

COMMENTARY

# A SERIOUS CHALLENGE IN FIGHTING THE COVID-19 PANDEMIC: SARS-COV-2 VACCINES IN ONCOLOGIC PATIENTS

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In 2020, the world started to face the rapid spread of a new coronavirus, SARS-CoV-2, that causes the severe respiratory syndrome called COVID-19. COVID-19 soon developed as a pandemic that, in just over a year and a half, has dramatically affected the lives, social behaviors, and economy globally. The COVID-19 pandemic has caused over 4 million deaths around the world, especially in patients with pre-existing medical conditions that make them more vulnerable. In this regard, patients with cancer are at higher risk of being infected by SARS-CoV-2 and develop severe disease. This is due to both their underlying immunosuppression and the cytotoxic regimens that they receive (1, 2). Furthermore, cancer patients are experiencing delays and modifica-

tions of their therapeutic plans due to disruption of the hospital workflows and access to care (3). Fortunately, several pharmaceutical companies, partly supported by the governments, rapidly started to develop COVID-19 vaccines. Indeed, vaccines are widely recognized as the main strategy to overcome the present pandemic and are particularly important for cancer patients. Several vaccines have been approved by local regulatory agencies, including mRNA BNT162b2 (Pfizer/BioNTech) (4), mRNA1273 (Moderna) (5) ChAdOx1 nCoV-19 (Oxford-AstraZeneca) (6), Ad26.COV2.S (Johnson & Johnson's Janssen) (7), CoronaVac (Sinovac Life Sciences) (8). Early in 2021, a pivotal study (4) was published reporting that the mRNA vaccine mRNA BNT162b2

(Pfizer/BioNTech) is safe and efficient in preventing COVID-19 infection in the adult general population. Two doses of this vaccine at a 21-day interval led to 95% effectiveness in preventing Covid-19 infection. Vaccine efficacy was maintained across subgroups analysis for age, sex, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Moreover, the safety profile of mRNA-BNT162b2 is characterized by fatigue, headache, and mild pain at the injection site. Given the optimal results achieved in phase III trial, mRNA-BNT162b2 was approved for clinical use by multiple local regulatory authorities, and vaccination programs began around the world. However, even if 3.9% of the 18,860 vaccinated individuals enrolled in this trial had a history of cancer, no patients receiving active systemic treatment with immunosuppressive or cytotoxic agents were included in this initial trial (4). Thus, the efficacy of mRNA-BNT162b2 in patients with cancer and in particular, receiving active treatment is unclear.

Of note, according to the guidelines, mRNA-BNT162b2 vaccination is also approved for cancer patients and it is administered according to the physician and local recommendation. To provide insight into the efficacy and safety of mRNA-BNT162b2 vaccination in cancer patients, single Institutions recently reported their experience in prospective studies. In particular, two studies (9, 10) evaluated the efficacy of the Pfizer/BioNTech vaccine in 102 and 232 solid cancer patients, respectively. Massarweh et al. compared the rates of anti-spike antibody response to mRNA-BNT162b2 vaccine in 102 solid cancer patients receiving systemic therapy and compared to 78 healthy controls (Petah Tikva, Israel). Ninety-two percent of the vaccinated cancer patients had detectable SARS-CoV-2 anti-spike IgG antibodies after the second vaccine dose, whereas in the control group, 100% were seropositive. Nevertheless, the authors observed significantly lower IgG titers in patients with cancer compared to healthy controls (1931 [IQR, 509-4386] AU/mL vs 7160 [IQR, 3129-11 241] AU/mL;  $P < .001$ ). The response to vaccination was not associated with specific cancer histology (9). In this study, the authors did not explore T-cell responses to the vaccine. These data suggest that, even if most of the patients were able to achieve a detectable response after a full schedule of vaccination, their antibody titer might not ensure complete protection.

Another single-center study again in Israel (Haifa) (10) evaluated 232 cancer patients who were receiving active treatment compared to 261 age-matched healthy controls. The authors observed that after the first dose of mRNA-BNT162b2, only 29% of neoplastic patients resulted seropositive compared to 84% of the control group. Similar results were observed also in subgroup analysis according to age lower or older than 60 years. Importantly, after the second dose of the vaccine 86% of tested patients turned seropositive, suggesting that a full vaccine schedule ensures a positive IgG titer even in a high-risk population. Notably, no serious adverse events related to the mRNA-BNT162b2 inoculation were observed, confirming its safety profile (10).

Finally, Monin et al. reported the experience of three institutions based in London (UK) (11). In this study, the authors compared the efficacy of the mRNA-BNT162b2 in cancer patients, in terms of the rate of seropositivity for anti-spike IgG antibodies against SARS-CoV-2, and the safety following each vaccine dose in a cohort of patients with a known diagnosis of cancer ( $n = 151$ ) compared to a healthy control group ( $n = 54$ ). Compared to the previous studies described, this cohort included also hematological cancer ( $n = 56$ ) in addition to solid cancer patients ( $n = 95$ ). All patients received the first dose of mRNA-BNT162b2 vaccine on day 1. Thereafter, 25 patients with solid cancer and 6 patients with hematological cancer received a second dose on day 21. Sixty-nine patients with solid cancer and 49 patients with hematological cancer received a delayed boost at around 12 weeks. Two patients (one with solid cancer and one with hematological cancer) died during the study period due to COVID-19 infection. Of the 134 individuals evaluated for anti-S IgG titers at 21 days following first dose vaccination, 32 (94%) of 34 healthy controls, 21 (38%) of 56 solid cancer patients, and eight (18%) of 44 hematological cancer patients turned seropositive. Response to vaccination was not associated with specific histology within solid cancer patients, but serological non-responders were enriched in patients receiving steroids at the time of vaccination (11). Remarkably, the rate of seroconversion was dramatically lower in hematological patients, suggesting that patients with impaired immune system will have partial or null immune protection after vaccination.

To address COVID-19 vaccine responses in hematological patients, several groups have retrospec-

tively studied their patients with leukemia, lymphoma, or myeloma receiving different vaccines. Hematological cancers are already known to be associated with lesser seasonal vaccine efficacy due to the disease condition or related to the immunosuppressive regimens administered (12). Indeed, differently than solid cancer patients, liquid cancer patients receiving treatments that specifically target immune cells, including B-cells, T-cells, and myeloid cells. Interestingly, impairment to generate a proper neutralizing response has been described with mRNA BNT162b2 used in multiple disease subtypes. In particular patients with B-cell malignancies are commonly treated with anti-CD20 monoclonal antibodies, resulting in prolonged lymphopenia and impairment to generate serological immunity against COVID-19 vaccine (13-20). Of note, CD19- and BCMA- targeted immunotherapies, including bispecific antibodies, CART and antibodies specifically ablate B-cells and plasma cells (21, 22) and could therefore potentially severely affect the response of hematological patients to COVID-19 vaccines. Other drugs used in liquid cancers, especially BTK inhibitors, such as ibrutinib, and venetoclax are associated with failure to respond to COVID-19 vaccine (13, 15-17). Finally, hematological patients undergoing or treated with allogeneic hematopoietic transplant are extremely vulnerable to severe COVID-19 infection, given their chronic exposure to immunosuppressive treatment, leading to a poor overall survival (23). Of note, COVID-19 pandemic, and the relative policies adopted by countries to reduce the spread of the virus, impacted the daily practice of the transplantation centers and their networks globally (24).

Overall, it is becoming clear from these pivotal studies that patients with hematological cancers and patients receiving immunosuppressive treatment are at higher risk of developing severe COVID-19 but also responding less to COVID-19 vaccines. These results suggest that all cancer patients should strictly follow social distancing, masking, and hygiene recommendations to avoid infection with COVID-19 (25, 26). Of course, timely vaccination and booster are essential to increase the chances of response to vaccination. In this regard,

we suggest when possible to vaccinate patients several weeks before starting their treatments and receive a third dose or booster upon completion and immune reconstitution. A guided strategy involving antibody-titer monitoring could help identify patients at higher risk of infection (low or absent SARS-CoV-2 antibodies) and recommend further actions. Among solid cancer patients, the solely first dose of mRNA BNT162b2 vaccination does not seem to be sufficient to generate a proper neutralizing response. However, after the second dose of vaccine, most of the patients became seropositive (9, 10). Thus, among solid cancer patients, it is imperative to respect the full schedule of vaccination in order to achieve proper protection.

In conclusion, the COVID-19 pandemic still represents a tremendous challenge for physicians treating neoplastic patients. The Delta variant of COVID-19 has even worsened this scenario as it can infect vaccinated patients (27). The most effective measures to reduce morbidity in this high-risk population are the same ones that are valid for the general population (social distancing, masking, hygiene) but should also include prompt testing in case of symptoms or exposure, use of the REGEN-COV (the combination of the two neutralizing monoclonal antibodies casirivimab and imdevimab) antibody treatment when indicated (28), vaccination of close family members, and adjustment of treatment schedules and vaccinations to enhance the chances of immune response.

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### Authors' contribution

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