Predictors of Humoral Response to SARS-CoV-2 Vaccination after Hematopoietic Cell Transplantation and CAR T-cell Therapy

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ABSTRACT
Cellular therapies including allogeneic hematopoietic cell transplant (allo-HCT) and autologous hematopoietic cell transplant (auto-HCT) and chimeric antigen receptor (CAR) T-cell therapy render patients severely immunocompromised for extended periods after therapy, and data on responses to COVID-19 vaccines are limited. We analyzed anti–SARS-CoV-2 spike IgG Ab (spike Ab) titers and neutralizing Ab among 217 recipients of cellular treatments (allo-HCT, n = 149; auto-HCT, n = 61; CAR T-cell therapy, n = 7). At 3 months after vaccination, 188 patients (87%) had positive spike Ab levels and 139 (77%) had positive neutralization activity compared with 100% for both in 54 concurrent healthy controls. Time from cellular therapy to vaccination and immune recovery post–cellular therapy were associated with response. Vaccination against COVID-19 is an important component of post–cellular therapy care, and predictors of quantitative and qualitative response are critical in informing clinical decisions about optimal timing of vaccines and the requirement for booster doses.

SIGNIFICANCE: Identifying predictors of response to vaccination against SARS-CoV-2 in patients following cellular therapy is critical to managing this highly vulnerable patient population. To date, this is the most comprehensive study evaluating quantitative and qualitative responses to vaccination, providing parameters most predictive of response and potentially informing booster vaccination strategies.

See related article by Chung et al., p. 568.

Note: Supplementary data for this article are available at Blood Cancer Discovery Online (https://bloodcancerdiscov.aacrjournals.org/).

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INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization in March 2020. Patients with cancer with hematologic malignancies, chronic lymphopenia, and/or corticosteroid use are at increased risk for hospitalization, severe respiratory illness, and increased mortality (1–4). Based on observed outcomes in the early part of the pandemic, factors including presence of lung infiltrates at presentation and neutropenia were identified as predictors for poor outcomes in recipients of cellular therapies for hematologic malignancies (5). Later, multicenter data from the Center of International Blood and Marrow Transplant Research reported that 27% of allogeneic hematopoietic cell transplantation (allo-HCT) recipients and 20% of autologous hematopoietic cell transplantation (auto-HCT) recipients with COVID-19 manifested moderate severity illness, whereas severe disease was reported in 15% and 13%, respectively, with an overall mortality of 21% (6). Our group has also reported the negative indirect effects of the pandemic on patients undergoing cellular therapies from delays in treatment leading to progression of disease and mortality (7).

Effective immunization is vital for protecting cellular therapy recipients from COVID-19 and mitigating spreading of the pandemic. There are currently two mRNA vaccines against SARS-CoV-2: the BNT162b2 (Pfizer–BioNTech; ref. 8), which is FDA approved, and mRNA-1273 (Moderna; ref. 9), which is approved under an Emergency Use Authorization protocol, both administered as two-dose series separated by 21 days (Pfizer–BioNTech) or 28 days (Moderna). Both mRNA vaccines are highly effective in healthy individuals, with >90% prevention of severe disease and mortality. However, among patients with malignancies (10, 11) and recipients of solid organ transplantation (12–14), emerging data suggest lower vaccine efficacy compared with the healthy population. Data for patients undergoing cellular therapies are sparse, with small studies reporting attenuated humoral and/or cellular immune responses (15–17).

We therefore aimed to assess immune responses to mRNA COVID-19 vaccines among patients who underwent cellular therapies at our center, with the goal of identifying predictors of response, determining the ideal timing for vaccination, and identifying patients at high risk for nonprotective immune responses who might benefit from additional doses (“boosters”) of vaccines.

RESULTS

Recipients of Cellular Therapy Have Lower Vaccine Responses than Healthy Donors

Between December 22, 2020, and February 28, 2021, 217 patients who were vaccinated against SARS-CoV-2 participated in this prospective observational study. Patient characteristics are summarized in Table 1. Patients were vaccinated as early as 2 months after cellular treatment (day 63), with a median time between treatment and the first dose of the vaccine of 1,007 days [interquartile range (IQR), 488–1,761; 2.75 years]. All patients received mRNA vaccines according to the recommended doses and timing, with 70% receiving the BNT162b2 (Pfizer–BioNTech) vaccine and 30% the mRNA-1273 (Moderna) vaccine. Fifty-two patients (23.9%) met our institutional immune recovery criteria for initiation of inactivated vaccines after transplant (CD4+ T-cell count >200 cells/μL, CD19+ B-cell count >50 cells/μL, IgG >500 mg/dL and PHA mitogen proliferation >40%), and 151 patients

| Variable                                      | N  | %    |
|-----------------------------------------------|----|------|
| Gender, male                                  | 129| 59.4%|
| Age, median years (range)                     | 66.4| 25.8–84.1 |
| Disease group                                 |    |      |
| Acute leukemia                                | 75 | 34.6%|
| MDS and MPN                                   | 41 | 18.8%|
| Chronic leukemia                              | 8  | 3.6% |
| MM and amyloid                                | 40 | 18.4%|
| Low-grade lymphoma                            | 8  | 3.6% |
| High-grade lymphoma and HD                    | 35 | 16.1%|
| T-cell lymphoma                               | 6  | 2.7% |
| Other: AA, systemic mastocytosis, BPD CN       | 4  | 1.8% |

Table 1. Patient characteristics

NOTE: Early allo, <1 year; mid-allo, 1–3 years; late allo >3 years; early auto, <1 year; late auto, >1 year.

Abbreviations: AA, aplastic anemia; BPD CN, blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; HD, Hodgkin disease; IMiD, immunomodulatory drug; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasms.
Response to SARS-CoV-2 Vaccination after Cellular Therapies

At 1 month after the first vaccine dose, 39 (18%) patients were tested for response. Twenty-four (61%) had a positive spike Ab defined as >50 AU/mL (median, 479.75 AU/mL; IQR, 170.4–3,658.8), and 15 (38.5%) had positive neutralization activity defined as >50% inhibition. The red lines denote the thresholds for positive assays (anti-SARS-CoV-2, 50 AU/mL, neutralization Abs: 30% inhibition). The three groups of allo-HCT, auto-HCT, and chimeric antigen receptor (CAR) T-cell therapy are represented in this graph. B, Ab responses to COVID-19 vaccines according to type of cellular therapy and timing posttreatment. Anti-SARS-CoV-2 spike IgG and neutralizing Ab titers were measured at 3 months after initial COVID-19 vaccination and summarized using scatter plots with median and IQR. Left, plots comparing anti-SARS-CoV-2 spike IgG categorized according to time for cellular treatment and type of cellular treatment (auto-HCT, allo-HCT, CAR T) compared with healthy controls (HC). Green dashed line denotes the threshold for a positive result (50.0 AU/mL). Right, circulating neutralizing Abs against SARS-CoV-2 were assessed at 3 months after initial COVID-19 vaccination. Plots comparing neutralizing Abs categorized according to time for cellular treatment and type of cellular treatment (auto-HCT, allo-HCT, CAR T) compared with healthy controls. Green dashed line denotes the threshold for a positive result (30% inhibition). *, P < 0.05; **, P < 0.01; ***, P < 0.001. ns, not significant. Early auto, first year; mid-allo, 1 to 3 years; late allo, >3 years; early auto, first year; late auto, >1 year. The number of patients is reported for spike Ab (S) and neutralizing Ab (N) for each group: healthy control (5.63/N25), early auto (5.20/N15), late auto (5.41/N37), early allo (5.19/N14), mid-allo (5.55/N49), late allo (5.75/N61), and CAR (5.7/N2). C, Ab responses to COVID-19 vaccines according to immune recovery. Anti-SARS-CoV-2 spike IgG and neutralizing Ab titers were measured at 3 months after initial COVID-19 vaccination and summarized using scatter plots with median and IQR. Left, plots comparing anti-SARS-CoV-2 spike IgG among patients meeting immune recovery posttreatment (green) versus patients not meeting criteria (red). Green dashed line denotes the threshold for a positive result (50.0 AU/mL). Right, circulating neutralizing Abs against SARS-CoV-2 were assessed at 3 months after initial COVID-19 vaccination. Plots comparing neutralizing Abs among patients meeting immune recovery posttreatment (green) versus patients not meeting criteria (red). Green dashed line denotes the threshold for a positive result (30% inhibition). **, P < 0.01; ***, P < 0.001. Pos, meeting all criteria, i.e., CD4+ T-cell count >200 cells/μL, CD19+ B-cell count >50 cells/μL, IgG >500 mg/dL, and PHA mitogen proliferation >40%. Neg S:52/N43, Pos S:52/N52.

(64.9%) initiated or completed standard posttransplant vaccinations prior to receiving a COVID-19 vaccine. As of August 1, 2021, none of the 217 vaccinated patients were diagnosed with COVID-19 disease after vaccination.

At 1 month after the first vaccine dose, 39 (18%) patients were tested for response. Twenty-four (61%) had a positive spike Ab defined as >50 AU/mL (median, 479.75 AU/mL; IQR, 170.4–3,658.8), and 15 (38.5%) had positive neutralization activity defined as >30% (median, 57.3%; IQR, 37.8%–89.6%). At 3 months after the first vaccine, 188 patients (87%) had a positive spike Ab (median, 5,379 AU/mL; IQR, 451–15,750), and 139 (77%) had a positive neutralization Ab assay (median, 93%; IQR, 36%–96%). A higher spike Ab titer was associated with higher neutralization activity, and neutralization activity was absent for spike Ab levels <250 AU/mL (Fig. 1A).

Fifteen patients (7%) had a documented COVID-19 infection or presence of N (nucleocapsid protein) Abs to SARS-CoV-2 prior to vaccination. Among these, seven had spike Ab level >50 AU/mL and neutralization Ab >30% detected prior to vaccination. Two patients with COVID-19 disease prior to their cellular treatment did not mount a measurable response to the vaccines given after treatment, whereas the remaining 13 generated very high spike Ab levels (25,000 AU/mL in 12 of 13 patients).

Sixty-nine healthy volunteers participated as a control group. The median age was 31 years (range, 22–67), with 78% female and 13% having COVID-19 disease prior to vaccination. Two patients with COVID-19 disease prior to their cellular treatment did not mount a measurable response to the vaccines given after treatment, whereas the remaining 13 generated very high spike Ab levels (25,000 AU/mL in 12 of 13 patients).
Time from Cellular Therapy to Vaccination Correlated with Humoral Response

Sixty-seven percent of patients vaccinated in the first 12 months after cellular therapy mounted a spike Ab response compared with 89% of patients vaccinated between 12 and 24 months, 91% of patients vaccinated between 24 and 36 months, and 93% of patients vaccinated after 36 months after cellular treatment ($P = 0.001$; Supplementary Table S1). Four patients were vaccinated before day 100 after cellular treatment, of whom only one had a positive spike Ab level of 1,016.6 and detectable neutralizing Ab. An additional 12 patients were vaccinated between days 100 and 180, and 6 mounted spike Ab (median, 409.4; IQR, 123.3–5,091.7), with 2 having detectable neutralizing Abs.

In a multivariate analysis (MVA) including type of cellular treatment (auto- and allo-HCT), time from transplant to vaccination, CD4 count, CD19 count, mitogen level, and IgG, CD19 (OR, 1.49; $P < 0.001$), mitogen levels (OR, 1.31; $P = 0.002$) and IgG (OR, 1.13; $P = 0.034$) remained independently associated with mounting a spike Ab response (Supplementary Table S2).

Response to Vaccine Varied between Different Types of Cellular Treatments

One hundred and forty-nine patients who underwent allo-HCT were vaccinated between days 63 and 5,186 (median, 1,109; IQR, 571–2,040) after therapy. Of the 25 for whom samples were available at 1 month after vaccination, 17 (68%) mounted a spike Ab response (median, 739.2; IQR, 219.5–3,051.3) and 11 of 21 (52%) had >30% neutralizing Ab (median, 57.29; IQR, 36.6–85.2%). At 3 months after vaccination, all patients were tested for spike Ab, with 89% mounting a response (median, 5,019.8; IQR, 635.4–15,914.5), and of the 122 who had neutralizing Ab tested, 78% were higher than the positive threshold (median, 90%; IQR, 41.7–96.3). This was significantly lower compared with HC ($P = 0.001$; Fig. 1C; Supplementary Table S1). In allo-HCT recipients, the response rates were 79% for patients vaccinated in the first year (early allo-HCT), 89% for those vaccinated between 1 and 3 years after allo-HCT defined above were significantly more likely to respond to vaccination by both titer and percentage neutralization. Among patients who did not meet criteria at time of vaccination, 37 (71%) had a positive spike Ab compared with 58 (98%) patients who met criteria ($P < 0.001$), and 26 (60%) patients who did not meet all criteria at time of vaccination had detectable neutralizing Ab compared with 47 (90%) patients who met criteria ($P = 0.001$; Fig. 1C; Supplementary Table S1).

**Table 2. Comparisons between patients post-allo-HCT and post-auto-HCT to healthy controls**

| Time from Treatment to Vaccination | Anti–SARS-CoV-2 spike IgG, median (IQR) | $P$ | Neutralizing Abs, median (IQR) | $P$ |
|-----------------------------------|----------------------------------------|----|--------------------------------|----|
| Healthy (N = 54)                  | 7,720 (3,885–9,746)                    |    | All cellular treatments (N = 217) |    |
| All cellular treatments (N = 217) | 3,292.7 (456.9–15,600.2)               | 0.001 | All cellular treatments (N = 180) |    |
| Healthy (N = 21)                  | 95.8 (94.5–96.3)                       |    | All cellular treatments (N = 122) |    |
| Allo-HCT (N = 149)                | 5,019.8 (635.4–15,914.5)               | 0.024 | Early allo (N = 19)              |    |
| Early allo (N = 19)               | 445.6 (112.3–5,728.2)                  | <0.001 | Early allo (N = 14)              |    |
| Mid-allo (N = 55)                 | 3,409.3 (683.8–20,901.2)               | 0.027 | Mid-allo (N = 49)                |    |
| Late allo (N = 75)                | 6,786.6 (1,833.5–17,535.7)             | 0.434 | Late allo (N = 61)               |    |
| Auto-HCT (N = 61)                 | 2,260.1 (419.4–10,598.8)               | <0.001 | Auto-HCT (N = 52)                |    |
| Early auto (N = 20)               | 718 (16.1–300.1)                       | 0.001 | Early auto (N = 15)              |    |
| Late auto (N = 41)                | 2,512.3 (673–10,598.8)                 | 0.005 | Late auto (N = 37)               |    |
|                                      |                                        |    |                                 |    |

NOTE: Early allo, <1 year; mid-allo, 1–3 years; late allo >3 years; early auto, <1 year; late auto, >1 year.

**Immune Recovery after Cellular Therapy Is Associated with Vaccine Response**

B cells and helper CD4 T cells are the primary drivers of vaccine responses in germinal centers. We therefore profiled immune subsets in the peripheral blood, responses to mitogen stimulus, and IgG levels as measures of immune reconstitution in our patient population. These factors have previously been identified to predict vaccine responses to influenza, pneumococcus, and shingles (18, 19), but their role in predicting response to mRNA-based vaccinations remains ill-defined. Immune function as assessed by CD4 or CD19 counts, mitogen proliferation response, and IgG levels found that each associated strongly with response to vaccine both for spike Ab and neutralizing Abs (Supplementary Table S1). Patients meeting all the criteria
(mid-allo-HCT), and 92% for those >3 years after allo-HCT (late allo-HCT), though this association was not statistically significant ($P = 0.282$). Titers were significantly lower among patients vaccinated in the first year posttransplant ($P = 0.019$; Table 3). Among seven patients vaccinated within the first 6 months posttransplant, three had a positive spike Ab, and in one patient, neutralizing Abs were detected. In comparison with HC, patients who were vaccinated >36 months after allo-HCT had an Ab response comparable with HC, whereas patients who were vaccinated in the first year and between 1 and 3 years posttransplant had significantly lower responses ($P \leq 0.001$ and $P = 0.027$, respectively; Table 2).

Immune function assessed by CD4, CD19, and IgG levels was available in 102 (68%) patients and strongly associated with response to vaccine for both spike Ab and neutralizing Abs. The median spike Ab levels for patients with CD4 count <200 cells/μL and >200 cells/μL were 422.6 (IQR, 13.2–2,427.2) and 6,651.7 (IQR, 1,258–2,082.6), respectively, with 71% versus 93% having a positive Ab ($P = 0.016$). Only 56% of patients with CD4 <200 cells/μL had detected neutralizing Abs (median, 53.7%; IQR, 2–93.3) versus 85% of patients with CD4 >200 cells/μL (median, 95.5%; IQR, 64.6–96.4; $P = 0.019$; Table 3). Among patients whose CD19 count was <50 cells/μL and >50 cells/μL at time of vaccination, 46% versus 94% had a positive spike Ab with medians of 27.5 (IQR, 5.2–373.2) and 6,425.7 (IQR, 1,258–2,082.6), respectively ($P < 0.001$). Only 20% of patients with CD19 <50 cells/μL had detected neutralizing Abs (median, 0; IQR, 0–20.7) compared with 87% patients with CD19 >50 cells/μL (median 95.5%; IQR, 67.4–96.3; $P < 0.001$; Table 3). Among patients whose IgG level was <500 mg/dL and >500 mg/dL at time of vaccination, 78% versus 95% had a positive spike Ab with medians of 1,156.5 (IQR, 373.4–24,333.3) versus 6,538.7 (IQR, 1,257.1–20,457.2; $P = 0.038$), whereas 67% patients with IgG level <500 mg/dL had detected neutralizing Abs (median, 49.3%; IQR, 12.9–96) compared with 85% with IgG level >500 (median, 94.7%; IQR, 66.7–96.3; $P = 0.133$; Table 3). Lastly, a significant difference in response to COVID-19 vaccine was seen among patients who met all criteria to initiate vaccinations compared with those who did not ($P = 0.002$; Table 3).

Forty-six allo-HCT patients (31%) were on immunosuppressive treatments (ruxolitinib, cyclosporine, or tacrolimus) at the time of vaccination, either for treatment of or as prophylaxis against graft-versus-host disease, and 14% were on oral steroids (all were on low dose, <0.5 mg/kg) for various indications. Treatments with immunosuppressive medications did not appear to decrease the likelihood of spike Ab response, but these patients were less likely to produce neutralizing Abs. Steroid use was associated with both lower spike Ab and neutralizing Ab response rates, with 67% of patients treated with steroids having positive spike Ab and 44% having a detectable neutralizing Ab compared with 93% ($P = 0.002$) and 84% ($P = 0.001$) among patients not treated with corticosteroids, respectively (Table 3).

In an MVA in patients who underwent allo-HCT including CD4 count, CD19 count, IgG, and steroid use, CD19 (OR, 1.53; $P < 0.001$) and IgG levels (OR, 1.15; $P = 0.023$) were associated with mounting a spike Ab response (Supplementary Table S2).

Sixty-one patients who underwent auto-HCT were vaccinated between days 79 and 3,784 (median, 774 days; IQR, 245–1,367) after therapy. Thirteen patients had samples available at 1 month after first vaccination, with 7 (54%) mounting spike Ab responses (median, 202.3; IQR, 109.3–296), and in 4 of 11 (36%), neutralizing Abs were detected (median, 46.3%; IQR, 36.13–85.8). At 3 months after vaccination, all patients tested for spike Ab, and 87% mounted a response (median, 2,260.1; IQR, 419.4–10,598.8) and 80% had >30% neutralizing Ab (median, 79.8%; IQR, 33.9–96). This was significantly lower compared with HC for the spike Ab and neutralizing Ab, respectively ($P < 0.001$ and 0.002; Table 2).

Patients vaccinated in the first year after auto-HCT (early auto) had significantly lower response rates for both the spike Ab ($P = 0.001$) and neutralizing Ab ($P = 0.025$) compared with patients vaccinated after the first year posttransplant (Table 3). Compared with HC, patients who were vaccinated early ($P < 0.001$) or late after an auto-HCT ($P = 0.009$) had a significantly lower response (Table 2).

Immune function assessed by CD4, CD19, mitogen, and IgG levels was available for 29 (47%) patients, and among these patients, only CD19 levels were associated with spike Ab response but not with neutralizing Ab response (Table 3).

Forty-three patients (71%) were on active treatment at the time of vaccination: immunomodulatory drugs (IMiD; lenalidomide and pomalidomide) in 20 patients (33%) and daratumumab in 12 (20%). Single-agent IMiDs were used mostly as maintenance treatment. Although response rates were not different between patients on treatments with either IMiDs or daratumumab compared with patients not on treatment, a significantly lower level of spike Ab ($P = 0.045$) but not neutralizing Abs ($P = 0.119$) was noted among patients treated with daratumumab (spike Ab median, 513 AU/mL; IQR, 226.6–1,486.9, and neutralizing Ab median, 59%; IQR, 8.8–81.4) versus those not on treatment (median, 3,297; IQR, 655–19,499, and median, 80.5%; IQR, 44.8–96.3, respectively).

Seven patients who underwent chimeric antigen receptor (CAR) T therapy were included in this analysis. The patients were vaccinated between days 66 and 825 (median, 218; IQR, 123–720). Response at 1 month was assessed in one patient, and the patient did not mount a response. At 3 months, only two of seven (28.5%) patients had a positive spike Ab response, with levels of 3,281 and 16,067 UA/mL. Immune function data were available on six patients with median CD4, CD19, mitogen, and IgG levels of 247 cells/μL, 0 cells/μL, 59%, and 710 mg/dL.

**Assessing Different Cutoffs for the Anti-SARS-CoV-2 Spike IgG Response**

A cutoff of 50 AU/mL was defined by the manufacturer as positive. Because the adequate titer threshold for predicting for neutralization capacity in vitro or clinically preventing disease is unknown, we evaluated for predictors of higher spike Ab titers. This analysis highlights that association between higher levels of spike Ab and the presence of neutralizing Ab as demonstrated in Fig. 1A. Immune function at the time of vaccination remained a significant predictor regardless of cutoff (Supplementary Table S3).
# Table 3. Allo-HCT and auto-HCT response characteristics

## Allo-HCT

| Variable | Group       | N    | Median (IQR) | <50 (IQR) | >50 (IQR) | P    |
|----------|-------------|------|--------------|-----------|-----------|------|
| Time groups per type of cellular treatment | Early allo | 19   | 445.6 (112.3–5,728.2) | 4 (21%) | 15 (79%) | 0.282 |
|         | Mid-allo | 55   | 3,409.3 (683.8–20,901.2) | 6 (11%) | 49 (89%) | 0.001 |
|         | Late allo | 75   | 6,786.6 (1,833.5–17,535.7) | 6 (8%) | 69 (92%) | 0.001 |
| CD4 count | <200 | 21   | 422.6 (13.2–2,247.2) | 6 (29%) | 15 (71%) | 0.001 |
|         | ≥200 | 81   | 6,651.7 (1,258–20,281.6) | 6 (7%) | 75 (93%) | 0.001 |
| CD19 count | <50 | 13   | 27.5 (5.2–373.2) | 7 (54%) | 6 (46%) | 0.001 |
|         | ≥50 | 89   | 6,425.7 (1,258–20,281.6) | 5 (6%) | 84 (94%) | 0.001 |
| IgG level | <500 | 18   | 1,156.5 (373.4–24,333.3) | 4 (22%) | 14 (78%) | 0.001 |
|         | ≥500 | 78   | 6,538.7 (1,257.1–20,457.2) | 4 (5%) | 74 (95%) | 0.001 |
| All immune criteria for vaccination met prior to COVID-19 vaccine | Not met | 35   | 916.5 (115.8–19,124) | 7 (20%) | 28 (80%) | 0.001 |
|         | Met | 48   | 7,638 (2,322.9–30,431) | 0 (0%) | 48 (100%) | 0.001 |
| Immune suppression with tacrolimus/cyclosporine or ruxolitinib | Yes | 46   | 4,430.4 (319.1–15,835.9) | 5 (11%) | 41 (89%) | 0.001 |
|         | No | 103  | 5,019.8 (936.8–17,529.2) | 11 (11%) | 92 (89%) | 0.001 |
| Steroids | Yes | 21   | 543.9 (16.1–5,786.1) | 7 (33%) | 14 (67%) | 0.001 |
|         | No | 128  | 5,960.4 (952–20,340.1) | 9 (7%) | 119 (93%) | 0.001 |

## Auto-HCT

| Variable | Group       | N    | Median (IQR) | <50 (IQR) | >50 (IQR) | P    |
|----------|-------------|------|--------------|-----------|-----------|------|
| Time groups per type of cellular treatment | Early auto | 20   | 718 (161.1–6,300.1) | 7 (35%) | 13 (65%) | 0.001 |
|         | Late auto | 41   | 2,564.2 (673.9–5,985.8) | 1 (2%) | 40 (98%) | 0.001 |
| CD4 count | <200 | 6    | 242 (35.4–490.7) | 2 (33%) | 4 (67%) | 0.001 |
|         | ≥200 | 23   | 2,390.8 (407.8–987.6) | 5 (22%) | 18 (78%) | 0.001 |
| CD19 count | <50 | 9    | 10.5 (4.4–41.9) | 6 (67%) | 3 (33%) | 0.001 |
|         | ≥50 | 20   | 3,123.9 (901.1–9,520.1) | 1 (5%) | 19 (95%) | 0.001 |
| IgG level | <500 | 14   | 487 (28.1–1,143.3) | 4 (29%) | 10 (71%) | 0.001 |
|         | ≥500 | 35   | 2,645.4 (584.9–10,405.8) | 3 (9%) | 32 (91%) | 0.001 |
| All immune criteria for vaccination met prior to COVID-19 vaccine | Not met | 13   | 554.5 (21.2–2,308.0) | 4 (31%) | 9 (69%) | 0.001 |
|         | Met | 11   | 3,603.2 (1,403.2–8,277.5) | 1 (9%) | 10 (91%) | 0.001 |
| IMiDs | Yes | 20   | 1,176.6 (417.3–3,370.1) | 2 (10%) | 18 (90%) | 0.001 |
|         | No | 41   | 2,757.1 (419.4–21,010.8) | 6 (15%) | 35 (85%) | 0.001 |
| Daratumumab | Yes | 12   | 513 (226.6–1,486.9) | 1 (8%) | 11 (92%) | 0.001 |
|         | No | 49   | 3,292.7 (655–19,499) | 7 (14%) | 42 (86%) | 0.001 |
DISCUSSION

In this largest analysis to date of humoral responses to anti-SARS-CoV-2 mRNA vaccines among recipients of cellular therapies, we demonstrate overall high response rates to mRNA vaccines, but with significant variability among the different cellular treatments based on immune reconstitution status. Transplant patients and patients after CAR T-cell therapy had inferior responses to the vaccines compared with HC, confirming the potential overall vulnerability of this population and the need to consider booster vaccination strategies.

Time from cellular therapy to vaccination was a strong predictor of response with less robust responses seen in patients vaccinated within the first year after transplant. Yet, it is important to note that among patients vaccinated within the first year, the response rates among allo-HCT and auto-HCT were 79% and 65%, respectively. Our cohort included 16 patients vaccinated within the first 6 months after transplant, a group where the spike Ab responses are particularly low, with 1 responder among 4 vaccinated in the first 100 days and 6 of 12 among those vaccinated between days 100 and 180. Since time posttransplant likely serves as a surrogate marker of immune recovery, our data suggest the use of more reliable predictors (particularly CD19 and IgG levels) to guide timing of vaccination and in patients with a good immune recovery vaccination should be offered as early as 3 months after cellular therapy.

Considering the immunosuppressive nature of cellular treatments, routine posttransplant vaccinations are often recommended based on immune recovery and time from transplant (18–20). However, in January 2021, the American Society of Hematology (ASH) and the American Society of Transplantation and Cellular Therapy (ASTCT) advised that SARS-CoV-2 vaccines be offered as early as 3 months following HCT or CAR T-cell therapies (https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients). We therefore applied the standard criteria to initiate vaccination and found that among patients who underwent allo-HCT, immune recovery was strongly associated with response to vaccination, whereas for patients post–auto-HCT, who routinely initiate vaccination at 1 year after transplant regardless of immune function status, only CD19 levels were associated with response. This is in agreement with findings reported by Greenberg and colleagues (21) in a nontransplant hematologic malignancy cohort, indicating a lower response to the vaccine among patients treated with B-cell–directed therapies. Additionally, in a cohort of 80 patients post–cellular therapies, Ram and colleagues (16) observed an association between higher CD19 levels and humoral response to the vaccine, whereas a higher CD4+/CD8+ ratio was associated with a cellular response. In another recent publication evaluating patients post–cellular therapies, Dhakal and colleagues (22) reported on a cohort of 130 patients and did not find a statistically significant association between immune recovery. The small sample size of this study likely limited the ability to observe the differences noted in our analysis. Our detailed analysis thus provides more granular information on immune recovery predictors to SARS-CoV-2 vaccination and highlights the differences between patients after allo-HCT, auto-HCT, and CAR T-cell therapies.

In this analysis, the positive cutoffs were 50.0 AU/mL for the SARS-CoV-2 IgG spike and 30% for the surrogate virus neutralization assay as determined by the manufacturer. However, a positive neutralization assay was not detected in any case with a SARS-CoV-2 IgG spike level lower than 250 AU/mL, and there was a strong correlation between the two tests, with higher levels of SARS-CoV-2 IgG spike correlating with higher neutralization capacity, as demonstrated when we applied higher levels of cutoffs for the SARS-CoV-2 IgG spike protein. These findings suggest that there was a group of patients who mounted a serologic response but remain vulnerable to SARS-CoV-2 infection in the absence of neutralizing Ab capacity.

Identifying the threshold that provides protection post-vaccination against SARS-CoV-2 remains a challenge also in the healthy population (23). Because postvaccination Ab response assessment with neutralizing assay is not readily available and established cutoffs for clinical protection are unknown, we strongly recommend that patients post–cellular treatments continue to use masks and practice social distancing as additional protective measures against emerging variants.

Optimizing humoral response in patients with low Ab titers or lack of serologic response, or revaccination of those who received COVID-19 vaccine before cellular therapy, is an area of ongoing investigation. To date, only a few studies have reported responses after a third mRNA dose and mostly among non–cancer immunocompromised patients. Werbel and colleagues (12) reported a cohort of 30 solid organ transplant patients who had suboptimal response to the first two doses of mRNA vaccines. Among patients who received a third dose of vaccine, a 40% response rate was observed (100% among patients with low positive titers after initial vaccination and only 25% among patients who had no response to the initial vaccine). Among another group of solid organ transplant patients in France (24) who received three doses of the Pfizer–BioNTech COVID-19 vaccine (BNT162b2), there was a 44% response rate among patients who had no response to the first two doses of the vaccine. Although the mRNA vaccines have high safety profiles among healthy individuals, the potential for worsening already present graft-versus-host disease and for new cytopenias are lingering safety concerns for cellular therapy patients (16, 25). Most recently, the Centers for Disease Control and Prevention recommended a booster vaccine dose to immunocompromised patients (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html), and this will likely be extended to the general population in light of evidence of an increased number of infections also among vaccinated healthy individuals (26). Our data suggest that an approach based on immune function can be a useful, practical guide for a third dose administration and particularly to identify those who are less likely to respond.

One limitation of this study is that all patients received mRNA-based vaccines; therefore, our findings may not apply to other types of vaccines. This analysis was also limited to early postvaccination assessment (3 months), and follow-up analysis over time in this patient population is warranted. Although the largest study to date, the number of eligible individuals early post–cellular therapy treatment was small, and we particularly had a small cohort of patients after CAR T therapy. Due to the heterogeneous nature of the cohort, it was not possible to examine the effects of other potential clinical predictors on vaccine-induced Ab levels. Additionally, our control cohort was not a matched control, and the age and gender of the HC were significantly younger than the
patient population. Lastly, with data supporting a critical role of cellular immunity against SARS-CoV-2 infection (27, 28), incorporating detailed analysis of cellular immunity response in patients after stem cell transplant and CAR T therapies undergoing vaccination is of high importance.

In summary, our study demonstrates high response rates to anti–SARS-CoV-2 mRNA vaccines among patients post-cellular therapy while highlighting the variability in degree of response based on immune reconstitution at that time. Moreover, this analysis underscores the importance of qualitative assessment provided by the neutralization assay, as many patients meeting thresholds for spike Ab titers did not have adequate neutralizing capacity. Because this is unlikely to be clinically available, our study provides guidance on anti-spike Ab levels that are likely to correlate with an adequate neutralization Ab response.

METHODS

Study Design

This observational study included adult patients who underwent cellular therapies including auto-HCT and allo-HCT and CAR T-cell therapy at Memorial Sloan Kettering Cancer Center (MSKCC) between October 2001 and November 2021 and remain under active follow-up. Patients were included in this study if they received the anti-SARS-CoV-2 vaccine between December 22, 2020, and February 28, 2021. Spike Ab titers and circulating neutralizing Abs were prospectively measured at 1 and 3 months after the first dose of vaccination. CD4 T-cell counts, CD19 B-cell counts, PHA mitogen proliferation responses, and IgG levels were collected in a subset of patients to assess immune recovery prior to vaccination. Patient demographics and clinical characteristics were retrospectively collected from the electronic medical record and institutional databases. Additionally, 69 healthy individual controls (HC) who were vaccinated over the same time period at our center were recruited and served as an HC group. The study was conducted through the Division of Hematologic Malignancies at MSKCC in accordance with the Declaration of Helsinki guidelines. Informed consent was waived under a retrospective research protocol (protocol 20-390) approved by the Institutional Review and Privacy Board of Memorial Hospital/MSKCC.

Ab Assays

Anti–SARS-CoV-2 Spike IgG Assay. The SARS-CoV-2 IgG spike Abs were measured using the AdviseDx SARS-CoV-2 IgG II assay on the Architect i2000 analyzer using chemiluminescent microparticle immunoassay (CMIA) technology. The resulting chemiluminescent reaction, measured as a relative light unit, was compared with a cutoff value of 50.0 AU/mL, defined during calibration of the instrument.

Surrogate Virus Neutralization Assay. The SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (Genescript) measured circulating neutralizing Abs against SARS-CoV-2 that block the interaction between the RBD of the viral spike glycoprotein with the ACE2 cell-surface receptor. The absorbance of the sample is inversely dependent on the titer of the anti-SARS-CoV-2 neutralizing Abs. Percentage inhibition was calculated per manufacturer’s instructions with a positive cutoff value of 30% and validated with a panel of confirmed COVID-19 patient and HC sera.

Statistical Analysis

Descriptive statistics for patient-, disease-, and transplantation-related variables as well as laboratory variables were reported using frequency and percentages for categorical variables and medians and IQRs for continuous variables.

Wilcoxon rank-sum tests compared the levels of anti-SARS-CoV-2 spike IgG and neutralizing Abs between healthy donors and recipients of cellular therapies, both overall and separated by the type and timing of the cellular therapy.

Fisher exact tests or chi-square tests, as appropriate, assessed the association between various factors and response to COVID-19 vaccine. Variables evaluated included age at time of vaccination (dichotomized as <60 years, 60–70 years, and ≥70 years), sex (male vs. female), disease groups (acute leukemia, myelodysplastic syndrome, myeloproliferative neoplasm; chronic leukemia, multiple myeloma, and amyloid; low-grade lymphoma, high-grade lymphoma, and Hodgkin disease; T-cell lymphoma and other; aplastic anemia, systemic mastocytosis, and blastic plasmacytoid dendritic cell neoplasm), time from cellular therapy to first vaccination dose (<12, 12–24, 24–36, and >36 months) as well as time from treatment to first vaccination dose within the subgroups of cellular treatments (auto-HCT, allo-HCT, and CAR T-cell therapies), prior COVID-19 infection, type of mRNA vaccine, use of immunosuppressive therapies among the allo-HCT patients only, disease-directed treatment among the auto-HCT only (IMiDs, monoclonal Ab, or other), as well as laboratory variables including CD4 count, CD19 count, IgG levels, and mitogen levels prior to vaccinations. CD4, CD19, IgG, and mitogen proliferation response levels were dichotomized based on ≥200, ≥50, ≥2500, and ≥40, respectively, as clinical thresholds used to define criteria for immunization. P < 0.05 was considered statistically significant.

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Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors’ Contributions

R. Tamari: Conceptualization, data curation, formal analysis, investigation, writing—original draft. I. Politikos: Conceptualization, writing—review and editing. D.A. Knorr: Conceptualization, data curation, investigation, writing—original draft. S.A. Vardhana: Conceptualization, supervision, writing—review and editing. J.C. Young: Investigation, writing—review and editing. L.T. Marcello: Investigation, writing—review and editing. S. Doddi: Validation, investigation, writing—review and editing. L.V. Ramanathan: Formal analysis, supervision, investigation, methodology, writing—review and editing. L.V. Ramanathan: Validation, investigation, writing—review and editing. L.V. Ramanathan: Validation, investigation, writing—review and editing. M.S. Pessin: Validation, investigation, writing—review and editing. E. Dunn: Investigation, writing—review and editing. M. Palazzo: Investigation, writing—review and editing. C.D. Bravos: Investigation, writing—review and editing. G.A. Papanicolaou: Conceptualization, writing—review and editing. M. Kamboj: Conceptualization, writing—review and editing. S. Doddi: Conceptualization, writing—review and editing. L.T. Marcello: Investigation, writing—review and editing. J.C. Young: Investigation, writing—review and editing. M.S. Pessin: Validation, investigation, writing—review and editing. E. Dunn: Investigation, writing—review and editing. M. Palazzo: Investigation, writing—review and editing. C.D. Bravos: Investigation, writing—review and editing. G.A. Papanicolaou: Conceptualization, writing—review and editing. M. Kamboj: Conceptualization, writing—review and editing.
supervision, writing–original draft. G.L. Shah: Conceptualization, data curation, formal analysis, supervision, investigation, visualization, writing–original draft.

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