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 (Biontech, 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 four and five 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 (χ², 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].
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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Notes and Insights
| 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)      | 1 (20)     |
| Monoclonal gammopathy             |             |            |
| 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) | 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 (n, %) | 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), extracorporeal photopheresis (ECP, n = 3).
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