VIEWPOINT

COVID-19 Vaccines in Patients With Cancer—A Welcome Addition, but There Is Need for Optimization

Eleni Korompoki, MD
Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

Maria Gavriatopoulou, MD
Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

Dimitrios P. Kontoyiannis, MD, ScD, PhD
Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Corresponding Author: Dimitrios P. Kontoyiannis, MD, ScD, PhD, Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1460, Houston, TX 77030 (dkontoyi@mdanderson.org).

The urgency of the COVID-19 pandemic led to the scientific triumph of rapid vaccine development against SARS-CoV-2 within less than a year, a period much faster to traditional vaccine development, which spans decades. That impressive speed is credited to a novel approach to vaccine development, with vaccines encoding genetic information in the form of messenger RNA (mRNA) and inducing the body to produce neutralizing antibodies against the SARS-CoV-2 spike protein, the attachment protein for viral entry to cells via the angiotensin-converting enzyme–2 receptor. There are currently 2 mRNA vaccines (Pfizer-BioNTech and Moderna) and 2 adenovirus-based vaccines (Oxford–AstraZeneca and Johnson & Johnson) for which phase 3 placebo-controlled randomized clinical trials (RCTs) published in high-profile journals show an impressive efficacy, although real world effectiveness remains to be further validated in postlicense assessment.[1] As very few patients with underlying cancer were enrolled in those studies,[2] many unanswered questions remain about the risk-benefit ratio of these new COVID-19 vaccines in patients with cancer.

Patients with cancer have high COVID-19–associated mortality rates, although there appears to be significant heterogeneity in risk among different cancer subgroups.[3] Although vaccines result in less risk for symptomatic and severe COVID-19 in the patients enrolled in RCTs, these studies were not powered to detect a signal for mortality protection from fatal COVID-19, and such data in high-risk subgroups, such as patients with cancer (especially the ones with frailty, old age, multiple comorbidities, active malignancy, and recent chemotherapy), are lacking. Furthermore, to our knowledge, there are no validated surrogate end points for assessing vaccine efficacy, such as specific SARS-CoV-2–neutralizing antibody titers in serum,[4] and there are no studies regarding the kinetics of antibody decay in patients with cancer. It is likely that SARS-COV-2, as most seasonal viruses (eg, influenza and respiratory syncytial virus) that infect mucosal surfaces and do not have a prominent viremic phase, would have suboptimal production and accelerating waning antibodies over time,[4] a problem that is exacerbated by cancer as the underlying disease, similar to the experience with influenza vaccines. Therefore, the protection of patients with cancer to severe primary SARS-CoV-2 infection and reinfection by various SARS-CoV-2 variants is unknown. Although mucosal surface antibodies, such as IgA and protective T-cell responses, might be similarly or even more important in protection following natural SARS-CoV-2 infection or vaccination, there are no such data for patients with cancer. Memory B-cell and T-cell responses might be substantially compromised in patients with cancer, such as those with hematologic malignancies.[3] It might be of interest to evaluate differences in dosing, dosing intervals, and the number of boosting doses in these patients, ideally in the context of adaptive multigroup platform trials or registries. In addition, some immunomodulating drugs administered in the cancer ecosystem, such as checkpoint inhibitors, might have a boosting effect on the vaccine efficacy, if one could extrapolate by recent experience with influenza,[5] realizing that the type of influenza vaccines (protein-based) is dissimilar to mRNA and/or DNA vaccines.

Furthermore, the effect of the long-term safety of these vaccines, although reassuring, will require careful postmarketing surveillance in patients with cancer, a population at high risk for intercurrent or synergistic toxic effects following chemotherapy. The association of genomic information encoding vaccines with carcinogenesis is likely very low, especially with mRNA vaccines, whose intracellular presence is very transient, although some concerns regarding DNA vaccine persistent might theoretically exist.[6] As mRNA vaccines are encapsulated into small liposomes, it has been hypothesized, but not proven, that lipid carriers and liposomes may accumulate in tumor tissues through the enhanced and permeation retention effect.[5,7]

In balance, in the absence of contraindications (eg, severe allergy), a careful endorsement of the new COVID-19 vaccines and counseling of patients with cancer seems appropriate, and the previously described approach has been adopted by the American Society of Clinical Oncology.[8] Going further, the Regulatory Agency in the UK should prioritize COVID-19 vaccination in patients with specific cancers, stem cell transplant, and immunosuppression due to disease or treatment, considering that they are at risk for severe morbidity and mortality from COVID-19.[9]

Although many unknowns remain regarding the optimal schedule of COVID-19 vaccines in patients with cancer (**Box**), it seems reasonable to administer COVID-19 vaccination before cytotoxic chemotherapy or chemoradiation and delay the second dose after the nadir of cytopenias and before the next cycle of chemotherapy to increase vaccine immunogenicity. Although there is substantial intrapatient variability as it relates to the kinetics of lymphocyte recovery, the same principle should be applied, if feasible, for patients with cancer (eg, patients with lymphoid malignancies or monoclonal gammopathies) who receive lympholytic agents, such as monoclonal antibodies (eg, rituximab) or long-term corticosteroids.

In addition to the urgency in vaccinating vulnerable patients with cancer, COVID-19 vaccination of their caregivers is also very important, as households have

Box. Unanswered Research Questions for Future Clinical Trials

- What is the response to COVID-19 vaccines in patients with cancer who have suboptimal humoral responses (eg, myeloma, lymphoma, leukemia, stem cell transplant, and corticosteroids) with conventional vaccines?
- Does the mRNA approach make a difference?
- What should be the optimal timing of vaccines in patients who are receiving chemotherapy?
- Do we need more than 2 doses and more frequent boosting?
- What about immune adjuvants?
- What should be the vaccination strategy (timing and dosing) in patients with cancer with predominant T-cell immunosuppression or cytopenias?
- What is the benefit (COVID-19 has higher mortality in patients with cancer) vs any perceived risk or futility (poor responses)?
- Are there any concerns of toxic effects in mRNA vaccines for patients with cancer? Should we consider that the conventional vaccine approach (heat-killed virus, protein-based SARS-CoV-2 vaccines) might be safer and more or less immunogenic?
- As patients with cancer have prolonged shedding and are prone to reinfections and relapses of SARS-CoV-2, should we administer vaccines to patients with cancer with a history of COVID-19? If so, when?
- Are there any concerns regarding antibody-mediated enhancement in these patients who have dysregulated immune systems?
- Do checkpoint inhibitors boost vaccination responses in patients with cancer? What is the optimal timing of COVID-19 vaccination in patients who are taking checkpoint inhibitors?
- How does prior convalescent serum or IVIG affect vaccine decision-making?
- What is the best vaccination strategy for patients with regional radiation, chemoradiation, or TBI?
- When is the optimal time for vaccination for patients with cancer who are to undergo surgery or in postsurgical setting?

Abbreviations: IVIG, intravenous immunoglobulins; mRNA, messenger RNA; TBI, total body irradiation.

emerged as a substantial venue for transmission of SARS-CoV-2. Finally, counseling patients as to the many unknowns of the new vaccines in terms of effectiveness and less, to some degree, safety, along with stressing the importance of continuing avoidance of exposure to SARS-CoV-2 (eg, good hand hygiene, social distancing, and mask wearing) are key.

ARTICLE INFORMATION

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