Annals of Research in Oncology
Vol. 1(3), 217-21, 2021

COMMENTARY

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

**G. Ghilardi [1,2], M. Ruella [1,2,3]**

[1] Division of Hematology-Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA
[2] Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA
[3] Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

## CORRESPONDING AUTHOR:

Marco Ruella
Division of Hematology-Oncology
Hospital of the University of Pennsylvania
3400 Spruce Street
19104 Philadelphia, PA
E-mail: mruella@upenn.edu
ORCID: 0000-0003-4301-5811

**Doi**: 10.48286/aro.2021.23

## KEY WORDS

*COVID-19; SARS-CoV-2; vaccines; mRNA vaccine; Pfizer/BioNTech; Oncology.*

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 modifications 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 mRNABNT162b2 (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 mRNABNT162b2

(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 mRNABNT162b2 is characterized by fatigue, headache, and mild pain at the injection site. Given the optimal results achieved in phase III trial, mRNABNT162b2 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 mRNABNT162b2 in patients with cancer and in particular, receiving active treatment is unclear.

Of note, according to the guidelines, mRNABNT162b2 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 mRNABNT162b2 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 mRNABNT162b2 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 mRNABNT162b2, 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 mRNABNT162b2 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 mRNABNT162b2 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 mRNABNT162b2 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 mRNABNT162b2 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 allogenic 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 CVID-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 stating 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 mRNABNT162b2 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.

## CONFLICT OF INTERESTS

The authors have declared no conflict of interests.

## REFERENCES


1. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020;26(8):1218-23.
2. Rugge M, Zorzi M, Guzzinati S. SARS-CoV-2 infection in the Italian Veneto region: adverse outcomes in patients with cancer. Nat Cancer 2020;1(8):784-8.
3. Rosenbaum L. The Untold Toll. The Pandemic's Effects on Patients without Covid-19. N Eng J Med 2020;382(24):2368-71.
4. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603-15.
5. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403-16.
6. Voysey M, Clemens SAC, Madhi SA, 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(10269):99-111.
7. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26. COV2.S Covid-19 Vaccine. N Engl J Med 2021;384(19):1824-35.
8. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21(2):181-92.
9. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer. JAMA Oncol 2021;7(8):1133-40.
10. Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer. JAMA Oncol 2021.
11. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol 2021;22(6):765-78.
12. Mazza JJ, Yale SH, Arrowood JR, et al. Efficacy of the influenza vaccine in patients with malignant lymphoma. Clin Med Res 2005;3(4):214-20.
13. Roeker LE, Knorr DA, Thompson MC, et al. COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia. Leukemia 2021;35(9):2703-5.
14. Herzog Tzarfati K, Gutwein O, Apel A, et al. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. Am J Hematol 2021;96(10):1195-203.
15. Benjamini O, Rokach L, Itchaki G, et al. Safety and efficacy of BNT162b mRNA Covid19 Vaccine in patients with chronic lymphocytic leukemia. Haematologica 2021.
16. Parry H, McIlroy G, Bruton R, et al. Antibody responses after first and second Covid-19 vaccination in patients with chronic lymphocytic leukaemia. Blood Cancer J 2021;11(7):136.
17. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137(23):3165-73.
18. McCaughan G, Di Ciaccio P, Ananda-Rajah M, et al. COVID-19 vaccination in haematology patients: an Australian and New Zealand consensus position statement. Intern Med J. 2021;51(5):763-8.
19. Lim SH, Campbell N, Johnson M, et al. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. Lancet Haematol 2021;8(8):e542-e4.
20. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 2021;39(8):1031-3.
21. Ghilardi G, Braendstrup P, Chong EA, Schuster SJ, Svoboda J, Ruella M. CAR-T TREK through the lymphoma universe, to boldly go where no other therapy has gone before. Br J Haematol 2021;193(3):449-65.
22. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Eng J Med 2021;384(8):705-16.
23. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation re-

cipients: an observational cohort study. Lancet Haematol 2021;8(3):e185-e93.
24. Algwaiz G, Aljurf M, Koh M, et al. Real-World Issues and Potential Solutions in Hematopoietic Cell Transplantation during the COVID-19 Pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee. Biol Blood Marrow Transplant 2020;26(12):2181-9.
25. Ljungman P, Mikulska M, de la Camara R, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant 2020;55(11):2071-6.
26. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood 2020;136(8):925-35.
27. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385(7):585-94.
28. 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 E J Med 2021.