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Letter

Enhanced SARS-CoV-2 breakthrough infections in patients with hematologic and solid cancers due to Omicron

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Patients with cancer are at high risk for severe clinical courses of COVID-19 and delays of antineoplastic treatment due to SARS-CoV-2 infections (Pinato et al., 2022). SARS-CoV-2 vaccinations were shown to be quite effective and well tolerated according to post-authorization data and real-life studies of hemato-oncological cohorts (Corti et al., 2022). However, we (Mair et al., 2022a; 2022b) and others have shown that antibody levels in patients with cancer are lower than in healthy controls, and specific subgroups such as patients receiving B cell-targeting treatments exhibit particularly low seroconversion rates.

With the emergence of immune-evading variants of concern (VOC) such as Delta (B.1.617.2) and Omicron (B.1.1.529), vaccination efficacy against symptomatic infections is considerably impaired in the general population, although protection against severe courses and hospital admission seems to be maintained (Andrews et al., 2022; Collie et al., 2022). Also in patients with cancer, disease severity in Omicron-infected individuals appears to be lower than with previous virus variants (Lee et al., 2022). Therefore, precautionary measures are gradually being lifted due to increasing vaccination coverage and the seemingly lower pathogenicity of the Omicron VOC in the general population. Nevertheless, mild SARS-CoV-2 infections and subsequent quarantine measures may disrupt anticancer treatment and thereby potentially impact survival prognosis in these patients. Data on the impact of VOC on vaccination efficacy and neutralizing ability of vaccination-induced antibodies, particularly the Omicron variant, are scarce in patients with different types of cancer with and without systemic treatment (Fendler et al., 2022).

Here, we analyzed the time course of the occurrence of SARS-CoV-2 infections in a large cohort of patients with cancer in Austria and Italy throughout the pandemic (Supplemental information). In total, 3,959 patients were included, of whom 3,036/3,959 (76.7%) had been diagnosed with a solid tumor and 923/3,959 (23.2%) with a hematologic malignancy. Of note, 2,737/3,959 (69.1%) did not undergo systemic antineoplastic treatment at the time of vaccination. Between February 24, 2020, and database lock (February 28, 2022), 950/3,959 (24.0%) patients had been infected with SARS-CoV-2. Moreover, 3,368/3,959 (85.1%) patients had received at least one vaccination dose, whereas 588/3,959 (14.9%) were unvaccinated. Baseline characteristics are shown in Table S1.

The weekly numbers of SARS-CoV-2 infections and COVID-associated hospitalizations according to vaccination status over time are illustrated in Figure S1A. With the emergence of the Delta VOC, 54/125 (43.2%) infected patients had been previously vaccinated. However, breakthrough infections were more common during the subsequent Omicron wave (204/289, 70.6%; odds ratio [OR]: 3.15, 95% confidence interval (CI): 1.99–4.99; $p < 0.001$, Fisher exact test, Figure S1B). Among all infected patients, breakthrough infections during the Delta and Omicron waves were more frequent in patients with cancer who were undergoing systemic antineoplastic treatment (79/95, 83.2%) as compared to patients without ongoing anticancer therapy (179/319, 56.1%, OR: 3.85, 95% CI 2.12–7.39; $p < 0.001$, Fisher exact test, Figure S1C), indicating a particularly impaired vaccination-induced immunity against VOCs in patients receiving systemic antineoplastic agents.

In addition, we observed that hospital admissions were less common during the Omicron wave than during the Delta wave, irrespective of vaccination status (Figure S1A). Vaccinated patients had a tendency for shorter hospital stays (median/range: 15 [1–41] days) than unvaccinated patients (median/range: 9 [1–79] days; $p = 0.126$, Mann-Whitney-U test, Figure S1D), suggesting a retained protection against severe COVID-19 in vaccinated individuals. In line, only 1/11 (9.1%) patients requiring intensive care unit

(ICU) admission was attributable to a breakthrough infection.

To gain deeper insights underlying the higher rate of breakthrough infections due to Omicron compared to Delta, we investigated humoral immunity after SARS-CoV-2 vaccination against VOCs. In particular, we measured levels of antibodies specific for the receptor-binding domain (RBD) on the SARS-CoV-2 spike protein of VOCs and their ability to inhibit the interaction of RBD with the human angiotensin-converting enzyme 2 (ACE2) receptor in a subgroup of patients with cancer undergoing antineoplastic treatment (Gattinger et al., 2022) (Supplemental information).

In total, 78 patients (28 with solid tumors, 26 with hematologic malignancies receiving B cell-targeted treatments, and 24 with hematologic malignancies receiving other therapy) and 25 healthcare workers (HCWs) as controls were included (Table S1). With regard to total anti-spike (S) protein IgG levels, there were significant differences between cohorts ($p = 0.009$, Kruskal-Wallis test, Figure S2A). Anti-S IgG levels were higher in HCWs (median optical density [OD]: 1.917, range: 1.513–2.793) than in patients with solid tumors (median OD: 1.787, range: 0.957–2.474, uncorrected $p = 0.036$) or hematologic malignancies receiving B cell-targeted agents (median OD: 1.750, range: 0.061–2.475, $p = 0.014$).

Differences between groups were more accentuated for RBD-specific antibodies. Antibody levels to RBD of wild-type (hu-1) were lowest in patients receiving B cell-targeted agents (median OD: 0.435, range: 0.058–2.435), followed by hematologic malignancies not receiving B cell targeted agents (median OD: 1.185, range: 0.123–2.441), solid tumors (median OD: 1.244, range: 0.088–2.406), and HCWs (median OD: 2.070, range: 0.442–2.883; $p < 0.001$, Kruskal-Wallis test, Figure S2B). Similar results were seen for RBD-Delta ($p < 0.001$, Figure S2C) and RBD-Omicron levels ($p < 0.001$, Figure S2D). Multivariate non-parametric analysis for RBD levels between groups confirmed these findings ($p < 0.001$), with significant differences ($p < 0.05$) for each VOC-specific RBD individually. Corrected pairwise comparisons between cohorts showed significant differences ($p < 0.05$) for each pair except between patients with hematologic malignancies without B cell-targeted treatment and patients with solid tumors. Of note, RBD-specific antibody levels numerically decreased from hu-1 to Delta and Omicron in all cohorts.

In addition, we performed molecular interaction assays to measure the inhibition of RBD-ACE2 binding by patients' sera. Most patients with solid tumors and hematologic malignancies without B cell-targeted treatment exhibited inhibition of RBD-ACE2 binding of more than 50% for hu-1 (median inhibition solid tumors: 98.5%, range: 15.7–100.6%; median hematologic malignancies: 91.8%, range: 22.7–100.6%; Figure S2E) and Delta VOC (median inhibition solid tumors: 94.4%, range: −13.7–100.6%; median hematologic malignancies: 59.2%, range: −49.7–100.8%, Figure S2F). In contrast, patients receiving anti-B cell treatment showed considerably lower values (median inhibition hu-1: 21.7%, range: −11.0–101.4%; median inhibition Delta: 13.1%, range: −48.4–100.9%). Of note, inhibition of RBD-ACE2 binding was markedly impaired for the Omicron variant in patients with solid tumors (median inhibition: 16.6%, range: −9.5–94.6%) as well as hematologic malignancies receiving B cell-targeting agents (median inhibition −1.07%, range: −62.6–81.0%) or other treatments (median inhibition: 5.6%, range: −43.6–99.2%), while HCWs as controls had considerably higher values (median inhibition: 79.4%, range: −1.7–99.8%; $p < 0.001$, Kruskal-Wallis test, Figure S2G) than the other groups. However, inhibition of the Omicron RBD-ACE2 interaction was considerably lower than for RBD of hu-1 and Delta. Multivariate non-parametric analysis for RBD-ACE2 inhibition levels between groups confirmed these findings ($p < 0.001$), with significant differences ($p < 0.05$) for each VOC-specific RBD individually. Corrected pairwise comparisons between cohorts showed significant differences ($p < 0.05$) for each pair except between patients with hematologic malignancies without B cell-targeted treatment and patients with solid tumors, as well as between both hematologic patient cohorts. Again, RBD-ACE2 binding inhibition decreased from hu-1 to Delta and Omicron within all cohorts.

Our data provide a comprehensive overview on SARS-CoV-2 infections and hospitalizations during the last Delta and Omicron waves of the pandemic in patients with different forms of cancer with and without treatment. We observed an increase of SARS-CoV-2 breakthrough infections with the occurrence of the Omicron variant as compared to the Delta wave, whereas hospital admissions decreased. However, as in the general population, our data do not allow conclusions on whether reduced hospitalization rates in patients with cancer were attributable to the seemingly lower pathogenicity of the Omicron variant or increasing infection and/or reduced vaccination coverage.

We found immunological evidence of highly impaired vaccine-induced neutralization of the Omicron variant, but not against the wild-type hu-1 strain and the previous Delta VOC in patients with hematologic and solid cancers in comparison to HCW. Indeed, comprehensive data on the neutralizing ability of vaccination-induced antibodies against VOCs are rare in hemato-oncologic patients, in particular concerning the Omicron variant (Fendler et al., 2022). While previous studies investigating prior virus variants showed impaired humoral responses mainly in the subpopulation of patients with hematologic malignancies receiving B cell-depleting therapies (Obeid et al., 2022), our immunological data indicate virtually lacking humoral vaccine response against the most recent Omicron VOC across a much broader population of patients with cancer.

Our study has some limitations, including the retrospective design, which is inherently linked to heterogeneity, as well as missing data. Whereas the number of received vaccinations was known in all patients, missing information on vaccination dates impeded further testing on time-dependent risks for infection and hospitalization. In addition, we only measured neutralizing RBD antibody levels and their inhibitory capacity on RBD-ACE2 binding, whereas immunity against VOCs may be based also on T cell-associated immunity and other factors.

In conclusion, the increasing rates of breakthrough infections and hospital admissions of vaccinated cancer patients associated with SARS-CoV-2 VOC highlight the need for further protective measures, not only for effective control of the

ongoing pandemic but also to prepare for the potential emergence of further immune-evading VOCs. The high rates of breakthrough infections in patients with hematologic and solid cancers documented in our study highlight the unresolved pandemic-related challenges in oncology, including a reduction and delay of routine care. In addition, adapted VOC-specific vaccines (Gattinger et al., 2022) might be needed to protect hemato-oncological patients and maintain cancer care during the ongoing pandemic.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.04.003.

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