIENTS AND METHODS

Patient Selection
We conducted a retrospective cross-sectional study of patients 18 years or older who had SARS-CoV-2 spike antibody (anti-S Ab) tests performed after 2 doses of SARS-CoV-2 mRNA vaccines between 12 and 90 days at the 3 Mayo Clinic sites in Minnesota, Florida, and Arizona between January 1, 2021, and May 10, 2021. The Elecsys Anti-SARS-CoV-2 S electrochemiluminescence immunoassay (Roche Diagnostics) was used to measure the antibody response. Patients with prior coronavirus disease 2019 (COVID-19) infection and patients receiving immunosuppressive therapy for an indication other than cancer were excluded. This study was approved by the Mayo Clinic Institutional Review Board.

Statistical Analyses
Categorical variables were summarized as frequencies (percentages), and continuous variables were reported as median with range. The Wilcoxon signed rank test was used to compare continuous variables between groups, and a $\chi^2$ or Fisher exact test was used to compare categorical variables. For box plot depiction, patients with anti-S Ab levels of greater than 2500 U/mL were assigned the value of 2500 U/mL and those with levels less than 0.4 U/mL were assigned the value of 0 U/mL. All tests were 2-sided with $P<.05$ considered statistically significant. The analysis was done using R statistical software, version 3.6.2 (R Project for Statistical Computing).

RESULTS

Patient Characteristics
Among 611 patients in whom anti-S Ab titers were assessed, 201 patients met the inclusion criteria and were included in this analysis (Table 1). Among 61 immunocompetent patients, 25 healthy individuals had no history of cancer and 36 patients had a history of solid malignancy but not immunosuppressive therapy.

| TABLE 1. Patient Characteristics and Cancer Types$^{a,b}$ |
|-----------------|-----------------|-----------------|-----------------|---|
| Variable        | Immunocompetent | Hematologic malignancy | Solid malignancy | $P$ value |
| Age (y), median (range) | 68.0 (28.0-90.0) | 71.0 (47.0-97.0) | 66.0 (38.0-81.0) | <.001 |
| Gender          |                 |                  |                 | <.001 |
| Female          | 53 (86.9)       | 28 (30.8)        | 47 (95.9)       |      |
| Male            | 8 (13.1)        | 63 (69.2)        | 2 (4.1)         |      |
| Healthy$^c$     | 25 (41.0)       | 0 (0.0)          | 0 (0.0)         |      |
| Cancer types    |                 |                  |                 |      |
| Breast cancer   | 35 (57.4)       | 0 (0.0)          | 44 (89.8)       |      |
| CLL             | 0 (0.0)         | 60 (65.9)        | 0 (0.0)         |      |
| CML             | 0 (0.0)         | 2 (2.2)          | 0 (0.0)         |      |
| Leukemia        | 0 (0.0)         | 2 (2.2)          | 0 (0.0)         |      |
| Lung cancer     | 0 (0.0)         | 0 (0.0)          | 5 (10.2)        |      |
| Lymphoma        | 0 (0.0)         | 9 (9.9)          | 0 (0.0)         |      |
| MDS             | 0 (0.0)         | 2 (2.2)          | 0 (0.0)         |      |
| MGUS            | 0 (0.0)         | 5 (5.5)          | 0 (0.0)         |      |
| Myeloma         | 0 (0.0)         | 9 (9.9)          | 0 (0.0)         |      |
| Prostate cancer | 1 (1.6%)        | 0 (0.0%)         | 0 (0.0%)        |      |
| Waldenstrom     | 0 (0.0)         | 2 (2.2)          | 0 (0.0)         |      |

$^a$CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; NA, not applicable; $^b$Data are presented as the number (percentage) of patients unless indicated otherwise. $^c$Healthy group included patients without previous diagnosis of cancer and not receiving immunosuppressive therapy.
Among 36 patients with cancer, 12 (33.3%) received no treatment, 13 (36.1%) received endocrine therapies, and 11 (30.6%) received trastuzumab with or without pertuzumab. Of 91 patients with hematologic malignancies, 60 patients (65.9%) had chronic lymphocytic leukemia (CLL). Forty-nine patients had solid malignancies while receiving treatments associated with cytopenia (solid malignancy group), including chemotherapy (35 patients [71.4%]) and cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i; 14 patients [28.6%]).

The median age in the hematologic malignancy group was older at 71 years compared with 68 years in immunocompetent group and 66 years in solid malignancy group (P<.001). More patients in the hematologic malignancy group were men (63 of 91 [69.2%]) vs 8 of 61 (13.1%) in the immunocompetent group and 2 of 49 (4.1%) with a solid malignancy (P<.001).

**Humoral Response to SARS-CoV-2 mRNA Vaccines**

Of the 201 study patients, 95 (47.3%) received mRNA-1273 and 106 (52.7%) received BNT162b2 (Table 2). More patients with hematology malignancy received BNT162b2—59 patients (64.8%) compared to 23 (37.7%) in the immunocompetent group and 24 (49.0%) in the solid malignancy group (P=.004). There was no significant difference in the median duration between the second vaccination and anti-S Ab testing, with a median of 28 days in the immunocompetent and hematologic malignancy groups and 26 days in the solid malignancy group (P=.38). Immunocompetent patients had significantly higher anti-S Ab levels than patients with hematologic malignancy and solid malignancy (Figure). A significantly greater proportion of immunocompetent patients had significantly higher anti-S Ab titers than patients with hematologic and solid malignancies (P<.001; Table 2). More patients with hematologic malignancy had extremely low antibody titers, with 48 of the 91 patients (52.7%) having negative results (<0.8 U/mL) and 67 (73.6%) having values of 50 U/mL or less. Of the 60 patients with CLL, 38 (63.3%) had negative results. Among patients with a negative result, 9 patients (8 with CLL and 1

| Variable | Immunocompetent (N=61) | Hematologic malignancy (N=91) | Solid malignancy (N=49) | P value |
|----------|------------------------|-------------------------------|------------------------|---------|
| Type of vaccine mRNA-1273 | 38 (62.3) | 32 (35.2) | 25 (51.0) | .004 |
| Anti-S Ab titer ≤2500 U/mL | 29 (47.5) | 88 (96.7) | 32 (65.3) | .001 |
| Anti-S Ab titer >2500 U/mL | 32 (52.5) | 3 (3.3) | 17 (34.7) | .001 |
| Anti-S Ab titer ≤1000 U/mL | 4 (6.6) | 85 (93.4) | 27 (55.1) | .001 |
| Anti-S Ab titer >1000 U/mL | 57 (93.4) | 6 (6.6) | 22 (44.9) | .001 |
| Anti-S Ab titer ≤500 U/mL | 2 (3.3) | 84 (92.3) | 22 (44.9) | .001 |
| Anti-S Ab titer >500 U/mL | 59 (96.7) | 7 (7.7) | 27 (55.1) | .001 |

*Anti-S Ab, anti-S protein antibody; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2. Type of SARS-CoV-2 mRNA Vaccine, Duration Between Vaccination and Anti-S Ab Test, and Anti-S Ab Levels**

Data are presented as the number (percentage) of patients unless indicated otherwise.

Difference between immunocompetent vs hematologic malignancy group and immunocompetent vs solid tumor group were both significant at P<.001.
with multiple myeloma) were not receiving any active therapy.

In the solid malignancy group, 4 of the 49 patients (8.2%) had negative results, and 10 (20.4%) had values of 50 U/mL or less. Among the 14 patients who received CDK4/6i, 4 (28.6%) patients had anti-S Ab titers of 500 U/mL or less compared to 20 of 37 (54.1%) who received chemotherapy. However, this difference did not reach a statistically significant level ($P = .1$; Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org).

Using multivariate logistic regression analysis adjusted for age, sex, and vaccine type, patients with hematologic malignancy (odds ratio [OR], 363.78; 95% CI, 71.32 to 3110.74; $P < .001$) and solid malignancy (OR, 35.51; 95% CI, 8.38 to 255.25; $P < .001$) were more likely to have anti-S Ab results of 500 U/mL or less compared to immunocompetent patients. There was no significant difference in age (OR, 1.02; 95% CI, 0.98 to 1.07; $P = .36$) and male sex (OR, 2.04; 95% CI, 0.47 to 7.97; $P = .31$) associated with anti-S Ab results of 500 U/mL or less. When comparing the 2 types of vaccines, more patients with hematologic malignancy received BNT162b2 than the immunocompetent and solid malignancy groups (64.8% [59 of 91], 37.7% [23 of 61], and 49.0% [24 of 49], respectively.) Nevertheless, after adjusting for age, sex, and treatment groups, receiving BNT162b2 was independently associated with anti-S Ab results of 500 U/mL or less (OR, 9.85 [95% CI, 3.61 to 30.86; $P < .001$]; Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org).

**Breakthrough Infections**

At the time of our report, 2 of the 201 patients had breakthrough infections after completion of 2 vaccinations. Both patients received BNT162b2. One of the patients was a 48-year-old woman with metastatic breast cancer receiving weekly paclitaxel. She experienced body ache and productive cough and was diagnosed as having COVID-19 3 months after the second vaccination. Her anti-S Ab titer was negative ($\leq 0.4$ U/mL). During active infection, the patient had to pause her systemic therapy.
Unfortunately, the patient developed rapidly progressive disease in her liver. She was not able to continue her treatment and was referred to hospice. The other patient, a 79-year-old woman in the immunocompetent group, developed COVID-19 pneumonia with a bacteria-superimposed infection requiring hospitalization approximately 4 months after the second dose of BNT162b2. This patient’s anti-S Ab level was 1635 U/mL. This patient recovered and was discharged home after 4 days of hospitalization.

DISCUSSION
Growing evidence suggests that patients with cancer who are receiving immunosuppressive therapy have a less robust immune response after SARS-CoV-2 infection or vaccination. Monin et al⁸ found that patients with cancer had poor response to BNT162b2, particularly after a single dose. However, only 31 of 151 patients with cancer in their study received the second vaccination, and a small number of patients received chemotherapy. This study also found lower levels of interferon-γ—producing or interleukin 2—producing T cells against S2 peptide in patients with cancer compared with healthy controls. Another study by Masarsweh et al⁶ reported a seroconversion rate of 90% in 102 patients with cancer after the second dose of BNT162b2 compared with 100% in the control group. Similar to our study, the anti-S Ab IgG titer was lower in patients with cancer than in healthy controls. However, a different anti-S Ab assay (ARCHITECT i2000SR platform; Abbott) was used in this particular study, possibly confounding the comparison. In another study by Herishanu et al⁷ patients with CLL appeared to have a worse immune response, with only 39.5% of patients with CLL having documented seroconversion after both doses of BNT162b2.

Similar to these studies, our study also found that patients with cancer, particularly those with hematologic malignancy, had substantially impaired humoral responses after both SARS-CoV-2 mRNA vaccines. Although the optimal cutoff for adequate protection against COVID-19 infection is currently unknown, only 8.8% of the hematologic malignancy group and 55.3% of the solid malignancy group had anti-S Ab titers greater than 500 U/mL. Because of the differences in anti-S Ab assays that were used in various studies, it is difficult to compare the results across studies. Only Herishanu et al⁷ used the same assay that we used (the Elecsys Anti-SARS-CoV-2 S electrochemiluminescence immunoassay) to evaluate anti-S Ab. Similar to their study, our study also documented a 36.7% seroconversion rate among patients with CLL after both doses of SARS-CoV-2 mRNA vaccines.

To the best of our knowledge, our study was the first to evaluate immune response in patients with cancer receiving either BNT162b2 or mRNA-1273 using the same anti-S Ab assay. Although receiving BNT162b2 was associated with lower anti-S Ab titers after adjusting for age, sex, and treatment groups, substantially more patients with hematologic malignancy received BNT162b2. Therefore, this result should be interpreted with caution. Furthermore, our study also illustrated breakthrough infections after full vaccination.

While CDK4/6i is not generally considered as immunosuppressive therapy, our study found that patients who receive immunosuppressive therapy may also have an impaired antibody-mediated response to SARS-CoV-2 mRNA vaccines. Compared with chemotherapy, there was a numerically lower percentage of patients receiving CDK4/6i with anti-S Ab titers of 500 U/mL or less (28.6%) vs those receiving chemotherapy (54.1%). Although this difference did not reach statistical significance, it is likely due to small sample size.

Our study has some limitations, particularly being a retrospective study, and there were imbalances in age, sex, and type of vaccine as described. While there were imbalances in sex and age between each of the groups, sex and age themselves were not significantly associated with lower anti-S Ab levels. In addition, our current study only focused on the levels of anti-S Ab. The neutralizing capacity of these antibodies and the
cellular T-cell responses to these vaccines remain unknown.

CONCLUSION
Our study highlights the importance of further evaluation of humoral responses to COVID-19 vaccines in patients with hematologic and solid malignancies receiving chemotherapies and CDK4/6i. Current guidelines pertaining to social distancing and face-covering do recommend caution after COVID-19 vaccination in immunosuppressed patients, as they may still be susceptible to COVID-19 infection despite full vaccination. Further evaluation of the T-cell response and the duration of humoral responses in these patients is currently ongoing at our institution (ClinicalTrials.gov identifier, NCT04865133). Additional studies are needed to further define the optimal antibody response that provides adequate protection from SARS-CoV-2 infection. Further clinical trials are also needed to evaluate the potential benefit of booster vaccinations, different vaccine doses or dosing intervals, and the comparative performance of different vaccine platforms in this group of vulnerable patients.

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Dr Chumsri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: Anti-S Ab, SARS-CoV-2 spike antibody; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor(s); CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; mRNA, messenger RNA; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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