Response to SARS-CoV-2 vaccination in patients after hematopoietic cell transplantation and CAR-T cell therapy

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Abstract:

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To the editor,

Coronavirus disease (COVID-19) caused by SARS-CoV-2 infection has affected tens of millions of people globally\(^1\). To overcome this pandemic, vaccination remains the most effective tool to prevent the disease and to limit the spread of infection. Several randomized trials have established the safety and efficacy of various types of vaccines in preventing severe symptomatic SARS-CoV-2 infection\(^2\)\(^-\)\(^5\). Data from phase III trials of messenger RNA (mRNA) vaccines through November 2020 showed 94.1% efficacy for the prevention of symptomatic severe acute SARS CoV-2 infection at 14 days after the second dose of mRNA1273 vaccine (Moderna)\(^2\) and 95% efficacy at 7 days after the second dose of BTN162b2 (Pfizer) vaccine\(^4\). Additionally, other vaccines using different platforms have shown efficacy ranging from 66% to 92%\(^3\)\(^,\)\(^5\). Although vaccines are effective, the actual benefit to patients with hematological malignancies remain to be determined as several reports suggest inadequate immune response in these patients\(^6\)\(^-\)\(^9\). Given the variable degree of immunosuppression associated with hematopoietic cell transplantation (HCT) and chimeric antigen receptor T-cell (CAR-T) therapy, patients are often recommended to receive these vaccines approximately 6 months after the procedure, to hopefully allow for adequate immune recovery. However, data are lacking for immune response to SARS-CoV-2 vaccination in patients after HCT and CAR-T therapy. Hence, we sought to assess the immune responses to COVID-19 vaccinations after received HCT and CAR-T therapy.

In the US, Pfizer, Moderna and Johnson and Johnson (J& J) vaccines have been approved by Food and Drug Administration (FDA) to be used in adults ≥18 years of age (≥12 years for Pfizer). Both Pfizer and Moderna are given 2 doses 3-4 weeks apart, while only one dose is given for J&J. We retrospectively assessed serological response following completed COVID-19 vaccination in patients after HCT and cellular therapy for hematological malignancies at our institution. Patients who were at least 2 weeks after vaccination scheme fully completed and had SARS-CoV-2 antibody checked were eligible. The blood samples were tested using
enzyme immunoassay (EUROIMMUN) that tests for antibodies to the S1 domain of the SARS-CoV-2 spike protein\textsuperscript{8,10}. The sensitivity and specificity of the EUROIMMUN assay is 87.1% and 98.9% respectively for detection of the anti-spike humoral response to SARS-CoV-2 infection\textsuperscript{10}. This semiquantitative assay has consistently correlated with neutralizing immunity\textsuperscript{10,11}. Patient-, disease- and treatment characteristics were compared by vaccine response using t-test for continuous variable and chi-square test for the categorical variables. Statistical significance was determined at $\alpha<0.05$, and all tests were two-sided. Data collection and analysis was approved by Medical College of Wisconsin Institutional Review Board.

A total of 130 patients (autologous [auto]-HCT n=45, allogeneic [allo]-HCT n=71 and CAR-T n=14) were included in the analysis (Table). Of the 130 patients, 79 (60%) tested positive for SARS-CoV-2 antibodies post vaccination. The positivity rate was 60%, 69% and 11% for auto-HCT, allo-HCT and CAR-T cell therapy recipients, respectively.

On subgroup analysis for auto-HCT, there was no difference in seropositivity rates based on patient age, interval between HCT and vaccination, disease type and immunoglobulin G (IgG) level. Similarly, for allo-HCT, the seropositivity rates did not differ by patient age, interval between allo-HCT and vaccination, immunosuppression (IST) status, presence of active graft-versus-host-disease (GVHD), recipient CD4 and CD8 counts at the time of vaccination. Among the 71 allo-HCT patients, higher IgG levels were seen among those who were seropositive [577 (189-2090) vs. 408 (153-1187); p=0.01]. Corticosteroids use for treatment of GVHD following allo-HCT was associated with significantly lower seropositivity rates compared to patients not receiving corticosteroids [4(31%) vs. 9 (69%); p=0.001]. For the small subset of patients who received vaccination <6 months after HCT (n=19, 4 auto-HCT; 8 allo-HCT and 7 CAR-T), the seropositivity rates were 2 (50%), 3 (37%) and 0% for auto-HCT, allo-HCT and CAR-T respectively.

To our knowledge, this is the first report describing the immunogenicity of SARS-CoV-2 vaccine in HCT and CAR-T recipients with hematological malignancies. Our results show that about one
third of HCT and 79% of CAR-T patients did not mount appreciable immune response to COVID-19 vaccinations. Antibody response was associated with higher IgG levels in allo-HCT patients, while no other predictors of vaccine response were identified for auto- or CAR-T patients.

Several factors may contribute to blunted immune response and affect vaccine efficacy in HCT and CAR-T recipients. Further investigations to determine factors impacting vaccine responses in these patients remains an unmet need. Consensus guidelines generally recommend initiating most vaccinations at ~6 months post HCT\textsuperscript{12,13} and while ASH/ASTCT statements recommend COVID vaccination as early as 3 months after HCT\textsuperscript{14}, our limited data indicated lower vaccine responses within 6 months.

Recent evidence points to inadequate immune response to COVID-19 vaccinations in patients with cancers including hematological malignancies\textsuperscript{6,9,15,16} and solid organ transplants\textsuperscript{8,17}. The seropositivity rates vary across these studies and this is attributed to different patient populations and variability in laboratory tests. It is important to note that CAR-T patients had low seroconversion rates in our study, but the small sample size precludes definite conclusions. Whether this is due to underlying immune suppression, disease characteristic or preceding cytokine release syndrome needs to be evaluated.

Limitations of our study include lack of concurrent control group without HCT and CAR-T, lack of serial measurements after vaccination and assessment of humoral response only with no information on B cell numbers.

The findings of low anti-spike antibody in HCT and CAR-T recipients after COVID-19 vaccinations suggest that such patients may remain at high risk of COVID-19 infection despite vaccination. Current guidelines do not recommend routine serologic testing in HCT, and CAR-T cell recipients given the lack of evidence. However, the results observed in this study underscore the importance of masking, social distancing, and vaccination of their households for HCT and CAR-T recipients despite the vaccination. Further studies looking at the wider
immune repertoire with characterization of memory B and T-cell immune responses over time and neutralizing antibody capacity are needed to better assess the immunological response and is the subject of recently activated trial by the Blood and Marrow Transplant Clinical Trials Network, in United States. In patients who fail to achieve optimal immune response, studies looking at the role booster doses, or revaccination are needed.
Author contribution and Disclosures: BD and MH designed the study. LB, TF, PH, AS, MH, BD collected data. BD and MH analyzed the data. BD wrote the first draft of manuscript, and all authors provided the critical input. Dr. Dhakal has served on the advisory board of Takeda, Amgen, and Jansen. He has received honorarium from Celgene. Mehdi Hamadani reports Research Support/Funding: Takeda Pharmaceutical Company; Otsuka Pharmaceutical; Spectrum Pharmaceuticals; Astellas Pharma. Consultancy: Medimmune LLC; Janssen R &D; Incyte Corporation; ADC Therapeutics; Cellerant Therapeutics; Celgene Corporation; Pharmacyclics, Magenta Therapeutics, Omeros, AbGenomics, Verastem, TeneoBio. Speaker’s Bureau: Sanofi Genzyme, AstraZeneca.
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Table: Comparisons of patient-, disease- and treatment characteristics by vaccine response in autologous hematopoietic cell transplantation (Auto-HCT), allogeneic (Allo-HCT) and chimeric antigen receptor T cell therapy (CAR-T)

|                        | Positive Vaccine Response | Negative Vaccine Response | P-value |
|------------------------|---------------------------|----------------------------|---------|
| **All Patients (N=130)** |                           |                            |         |
| Vaccine types          |                           |                            |         |
| Pfizer                 | 43 (56%)                  | 34 (44%)                   | 0.38    |
| Moderna                | 32 (68%)                  | 15 (32%)                   |         |
| Johnson & Johnson      | 4 (67%)                   | 2 (34%)                    |         |
| **Auto-HCT (N=45)**    |                           |                            |         |
| All auto-HCT recipient | 27 (60%)                  | 18 (40%)                   |         |
| Median age (range)     | 65 (48-70) yrs            | 65 (45-75) yrs             | 0.50    |
| Interval between auto-HCT & vaccination | | | |
| <12 months             | 11 (73%)                  | 4 (27%)                    | 0.20    |
| ≥12 months             | 16 (53%)                  | 14 (47%)                   |         |
| Auto-HCT indication    |                           |                            |         |
| Lymphoma               | 8 (53%)                   | 7 (47%)                    | 0.52    |
| Myeloma                | 19 (63%)                  | 11 (37%)                   |         |
| Patients on Maintenance therapy¹ | | | 0.58 |
| Disease relapse prior to vaccine | 8 (47%) | 9 (53%) | 0.18 |
| Prior COVID infection  | 1                         | 1                          | -       |
| Patients with IgG<400  | 8 (57%)                   | 6 (43%)                    | 0.79    |
| Median time from auto-HCT to vaccine, months (range) | 30 (3-173) | 30 (2-96) | 0.50 |
| Median IgG level (range) | 474 (146-1481)          | 429 (40-990)               | 0.29    |
| **Allo-HCT (N=71)**    |                           |                            |         |
| All allo-HCT recipients | 49 (69%)                  | 22 (31%)                   |         |
| Median age (range)     | 64 (25-70) yrs            | 68.5 (37-77) yrs           | 0.07    |
| Interval between allo-HCT & vaccination | | | |
| <12 months             | 11 (58%)                  | 8 (42%)                    | 0.22    |
| ≥12 months             | 38 (73%)                  | 14 (27%)                   |         |
| Allo-HCT recipient & IST status | | | |
| Off IST                | 18 (72%)                  | 7 (28%)                    | 0.69    |
| Ongoing IST drugs²    | 31 (67%)                  | 15 (33%)                   |         |
| Allo-HCT recipient’s GVHD status | | | |
| No active GVHD         | 20 (69%)                  | 9 (31%)                    | 0.99    |
| Active GVHD            | 29 (69%)                  | 13 (31%)                   |         |
| Active chronic GVHD    | 23 (65%)                  | 12 (34%)                   | 0.55    |
| Disease relapse prior to vaccine | 4 (57%) | 3 (43%) | 0.47 |
| Positive patients with either CD4<100/ul; CD8 <100/ul and/or IgG<400 | | | 0.08 |
| Median time from allo-HCT to | 26 (4-154) | 25 (3-155) | 0.68 |
| vaccine, months (range)          | 4 (31%) | 9 (69%) | 0.001 |
|----------------------------------|---------|---------|-------|
| Prednisone use at the time of vaccination |         |         |       |
| Prior COVID infection            | 3       | 0       |       |
| Median CD4 count (range) / uL     | 327 (44-1165) | 274 (56-576) | 0.10  |
| Median CD8 count (range) / uL     | 278 (46-1739) | 276 (34-1440) | 0.73  |
| Median IgG level (range) / uL     | 577 (189-2090) | 408 (153-1187) | 0.01  |
| CAR-T (N=14)                     |         |         |       |
| All CAR-T recipients             | 3 (21%) | 11 (79%) | N/A   |
| Prior COVID infection            | 1       | 0       |       |
| Median time from CAR-T to vaccine, months (range) | 24 (8-31) | 6 (3-37) | 0.09  |
| Disease relapse prior to vaccine  | 0       | 1       | 0.59  |
| Median IgG level (range) / uL     | 535 (191-1562) | 535 (191-4843) |       |

1. Maintenance therapy included: lenalidomide +/- others (9), rituximab (2), nivolumab (1).
2. Immuno suppressive therapy (IST) in vaccine responders (n=29; ruxolitinib +/- others -16, sirolimus +/- others -5, mycophenolate moefetil-3, tacrolimus-2, prednisone-2 and ibrutinib-1) and non-responders (n= 14; ruxolitinib +/- others-6, mycophenolate moefetil-4, tacrolimus-3, prednisone- 1).
3. Active acute or chronic GVHD defined as either active signs or symptoms of GVHD, or ongoing IST drugs used to treat GVHD. Ongoing use of GVHD prophylaxis in the absence of signs or symptoms of GVHD was not considered active GVHD. Group off IST consisted of patients off of all systemic medications to treat or prevent GVHD for 2 or more weeks.