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Letter

Longitudinal COVID-19-vaccination-induced antibody responses and Omicron neutralization in patients with lung cancer

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During the global pandemic with COVID-19, early reports indicated that cancer patients in general, and lung cancer patients in particular, who were infected with SARS-CoV-2 had high mortality rates, with a reported 25%–40% case fatality rate (CFR) (Rolfo et al., 2022). The underlying clinical, demographic, and tumor-biologic factors contributing to the aggressive course of infection in this vulnerable cancer population have not been fully elucidated and could arise through multiple mechanisms, including the immunosuppressive activity of lung cancer therapeutics, lung cancer itself, or other co-morbidities particularly related to the respiratory system (Kuderer et al., 2020; Zhang et al., 2021; Lievre et al., 2020). In December 2020, phase III randomized clinical trials demonstrated strong clinical efficacy of SARS-CoV-2 mRNA vaccines, which subsequently became available to the public in the United States, but did not specifically evaluate lung cancer patients (Baden et al., 2021; Chavez-Macgregor et al., 2022). Additionally, the recently emergent Omicron variants largely evade vaccination-induced immunity. It has been shown that third mRNA vaccine doses increase Omicron antibody neutralization in the general population; however, the efficacy of this third dose remains unknown in patients with lung cancer (Planas et al., 2022; Wu et al., 2022; Nemet et al., 2022). Thus, there are major knowledge gaps for managing patients with lung cancer in the COVID-19 era which need to be filled.

To address these key issues, we prospectively studied the magnitude and kinetics of the humoral response to COVID-19 mRNA vaccination in a well-annotated lung cancer population of 176 individuals, compared to an age-matched control series. Of the full cohort, 114 patients received two doses of mRNA vaccine, with 66% receiving the BNT162b2 (Pfizer/BioNTech), while 34% received mRNA-1273 (Moderna). Participant demographics are shown in Table S1. The median age was 69, with 54% female and 54% with stage 4 disease. Across all stages and histologies, 68% of patients were actively receiving systemic treatment for lung cancer. For comparison, information and specimens from 140 control participants were recruited from two sources at the Mount Sinai Health System: the Early Lung Cancer Action Program (ELCAP) screening center and the Protection Associated with Rapid Immunity to SARS-CoV-2 (PARIS) study (Krammer et al., 2021). The control group coming from ELCAP screening participants (n = 51) was well matched in terms of age and ethnicity and was comprised of 43% women. The PARIS control group from healthcare workers (n = 67) had no ethnicity data recorded and was comprised of 69% women. Overall, following the same exclusion criteria, the combined control groups had 64% of participants receiving BNT162b2 mRNA vaccine and 36% of participants receiving mRNA-1273 vaccine.

The evolution of humoral response over time in patients and controls who received two doses of mRNA vaccine (prior to booster) is represented in Figure S1A. Linear regression analysis revealed that lung cancer patient antibody titers had a significantly reduced area under the curve (AUC) per day compared to control antibody titers ($p = 0.0018$). Critically, there

were significantly more post-vaccinated lung cancer patients with titers measured at zero compared to controls (patients, 6/103; control, 0/105; $p < 0.0001$). Additionally, there was significantly more intra-patient variance in antibody titers within the cancer group compared to the controls ($p = 0.002$) (Figure S1B). Longitudinal analyses of individual cancer patients and controls are shown in Figures S1C and S1D, respectively. In this patient set, 34.9% (n = 44) received a booster (third) vaccination. Overall, booster vaccinations resulted in a significantly positive increase in the trajectory of patient antibody titers, emphasized in Figure S1E by the darker blue circles ($p < 0.001$). Of the six patients who had zero titers after initial vaccination, two were deceased prior to availability of a third (booster) vaccination. However, booster vaccinations resulted in increased titers to detectable levels in three of the three patients for whom post-booster blood draws were available, shown in Figure S1F as a time course relative to treatment and vaccination.

A relevant question for patients with lung cancer is whether the third mRNA vaccine-induced immune response will protect against SARS-CoV-2 variants. We assessed the neutralization ability of antibodies against the Omicron variant in comparison to ancestral (wild-type) SARS-CoV-2 in a subset of 28 lung cancer patients and 30 healthy controls who received their third mRNA vaccine prior to the latest blood draw. Both patients and healthy controls had significantly lower Omicron neutralization ability compared to ancestral SARS-CoV-2 (Figures S1G and S1H, $p < 0.01$). The differential drop between ancestral and Omicron neutralization was numerically but not significantly greater in patients compared to controls ($p = 0.07$). Post-booster anti-spike binding antibody titers correlated significantly with neutralizing antibody titers (NAbTs) observed for both wildtype and Omicron variants ($p < 0.0001$ and $p = 0.0004$, respectively) (Figures S1I and S1J), which correlated with each other as well ($p = 0.0004$) (Figure S1K). For the Omicron variant, of the 28 patients, six (21%) had NAbT readings at the minimum level of detection (essentially undetectable neutralizing activity), in contrast to only one of 30 controls (3%) (Figure S1G). There was one lung cancer patient who also had undetectable wild-type neutralization activity. This patient was also undetectable for Omicron neutralization and was one of the patients identified as having compromised anti-spike antibody titers discussed above. Thus, lung cancer patients as well as the controls had significantly less NAbTs against Omicron compared to ancestral virus, and a substantial subset (6/28) of lung cancer patients failed to develop anti-Omicron NAbTs. Although there was an overall significant correlation between neutralization and anti-spike binding Ab titers, the six cases with complete failure of Omicron neutralization did not necessarily have low binding titers (Figure S1J) such that it would not have been possible to infer or predict a patient's Omicron neutralization ability from their anti-spike antibody titer readings.

For patients with cancer and the oncology patient care community, it is important to know what the impact of anticancer therapeutics is on the immune response to SARS-CoV-2 infection and/or vaccination. This is obviously relevant given the immunosuppressive nature of many anticancer drugs and the need, in most patients with stage IV lung cancer, to continue receiving anticancer therapy for the remainder of their lives. Thus, it was important to learn that there were no significant differences across stages in the relationships between cancer therapy category (targeted therapy, chemotherapy, immunotherapy, no therapy) and anti-spike antibody titers as shown in Figure S1L for lung cancer patients who received mRNA vaccination. Overall, we observed no statistical relationships in this initial dataset between treatment and post-vaccination changes in antibody levels. Nevertheless, to be conservative, we cannot rule out the possibility that the compromised immune responses observed in the small percentage of patients on this study were the product of cancer treatment effects, and we continue to study this issue in our expanding longitudinal cohort.

In summary, we found that the majority of patients with lung cancer mounted an adequate antibody titer in response to vaccination, comparable to healthy control values, but a subset (5%) displayed a diminished antibody response to COVID-19 vaccination, as indicated by antibody titers below the level of detection. Recovery of antibody levels after the third mRNA vaccine dose suggests that repeat vaccination is important in obtaining and/or maintaining antibody titers in patients with lung cancer and supports the concept of continued serial vaccination dosing. Of particular concern is the increased fraction of post-booster patients with lung cancer that failed to produce NAbTs against Omicron. In this small subset, we were not able to statistically evaluate causative factors contributing to the seroconversion failure, nor could we conclusively rule out the involvement of cancer treatment or advanced stage disease. The small fraction of lung cancer patients with absent antibody responses is overall good news; however, it highlights the urgent need to study large populations longitudinally to identify characteristics underlying this effect and to investigate the potential benefits of booster vaccinations in the context of new variants in this constantly evolving pandemic.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.04.012.

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DECLARATION OF INTERESTS

The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays and NDV-based SARS-CoV-2 vaccines, which list F.K. as co-inventor. V.S. is also listed on the serological assay patent application as co-inventor, and A.G.-S. is listed on the NDV-based SARS-CoV-2 vaccine as co-inventor. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2. F.K. has consulted for Merck and Pfizer (before 2020) and is currently consulting for Pfizer, 3rd Rock Ventures, Seqirus, and Avimex. The Krammer laboratory is also collaborating with Pfizer on animal models of SARS-CoV-2. The Adolfo García-Sastre laboratory has received research support from Pfizer, Senhwa Biosciences, Kenall Manufacturing, Avimex, Johnson & Johnson, Dynavax, 7Hills Pharma, Pharmamar, ImmunityBio, Accurius, Nanocomposix, Hexamer, N-fold LLC, Model Medicines, Atea Pharma, and Merck, outside of the reported work. A.G.-S. has consulting agreements for the following companies involving cash and/or stock: Vivaldi

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