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Letter

Humoral and cellular immune responses in SARS-CoV-2 mRNA-vaccinated patients with cancer

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https://doi.org/10.1016/j.ccell.2021.08.001

Patients with cancer, particularly those under active therapy, are at increased risk of morbidity and mortality when infected with SARS-CoV-2 (Bakouny et al., 2020; Grivas et al., 2021). Their ability to launch adequate immune responses during COVID-19 or upon SARS-CoV-2 vaccination might be impaired to varying degrees (Greenberger et al., 2021; Thakkar et al., 2021; see also Griffiths and Segal, 2021, and references therein). While both SARS-CoV-2 infection and vaccination evoke antibody- and cell-based responses (Sahin et al., 2021), less is known about individual humoral and cellular immune response profiles in patients with solid and hematologic cancers (Ehmsen et al., 2021). This is of particular importance since discordant humoral and cellular immune responses in the same individuals may still result in mitigated COVID-19 severity or disease protection (Bange et al., 2021).

We assessed the SARS-CoV-2 spike protein-specific (anti-S) IgG antibody (using a quantitative anti-S IgG assay [Abbott]) and activated $CD4^+$/$CD8^+$ T cell status (applying a spike-derived pooled activator peptide T cell analysis [Miltenyi Biotec]; see Supplemental Information) in 87 freshly vaccinated patients with hematologic and solid tumors (T group), out of which 70 were under anticancer therapy (subgroup T_{tx})—currently or within the last 3 months (or 6 months regarding the anti-CD20 antibody treatment) —and 17 were untreated (subgroup T_{ut}). Thirty-nine patients were diagnosed with solid cancer, among them most often gastrointestinal malignancies (n = 14) and breast (n = 11) and ovarian cancer (n = 6). Hematologic malignancies were diagnosed in 48 patients: most frequently as Hodgkin's or non-Hodgkin's lymphoma (n = 23), chronic myeloproliferative neoplasia (n = 7), and multiple myeloma (n = 6). Systemic treatment included conventional chemotherapeutics in 40 cases, an anti-CD20 antibody in 11 cases, and small molecule inhibitors in 20 cases. Additional detailed clinical characteristics of the patients are provided in Table S1A. Forty-four patients and virtually all 29 vaccinated control participants (all with no evident cancer diagnosis) received two doses of the mRNA vaccine BNT162b2 (Pfizer/BioNTech), and another 43 patients with cancer received mRNA-1273 vaccine (Moderna). Responses were monitored 3 weeks after the second vaccination, compared to baseline and the overall 44 control participants (C group), comprised of vaccinees (subgroup C_{vax}, n = 23), non-vaccinated COVID-19-convalescents (subgroup C_{con}, n = 15), and convalescents that were vaccinated after confirmed COVID-19 (subgroup C_{cox}, n = 6) (Table S1).

When comparing the vaccination-evoked humoral responses in the evaluable 83 (4 had no complete response data) patients with cancer (T) and 44 control participants (C) globally or across subgroups, spike-specific IgG concentrations scattered over several orders of magnitude, with a bigger percentage of participants without elicited humoral responses among T (Figure S1A). There were no statistically significant differences regarding cellular responses between T and C groups, indicating preserved SARS-CoV-2-specific T cell immunity despite compromised antibody responsiveness in the T group. Of the 38 evaluable patients with solid cancer, 34 (89.5%) achieved a humoral and 34 (89.5%) at least a $CD4^+$ or a $CD8^+$ T cell response; of the 45 evaluable patients with hematologic malignancies, 26 (57.8%) had a positive antibody, and 34 (75.6%) had a positive $CD4^+$ or $CD8^+$ response (Figure S1A; see bottom panel regarding subgroup results).

The determination of individual triads comprising spike-specific IgG, activated $CD4^+$, and $CD8^+$ responses unveiled triple non-responders to vaccination exclusively among T_{tx}, almost exclusively related to anti-CD20 therapy, but none in C (Figures S1B and S1C). Overall, 12 of 36 vaccinated patients with solid tumor under therapy (8 of 18 in the BNT162b2 and 4 of 18 in the mRNA-1273 cohorts) achieved a complete triple response, whereas such result was accomplished in only 6 of 30 patients with hematologic cancer under therapy (3 of 16 BNT162b2 and 3 of 14 mRNA-1273), and never in the context of an anti-CD20 antibody (Figure S1B). In total, 60 (72.3%) and 68 (81.9%) of the evaluable 83 patients with cancer presented with humoral or cellular responses, respectively, comparing to 29 of 29 (100%) and 28 of 29 (96.6%) responses in vaccinated controls.

Importantly, humoral and cellular responses were often found to be discordant in patients with cancer. Particularly, T_{tx} patients exhibited no IgG, but a $CD4^+$

or $CD8^+$ cellular response, or, conversely, neither a $CD4^+$ nor a $CD8^+$ cellular but a humoral response in 12 of 34 (BNT162b2) and 7 of 32 (mRNA-1273) cases. Cellular responses without humoral responses were exclusively observed in patients with cancer, with higher frequency in actively treated patients (13 of 66 in T_{tx} versus 2 of 17 in T_{ut}). In addition, 3 of 8 BNT162b2-vaccinated and 0 of 9 mRNA-1273-vaccinated T_{ut} patients presented with discordant responses, suggesting the potentially higher capacity of the mRNA-1273 vaccine to concordantly evoke both humoral and cellular responses. Specific $CD4^+$ or $CD8^+$ T cell immunity was found in 73.2% (30 of 41) of mRNA-1273-vaccinated patients with cancer, as compared to only 54.8% (23 of 42) of BNT162b2-vaccinated patients in T (Figure S1C).

Moreover, we scrutinized our data to unveil predictors of concordant and discordant immune responses in patients with cancer (Table S1B). Despite a large proportion of concordantly positive vaccine results achieved in the T group (Figure S1B), odds ratios comparing their concordant results to vaccinated controls were significantly reduced across many clinical parameters (Table S1B). Patients with hematologic cancer were at explicit risk for a concordantly negative response, which further increased in the context of an anti-CD20 antibody. Discordant responses were predicted, again, by hematologic malignancies and treatment with CD20 antibodies, but also with small molecule inhibitors and advanced age. Notably, mRNA-1273, unlike BNT162b2, was not statistically associated with discordant responses, indicating it might have the capacity to robustly produce concordant responses, especially in patients with hematologic cancer (Figure S1B; Table S1B).

Triad analyses of control participants unveiled differences between non-vaccinated COVID-19 convalescents (C_{con}) and vaccinated (C_{vax}) controls. Discordant positive humoral, but no cellular, responses were found in 8 of 15 C_{con} but 1 of 29 C_{vax} (Figure S1B). Notably, vaccinated control participants were significantly younger when compared to COVID-19 convalescents or the patients with cancer (50 versus 72 versus 66 years on average; Table S1A), thereby possibly accounting for a stronger vaccine response due to younger ages. BNT162b2-based vaccination in 6 post-COVID-19 patients led to uniformly concordant responses, thereby implying a strong boosting effect of an additional vaccination in a SARS-CoV-2-primed non-cancer population.

Our data provide evidence for compromised immune responses to BNT162b2 and mRNA-1273 SARS-CoV-2 vaccines in patients with cancer, particularly with anti-CD20 exposure, and unveil discordant responses in a substantial fraction of patients under anticancer therapy, often as a specific $CD4^+$ or $CD8^+$ response in the absence of an IgG response. Our findings agree with a recent study by Ehmsen et al., which reports impaired humoral and cellular responses to the two mRNA vaccines, especially in patients with hematologic malignancies (Ehmsen et al., 2021). The difference of the frequencies of individuals with detectable activated T cell responses in our study and Ehmsen et al. could be explained by the sensitivity level of the isolation procedure and spike peptide cocktail in the T cell assay applied. Importantly, while their work focused on the long-term decline of the vaccine-evoked humoral and cellular responses, we present here individually resolved triad response data across all study participants. Vaccine-induced T cells complement the defense line to primary SARS-CoV-2 infection (Sahin et al., 2021), albeit with unclear relative contributions of $CD4^+$ versus $CD8^+$ T cells, especially in vaccinees without a sufficiently neutralizing antibody titer. How to convert measurable IgG antibody levels into virus-neutralizing *in vivo* activity is currently under investigation (Khoury et al., 2021). How to interpret the *in vivo* protective potential from *ex vivo*-detectable frequencies of activated SARS-CoV-2-specific T cells imposes a similarly important translational task (Bange et al., 2021). Given the significant proportion of individual patients with cancer with a cellular and often just a sole activated $CD4^+$ or $CD8^+$ response in the absence of anti-S antibodies, long-term follow-up of this particularly vulnerable population with respect to emerging SARS-CoV-2 variants and third-dose vaccination is urgently needed. The extent of clinical disease protection based on concordant versus discordant vaccination responses in patients with cancer deserves specific attention in the future course of the pandemic.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.08.001.

ACKNOWLEDGMENTS

This study was supported by the Förderverein Hämatologie und internistische Onkologie (Tyle Private Foundation, Linz, Austria) and a grant from the Medical Faculty of the Johannes Kepler University to C.A.S. We express our gratitude to the patients and participants for their active involvement.

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