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Letter

Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer

Sidse Ehmsen,[1,2,3] Anders Asmussen,[4] Stefan S. Jeppesen,[1,2,3] Anna Christine Nilsson,[2,5] Sabina Østerlev,[1] Hanne Vestergaard,[4] Ulrik S. Justesen,[2,6] Isik S. Johansen,[2,7] Henrik Frederiksen,[2,3,4] and Henrik J. Ditzel[1,2,3,8,9,*]

[1]Department of Oncology, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]Academy of Geriatric Oncology, Odense University Hospital, Odense, Denmark
[4]Department of Hematology, Odense University Hospital, Odense, Denmark
[5]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark
[6]Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark
[7]Department of Infectious Disease, Odense University Hospital, Odense, Denmark
[8]OPEN—Open Patient data Exploratory Network, Odense University Hospital, Odense, Denmark
[9]Department of Molecular Medicine, University of Southern Denmark, Odense, Denmark
*Correspondence: hditzel@health.sdu.dk
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Patients with solid and hematologic cancer are more vulnerable to SARS-CoV-2 infection and have poorer prognoses of COVID-19 because of their general health status, immunosuppression caused by cancer itself, and/or cancer therapies (Bakouny et al., 2020, Verma et al., 2016, Ewertz et al., 2016, Ehmsen et al., 2021). COVID-19 vaccination induces both antibody and T cell immune responses, and both mRNA vaccines, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), are efficacious in healthy individuals in preventing COVID-19 illness, including severe disease (Baden et al., 2021, Mulligan et al., 2020). It has been shown that patients with certain hematologic malignancies and patients with solid cancer who receive certain therapies do not adequately elicit an anti-SARS-CoV-2 IgG antibody response following vaccination (Griffiths and Segal, 2021). However, anti-SARS-CoV-2-specific T cell responses in these cancer patients have not been detailed, nor has the durability of the anti-SARS-CoV-2 IgG antibody response.

To assess both the humoral and cellular immune responses and to determine the durability of the antibody response, we assessed both anti-SARS-CoV-2 spike (anti-S) IgG antibody and SARS-CoV-2-specific CD8+ and CD4+ T cell responses following mRNA vaccination in patients with solid and hematologic malignancies.

Overall, 524 patients with cancer had blood drawn at median 36 days (interquartile range [IQR]: 29–43 days) after the second dose of vaccine, and these blood samples were analyzed for anti-S IgG and CD4+/CD8+ T cell responses. Of those, 247 (47%) had a second blood sample drawn 3 months (median 81 days [IQR: 75–87 days]) after the second vaccine dose, and that blood sample was also analyzed for anti-S IgG.

The patients included in the study were grouped based on primary cancer diagnoses, with 201 (38%) having solid cancer and 323 (62%) hematologic cancer. The clinical characteristics are provided in Table S1A. Patients with hematologic cancer were mainly selected among lymphoid and plasma cell neoplasm patients, and consequently, most patients selected were diagnosed with either chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (37%) and multiple myeloma (32%). The majority of patients with solid cancer had an active cancer (i.e., in curative or palliative treatment) at the time of their first vaccination dose, including 29% with progressive disease, while 41% had a cancer in remission (complete or partial response). Of the patients with hematologic cancer, only 3% had progressive disease, while 51% were in remission. All patients with solid cancer were in active cancer therapy (by study definitions). Among patients with hematologic cancer, 39% were in active cancer therapy, with the most prevalent therapy being chemotherapy, and anti-CD20 or anti-CD38 antibody therapies, and 17% had received stem cell transplants. Prednisolone treatment (>10mg) prior to vaccination and the first blood draw was ongoing in 15% of patients with solid cancer and 13% of patients with hematologic cancer (Table S1A).

The seropositivity rate for anti-S IgG 36 days after vaccination in patients with solid cancer was high (n = 187, 93%); and only 2% (n = 4) exhibited no detectable antibodies, and 5% (n = 10) exhibited borderline levels. For the group of patients with hematologic cancer, the seropositive rate was significantly lower: 215 (66%) were seropositive, 75 (23%) had no measurable antibodies, and 33 (10%) exhibited borderline levels ($p = 0.004$, χ^2 test) (Table S1B). For the total cohort, titers declined significantly between 36-day and 3-month samples, declining from median 429 BAU/mL (IQR: 68–1,147) to median 139 BAU/mL (IQR: 15–439) ($p = 0.03$, Student's t test). For patients with solid cancer, a drop from 93% to 86% in seropositivity rates was observed, and for patients with hematologic cancer, a drop from 66% to 53% was observed. A total of 24 original seropositive patients (10%), 5 with solid cancer and 19 with hematologic cancer, converted to seronegative status. In addition, 8 patients (24%) who initially exhibited borderline levels had no measurable antibodies in the 3-month samples. Only 1 patient with no measurable antibodies observed in the 36-day sample had a measurable level in the 3-month sample.

The diagnoses and treatments for the 14 patients with solid cancer who exhibited no or borderline (seronegative) anti-S IgG 36 days after the second vaccination are listed in Table S1C. For 4 of the 14 patients, the anti-S IgG response was

also evaluated in the 3-month sample, but no change in the levels was observed. All but 4 seronegative patients with solid cancers received chemotherapeutic or targeted agents, and this could explain the lack of response (Table S1C). However, other patients with solid cancer received the same drugs and did develop antibody responses. Among patients in standard immunotherapy with anti-PDL1/PD1 or anti-CTLA4, only 1 of 24 was seronegative, and among patients in radiotherapy, only 1 of 29 was seronegative.

A total of 108 patients with hematologic cancers were seronegative. Only 11% (1 of 9) of patients with Mantle cell lymphoma, 55% (66 of 121) with CLL/SLL, and 62% (24 of 39) with follicular lymphoma were seropositive ($p < 0.001$, χ^2 test) (Table S1D). Slightly higher seropositivity rates of 72% (13 of 18) were seen for marginal zone lymphoma, 80% (82 of 103) for multiple myeloma, and 85% (29 of 34) for diffuse large B cell lymphoma. Importantly, significantly more seronegative patients had progressive disease compared to seropositive patients, who most often had a cancer in remission ($p = 0.005$ χ^2 test) (Table S1D).

When analyzing the association between seronegative rates and immunosuppressive therapies—such as anti-CD20, Bruton Tyrosine Kinase inhibitors (BTKi) and anti-CD38 therapies, steroids, and stem cell transplantation—we identified a significant association across immunosuppressive therapies ($p < 0.008$, χ^2 test). More seronegative patients were treated with anti-CD20 therapy (28%, $p < 0.008$, Fisher's exact test), BTKi therapy (11%, $p = 0.002$), or chemotherapy (25%, $p = 0.02$), and fewer seronegative patients had stem cell transplants ($p = 0.03$) compared with seropositive patients. Anti-CD38 therapy was not significantly associated with anti-S IgG status (14%, $p = 0.07$). Our cohort included 43 patients with hematologic cancer who had used prednisolone (>10 mg, daily or occasionally) at time of vaccination and/or at time of blood draws. Of these, 23 patients were seronegative, and a statistically significant association between steroid use and seronegativity was observed ($p = 0.005$, Fischer's exact test) (Table S1D). Multivariate logistic regression analysis using key confounding variables that were biologically plausible affecters of seroconversion were included in the analysis. Overall, our results indicate an association between seronegative rates and steroid use, stem cell transplantation, type of cancer therapies, and cancer diagnosis ($p < 0.001$) for patients with hematologic cancer.

Regarding SARS-CoV-2-specific T cell reactivity, 92 (46%) patients with solid cancer elicited such a response, 70 of whom (76%) mounted both CD4+ and CD8+ T cell responses, and 21 (23%) only elicited a CD8+ T cell response (Table S1B). For patients with hematologic cancer, 144 (45%) exhibited positive T cell responses, 81% of whom were positive for both CD4+ and CD8+ T cells, and 26 (18%) only elicited a CD8+ T cell response (Table S1B). Importantly, most seronegative patients (76%) did not elicit a T cell response. For patients with solid cancer, only 1 of the 14 seronegative patients elicited a T cell response, and among patients with hematologic cancer, 80 of the 108 seronegative patients (74%) elicited no T cell response, but 28 patients (26%) did.

Serological status and T cell response data were used in association studies between cancer subtypes and treatments. A significant association between patients with hematologic cancer who lacked a T cell response and steroid use was observed, but no association was observed for other treatments, diagnoses, or extents of disease (Table S1E).

Collectively, our data indicate that patients with solid cancer generally elicited excellent humoral, but insufficient cellular, immune responses following completion of COVID-19 mRNA vaccine, and patients with hematologic malignancies less frequently elicited adequate humoral and cellular responses. It has been proposed that patients with cancer who exhibited a poor humoral immune response may be protected by a good cellular immune response; however, our data suggest that the majority of the seronegative cancer patients did not elicit CD8+/CD4+ T cell responses. We also observed that titers of the antibody rapidly decreased from 36-day to 3-month for most patients with cancer, resulting in seroconversion of approximately 10% of the seropositive to seronegative, most prominently for patients with hematologic cancer, but this was also observed in patients with solid cancer. For patients with hematologic cancer, seronegativity was significantly associated with certain diagnoses, remission statuses, and treatments, but the lack of T cell responses was only significantly associated with steroid use.

Antibody reactivity correlates with virus neutralization and hence with immunity (Kristiansen et al., 2021), but an absolute protective threshold has yet to be established. In the present study, a borderline level of anti-S IgG antibodies was defined as $\leq$54 BAU/mL, a level previously reported to confer an estimated 50% protective antibody level in standardized units (Khoury et al., 2021). The SARS-CoV-2 specific T cell assay has not yet been approved for clinical use, and although it does not evaluate the full T cell repertoire, it provides reliable data on the T cell response (Martínez-Gallo et al., 2021). Further studies elucidating the clinical consequences of no or low antibody and T cell activation and their limited durability are required.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.07.016.

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DECLARATION OF INTERESTS

All authors declare no competing interests.

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