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Letter

Efficacy of a third SARS-CoV-2 mRNA vaccine dose among hematopoietic cell transplantation, CAR T cell, and BiTE recipients

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<https://doi.org/10.1016/j.ccell.2022.02.010>

Hematopoietic cell transplantation (HCT) and cellular therapy (CT) recipients have poor outcomes after developing COVID-19 (Spanjaart et al., 2021, Meir et al., 2021). HCT and/or CT recipients also have blunted responses to SARS-CoV-2 vaccines (Dhakal et al., 2021). Several groups, including ours, have indicated a response rate of 50%–80% among HCT recipients and 20%–30% among chimeric antigen receptor (CAR) T cell recipients (Dhakal et al., 2021, Meir et al., 2021, Abid and Abid, 2021). The general population has demonstrated sustained and durable immune responses to an additional mRNA vaccine dose (“booster”) to counteract the waning immunity to the primary vaccination series (Nemet, Kliker, Lustig, Zuckerman, Erster, Cohen, Kreiss, Alroy-Preis, Regev-Yochay, Mendelson, Mandelboim, 2022). It remains unknown whether HCT and/or CT recipients respond to the additional primary or booster dose and/or seroconvert after booster.

We examined serological responses to the third vaccine dose among those HCT (both allogeneic HCT [alloHCT] and autologous HCT [autoHCT]), CAR T cell, and bispecific T cell engager (BiTE) recipients who had not seroconverted after the primary series with an mRNA-based (BNT162b2 [Pfizer-BioNTech] or mRNA1273 [Moderna]) vaccine. We included patients who had not seroconverted after the primary series (no response per the assay cutoff described below), had received a booster, and had serological response examined after the primary series as well as after the booster.

Patients were required to have at least 28 days between the second dose and the booster and 14 days to antibody titer testing after receiving the booster. Patients with SARS-CoV-2 antibody testing within 2 weeks of the booster or COVID-19 infection any time prior to the booster dose were excluded from the analysis.

The AdviseDx SARS-CoV-2 IgG II assay was used to detect immunoglobulin G (IgG) antibodies (Ab) directed against the receptor-binding domain (RBD) of the SARS-CoV-2 S1 subunit of the spike protein, and the assay was performed on Abbott's ARCHITECT i2000SR System. This semiquantitative assay has consistently been correlated with neutralizing immunity. The cutoff value is 50 AU/mL, with < 50 AU/mL values reported as negative and a maximum value of 50,000 AU/mL. Patient-, disease-, and treatment characteristics were compared based on vaccine response by using Wilcoxon's rank-sum for continuous variables and Fisher's exact test for the categorical variables. A p value < 0.05 at two-sided testing was considered significant. The study was approved by the Medical College of Wisconsin Institutional Review Board, and informed consents were obtained from the patients.

A total of 75 patients (alloHCT, n = 30; autoHCT, n = 26; CAR-T, n = 10; BiTE, n = 9) did not seroconvert after their primary vaccination series with an mRNA-based vaccine (Table S1). Among these, 44 (59%) developed protective antibodies after the booster. The seroconversion rates were 63%, 58%, 40%, and 67% among autoHCT, alloHCT, CAR-T, and

BiTE recipients, respectively. Median age among seroconverters with booster was older than among non-seroconverters (70 [31–77] versus 66 [35–81]; p = 0.04). Although there were no significant differences in seroconversion rates between males and females, the antibody titers were significantly lower in males compared to females (p = 0.046). Also, corticosteroid usage was significantly lower among seroconverters than non-seroconverters (41% versus 59%; p = 0.04) and the antibody titers were significantly lower among corticosteroid recipients (p = 0.012) (Figure S1). No significant differences were noted in the three vaccine strategies (BNT162b2, mRNA1273, and mix-and-match).

We found no significant differences in seroconversion based on age, interval between immunotherapy and vaccination, corticosteroid usage, active graft versus host disease (in alloHCT), immunosuppression status (including active immunosuppressant use), disease relapse prior to booster, absolute lymphocyte count (ALC), or CD4, CD8, or IgG levels. Among autoHCT recipients, the response to the booster in patients with multiple myeloma (MM) was significantly superior compared to the response in patients with lymphoma (80% versus 30%; p = 0.01).

Three other studies so far have reported the efficacy of a third vaccine dose exclusively in alloHCT recipients. Redjoul et al. (2021) showed that a third dose of BNT162b2 mRNA vaccine led to a significant increase in anti-SARS-CoV-2 IgG antibodies (from 737 AU/mL to 11,099 AU/mL; p = 0.00069) in 42



alloHCT recipients. Maillard et al. (2022) showed that 41% of patients (29/70) developed a detectable response after the third dose after not responding to the first two doses. Canti et al. (2022) showed that 87% of alloHCT recipients (33/38) seroconverted after three vaccine doses and that there were strong correlations between Abs against RBD and neutralizing Ab titers.

Continued blunted humoral responses even after the booster among CAR T recipients are concerning and are in alignment with other reported literature. Our systematic review reported antibody responses in 40 CAR-T recipients from five studies and demonstrated a pooled response rate of only 30% (Abid and Abid, 2021). Bange et al. (2021) showed that patients with T cell depletion have the highest risk of death independent of cancer subtype or presence of B cell responses. In contrast, patients with hematologic malignancies and higher CD8⁺ T cell numbers have higher detectable SARS-CoV-2-specific T cell responses and improved survival. These findings provide insight into why severely lymphodepleted CAR T recipients, independent of their remission status, may have high mortality. Given that the COVID-19-attributable mortality rate in the European Bone Marrow Transplant (EBMT) registry study was 41% (Spanjaart et al., 2021), and continued blunted humoral responses despite one and two additional vaccine doses demonstrated in a recent study (Sesques et al., 2022), the results of our analysis, showing at least partial success in seroconversion with booster among CAR T recipients, are encouraging.

Several factors, indigenous to CAR T recipients, may account for consistently blunted vaccine responses, including pre-existing, profound immunosuppression. Heavily pretreated status, often including prior HCT, lymphodepletion chemotherapy, bridging chemotherapy, prolonged B cell aplasia, preceding on-target off-tumor toxicities such as cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome requiring corticosteroids and tocilizumab may contribute to blunted vaccine responses (Meir et al., 2021, Abid, 2022).

Given the lack of data in this regard, a substantial seroconversion rate to the booster vaccine dose among BiTE recipi-

ents is encouraging. This finding aligns with other recent studies that demonstrate a superior response to primary vaccine series among recipients of BCMA-targeted CAR T compared to those directed against CD19 (Abid and Abid, 2021). This is also likely a function of the underlying disease. Our results are congruent with other data which show that patients with myeloma respond better to mRNA vaccines than do patients with lymphoma (Meir et al., 2021, Van Oekelen et al., 2021).

Besides the retrospective design, limitations of our study include the lack of a concurrent control group without HCT and/or CT and BiTE. Other limitations include the lack of serial assessment of humoral response at various time points, robust immune reconstitution data, B cell numbers, and T cell responses. Further, no conclusion may be drawn from our results in terms of protection against clinical breakthrough infection—especially of the B.1.1.529 (omicron) variant of SARS-CoV-2. Although our study did not sequence the viral genome to the variant level, eight patients received a booster either after or on November 26, 2021, when the World Health Organization (WHO) named omicron as a variant of concern. However, emerging data have demonstrated the importance of a third BNT162b2 vaccine dose and have shown higher neutralization efficiency (by a factor of 100) against omicron after the third dose than after the second dose (Nemet, Kliker, Lustig, Zuckerman, Erster, Cohen, Kreiss, Alroy-Preis, Regev-Yochay, Mendelson, Mandelboim, 2022), including in patients with cancer (Zeng, Evans, Chakravarthy, Qu, Reisinger, Song, Rubinstein, Shields, Li, Liu, 2022).

Overall, our findings can guide patients and physicians, particularly in the setting of emerging highly transmissible variants of concern. Vaccination remains the cornerstone in protecting vulnerable HCT and/or CT patients against COVID-19, and these results strongly support the role of the booster and/or third vaccine dose and pave the way for larger prospective studies. Other novel strategies, such as the use of monoclonal antibodies that have demonstrated efficacy against the omicron variant, either authorized for preexposure prophylaxis or to prevent severe COVID-19, may be utilized earlier in

this immunocompromised patient cohort. Although the results of prospective vaccine studies such as CIBMTR study SC21-07/BMT-CTN 2101 are awaited, other mitigation approaches, including vaccination of close contacts, social distancing, and masks, should be continued for the foreseeable future.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.ccell.2022.02.010>.

DECLARATION OF INTERESTS

N.N.S reports participation in advisory boards and/or consultancy for Kite Pharma, TG Therapeutics, Miltenyi Biotec, Lilly, Epizyme, Legend, Incyte, Novartis, and Umaja, as well as research funding and honoraria from Miltenyi Biotec. T.S.F reports research funding from Novartis, Portola, Curis, and TG Therapeutics and consultancy and/or speaking for Adaptive Biotechnologies, ADC Therapeutics, AbbVie/Pharmacyclics, AstraZeneca, Beigene, Bristol-Myers Squibb, Biogen, CSL Therapeutics, KaryoPharm, Kite (Gilead), MorphoSys, Pharmacyclics, Sanofi, Servier Pharmaceuticals, TG Therapeutics, Kyowa, and Veristem. A.D. has served on the advisory boards of BMS and Pfizer, and she reports consultancy for Janssen, travel support from Imbrium, and research support and/or funding from Janssen, TNB-383B, Abbvie, Regeneron, Takeda, Sanofi, Prothena, and Caelum (Funding to Institution for Clinical Trial). B.D. reports honoraria from and/or consultancy for BMS, Karyopharm, GSK, Janssen, Arcellx, Genentech, Natera, Sanofi, Takeda, and Amgen, as well as research funding from Amgen, Sanofi, Arcellx, Carsgen, Cartesian, Fate, Janssen, and BMS. S.C. reports research funding from Amgen, Janssen, Sanofi, and Syndax and has served on the advisory boards of GSK and Sanofi. M.H. reports consultancy for Incyte Corporation, ADC Therapeutics, Magenta Therapeutics, Omeros, AbGenomics, MorphoSys, Kite, Novartis, GenMab, Seattle Genetics, Gamida Cell, Legend Biotech, and Kadmon and has served on speaker's bureaus for Sanofi Genzyme, Astrazeneca, BeiGene, and ADC Therapeutics. The remaining authors declare no competing financial interests.

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