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Original Research

Third dose of SARS-CoV-2 vaccination in hemato-oncological patients and health care workers: immune responses and adverse events — a retrospective cohort study

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Abstract  Background: Due to potentially immune-escaping virus variants and waning immunity, a third SARS-CoV-2 vaccination dose is increasingly recommended. However, data in patients with cancer are limited.

Patients and methods: We measured anti-SARS-CoV-2 spike protein antibody levels after the third vaccination dose in 439 patients with cancer and 41 health care workers (HCW) at an academic centre in Austria and a rural community hospital in Italy. Adverse events were retrieved from questionnaires.

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Results: Overall, 439 patients and 41 HCW were included. SARS-CoV-2 infections were observed in 62/439 (14.1%) patients before vaccination and in 5/439 (1.1%) patients after ≥1 dose. Longitudinal analysis revealed a decrease of antibody levels between 3 and 6 months after second vaccination in patients with solid tumours (p < 0.001) and haematological malignancies without anti-B cell therapies (p < 0.001). After the third dose, anti-S levels increased compared to the first/second dose. Patients receiving B cell-targeted agents had lower antibody levels than patients with haematological malignancies undergoing other treatments (p < 0.001) or patients with solid tumours (p < 0.001). Moreover, anti-S levels correlated with CD19+ (B cell) and CD56+ (NK cell) counts in peripheral blood. The most frequent adverse events after the third dose were local pain (75/160, 46.9%), fatigue (25/160, 15.6%) and fever/chills (16/160, 10.0%). Patients with cancer had lower anti-S levels than HCW (p = 0.015).

Conclusions: This study in patients with cancer shows improved antibody levels after the third vaccination dose at an acceptable side-effect profile. Lower antibody levels than in controls underline the need for further follow-up studies and dedicated trials.

1. Introduction

Patients with cancer are particularly affected by the COVID-19 pandemic. They are not only prone to adverse outcomes and severe COVID-19 when infected with SARS-CoV-2 but also at risk of disruptions of anticancer treatment or monitoring visits because of SARS-CoV-2 infections [1–4]. Therefore, large oncolo-gical societies recommend SARS-CoV-2 vaccination for all patients with cancer [5].

Overall, SARS-CoV-2 vaccines are highly effective and well tolerated [6–8]. Although SARS-CoV-2 vaccination shows immunogenicity in patients with cancer, seroconversion rates and antibody levels are lower than healthy cohorts, especially in patients undergoing antineoplastic treatment [9–14]. Similar results were observed in patients with immunosuppression due to organ transplantation [15].

With the emergence of variants of concern with increased immune evasion abilities, expanding the overall vaccination coverage and administration of a third booster vaccination is needed to avoid prolonging the pandemic [16]. A third vaccination dose shows the ability to lower the rates of SARS-CoV-2 infection and severe COVID-19 in comparison to non-boostered elderly populations [17]. Studies in immunosuppressed transplant recipients report improved antibody responses after the third dose [18,19]. Similarly, first data after the booster dose in patients with cancer show higher antibody titers, especially in patients with minimal to moderate responses after the second dose [20–22].

However, the existing data are limited by small sample sizes, and large-scale real-life data assessing the immune response after the third dose in patients with haemato-oncological diseases are scarce. Therefore, we aimed to assess clinical factors impacting humoral immune responses after the third SARS-CoV-2 vaccination dose in a large real-life cohort of patients with haemato-oncological malignancies.

2. Materials and methods

2.1. Patient cohorts

In this retrospective cohort study, we included samples from two cohorts of patients with haemato-oncological malignancies undergoing antineoplastic treatment and/ or regular follow-up visits as well as from one control group of health care workers (HCWs) as described previously [9]. This study was reviewed and approved by the ethics committees of the Medical University of Vienna (protocol no. 1164/2019, 1296/2020, 1349/2020, 1073/2021) and the Südtiroler Sanitätssbetrieb (South Tyrolean Healthcare Service, amended protocol no. 35/2020, 139/2021). The study has been conducted according to the Declaration of Helsinki, all its later amendments and in compliance with local and institutional guidelines. All individuals provided informed consent prior to study inclusion.

2.1.1. Vienna patient cohort

The Vienna patient cohort includes patients with solid tumours undergoing systemic treatment, who participate in the Biobanking Program at the Division of Oncology, Department of Medicine I (Medical University of Vienna). Regular SARS-CoV-2 testing prior to outpatient visits was performed as previously published and according to institutional practice [23]. Blood samples were stored by the ‘MedUni Wien Biobank’ facility in accordance with Standard Operating Procedures in an ISO 9001:2015-certified environment [24]. Patients were included if blood samples after the third SARS-CoV-2 vaccination dose were available. Sampling
was performed at 15.5 days after vaccination in the median (range: 1–70). Anti-SARS-CoV-2 nucleocapsid (anti-NC) and anti-SARS-CoV-2 spike protein (anti-S) antibodies were measured using Roche Elecsys assays at the Department of Laboratory Medicine as outlined previously and according to institutional practice [9].

2.1.2. Meran patient cohort
The Meran patient cohort includes patients with haematological diseases and solid tumours who underwent systemic treatment and/or regular follow-up visits between 24/09/2021 and 03/12/2021 at the haemat-oncological day hospital ward of the ‘Franz Tappeiner’ Hospital in Meran/Merano, Italy. All patients in this cohort received the BNT162b2 vaccine as first, second and third doses. According to national guidelines, the second dose was considered as booster dose in patients with previous SARS-CoV-2 infection. Anti-NC/S antibodies were measured 21 days after the first dose, while a further analysis was performed 21 days after the second dose in patients who did not show seroconversion (anti-S < 50 AU/ml) after the first dose. Moreover, to assess the timely variations of antibody levels, repeated blood sampling at pre-defined time-points (in median 3, 4.5 and 6 months after the second vaccination) was performed in a longitudinal cohort. Furthermore, lymphocyte subset counts were assessed 6 months after the second vaccination in this cohort. Antibody measurements after the third dose were performed at a median of 18 days (range: 3–66) after vaccination. Anti-NC and anti-S levels were determined using the Abbott SARS-CoV-2 IgG assays on the Abbott Alinity system as published previously [9].

Patient-reported adverse events (AEs) after vaccination were collected using a standardised questionnaire.

2.1.3. HCWs cohort
A cohort of HCWs was included as control group. This cohort included physicians, nurses as well as scientific and administrative staff employed at the Division of Oncology, Department of Medicine I (Medical University of Vienna). Blood biobanking was performed as described previously [9, 25], and antibody levels were measured as outlined for the Vienna patient cohort.

2.2. Statistical analysis
To compare distributions between metric variables, the Mann-Whitney-U, Kruskal–Wallis and Wilcoxon signed-rank tests were used as appropriate, supplemented by non-parametric methods for longitudinal data [26]. A two-sided p < 0.05 was considered as a significance threshold. Due to the exploratory and hypothesis-generating design of the present study, no adjustment for multiple testing was applied [27].

Table 1
Baseline characteristics of the patient cohorts.

| Vienna cohort (n = 26) | Meran cohort (n = 413) |
|-----------------------|-----------------------|
| **Age (median, range)** | 63 (28–85) | 70 (24–90) |
| **Gender** | | |
| Male | 17 (65.4%) | 196 (47.5%) |
| Female | 9 (34.6%) | 217 (52.5%) |
| **Solid tumours** | | |
| Lung cancer | 6 (23.1%) | 32 (13.3%) |
| Breast cancer | 5 (19.2%) | 51 (21.3%) |
| Head and neck cancer | 3 (11.5%) | 1 (0.1%) |
| Pancreatic cancer | 4 (15.4%) | 8 (3.3%) |
| Colorectal cancer | 0 (0.0%) | 29 (12.1%) |
| Upper gastrointestinal cancer | 3 (11.5%) | 10 (4.2%) |
| Renal cancer | 0 (0.0%) | 14 (5.8%) |
| Ovarian cancer | 0 (0.0%) | 22 (9.2%) |
| Prostate cancer | 0 (0.0%) | 31 (12.9%) |
| Other | 5 (19.2%) | 42 (17.5%) |
| **Haematological malignancy** | 173 (41.9%) | |
| Essential | 32 (18.5%) | |
| Thrombocytopenia | | |
| Chronic lymphatic leukaemia | 26 (15.0%) | |
| Multiple myeloma | 22 (12.7%) | |
| Chronic myeloid leukaemia | 15 (8.7%) | |
| Polycythaemia vera | 11 (6.4%) | |
| Follicular lymphoma | 11 (6.4%) | |
| Myelodysplastic syndrome | 11 (6.4%) | |
| Diffuse large B cell lymphoma | 10 (5.8%) | |
| Other | 35 (20.2%) | |
| **Ongoing treatment** | | |
| Chemotherapy | 8 (30.8%) | 151 (36.6%) |
| Targeted therapy | 3 (11.5%) | 96 (23.2%) |
| Immune checkpoint inhibition (ICI) | 8 (30.8%) | 32 (7.7%) |
| Chemotherapy | 2 (7.7%) | 44 (10.7%) |
| + targeted therapy | 5 (19.2%) | 4 (0.1%) |
| Chemotherapy + ICI | 0 (0.0%) | 58 (14.0%) |
| No ongoing antineoplastic treatment | 0 (0.0%) | 28 (6.8%) |
| Other | 0 (0.0%) | 39 (9.4%) |
| **Used vaccine** | | |
| 3x BNT162b2 | 19 (73.1%) | 413 (100.0%) |
| 3x mRNA-1273 | 3 (11.5%) | |
| 2x BNT162b2 | 1 (3.8%) | |
| → 1x mRNA-1273 | | |
| 2x mRNA-1273 | 2 (7.7%) | |
| → 1x BNT162b2 | | |
| 2x AZD1222 | 1 (3.8%) | |
| → 1x mRNA-1273 | | |
| **Confirmed SARS-CoV-2 infections** | | |
| Prior to vaccination | 0 (0.0%) | 62 (15.0%) |
| Between 1st and 2nd dose | 0 (0.0%) | 57 (91.9%) |
| After 3rd dose | 0 (0.0%) | 2 (3.2%) |
| - | 0 (0.0%) | 3 (4.8%) |
Statistical analysis was performed using GraphPad Prism 9.3.0 (La Jolla, CA, USA) and R 4.1.2 (The R Project for Statistical Computing, Vienna, Austria) with RStudio 2021.09.1 (RStudio Inc., Boston, MA, USA).

3. Results

3.1. Patients’ characteristics

In total, 26 patients were included in Vienna, while 413 patients were enrolled in Meran. In the Vienna cohort, the median age was 63 years (range: 28–85) and all patients were treated for solid tumours. The most frequently applied treatments were chemotherapy and immune checkpoint inhibitors (ICI) in 8/26 (30.8%) patients each.

In the Meran cohort, the median age was 70 years (range: 24–90). Overall, 240/413 (58.1%) patients were diagnosed with a solid tumour, while 173/413 (41.9%) patients with haematological malignancies were included. In Meran, chemotherapy was the most frequently applied treatment modality (151/413, 36.6%), while 39/413 (9.4%) received a B cell-targeted agent. Detailed patient characteristics are given in Table 1.

3.2. Used vaccinations and COVID-19 infections

In Vienna, 19/26 (73.1%) patients received three doses of the BNT162b2 vaccine, while 3/26 (11.5%) were vaccinated three times with mRNA-1273. A heterologous vaccination regimen was applied in 4/26 (15.4%) patients. Of note, there were no documented previous SARS-CoV-2 infections as verified by RT-PCR of respiratory specimens until 30/11/2021 (Table 1).

In Meran, all patients were vaccinated with three doses of the BNT162b2 vaccine. Notably, 62/413 (15.0%) patients had a confirmed SARS-CoV-2 infection; however, 57/62 infections (91.9%) occurred prior to vaccination (Table 1). Still, breakthrough infections could be observed in 5 patients. Two patients with confirmed SARS-CoV-2 infection between the first and second dose had a mild clinical course and could be managed in an outpatient setting. In total, three patients were infected after the third dose (3 days, 3 weeks and 4 weeks after vaccine administration, respectively). One patient suffered from acute myeloid leukaemia and received 5-azacytidine treatment, another individual was under active ibrutinib treatment for CLL. Both were admitted to the hospital but did not need admission to the intensive care unit (ICU). In the third patient, rituximab maintenance therapy due to follicular lymphoma had been stopped 6 months prior to infection. Still, the patient had no detectable SARS-CoV-2 antibodies after vaccination and experienced a severe course with ICU admission.

3.3. Humoral immune responses after the third vaccination in patients with cancer

In the Vienna patient cohort, the median anti-S level after the second vaccination was 236 U/ml (range: 0–2500 U/ml; below the detection range (0.4 U/ml): 2/24 patients, 8.3%). After the third vaccination, the anti-S concentrations of these patients increased to a median of 2500 U/ml (range: 2–2500 U/ml; <0.4 U/ml: 0/26 patients, 0.0%; p < 0.001, Wilcoxon signed-rank test, Fig. 1A).

In the Meran cohort, median anti-S levels after the first vaccination were 222.8 AU/ml (range: 0–40000 AU/ml; <50 AU/ml: 115/411, 28.0%). Sampling after the second vaccination was only performed in patients with anti-S values < 50 AU/ml. Median anti-S level after the second dose reached 48.35 AU/ml (range: 0–40000; <50 AU/ml: 56/112, 50.0%). After the third vaccination, antibody levels increased (median levels 12924 AU/ml, range: 0–40000; <50 AU/ml: 39/413, 9.4%) compared to the first and second dose (p < 0.001, Wilcoxon signed-rank test, Fig. 1B). Antibody levels after the third vaccination were lower in patients with haematological malignancies receiving anti-B cell therapies (median: 4 AU/ml, range: 0–40000) than those receiving other treatments (median: 11124 AU/ml, range: 1.7–40000, p < 0.001, Mann-Whitney-U) or patients with solid tumours (median: 18624 AU/ml, range: 3.2–40000, p < 0.001, Fig. 1C). Of note, 26/39 (66.7%) patients with ongoing anti-B cell treatment did not develop anti-S antibodies, whereas this was the case in 10/134 (7.5%) patients with haematological cancers without anti-B cell therapy and 3/240 (1.3%) patients with solid tumours. In the latter, no difference according to applied treatments could be detected overall (p = 0.199, Kruskal Wallis); still, in uncorrected pairwise comparisons, patients receiving chemotherapy had somewhat lower levels (median 13383 AU/ml, range: 32–40000, <50 AU/ml: 1/98, 1.0%) than those with no active antineoplastic treatment (median: 34288 AU/ml, range: 7112–40000, <50 AU/ml: 0/17, 0.0%, p = 0.022, Fig. 1D). There were no differences in time between the third vaccination and blood sampling between these subgroups (pairwise p > 0.999, Mann-Whitney-U).

3.4. Longitudinal analysis of antibody levels after SARS-CoV-2 vaccination

In 178/413 patients of the Meran cohort, longitudinal measurements of anti-S levels after the second vaccination were performed. Patients’ characteristics of this subcohort are given in Supplementary Table 1. In 58/178
Fig. 1. (A) Anti-S levels after the second and third vaccination dose in the Vienna cohort. (B) Anti-S levels after the first, second and third vaccination dose in the Meran cohort. Anti-S levels after the second dose were only determined if no seroconversion was seen after the first dose. P-values as determined by Wilcoxon signed-rank test. (C) Anti-S levels after the third dose in patients with solid tumours and haematological malignancies with/without B cell-targeted treatment in the Meran cohort. (D) Anti-S levels in patients with solid tumours of the Meran cohort according to applied treatment modalities. P-values as determined by Mann-Whitney-U/Kruskal–Wallis test.

Fig. 2. Anti-S levels 3, 4.5 and 6 months after the second as well as after the third dose in patients with solid tumours and haematological malignancies with/without B cell-targeted therapy (A) and patients with/without prior SARS-CoV-2 infection (B). P-values as determined by Wilcoxon signed-rank test.
(32.6%) of these patients, a SARS-CoV-2 infection was observed prior to vaccination.

Overall, antibody levels decreased from 3 months to 4.5 and 6 months in the Meran cohort (non-parametric relative effects 0.556, 0.497, 0.464; \(p < 0.001\)), with time profiles not differing between the cohorts (\(p = 0.062\)). In patients with solid tumours, antibody levels decreased from 3 months (median 2220 AU/ml, range: 0—40000) to 4.5 (median: 1070, range: 0—40000) and 6 months (median 743.5, range: 0—40000) after the second vaccination (\(p < 0.001\), Wilcoxon signed-rank, Fig. 2A). Similarly, in patients with haematological malignancies and no ongoing B cell-targeted treatment, antibody levels decreased (3 months: median 5537 AU/ml, range: 0—40000; 4.5 months: median 4559 AU/ml, range: 0—40000; 6 months: median 2328 AU/ml, range: 0—40000; \(p < 0.001\)). In contrast, there was no time-dependent change in patients with haematological disease under anti-B cell treatment (3 months: median 0.15 AU/ml, range: 0—28102; 4.5 months: median 2.9 AU/ml, range: 0—18428; 6 months: median 3.9 AU/ml, range: 0—14470; \(p > 0.05\)) who had lower antibody levels after the second vaccination as reported previously [9]. In these patients, the third vaccination dose did not result in higher antibody levels (median: 3.6 AU/ml, range: 0—40000, \(p = 0.325\)). In contrast, antibody levels increased in solid tumours (median: 23074 AU/ml, range: 7.2—40000, \(p < 0.001\)) and haematological patients without B cell-targeted therapy (median: 11261 AU/ml, range: 1.7—39998) after the third vaccination. In both patient cohorts with and without prior SARS-CoV-2 infection, antibody levels decreased over time and increased after the third shot. In addition, patients with prior COVID-19 overall reached higher antibody levels after the third dose (median: 37620.9 AU/ml; range: 1969.6—40000; \(<50\) AU/ml: 0/58, 0.0%) than patients with no documented COVID-19 (median: 7426.95, range: 0—40000; \(<50\) AU/ml: 24/120, 20.0%, Fig. 2B). There was no difference in time between the third vaccination and blood sampling between patients with and without prior COVID-19 (\(p = 0.494\), Mann-Whitney-U).

3.5. Correlation of lymphocyte subtype counts with humoral immune responses

In 149/178 (83.7%) patients of the longitudinal cohort, lymphocyte subtype analyses were performed 6 months after the second vaccination dose. Of these patients, 56/149 (37.6%) patients had previously been infected with SARS-CoV-2. These individuals had higher total lymphocyte counts (\(p = 0.031\), Mann-Whitney-U) and CD19+ counts (\(p < 0.001\)) as well as numerically higher CD56+ cell counts (\(p = 0.051\)) than their counterparts who had not previously been tested positive for SARS-CoV-2 (Fig. 3). Overall, antibody levels 6 months after the second vaccination weakly correlated with CD19+ counts (Spearman’s \(r = 0.325\), \(p < 0.001\)) and CD56+ counts (Spearman’s \(r = 0.220\), \(p = 0.008\)), as did antibody levels after the third dose (CD19+: \(r = 0.288\), \(p < 0.001\); CD56+: \(r = 0.250\), \(p = 0.002\)). This association remained significant in patients who were not infected, while there was no correlation in previously infected patients (detailed correlation plots are given in Supplementary Figure 1).

3.6. Reported AEs after SARS-CoV-2 vaccination in patients with cancer

Possibly vaccination-associated AEs were reported in 413 patients of the Meran cohort after the first dose as well as in 361/413 (87.4%) patients after the second...
and 160/461 (34.7%) patients after the third dose. Higher-grade AEs were overall rare, with only 9 Grade 3 AE after the first, 6 Grade 3 AE after the second and 5 Grade 3 AE after the third dose. Most patients experienced local pain after the first (Grade 1: 150/413, 36.3%), second (131/361, 36.3%) and third (75/160, 46.9%) dose, followed by fatigue (first dose: 60/413, 14.5%; second dose: 52/361, 14.4%; third dose: 25/160, 15.6%) and myalgia (first dose: 20/413, 4.8%, second dose: 28/361, 7.8%, third dose: 13/160, 8.1%). Further details on reported AEs are given in Table 2.

3.7. Humoral immune responses after the third vaccination in patients with cancer versus HCW

In the HCW cohort, 41 samples after the third vaccination dose were available, with full longitudinal follow-up after all vaccination doses in 19 HCWs. Baseline characteristics of the HCW cohort are given in Supplementary Table 2. One confirmed SARS-CoV-2 infection was reported, 2/41 (4.9%) HCW had anti-NC antibodies without a positive SARS-CoV-2 RT-PCR.

In HCW, antibody levels increased between the first (median: 54.2 U/ml, range: 0–376, <0.4 U/ml: 4/19, 21.1%) and second (median: 2500 U/ml, range: 34.1–2500, <0.4 U/ml: 0/19, 0.0%; p < 0.001) as well as between the second and third (median: 2500 U/ml, range: 164–2500, <0.4 U/ml: 0/41, 0.0%; p = 0.004) vaccination dose (Fig. 4A).

Due to different assays used in Vienna and Meran, a comparison between patients with cancer and HCW as control group was only feasible in the Vienna cohort. Notably, patients with cancer had lower anti-S levels after the third dose (median: 2500 U/ml, range: 2–2500, <0.4 U/ml: 26, 0.0%) as compared to HCW (median: 2500, range: 164–2500, <0.4 U/ml: 0/41, 0.0%; p = 0.015). Indeed, antibody levels in patients after the third dose were comparable with those in HCW after the second dose (median: 2500 U/ml, range: 34.1–2500, <0.4 U/ml: 0/19, p = 0.257, Fig. 4B). However, blood sampling was performed somewhat later in HCW (median: 22 days, range: 15–62) than in patients with cancer (median: 15.5 days, range: 1–70; p = 0.01, Mann-Whitney-U).

4. Discussion

Previous research has shown that patients with cancer show immune responses after the first and second SARS-CoV-2 vaccination doses, albeit to a lesser extent than healthy individuals [9–14]. However, with the emergence of novel SARS-CoV-2 variants such as the recent B.1.1.529 (‘Omicron’) variant, the efficacy of the available vaccines may be further impaired [28,29]. Early reports suggest that three doses of the BNT162b2 vaccine result in sufficient amounts of antibodies neutralising the B.1.1.529 variant, whereas levels of these antibodies are markedly lower in individuals who had only received two doses [29,30]. These results underscore the importance of a third ‘booster’ vaccination dose. However, respective data after the third dose are limited in immunosuppressed patients such as those undergoing cancer treatments.

Here, we show in one of the largest published cohorts so far that anti-S levels increased after the third vaccination in patients with cancer. These results are in line with recent publications of smaller cohorts, where a meaningfully strengthened humoral immune response after the third vaccination dose was suggested [20–22,31,32]. However, and in accordance with other published data, patients with haematological-oncological diseases still show lower antibody levels than controls [20]. In fact, antibody concentrations after the third dose in our cohort of patients with cancer were comparable to those after the second vaccination in the HCW control group. Further follow-up studies will be needed to evaluate whether the administration of additional vaccination doses will be necessary in the further course of the pandemic, especially in immunocompromised patients at high risk for severe clinical courses of COVID-19.

Once again, haematological patients receiving anti-B cell therapies showed impaired humoral immune responses compared to patients undergoing other treatment modalities. This is particularly concerning as one
In our study, we observed a breakthrough infection with severe course and ICU admission 6 months after prior rituximab treatment for follicular lymphoma. Of note, no anti-S antibodies were detected in this patient after the third vaccination. Interestingly, previous reports have shown that T cell priming and reactivity are still preserved in patients with rheumatic diseases or multiple sclerosis [33,34]. In a recent publication, the correlation between neutralising antibodies and spike protein-specific T cell responses was weak in patients with cancer, indicating that cellular immunity against SARS-CoV-2 may mount independently from humoral immune responses [20].

Notably, we found correlations between antibody levels and lymphocyte subset counts, specifically CD19+ B cells and CD56+ natural killer (NK) cells. In line, patients with prior SARS-CoV-2 infection (and subsequently higher antibody levels) had higher B cell and NK cell counts. Still, the correlation of CD19+ and CD56+ cell counts with antibody levels remained also significant in patients who had not been infected. These data confirm previous findings where a link between CD56+ NK cell counts and immune responses towards mRNA-based vaccines has been postulated [41,42]. However, the underlying immunological mechanisms remain elusive and further investigations including antigen-specific T cell assays would be needed to obtain deeper insights into vaccination-induced immunity in patients with cancer.

In our cohorts, 14% of the included patients were infected before vaccination, while breakthrough infections were seen in only ~1%. Although the inferences of our retrospective observations on vaccine efficacy have to be taken cautiously, these data underline that the combination of SARS-CoV-2 vaccination with general protective measures (including personal, institutional and governmental safety measures [23,43]) helps to limit compromised immune systems due to immunosuppressive medications who are not able to mount an adequate immune response to the COVID-19 vaccination [38]. Further monoclonal antibodies for post-exposure prophylaxis and early outpatient treatment in patients with risk factors have been studied [39,40].

Table 2
Reported possibly vaccination-related adverse events in patients with cancer.

|                  | First dose (n = 413) | Second dose (n = 361) | Third dose (n = 160) |
|------------------|----------------------|-----------------------|----------------------|
|                  | Grade 1 | Grade 2 | Grade 3 | Grade 1 | Grade 2 | Grade 3 | Grade 1 | Grade 2 | Grade 3 |
| Local pain       | 141 (34.1%) | 16 (3.9%) | 3 (0.7%) | 120 (33.2%) | 10 (2.8%) | 1 (0.3%) | 69 (43.1%) | 5 (3.1%) | 1 (0.6%) |
| Local redness    | 12 (2.9%)   | 1 (0.2%) | 0 (0.0%) | 6 (1.7%)   | 1 (0.3%) | 0 (0.0%) | 5 (3.1%)   | 1 (0.6%) | 0 (0.0%) |
| Local swelling   | 16 (3.9%)   | 1 (0.2%) | 0 (0.0%) | 8 (2.2%)   | 1 (0.3%) | 0 (0.0%) | 4 (2.5%)   | 1 (0.6%) | 0 (0.0%) |
| Local itching    | 9 (2.2%)    | 0 (0.0%) | 0 (0.0%) | 4 (1.1%)   | 0 (0.0%) | 0 (0.0%) | 3 (1.9%)   | 0 (0.0%) | 0 (0.0%) |
| Allergic reaction| 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) |
| Feverchills      | 13 (3.1%)   | 1 (0.2%) | 0 (0.0%) | 25 (6.9%)  | 2 (0.6%) | 2 (0.6%) | 14 (8.8%)  | 2 (1.3%) | 0 (0.0%) |
| Flushing         | 6 (1.4%)    | 2 (0.5%) | 0 (0.0%) | 5 (1.4%)   | 3 (0.8%) | 0 (0.0%) | 3 (1.9%)   | 1 (0.6%) | 0 (0.0%) |
| Dizziness        | 10 (2.4%)   | 3 (0.7%) | 0 (0.0%) | 4 (1.1%)   | 2 (0.6%) | 0 (0.0%) | 3 (1.9%)   | 1 (0.6%) | 0 (0.0%) |
| Fatigue          | 54 (13.1%)  | 4 (1.0%) | 2 (0.5%) | 48 (13.3%) | 3 (0.8%) | 1 (0.3%) | 21 (13.1%) | 2 (1.3%) | 2 (1.3%) |
| Insomnia         | 8 (1.9%)    | 1 (0.2%) | 0 (0.0%) | 5 (1.4%)   | 1 (0.3%) | 0 (0.0%) | 5 (3.1%)   | 0 (0.0%) | 0 (0.0%) |
| Sweating         | 7 (1.7%)    | 1 (0.2%) | 0 (0.0%) | 5 (1.4%)   | 1 (0.3%) | 0 (0.0%) | 3 (1.9%)   | 1 (0.6%) | 0 (0.0%) |
| Rash             | 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) |
| Sore throat      | 3 (0.7%)    | 0 (0.0%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 1 (0.6%)   | 0 (0.0%) | 0 (0.0%) |
| Headache         | 21 (5.1%)   | 8 (1.9%) | 1 (0.2%) | 18 (5.0%)  | 4 (1.1%) | 1 (0.3%) | 6 (3.8%)   | 3 (1.9%) | 1 (0.6%) |
| Myalgia          | 17 (4.1%)   | 3 (0.7%) | 0 (0.0%) | 22 (6.1%)  | 6 (1.7%) | 0 (0.0%) | 10 (6.3%)  | 3 (1.9%) | 0 (0.0%) |
| Arthralgia       | 17 (4.1%)   | 0 (0.0%) | 0 (0.0%) | 8 (2.2%)   | 12 (3.3%) | 0 (0.0%) | 9 (5.6%)   | 1 (0.6%) | 0 (0.0%) |
| Lymphadenopathy  | 3 (0.7%)    | 1 (0.2%) | 0 (0.0%) | 4 (1.1%)   | 0 (0.0%) | 0 (0.0%) | 2 (1.3%)   | 0 (0.0%) | 0 (0.0%) |
| Decreased appetite| 9 (2.2%)  | 0 (0.0%) | 0 (0.0%) | 10 (2.8%)  | 0 (0.0%) | 0 (0.0%) | 4 (2.5%)   | 0 (0.0%) | 0 (0.0%) |
| Nausa            | 6 (1.4%)    | 2 (0.5%) | 0 (0.0%) | 5 (1.4%)   | 2 (0.5%) | 0 (0.0%) | 3 (1.9%)   | 0 (0.0%) | 0 (0.0%) |
| Diarrhea         | 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 3 (0.8%)   | 0 (0.0%) | 1 (0.3%) | 4 (2.5%)   | 0 (0.0%) | 1 (0.6%) |
| Cough            | 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 2 (1.3%)   | 0 (0.0%) | 0 (0.0%) |
| Dyspnea          | 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 1 (0.6%)   | 0 (0.0%) | 0 (0.0%) |
| Chest pain       | 3 (0.7%)    | 0 (0.0%) | 1 (0.2%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 1 (0.6%)   | 0 (0.0%) | 0 (0.0%) |
| Tachycardia      | 5 (1.2%)    | 1 (0.2%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) |
| Anosmia          | 1 (0.2%)    | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%) | 0 (0.0%) |
| Hypoesthesia     | 2 (0.5%)    | 0 (0.0%) | 0 (0.0%) | 2 (0.6%)   | 0 (0.0%) | 0 (0.0%) | 1 (0.6%)   | 0 (0.0%) | 0 (0.0%) |
uncontrolled viral spread in patients with cancer. To add 

further, AE rates after vaccine administration in our 

cohort were comparable to those observed in the general 

population [7]. Overall, our data corroborate the 

favourable safety profile of the available vaccines in pa-

tients with haemato-oncological diseases, confirming 

the beneficial risk-benefit ratio of SARS-CoV-2 vaccination.

4.1. Limitations

Clearly, our study has important limitations. As in our 

previous report [9], pooled analyses between both pa-

tient cohorts were not feasible due to different assays 

used in both centres. Again, only patients who were 

seronegative after the first dose underwent antibody 

measurements after the second dose in the Meran 

cohort. Consequently, the increase in antibody levels 

between the second and third cohort could not be 

evaluated in all patients. Moreover, anti-S antibody 

levels are a mere surrogate parameter for humoral im-

munity, whereas a further investigation on the levels of 

neutralising antibodies could more precisely reflect the 

actual anti-SARS-CoV-2 immune responses, especially 

in the light of emerging virus variants potentially 

hampering vaccination-induced immunity. In addition, 

further studies on cellular immune responses could 

provide a more comprehensive picture on immune re-

sponses after vaccination, particularly in patients un-

dergoing anti-B cell therapies. Furthermore, differences 

in national vaccination regulations between Austria and 

Italy limit the comparability of both cohorts. While the 

administration of the third dose is endorsed in both 

countries, these recommendations were issued earlier in 

Austria than in Italy, and current or future vaccination 

mandates may impact the vaccination behaviour of the 

general population and patients with cancer. Lastly, our 

study has the inherent shortcomings of a retrospective 

real-life study such as incompleteness of data and het-

erogeneous cohorts. In line, the validity of data on 

possibly vaccination-induced AEs as collected by a 

questionnaire is limited by a reporting bias.

5. Conclusion

Taken together, our real-life data support the timely 

administration of the third SARS-CoV-2 vaccination 

dose in patients with cancer. Our results based on two 

independent cohorts of patients with haemato-onco-

logical malignancies treated at an academic tertiary care 

centre in Austria and a communal hospital in a rural 

area in Italy show that antibody levels considerably in-

crease after the third vaccination dose. Moreover, our 

data suggest that humoral immune responses do not 

only correlate with CD19+ (B cell) but also CD56+ 

(NK cell) counts in peripheral blood. The combination 

of diminishing antibody levels in the months following 

the second vaccination and the emergence of viral vari-

ants further underscores the necessity of a ‘booster’ 

dose in this vulnerable cohort. As antibody levels are 

still lower than controls and particularly low in specific 

subgroups such as patients receiving anti-B cell ther-

apies, dedicated trials on SARS-CoV-2 vaccinations and, 

potentially, additional vaccination doses will be needed.

Authors contributions

Contribution to study design and its implementation: 

MJM, JMB, MM, MG, ACB, WT, ASB, TP, HH, 

WWL, MR, ST, TF, TB, DF, MP; data analysis and 

interpretation: MJM, JMB, MM, MG, ACB, TT, DF, 

MP; Manuscript writing and editing: MJM, JMB, MM, 

MP. All authors read and approved the final version of 

the manuscript. MJM and JMB as well as DF and MP 

contributed equally and should be regarded co-first/co-

last authors.

Access to data statement

M JM and MP had full access to all the data in the study 

and take responsibility for the integrity of the data and 

the accuracy of the data analysis.

Ethical approval

This study was approved by the ethics committee of the 

Medical University of Vienna (protocol no. 1164/2019, 

1296/2020, 1349/2020 and 1073/2021) and the Südtiroler 

Sanitätsbetrieb (South Tyrolean Healthcare Service, 

amended protocol no. 35–2020, 139/2021).

Data availability

Data are available from the corresponding author/lead 

contact (Matthias Preusser, matthias.preusser@ 

meduniwien.ac.at) upon reasonable request and 

necessary regulatory approvals.

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had no role/influence in design and conduct of the study; 

collection, management, analysis and interpretation of 

the data; preparation, review, or approval of the 

manuscript and decision to submit the manuscript for 

publication.

Conflict of interest statement

Anna Sophie Berghoff has received research support 

from Daiichi Sankyo, Roche, and honoraria for
lectures, consultation or advisory board participation from Roche, Bristol-Meyers Squibb, Merck, Daiichi Sankyo as well as travel support from Roche, Amgen and AbbVie.

Thorsten Fuereeder has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: MSD, Merck Darmstadt, Roche, Bristol-Myers Squibb, Accord, Sanofi, Boehringer Ingelheim as well as travel support from Roche, MSD and Bristol-Myers Squibb. The following for-profit companies have supported clinical trials and contracted research conducted by TF with payments made to his institution: MSD, Merck Darmstadt, Bristol-Myers Squibb.

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All other authors declare that they have no conflict of interest related to the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.019.

References

[1] Tagliamento M, Agostinetti E, Bruzzone M, Ceppi M, Saini KS, de Azambuja E, et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2021;163:103365. https://doi.org/10.1016/j.critrevonc.2021.103365.

[2] Pinato DJ, Tabernero J, Bower M, Scotti L, Patel M, Colomba E, et al. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. Lancet Oncol 2021;22:1669–80. https://doi.org/10.1016/S1470-2045(21)00573-8.

[3] Pinato DJ, Patel M, Scotti L, Colomba E, Dolly S, Loizidou A, et al. Time-dependent COVID-19 mortality in patients with cancer. JAMA Oncol 2022;8:114. https://doi.org/10.1001/jamaoncol.2021.6199.

[4] Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020;395:1907–18. https://doi.org/10.1016/S0140-6736(20)31187-9.

[5] Corti C, Crimini E, Tarantino P, Pravettoni G, Eggermont AMM, Delaloge S, et al. SARS-CoV-2 vaccines for cancer patients: a call to action. Eur J Cancer 2021;148:316–27. https://doi.org/10.1016/j.ejca.2021.01.046.

[6] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16. https://doi.org/10.1056/NEJMoa2035389.

[7] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383:2603–15. https://doi.org/10.1056/nejmoa2034577.

[8] Voysey M, Clemens SAC, Madhu S, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111. https://doi.org/10.1016/S0140-6736(20)32661-1.

[9] Mair MJ, Berger JM, Berghoff AS, Starzer AM, Ortmayr G, Puhr HC, et al. Humoral immune response in hematopoietic patients and health care workers who received SARS-CoV-2 vaccinations. JAMA Oncol 2022;8:1016. https://doi.org/10.1001/jamaoncol.2021.5437.

[10] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137:3165–73. https://doi.org/10.1182/blood.202111588.

[11] Corti C, Antonarelli G, Scotté F, Spano JP, Barrière J, Michot JM, et al. Seroconversion rate after vaccination against COVID-19 in patients with cancer—a systematic review. Ann Oncol 2022;33:158–68. https://doi.org/10.1016/j.annonc.2021.10.014.

[12] Di Noia V, Pimpinelli F, Renna D, Barberi V, Macellini MT, Gariazzo L, et al. Immunogenicity and safety of COVID-19 vaccine BNT162b2 for patients with solid cancer: a large cohort prospective study from a single institution. Clin Cancer Res 2021;27:6815–23. https://doi.org/10.1158/1078-0432.CCR-21-2439.

[13] Becerril-Gaitan A, Vaca-Cartagena BF, Ferrigno AS, Mescavage F, Barrientos-Gutiérrez T, Tagliamento M, et al. Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis. Eur J Cancer 2022;160:243–60. https://doi.org/10.1016/j.ejca.2021.10.014.

[14] Saini KS, Martins-Branco D, Tagliamento M, Vidal L, Singh N, Punie K, et al. Emerging issues related to COVID-19 vaccination in patients with cancer. Oncol Ther 2021;9:255–65. https://doi.org/10.1007/s40487-021-00157-1.

[15] Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Aley PK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA 2021;325:2204–6. https://doi.org/10.1001/jama.2021.7489.

[16] Pappas G, Saloustros E, Boutis A, Tsoukalas N, Nikolaou M, Christopoulou A, et al. Vaccine third dose and cancer patients: necessity or luxury? ESMO Open 2021;6:100306. https://doi.org/10.1016/j.esmoop.2021.10.006.

[17] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkestein N, et al. Protection of BNT162b2 vaccine booster against covid-19 in Israel. N Engl J Med 2021;385:1393–400. https://doi.org/10.1056/NEJMOA2114255.
Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Bello ADe. Three doses of an mRNA covid-19 vaccine in solid-organ transplant recipients. N Engl J Med 2021;385:661–2. https://doi.org/10.1056/NEJMCI2018881.

Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Rottenberg Y, Grinshpun A, Ben-Dov IZ, Djian EO, Wolf DG, Fenioux C, Teixeira L, Fourati S, Melica G, Lelievre JD, Haslacher H, Gerner M, Hofer P, Jurkowitsch A, Hainfellner J, Chen J, Wang R, Gilby NB, Wei G-W. Omicron (B.1.1.529): a severe acute respiratory syndrome coronavirus 2 inpatients treated with anticancer agents. JAMA Oncol 2021;2021.7777.

Bender R, Lange S. Adjusting for multiple testing - when and how? J Clin Epidemiol 2001;54:343–9. https://doi.org/10.1016/S0895-4356(00)00314-0.

Chen J, Wang R, Gilby NB, Wei G-W. Omicron (B.1.1.529): infectivity, vaccine breakthrough, and antibody resistance. ArXiv 2021. 2112.01318.

Muñ A, Lui BW, Wallisch A-K, Bacher M, Mühl J, Reinholz J, et al. Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-elicited human sera. Science 2022. https://doi.org/10.1126/science.abc7591, eabc7591.

Pfizer Inc. Press release: pfizer and BioNTech update on omicron variant. 2021.

Greenberger LM, Saltzman LA, Seneffeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies. Cancer Cell 2021;39:1297–9. https://doi.org/10.1016/j.ccell.2021.09.001.

Shapiro LC, Thakkar A, Campbell ST, Forest SK, Pradhan K, Gonzalez-Lugo JD, et al. Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer. Cancer Cell 2022;40:3–5. https://doi.org/10.1016/j.ccell.2021.11.006.

Bonelli MM, Mruk D, Perkmann T, Haslacher H, Aletaha D. SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response. Ann Rheum Dis 2021;80:1355–6. https://doi.org/10.1136/annrheumdis-2021-220408.

Apostolidis SA, Kakara M, Painter MM, Goel RR, Mathew D, Lensi K, et al. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat Med 2021;27:1990–2001. https://doi.org/10.1038/s41591-021-01507-2.

Seikine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 2020;183:158–168.e14. https://doi.org/10.1016/j.cell.2020.08.017.

Di Noia V, Pimpinelli F, Renna D, Barberi V, Pellini R, Moretone A, et al. Clinical characteristics limiting the durability of humoral response to BNT162b2 in patients with solid cancer. Ann Oncol 2021;2021.e1016. https://doi.org/10.1016/j.annonc.2021.11.015.

Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, et al. Duration of antiviral immunity after smallpox vaccination. Nat Med 2003;9:1131–7. https://doi.org/10.1038/nm917.

FDA. FDA news release: coronavirus (COVID-19) update: FDA authorizes new long-acting monoclonal antibodies for pre-exposure prevention of COVID-19 in certain individuals 2021.

Wenreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. N Engl J Med 2021;385:e81. https://doi.org/10.1056/NEJMoa2108163.

O’Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV antibody combination to prevent covid-19. N Engl J Med 2021;385:1184–95. https://doi.org/10.1056/NEJMoa2109682.

Molica S, Giannarelli D, Mair MJ, Lanthaler F, Alber M, Mitterer M. Mobility as a driver of severe acute respiratory syndrome coronavirus 2 in cancer patients during the second coronavirus disease 2019 pandemic wave. Int J Cancer 2022;150:431–9. https://doi.org/10.1002/ijc.33838.