Longitudinal SARS-CoV-2 mRNA Vaccine-Induced Humoral Immune Responses in Patients with Cancer

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ABSTRACT

Longitudinal studies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine-induced immune responses in patients with cancer are needed to optimize clinical care. In a prospective cohort study of 366 (291 vaccinated) patients, we measured antibody levels [anti-spike (IgG-(S-RBD) and anti-nucleocapsid immunoglobulin] at three time points. Antibody level trajectories and frequency of breakthrough infections were evaluated by tumor type and timing of treatment relative to vaccination. IgG-(S-RBD) at peak response (median = 42 days after dose 2) was higher ($P = 0.002$) and remained higher after 4 to 6 months ($P = 0.003$) in patients receiving mRNA-1273 compared with BNT162b2. Patients with solid tumors attained higher peak levels ($P = 0.001$) and sustained levels after 4 to 6 months ($P < 0.001$) compared with those with hematologic malignancies. B-cell targeted treatment reduced peak ($P = 0.001$) and sustained antibody responses ($P = 0.003$). Solid tumor patients receiving immune checkpoint inhibitors before vaccination had lower sustained antibody levels than those who received treatment after vaccination ($P = 0.043$). Two (0.69%) vaccinated and one (1.9%) unvaccinated patient had severe COVID-19 illness during follow-up. Our study shows variation in sustained antibody responses across cancer populations receiving various therapeutic modalities, with important implications for vaccine booster timing and patient selection.

Significance: Long-term studies of immunogenicity of SARS-CoV-2 vaccines in patients with cancer are needed to inform evidence-based guidelines for booster vaccinations and to tailor sequence and timing of vaccinations to elicit improved humoral responses.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to cause significant morbidity and mortality, in particular among vulnerable immunosuppressed patients with cancer (1, 2). From observational studies, messenger RNA (mRNA) SARS-CoV-2 vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna/NIH), show reduced antibody response in patients with cancer compared with healthy individuals (3–18). Patients with selected hematologic malignancies (7, 8, 13, 14, 19, 20), and those receiving specific anticancer treatments [e.g., anti-CD20 (3, 9, 15), anti-CD38 (13, 21), and chemotherapy (16)] may have low or no antibody response following vaccination. Although it is believed that vaccine-induced responses are robust up to 6 months (22), and clinically significant breakthrough infections appear to be rare in healthy individuals (23), the kinetics of immune response and incidence of breakthrough infections are unclear in patients receiving concurrent therapy for malignancy (24). Novel variants such as B.1.617.2 (Delta) with higher

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transmission rates and reduced sensitivity to antibody neutralization increase risk of infection (25, 26). There is an urgent need to understand long-term immunogenicity of SARS-CoV-2 vaccines among patients with cancer to inform evidence-based guidelines for subsequent timing and frequency of booster vaccinations.

We report data on the longitudinal durability of two dose mRNA vaccination and frequency of breakthrough infections in patients with solid and hematologic malignancies receiving various treatments from the United States NCI-funded Serological Sciences Network (SeroNet)-Coronavirus Risk Associations and Longitudinal Evaluation (CORALE) study.

Patients and Methods

Study setting

The Cedars Sinai Health System is located in the diverse metropolis of Los Angeles, serving a catchment area over 5.7 million (57.6% of the total Los Angeles County population; ref. 27). Cedars-Sinai Cancer includes the main campus (Cedars-Sinai Medical Center), The Angeles Clinic and Research Institute, and other affiliated sites. The study was approval by the Institutional Review Board and all participants provided written informed consent.

Study design and population

SeroNet-CORALE is a prospective repeated-measurement cohort study established on November 3, 2020 (28). Patients with cancer over age 18 with histologically confirmed solid tumors or hematologic malignancies were recruited in the clinical setting and through direct email (Supplementary Fig. S1). Patients undergoing active anticancer treatment and under clinical surveillance or had receive a bone marrow transplant (allogeneic or autologous) were accrued. To focus on patients with cancer with altered immunity, we oversampled patients with B-cell/plasma cell malignancies (B-cell) and any patient with cancer receiving immune checkpoint inhibitors (ICI). Unvaccinated patients and those receiving either BNT162b2 or mRNA-1273 vaccines (two doses) were included. As a referent population, we used data from health care workers (HCW) at Cedar-Sinai Health System over age 18 without a history of cancer. The CORALE-HCW cohort has been described previously (29).

Data and sample collection

Participants were asked to complete self-administered questionnaires about demographics, lifestyle/behaviors, COVID-19-related exposures, and medical histories. Electronic medical records were reviewed to extract clinical data including tumor type (ICD-10 codes), treatment regimens, and timing of administration. Treatment was defined relative to the time of vaccination as active (within 6 months) or nonactive and categorized as ICI; ICI + chemotherapy; B-cell therapy(ies); B-cell therapy(ies) + chemotherapy; chemotherapy; and hormonal therapy. SARS-CoV-2 vaccination status and dates of administration were obtained from patient reports, vaccine cards, and immunization records. Discrepancies in medical information were adjudicated by N.M. Merin and K.L. Reckamp, and verified through the California Immunization Registry.

Blood draws occurred at clinical visits at three time points: (i) enrollment (prior to dose 1 vaccination for vaccinated patients, $n = 112$); (ii) peak response (2–12 weeks post two-dose for vaccinated patients, $n = 147$); and (iii) sustained response (16–28 weeks after two-dose for vaccinated patients, $n = 124$). The cut point for separating peak and sustained response was selected to align with data from previous studies suggesting divergence in humoral immune response after 120 days (30). Not all individuals had blood draws at all three time points due to different dates of study enrollment, vaccination date, and frequency of clinic visits. We did not impute missing data.

Serologic testing for antibodies to the receptor binding domain (RBD) of the S1 subunit of the viral spike protein [IgG(S-RBD)] and antibodies targeting the viral nucleocapsid protein (IgG(N)) was performed using the SARS-CoV-2 IgG II and SARS-CoV-2 IgG assays, respectively, manufactured by Abbott Diagnostics. We present findings in AU/mL. On the basis of the results from the first WHO International Standard study (31), the mathematical relationship of the Abbott AU/mL unit to WHO unit [binding antibody unit per mL (BAU/mL)] is: BAU/mL = 0.142*AU/mL. The minimal threshold for seroconversion in response to vaccination was defined as IgG(S-RBD) = 50 AU/mL or 7.1 BAU/mL (32). For assessing potential response of neutralizing antibodies, we considered a high IgG(S-RBD) threshold of 4,160 AU/mL (590.72 BAU/mL) as a correlate of neutralization (33). The 4,160 AU/mL threshold has been shown to correspond to a 0.95 probability of obtaining a PRNT ID50 at a 1:250 dilution as a representative high titer (33).

Prior SARS-CoV-2 infection was defined as patient self-report, medical chart confirmation or based on the previously established cutoff of IgG(N) S/C ≥1.4 (32), prior to the time of vaccination. A definitive breakthrough infection was defined as IgG(N) S/C ≥1.4, documentation of COVID-19 infection in medical records, or the detection of SARS-CoV-2 on RT-PCR assay performed 14 or more days after receipt of a second dose. Medical charts were reviewed by K.L. Reckamp, N.M. Merin, and O. Hamid to adjudicate cases.

Statistical analysis

Demographic and clinical information are described for both patients with cancer and HCW. Among vaccinated recipients who received two doses of either mRNA vaccine, we examined two time points representing peak and sustained responses. We constructed categories using peak quantitative IgG(S-RBD) levels to define the proportion of vaccine recipients who were seronegative [IgG(S-RBD) < 50 AU/mL], intermediate seropositive [gG(S-RBD) range 50–4,160 AU/mL] and high seropositive with IgG(S-RBD) ≥ 4,160 AU/mL. To examine differences in clinical characteristics by these categories of seropositivity, we used Kruskal–Wallis tests to compare continuous variables and Fisher exact tests for categorical variables. We built multivariable ordinal logistic regression models to assess peak and sustained seropositivity adjusting for age, sex, ethnicity, days after two-dose vaccination, vaccine type, cancer type, ECOG performance status, prior SARS-CoV-2 infection, and treatment type. The covariates of interest were selected a priori based on the hypothesized associations with serologic response. To visualize overall trajectories, we used loess curves with 95% confidence bands of $\log_{10}$ transformed IgG(S-RBD)+1 antibody response over time. We investigated timing of the initiation of treatment before and after vaccine administration among those with solid tumors treated with ICI and those with hematologic malignancies treated with B-cell–targeted therapies and anti-CD38. Timing of other treatments were not investigated due to limited sample size. Demographic and clinical information are described for individuals with breakthrough infections. Clinical timelines are provided for hospitalized/deceased cases. P value <0.05 was considered statistically significant. Statistical analysis was performed in R, version 4.1.1.

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Characteristics of the patient cohort

From December 22, 2020 to August 30, 2021, a total of 366 patients with cancer were enrolled and donated blood for antibody testing (54 unvaccinated; 291 vaccinated with two doses mRNA vaccine, Supplementary Table S1). Compared with vaccinated HCW, vaccinated patients with cancer were older [median = 65 (56–73) vs. median = 38 (32–49) years], less likely to be female (46.4% vs. 65.3%), and self-identify as a non-White minority (39.5% vs. 55.7%). Among patients with cancer, the frequency of prior SARS-CoV-2 infection at time of enrollment was lower in vaccinated than unvaccinated patients (6.2% vs. 22.2%). Unvaccinated patients were also more likely to be younger [median = 56 (41–65) vs. median = 65 (56–73) years], female (61.1% vs. 46.4%), self-identify as a non-White minority (64.8% vs. 39.5%), have a hematologic malignancy (64.8% vs. 50.2%) and poor ECOG status (63.0% vs. 54.6%) compared with vaccinated patients.

Among vaccinated patients with cancer (49.8% solid tumors, 50.2% hematologic malignancies), 163 (56.0%) received BNT162b2 (two doses) and 128 (44.0%) received mRNA-1273 (two doses). There was no statistically significant differences in patient demographics or clinical characteristics between those receiving BNT162b2 and mRNA-1273. The most common solid malignancies were thoracic (26.9%), melanoma (24.8%), breast (14.5%), and gastrointestinal (13.1%). Among hematologic malignancies, 65.1% had multiple myeloma, 13.7% lymphoma, and 21.2% leukemia or myeloproliferative neoplasms. Nearly all vaccinated patients were on treatment (ICI: 25.4%; ICI + chemotherapy: 11.3%; B-cell therapies: 32.0%, B-cell therapies + chemotherapy: 5.8%; chemotherapy: 16.5%); 85 (29.2%) had received an allogeneic (41.2%) or autologous (58.8%) transplant.

Longitudinal changes in seropositivity and antibody levels in patients with cancer

Following two-dose mRNA vaccination, peak IgG(S-RBD) antibody levels were lower in patients with cancer [solid: median = 8,581 (IQR = 2,375–26,799) AU/mL; hematologic: median = 1,128 (IQR = 188–11,115) AU/mL] compared with HCW [median = 11,794 (IQR = 6,504–20,698) AU/mL, **Fig. 1**]. After a median follow-up of 42 days (IQR = 26–57) after dose 2, patients with higher antibody levels were younger ($P = 0.018$), Hispanic ethnicity ($P = 0.010$), diagnosed with solid tumors ($P = 0.007$), or on clinical surveillance/hormonal therapies ($P < 0.001$; **Table 1**). A higher proportion of patients who received mRNA-1273 had antibody levels ≥4,160 AU/mL compared with those receiving BNT162b2 (61.3% vs. 37.6%, $P = 0.018$). No significant differences in peak antibody levels were observed across solid tumor subtypes. Among patients with hematologic malignancies, multiple myeloma patients had significant lower antibody levels (median = 794; IQR = 100–4,102 AU/mL; $P < 0.001$).

With longer follow-up [median = 145.5 days (IQR = 118–179.2) after dose 2], antibody levels significantly decreased [proportion of individuals with levels ≥4,160 AU/mL: 24.1% (solid) and 16.7% (hematologic), **Fig. 2**; Supplementary Table S2]. Consistent with peak levels, levels after 4–6 months were higher in younger patients ($P = 0.01$), patients with solid malignancies ($P = 0.011$) and those not on active anticancer treatment ($P < 0.001$). In multivariable models, treatment was a consistent predictor of seropositivity at both peak and sustained time points (Supplementary Table S3). Hispanic ethnicity was associated with 6.34-fold increase in odds of higher seropositivity at peak levels ($P = 0.002$). Younger age and good ECOG performance status were significant predictors of higher seropositivity after 4 to 6 months.

Overall, patients receiving mRNA-1273 had higher peak IgG(S-RBD) antibody levels compared with BNT162b2 (median = 9,896; IQR = 1,214–28,066 vs. median = 2,259; IQR = 290–11,691, respectively; $P = 0.002$, **Fig. 2A**) and this pattern persisted after 4–6 months (median = 1,450; IQR = 363–4,480 vs. median = 390; IQR = 95–2,173, respectively; $P = 0.003$). In multivariable models, patients receiving mRNA-1273 were 2.62-fold more likely to maintain higher seropositivity after 4 to 6 months compare those receiving BNT162b2 ($P = 0.03$).

Timing of anticancer treatments in relation to vaccine administration

Among patients with hematologic malignancies, patients receiving B-cell therapies had significantly lower peak [median = 824

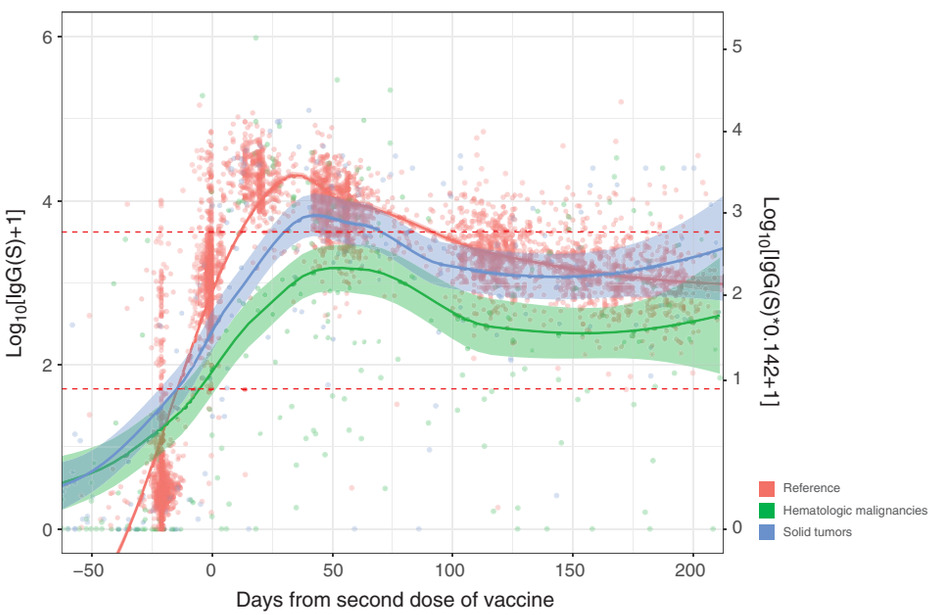

Figure 1.
Trajectories of IgG (S-RBD) antibody levels after two-dose mRNA vaccination among cancer patients. Blue, data for patients with solid tumors; green, for patients with hematologic malignancies; red, for the referent population (HCW). Dotted red lines represent the minimal cutoff for seroconversion defined as IgG(S-RBD) = 50 AU/mL and correlate of neutralization [IgG(S-RBD) = 4,160 AU/mL].

Table 1. Demographic and clinical characteristics of patients by peak antibody response after two-dose mRNA vaccination.

	IgG(S-RBD) antibody levels[a]			
	No seroconversion 0 < 50 AU/mL	**Intermediate seropositivity 50–4,160 AU/mL**	**High seropositivity ≥4,160 AU/mL**	***P* value**
N	17	60	70	
IgG(S-RBD) median (IQR)	11.7 (2.1, 15.0)	1000.3 (394.6, 2435.8)	20,997 (10,314, 34,489)	<0.001
Age, median (IQR) years	64 (56, 72)	68 (59.5, 73)	61 (50.5, 67.8)	0.018
Sex				0.094
Female	4 (5.8%)	28 (40.6%)	37 (53.6%)	
Male	13 (16.7%)	32 (41.0%)	33 (42.3%)	
Race/ethnicity				0.010
Non-Hispanic White	11 (12.6%)	37 (42.5%)	39 (44.8%)	
Hispanic	0 (0.0%)	6 (23.1%)	20 (76.9%)	
Non-Hispanic Black	2 (14.3%)	9 (64.3%)	3 (21.4%)	
Asian	2 (14.3%)	6 (42.9%)	6 (42.9%)	
Other	2 (40.0%)	2 (40.0%)	1 (20.0%)	
Unknown	0 (0.0%)	0 (0.0%)	1 (100.0%)	
Type of malignancy				0.007
Solid tumor	2 (3.1%)	25 (39.1%)	37 (57.8%)	0.381
Breast	1 (7.7%)	2 (15.4%)	10 (76.9%)	
Gastrointestinal	0 (0.0%)	5 (41.7%)	7 (58.3%)	
Melanoma	1 (8.3%)	4 (33.3%)	7 (58.3%)	
Thoracic	0 (0.0%)	7 (53.8%)	6 (46.2%)	
Other	0 (0.0%)	7 (50.0%)	7 (50.0%)	
Hematological malignancies	15 (18.1%)	35 (42.2%)	33 (39.8%)	0.002
Lymphoma	2 (25.0%)	2 (25.0%)	4 (50.0%)	
Leukemia/MDS/MPN	1 (5.0%)	4 (20.0%)	15 (75.0%)	
Myeloma	12 (21.8%)	29 (52.7%)	14 (25.5%)	
Type of anticancer treatment				<0.001
Clinical surveillance (±hormone)	0 (0.0%)	2 (15.4%)	11 (84.6%)	
ICI	2 (6.9%)	11 (37.9%)	16 (55.2%)	
ICI + chemotherapy	1 (5.3%)	11 (57.9%)	7 (36.8%)	
B-cell therapy	10 (20.0%)	23 (46.0%)	17 (34.0%)	
B-cell therapy + chemotherapy	4 (40.0%)	6 (60.0%)	0 (0.0%)	
Chemotherapy (±hormone)	0 (0.0%)	7 (26.9%)	19 (73.1%)	
ECOG status				0.341
0	4 (6.6%)	23 (37.7%)	34 (55.7%)	
1	12 (15.4%)	33 (42.3%)	33 (42.3%)	
2–3	1 (12.5%)	4 (50.0%)	3 (37.5%)	
SARS-CoV-2 vaccine				0.018
BNT162b2	11 (12.9%)	42 (49.4%)	32 (37.6%)	
mRNA-1273	6 (9.7%)	18 (29.0%)	38 (61.3%)	
Prior SARS-CoV-2 infection				>0.999
No	16 (11.7%)	56 (40.9%)	65 (47.4%)	
Yes	1 (10.0%)	4 (40.0%)	5 (50.0%)	
Days from dose 2 (median, IQR)	42 (33, 55)	48 (34, 62)	38 (23, 54)	0.119
Days from dose 1 (median, IQR)	68 (54, 78)	70 (58, 85)	62 (50, 81)	0.248

[a]Row percent.

(IQR = 81–5,539) AU/mL vs. median = 11,173 (IQR = 1,938–31,397) AU/mL, respectively; $P = 0.001$] and sustained antibody levels [median = 225 (IQR = 37–1,006) AU/mL vs. median = 1,022 (IQR = 862–4,480) AU/mL, respectively; $P = 0.003$, **Fig. 2C**] compared with those not receiving B-cell therapies. Vaccination after 4 weeks from any type of B-cell therapy yielded significantly higher peak levels (median = 14,131; IQR = 4,227–23,870 AU/mL) compared with earlier vaccination. The proportion of those with high seropositivity increased with the interval between treatment and vaccination (up to 2 weeks after treatment: 23.7%; 2–4 weeks: 40.0%; and 4+ weeks: 75.0%). Among those receiving anti-CD38 therapies, 100% seroconverted if vaccinated more than 2 weeks after first dose whereas no seroconversion was observed among 26.3% of cases vaccinated within two weeks of treatment.

Among patients with solid tumors, we observed a nonstatistically significant lower peak antibody levels among those receiving ICI with or without chemotherapy compared with those treated with chemotherapy or other therapies ($P = 0.072$, **Fig. 2D**). There was a significant drop in antibody levels at 4 to 6 months among patients on ICI compared with those receiving only chemotherapy and other treatments ($P = 0.004$). Drop in antibody levels was more pronounced among patients who were vaccinated after starting ICI compared with before treatment (median = 278; IQR = 202–958 vs. median = 1,327; IQR = 913–2,627, respectively; $P = 0.043$, **Fig. 3**).

Breakthrough infections

Among vaccinated patients with, there were two (0.69%) breakthrough cases of severe COVID-19 illness requiring hospitalization

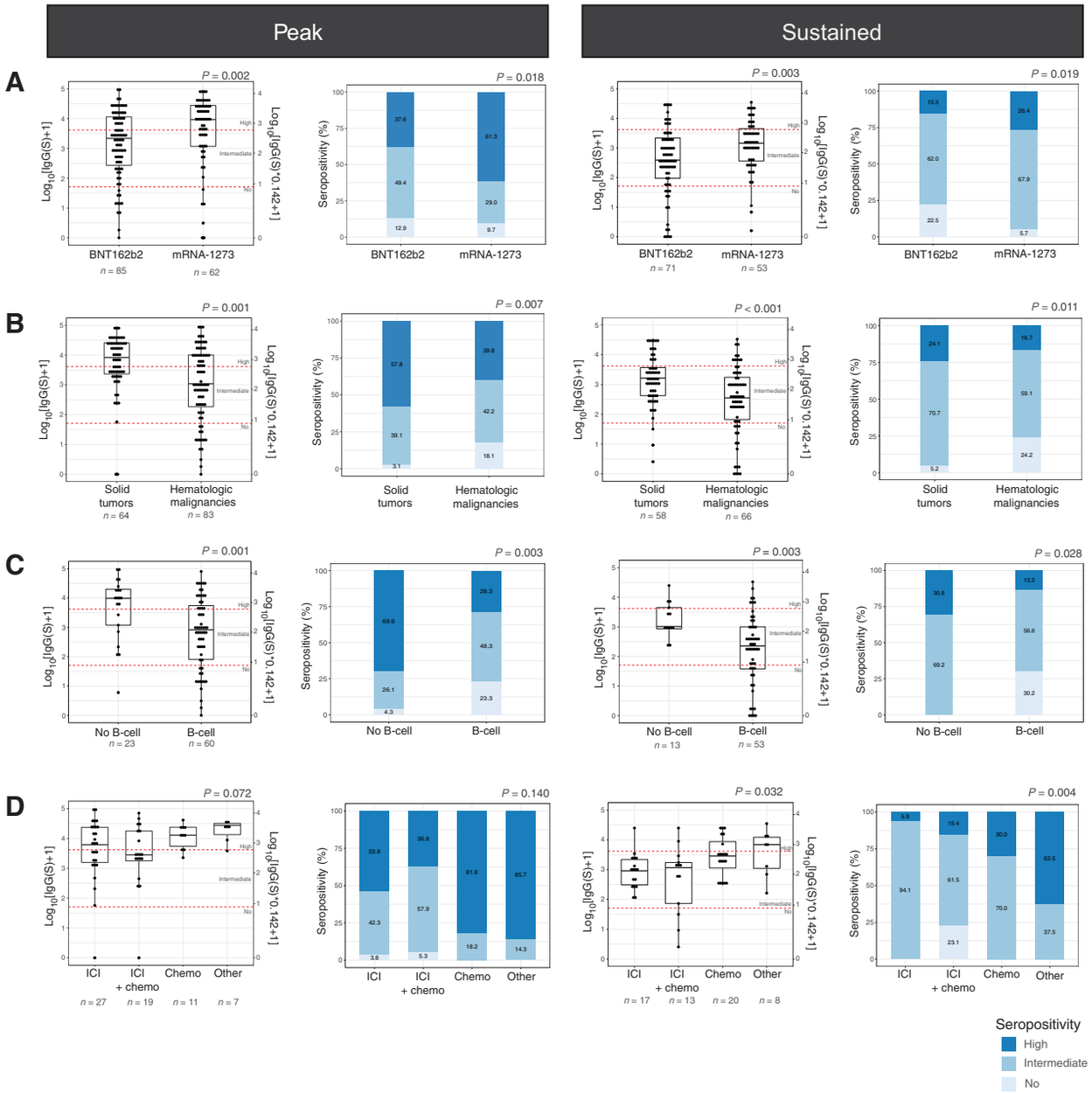

Figure 2.

Post-vaccination IgG(S-RBD) antibody levels at peak and sustained time points among cancer patients by vaccine type: BNT162b2 vs. mRNA-1273 (**A**); tumor type: solid tumor vs. hematologic malignancy (**B**); treatment among individuals with B-cell malignancies: B-cell targeted vs. no B-cell targeted (**C**); and treatment among individuals with solid tumors: ICI, ICI + chemotherapy, chemotherapy vs. other (**D**). Dots in box plots depict IgG(S-RBD) antibody levels; boxes represent the first quartile, median, and third quartile; whiskers represent minimum and maximum values. Stacked bar chart denote seropositivity (high, solid blue; intermediate, light blue; none, white). Dotted red lines represent the minimal cutoff for seroconversion [IgG(S-RBD) = 50 AU/mL] and correlate of neutralization [IgG(S-RBD) = 4,160 AU/mL].

(Supplementary Table S4; Supplementary Fig. S2). An additional 9 (3.1%) vaccinated patients were suspected of asymptomatic illness. Among unvaccinated patients, 1 (1.9%) case of severe COVID-19 illness and death occurred. All cases of severe COVID-19 illness occurred in patients with hematologic malignancies (mantle cell lymphoma: 1; multiple myeloma: 2).

Discussion

In this prospective cohort study, we show significant variability in peak and sustained IgG(S-RBD) antibody levels in vaccinated patients undergoing cancer treatment. Many patients do not seroconvert, and at 4 to 6 months of follow up only 24% of solid tumor patients and 17% of hematologic malignancy patients maintained

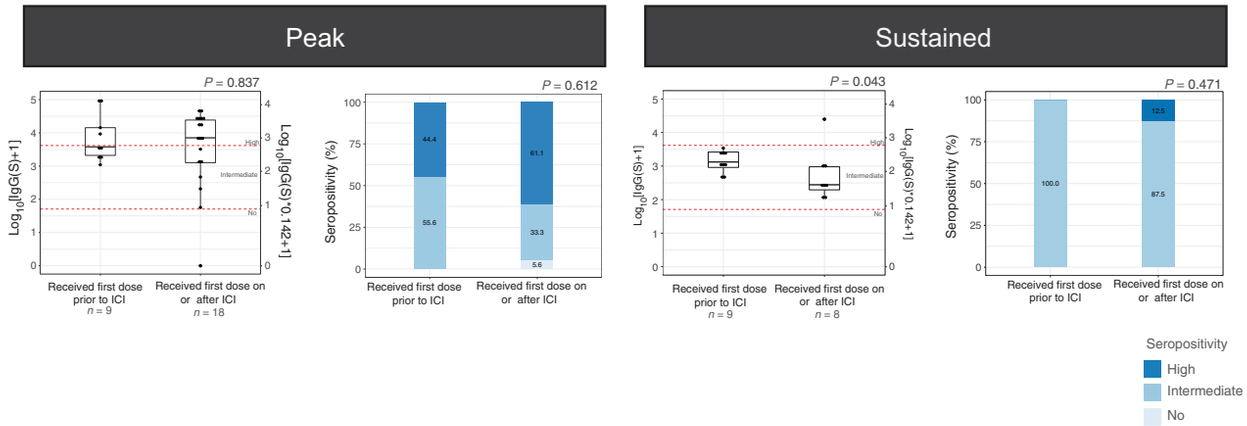

Figure 3.

Post-vaccination IgG(S-RBD) antibody levels at peak and sustained time points among patients with solid tumors treated with immune checkpoint inhibitors by timing of vaccination administration. Dots in box plots depict IgG(S-RBD) antibody levels; boxes represent the first quartile, median, and third quartile; whiskers represent minimum and maximum values. Stacked bar chart denote seropositivity (high, solid blue; intermediate, light blue; none, white). Dotted red lines represent the minimal cutoff for seroconversion [IgG(S-RBD) = 50 AU/mL] and correlate of neutralization [IgG(S-RBD) = 4,160 AU/mL].

high antibody levels. Differences in antibody responses were partly explained by differences in treatment regimens, timing between vaccination and treatment, mRNA vaccine type, age and ethnicity. Despite variability in antibody responses among vaccinated patients with cancer, breakthrough infections resulting in severe COVID-19 illness and hospitalization were uncommon up to 6 months, similar to findings reported in HCW (22). All cases of severe illness/death occurred in hematologic malignancy patients; additional approaches may be needed to protect these individuals from COVID-19.

A strength of this study is the long-term follow up of patients on specific anticancer treatments. Our results confirm previous reports of lower rates of seroconversion and antibody levels among individuals with hematologic malignancies and patients on chemotherapy (3, 6–8, 11–14, 16, 21, 34). Unexpectedly, we observed that fewer patients treated with ICI achieve high-peak antibody levels after vaccination, when compared with patients on chemotherapy alone and other treatments. Antibody levels quickly dropped after peak levels, with only 5.9% of ICI patients maintaining high antibody levels at 4 to 6 months follow up. This was unexpected because ICI are thought to broadly work through immune stimulation (35), and we hypothesized that ICI patients would have normal or higher responses to vaccination.

A key dilemma facing clinicians is when to administer vaccinations or boosters in patients undergoing immunosuppressive therapy. Some clinicians may decide to delay cancer treatment to allow a window for vaccination, whereas others may delay vaccination until treatment is complete to ensure a robust vaccine response. There are currently very little data to help with such decision making. As expected, we observed that B-cell and plasma cell targeting therapy had the strongest effect on antibody levels after vaccination, but that delaying treatment for as little as 2 to 4 weeks after vaccination improved humoral responses. For patients receiving anti-CD38 therapy, all patients with a gap of at least 2 weeks between vaccination and treatment seroconverted. Two recent studies in patients receiving the CD20 targeting antibody rituximab demonstrated reduced seroconversion for up to 6 to 9 months after treatment (34, 36). Differences in timing of administration between vaccination and anticancer treatments are likely due to different pharmacokinetics between the two agents, and the specific types of immune cells targeted by anti-CD38 and anti-CD20 antibodies.

When we examined the effect of vaccine timing on patients treated with ICI, we observed that patients pretreatment with ICI had reduced antibody responses compared with those who received treatment after vaccination. Although PD-1 targeting in cancer has primarily focused on its role in T cells, PD-1 is expressed on naïve B cells, and PD-1/PD-L1 signaling is a critical part of the germinal center response (37). Preclinical vaccine studies have also shown that treatment with ICI prior to vaccine abolishes vaccine induced T-cell responses due to apoptosis of overactivated T cells (38). Further studies that examine vaccine immune response in ICI-treated patients are urgently needed.

Data comparing mRNA vaccines are limited. A study among HCW showed higher antibody levels in participants vaccination with mRNA-1273 compared with BNT162b2 (39). A comparative effectiveness study among adults without immunocompromising conditions showed that vaccine effectiveness decreased to 77% with BNT162b2, but remained around 92% for mRNA-1273 after 120 days (30). Protection against COVID-19 hospitalization was also higher for the mRNA-1273 vaccine (93%) than BNT162b2 (88%; ref. 30). The higher mRNA content in mRNA-1283 compared with BNT162b2 and longer interval between priming and boosting compared with BNT162b2 is suspected to explain this difference in humoral response. We also demonstrated significantly higher response from mRNA-1273 compared with BNT162b2 in patients with cancer across tumor types. However, there are many challenges to interpreting comparative responses between the two mRNA vaccines based on real-world studies where vaccination is not assigned on the basis of randomization. This includes the potential for unaccounted sources of bias, and results should be interpreted with caution and validated in randomized clinical trials. If confirmed, these findings may be clinically relevant, especially for patients with cancer that mount low or

intermediate serologic responses due to their disease state or anticancer regimens.

Consistent with findings among HCW, we observed <1% of breakthrough infections resulting in hospitalization among vaccinated patients with cancer. The frequency of severe COVID-19 illness was higher in unvaccinated patients with cancer. Heudel and colleagues (24) observed 0.4% patients with cancer developed COVID-19 symptoms with documented SARS-CoV-2 on RT-PCR after two doses. Mortality within 2 months was significantly higher in patients with hematologic malignancies (24). In our study, all hospitalized patients with COVID-19 had hematologic malignancies. The two vaccinated patients recovered with treatment and the unvaccinated patient died.

This study has several limitations. First, this cohort represents a sample of the cancer population receiving care at a single health care system. Real-world observational studies are subject to potential selection biases, missing data, and other unmeasured confounders. In this study, we did not have complete serological data at all timepoints, and we were not able to adjust for all covariates across subgroup analyses. Second, the number of unvaccinated patients in the cohort was small making estimates of vaccine efficacy challenging. Incomplete sampling may have underestimated asymptomatic infections during follow-up. Sample size limitations precluded analysis of certain subgroup of interest. Our report focused only on humoral immunity and would have been strengthened with corresponding data on cellular immunity. Finally, the follow-up period is relatively short and does not allow us to estimate the risk of breakthrough infections beyond 6 months.

Understanding longitudinal trajectories of immune response following vaccination among patients with cancer is critical. The U.S. FDA recommends booster vaccination after 6 months of second dose in immunocompromised individuals. However, the optimal timing and frequency of booster vaccinations is unclear. Boosters may also only be useful in those with an initial response. Alternative approaches, such as heterologous vaccination (40) and mAbs, may be needed for patients lacking a response. Further studies will help determine optimal approaches including timing of vaccination and anticancer treatments in patients with cancer.

Authors' Disclosures

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