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Notes and Insights

SARS-CoV-2-specific T cells are generated in less than half of allogeneic HSCT recipients failing to seroconvert after COVID-19 vaccination

SARS-CoV-2 vaccines induce humoral and cellular immune responses [1, 2], protecting against infection, severe disease, and death [1]. Which compartment bears greater relevance for protection is unclear. Most vaccinees are not tested for humoral, let alone cellular responses; most healthy individuals will respond with both [2–4]. Clinical experience confirms an excessive risk of immunocompromised patients for severe COVID-19 [5–7], giving them priority access to vaccination, although suboptimal responses were predicted. Humoral responses are easily detected, and cellular responses are less so [8]. Hematopoietic stem cell transplantation (HSCT) recipients remain immunocompromised after numeric T-cell recovery and immunosuppressant withdrawal [9]. In contrast to healthy SARS-CoV-2 vaccinees, immunocompromised patients' vaccine responses should be monitored to identify failure to develop protection [2]. In a cohort of vaccinated, nonseroconverted HSCT patients, induction of S1 domain of spike protein (S1-) specific T-cell responses was assessed to distinguish isolated B cell from combined adaptive immune incompetence.

Vaccination was initiated ≥3 months post-HSCT. Adult post-HSCT patients after two doses of Comirnaty (Biontec, Mainz, D) or Vaxzevria (Astra-Zeneca, Gothenburg, S) were monitored for anti-Spike-antibodies. Nonseroconverters beyond week 3 could participate in this study. B-non-Hodgkin's lymphoma (B-NHL) patients with isolated pharmacological B-cell depletion and healthy vaccinees served as controls. A conventional commercial in vitro T-cell stimulation assay determined T-cell response to S1-peptide (Supporting Information Methods).

Of 152 double-vaccinated patients, 27 (17.8%) developed no antibodies; 17 thereof (13 2xComirnaty, 3 2xVaxzevria, 1 1xheterologous) participated in our study. At the time of vaccination, 16 of 17 patients were >6 (median 47, range 5–1409) months out from HSCT and were full donor-type chimeras with adequate graft function.

Peripheral blood was analyzed for lymphocyte subpopulations and SARS-CoV-2-specific T cells for 55 days (median; range, 21–127) after the second vaccination. B cells were detected or normal in 14 or 10 of 17 patients. $CD8^+$ T cells were at least normal in 16 of 17 patients, and absolute $CD4^+$ T-cell lymphopenia was prevalent (14/17). Even the three patients with low-normal $CD4^+$ cell counts had skewed CD4:CD8 ratios (Fig. 1A and B). Patients' response to the TCR-MHC-cross-linking reagent was normal (n.s.) [9]; SARS-CoV-2 vaccination-specific responses, however, were diminished (Fig. 1C and D). Patients 2, 4, and 1 demonstrated isolated helper T-cell, cytotoxic T-cell, and combined T-cell responses; the total probability of SARS-CoV-2-specific T-cell responses was 7/17 (41%), 5/13, and 2/3 after 2xComirnaty and 2xVaxzevria. All patients with iatrogenic B-cell aplasia were responders. Unifying features of the remaining responders were not apparent. Thus, the absence of humoral responses does not preclude posttransplant cellular vaccination responses.

We next tested specifically B-cell depleted, inherently seronegative B-NHL patients (Table 1); responses of $CD4^+$ and $CD8^+$ T cells were observed in five of five and four of five (Fig. 1D). Of 22 healthy, antibody-positive vaccinees, 20 of 22 and 16 of 22 had antigen-responsive $CD4^+$ and $CD8^+$ cells. Only one had no T-cell response (Fig. 1D), in agreement with published data [8]. Of patients receiving systemic immunosuppressive therapy ("IS") or not ("no IS") concurrent to vaccination, four of 12 and three of five generated spike-protein-specific T cells (χ^2, $p = 0.54/0.12$ for $CD4^+/CD8^+$ T cells; Fig. 1D). T-cell responses were less frequent in post-HSCT patients, but, where observed, were of normal magnitude.

COVID-19-related mortality for patients with hematological cancer dramatically exceeds that for the general population including the elderly [5–7]. The effectiveness of SARS-CoV-2 vaccines in such vulnerable cohorts was not robustly established.

As shown here for the SARS-CoV-2 vaccine, adaptive immunity after HSCT often remains insufficient even after the withdrawal of immunosuppressants. A total of 17.8% of post-HSCT patients generated no vaccine antibodies. The majority thereof additionally did not develop T-cell responses, remaining unprotected against the SARS-CoV-2 virus.

The concurrently performed positive control, CytoStim, demonstrates patients' overall unimpaired T-cell responsiveness, while sensitization to new antigen (spike protein) is deficient. After HSCT, low CD4:CD8 ratios indicate incomplete T-cell reconstitution with defective thymic recovery of $CD4^+$ and predominant homeostatic expansion of peripheral $CD8^+$ T cells. Limited T-cell receptor diversity precludes adequate vaccination responsiveness [9].

No systemic immunosuppressive therapy ("no IS") patients and patients receiving systemic immunosuppressive therapy ("IS") among the humoral non-responders were not relevantly different re. lymphocyte counts or CD4:CD8 ratios. Nonseroconverting "no IS" were also no more likely than "IS" patients to mount S1-specific T-cell responses (3/5 vs. 4/12, n.s.). Our data thus confirm and expand on recent reports in a similar cohort [10].

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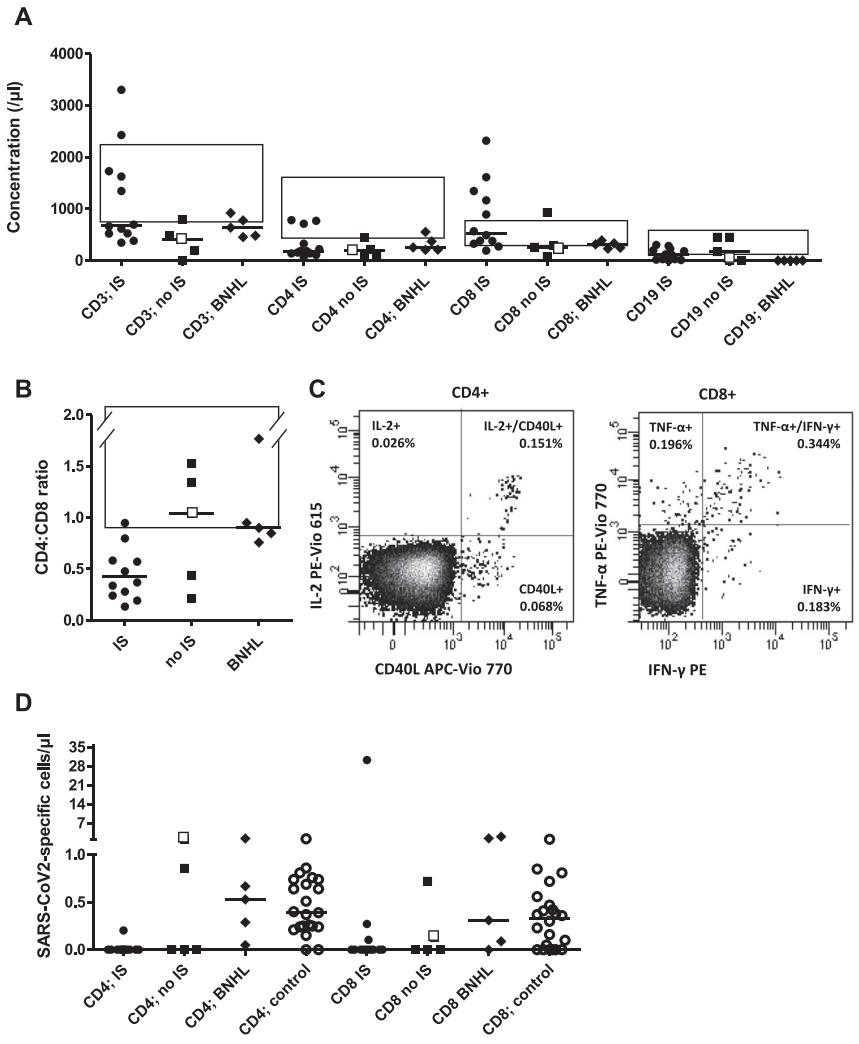

Figure 1. Lymphocyte subpopulations and T-cell response after two doses of SARS-CoV-2 vaccination. Lymphocyte concentrations ($CD3^+/CD4^+/CD8^+/CD19^+$ cells) were measured by flow cytometry and are shown for HSCT recipients ($n = 17$) with ("IS", circles; $n = 12$) or without ("no IS", squares; $n = 5$) systemic immunosuppressive therapy for chronic GVHD and for untransplanted B-cell aplastic B-NHL patients ($n = 5$) ("BNHL", diamonds), all three patient groups without a humoral response to SARS-CoV-2 vaccination (A). For the same patient groups, CD4:CD8 ratios are displayed (same symbols, B). The boxes in (A, B) indicate normal ranges for German adults. A representative positive flow-cytometry analysis is shown in (C). Vaccine-specific T-cell responses for the three patient groups (same symbols as above), as well as healthy vaccinated volunteers, (empty circles) are shown (D). In all panels, the black line marks the median. Empty squares in panels (A, B, D) represent the one patient developing both CD4 and CD8 responses.

It is difficult to know if isolated T-cell responses provide protection against SARS-CoV-2. The 59% of our cohort (12% of the total posttransplant cohort) mounting neither humoral nor cellular responses presumably remain immunologically unprotected and should be counseled accordingly.

Besides the small sample size, a shortcoming of our analysis is its limitation to nonseroconverters. Possible divergence of T- and B-cell responses would be interesting but was not covered by the protocol. Profound lymphopenia precluded deeper phenotyping of (responding) T cells.

We conclude that the majority of allogeneic HSCT patients not showing humoral responses to SARS-CoV-2 vaccination also fail to mount antigen-specific T-cell responses. Immunosuppressive treatment postallogeneic HSCT does not preclude vaccination responses. High-nonresponse rates of HSCT patients to SARS-CoV-2 vaccination mandate testing for humoral and cellular responses to provide tailored guidance.

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Andrea Jarisch[1], Eliza Wiercinska[2], Shabnam Daqiq-Mirdad[2], Helen Hellstern[2], Salem Ajib[3], Anjali Cremer[3,4,5], Ngoc Thien Thu Nguyen[3], Alexandra Dukat[6], Evelyn Ullrich[1,4,5,7], Sandra Ciesek[8], Kai-Uwe Chow[4], Hubert Serve[3,4,5], Erhard Seifried[2,9], Peter Bader[1], Halvard Bonig[2,9] and Gesine Bug[3,4,5]

[1] Division of Pediatric Stem Cell Transplantation and Immunology, Goethe University, Frankfurt, Germany
[2] German Red Cross Blood Service BaWüHe, Frankfurt, Germany

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Table 1. Patient characteristics

	HSCT cohort	NHL cohort
Age (median, range), years	58 (19–73)	57 (29–72)
Sex (male/female)	10/7	3/2
Diagnosis (*n*, %)		
ALL	6 (35)	
AML	8 (47)	
MDS/MPN	3 (18)	
NHL (FL/MCL)		4 (80)
Monoclonal gammopathy		1 (20)
Stem-cell donor (*n*, %)		
MSD	6 (35)	
MUD (≥ 9/10 HLA matched)	11 (65)	
In vivo T-cell depletion (*n*, %)		
ATG	10 (59)	
Alemtuzumab	1 (6)	
None	6 (35)	
Vaccine		
Comirnaty, BioNTech Pfizer (*n*, %)	13 (76)	5 (100)
Vaxzevria, AstraZeneca (*n*, %)	4 (24)	
Time from HSCT to vaccination (median, range), months	47 (5–1409)	
>6 months (*n*, %)	16 (94)	
Disease status at vaccination (*n*, %)		
CR	17 (100)	5 (100)
Prior CAR T-cell therapy (*n*, %)	2 (12)	
Exposure to anti-CD20/22 antibodies within 6 months prior to vaccination (*n*, %)	3 (18)	5 (100)
IST status at vaccination (n, %)		
Off	5 (29)	
Ongoing*	12 (71)	
One IST	4 (33)	
Combination of 2 IST	7 (58)	
Combination of 3 IST	1 (8)	
GVHD status at vaccination (*n*, %)		
No active GVHD	5 (29)	
Late onset acute GVHD (grade 2)	2 (12)	
Chronic GVHD (moderate/severe)	10 (1/9), (59)	
Substitution of IVIG within 6 months of vaccination (*n*, %)	8 (47)	0 (0)
Prior exposure to SARS-CoV-2	0 (0)	0 (0)

Data presented as *n* (%) unless otherwise indicated.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; CR, complete remission; FL, follicular lymphoma; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; IVIG, intravenous immunoglobulins; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasia; MSD, matched sibling donor; MUD, matched unrelated donor; NHL, non-Hodgkin's lymphoma; *IST, immunosuppressive therapy: prednisolone ($n = 6$), everolimus ($n = 4$), ruxolitinib, tacrolimus, tocilizumab, abatacept ($n = 2$ for each drug), extracorporal photopheresis (ECP, $n = 3$).

[3] Department of Medicine, Hematology/Oncology, Goethe University, Frankfurt, Germany
[4] Frankfurt Cancer Institute (FCI), Goethe University, Frankfurt, Germany
[5] German Cancer Consortium (DKTK) Frankfurt/Mainz and German Cancer Research Center (DKFZ), Heidelberg, Germany
[6] Outpatient Cancer Clinic AKS Schaubstraße, Frankfurt, Germany
[7] Experimental Immunology, Department for Children and Adolescent Medicine, Goethe University, Frankfurt, Germany
[8] Institute for Medical Virology, Goethe University, Frankfurt, Germany
[9] Institute for Transfusion Medicine and Immunohematology, Goethe University, Frankfurt, Germany

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Full correspondence: Dr. Andrea Jarisch, Division of Pediatric Stem Cell Transplantation and Immunology, Department for Children and Adolescents Medicine, University Hospital Frankfurt, Theodor-Stern-Kai 5, 60590 Frankfurt am Main, Germany
e-mail: andrea.jarisch@kgu.de

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