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Cancer or COVID-19? A Review of Recommendations for COVID-19 Vaccination in Cancer Patients

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Opinion statement

While emergency use is authorized for numerous COVID-19 vaccines and the high-risk population including cancer patients or those with immunosuppression due to disease or therapy is prioritized, data on this group's specific safety and efficacy of these vaccines remains limited. Safety data from clinical trials and population data may be extrapolated, and these vaccines may be used for cancer patients. However, concerns of efficacy due to the variable immune response in patients with active cancers undergoing active therapy and cancer survivors with chronic immunosuppression remain. The authors aim to discuss the current recommendations for use of COVID-19 vaccination in patients with cancer.

Introduction

Across the globe, multiple vaccines have received emergency use authorizations for SARS-CoV-2 prevention. Various technology platforms for vaccination are being used to tackle this COVID-19 pandemic, and while each vaccine has its demerits, the merits of vaccination outweigh the risk of infection in most cases. However, the challenge remains in patients dealing with cancer, due to the lack of vaccination data in cancer patients during or following cancer therapy. It is known that COVID-19 results in more severe and higher mortality in patients with active cancer; cancer survivors infected with SARS-CoV-2 tend to have poorer prognosis too [1••, 2, 3]. While priority vaccination has been offered for patients with comorbidities including cancer, the authors aim to review the recommendations and address the challenges in vaccine safety in cancer patients, ability to develop a successful immune response while on immunosuppressive/myelosuppressive therapy, and the effect of vaccination on cancer management.

Vaccination challenges in cancer patients

Safety

Accelerated phase III trials for COVID-19 vaccine safety and efficacy were aimed at the general population with an urgent need to reduce the disease incidence. Therefore, vaccination data in dedicated subgroups including cancer patients was not studied, and the recommendations for vaccine administration in cancer patients come from extrapolated population data or limited prospective data following emergency use approvals for vaccine use in the general population [4]. Cancer patients or patients receiving immunosuppressive therapy included 0.5 to 4% of all phase III vaccine trials and were not subjected to a separate analysis for efficacy or immune response assessment [5–7]. The general population safety of COVID-19 vaccines has been studied in detail, and none of the approved vaccines contains a live or attenuated SARS-CoV-2 capable of infection. The live adenoviral vector vaccine technology is nonreplicative and therefore considered safe in immunocompromised states. Vaccine-specific safety concerns including thromboembolic events following the AstraZeneca [8] or Jansen COVID-19 vaccines [9], myocarditis or pericarditis following mRNA vaccines [10], and neurological manifestations (Bell's palsy or Guillain-Barré-type presentation) among others have been reported. The association of genomic information encoding vaccines with carcinogenesis is likely very low, especially with mRNA vaccines [11]. However, these concerns have not been more prevalent in immunocompromised or cancer patients, and the benefits of vaccination outweigh the concerns or these rare adverse effects [12]. "Enhanced permeation and retention" of mRNA encapsulated in liposomal nanoparticles has raised concerns about dose modification or vehicle carriers for mRNA in active cancer patients [13, 14], but more data is required before a recommendation or practice change is advised. Although the long-term safety of these vaccines is reassuring, we will require careful post-marketing surveillance in patients with cancer [15].

Efficacy

Ongoing therapy and its impact on immunization response

While the safety of these vaccines does not seem to be a major concern, the efficacy of immunization in cancer patients has been variable. Detection of antibodies has been shown to be significantly lower in patients receiving anti-CD20 therapy or bone marrow/stem cell transplantation [16]. Impaired immunization response and low antibody titer are reported in patients with chronic lymphocytic leukemia as a result of disease activity as well as therapy (anti-CD20) [17•]. Similar inadequacies in immunization have been demonstrated in patients on treatment with monoclonal antibodies to CD20 [18], Bruton tyrosine kinase inhibitors [19], and bone marrow/stem cell transplantation due to the blunted immune response. The likelihood of a desired post-vaccine immune response within 6 months of receiving myelosuppressive therapy is low; however, since there is no contraindication, the benefit of protection from SARS-CoV-2 at the earliest in high-prevalence areas requires a case-based approach. Inactivated vaccines for various infections (influenza, herpes zoster, etc.) have been used after 6 months of bone marrow/stem cell transplantation [20], and the same can be extrapolated for the use of COVID-19 vaccines in patients undergoing cancer treatment.

Vaccination and its impact on ongoing therapy

While the loss of the efficacy of vaccination has been discussed, the loss of treatment efficacy resulting from vaccination and induction of immune response needs to be addressed. The effect of a provoked immune response resulting in incited graft versus host disease following influenza vaccination has been studied in patients undergoing bone marrow/stem cell transplantation. Limited data also mentions adverse outcomes in immunotherapy or checkpoint inhibitor therapy resulting from induced immune response following vaccination [21•]. However, the benefits of immunization against COVID-19 may outweigh the current known risks when associated with checkpoint inhibitors. Larger prospective data will be required to assess the safety of their concomitant use. In the current recommendation, neither COVID-19 vaccination nor checkpoint inhibitors are contraindicated for simultaneous use [22].

Cancer management post-vaccination

Since the possibility of SARS-CoV-2 infection remains even post-vaccination, the recommendation for testing prior to surgical or medical (mainly myelosuppressive type) therapies is unclear. It is advisable to routinely test patients

undergoing cancer therapies since the vaccine-derived protection from infection is of variable duration and "successful immunization" may differ in cancer patients as compared to that in the normal population. Patients expected to receive immunosuppressive therapy should complete vaccination up to 4 weeks prior to initiation, to allow immunity development. Fully vaccinated cancer patients undergoing surgery or medical therapy are prone to loss of vaccine immunity due to suppressive therapy and general blunting of antibody response. Therefore, adherence to mask protocol, social distancing, and vaccination of caregivers and close contacts decrease the patient's risk of exposure and contraction of COVID-19.

Expert recommendations/guidelines for COVID-19 vaccination in cancer patients

A review of recommendations from expert groups is tabulated in Table 1.

Suggested COVID-19 vaccine timing in patients undergoing active cancer therapy is in Table 2.

Documentation of immune response to vaccination

There is no role of post-vaccination antibody testing either in the general population or in immune-compromised patients. Routine serological tests are unable to detect vaccine-induced antibodies. Specific antibody titers to SARS-CoV-2 surface spike protein are required to assess vaccine-mediated antibody response. However, the level of protection and its corresponding antibody levels need to be evaluated yet. Studies from Israel [29] and Japan [30] have shown that up to 90% patients with cancer had an immune response as compared to healthy controls. Cellular T-cell immunity cannot be tested and may be the key to lasting vaccine immunity in the absence of adequate antibody titers. Positive antibodies to nucleocapsid protein for SARS-CoV-2 are useful to detect prior infection, but the role of antibody testing for assessment of immunity is limited and not recommended. Yazaki et al. [30] demonstrated similar seroprevalence while developing lower serum IgG levels to SARS-CoV-2 spike protein in cancer patients. Therefore, post-vaccination levels of antibodies tell only a part of the story while protection may be offered by memory T cells in seronegative patients [31]. Currently, there is no recommendation for revaccination after immune competence is regained in persons who received COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs [32].

Table 1. Review of recommendations from expert groups

Society/expert group	Precautions	Suggestion	Recommendation
American Society of Clinical Oncology (ASCO) [23]	Patients to be counseled about lack of safety data in cancer	Vaccination may be offered to active cancer patients, and survivors must be offered COVID-19 vaccination	Essential to continue protection with masking, social distancing, and hand hygiene even after vaccination
NCCN COVID-19 Vaccination Advisory Committee [24]	Attenuated response may be seen in patients on maintenance therapies	The current data suggests immunization for all patients receiving active therapy. Patient counseling that there is emerging efficacy data in these patients and may need revaccination with a booster in the future	Wait at least 3 months after bone marrow/stem cell transplantation to maximize vaccine efficacy
American Society for Hematology [25]	Vaccination may induce an inflammatory reaction and could elevate the risk for treatment failure, e.g., graft versus host reaction	Vaccination should be offered at least 2 weeks prior to therapy in patients undergoing B-cell depleting treatments	Vaccination between cycles of intermittent cytotoxic chemotherapy or 3 months after stem cell transplantation/CAR-T cell therapy
Joint Committee on Vaccination and Immunisation (UK) [26]		Priority vaccination for patients with cancer, bone marrow and stem cell transplant recipients, and people with immunosuppression due to disease or treatment	
Infectious Disease Working Party of the German Society for Haematology and Medical Oncology [27]	Healthcare workers caring for patients with cancer should be prioritized in receiving the vaccination to reduce nosocomial transmission	Six-month interval for vaccinating patients who have received allogenic bone marrow transplant or anti-CD20 antibodies	Patients with cancer should be offered vaccination against COVID-19 using an mRNA vaccine
French Society for Immunotherapy of Cancer [28]	Anti-SARS-CoV-2 vaccination should be made available to cancer patients under immunotherapy but considered individually	Continued research to generate more data on vaccine efficacy/safety in immunotherapy-treated cancer patients	Vaccination 3 weeks prior to therapy OR 3 months after CAR-T cell/bone marrow transplant therapy

Table 2. Suggested COVID-19 vaccine timing in patients undergoing active cancer therapy

Timing	Therapy	Considerations
2 weeks prior	Elective surgery	Allow work-up period to mount immune response
4 weeks after	Emergency surgery	Recovery to ambulatory and return to activities of daily life prior to vaccination
Towards end of therapy cycle (NOT on first day of next cycle)	Cytotoxic chemotherapy Immunomodulators Proteasome inhibitors CDK4/6 inhibitors	When blood counts have maximally recovered
No specific timing consideration	Monoclonal antibodies without cytotoxic chemotherapy Immunotherapy without cytotoxic chemotherapy Tyrosine kinase inhibitors PARP inhibitors Hormone treatments Radiation therapy	Complete blood counts within normal range
Completion of therapy	Continuous or short intermittent breaks between treatments	Premature cessation of therapy and waiting for vaccine immune response may leave the patient without any cancer protection or lead to failure of treatment
3 to 6 months after	CAT-T cell therapy or bone marrow/stem cell transplant patients	Essential to prevent failure of treatment

Summary

Prioritizing vaccination for cancer survivors may be necessitated as they may be at high risk for severe or fatal COVID-19 resulting from a long-term weakened immune system. It is clear that immune response to COVID-19 vaccines may be attenuated in cancer and immunocompromised patients; however, the recommendations do not list the use of a vaccine as a contraindication. In theory, a sub-optimal immune response may be better than no immunity to COVID-19. However, the timing of vaccination needs to be staged in regard to ongoing therapy to allow maximal benefit without loss of treatment efficacy and disease control. To conclude, COVID-19 vaccination should be considered a standard of care for patients with cancer as the benefits likely outweigh the risks of vaccine-related adverse effects [33••].

Author contribution

Manit K. Gundavda, Contribution: Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review.
Kaival K. Gundavda, Contribution: Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review.

Declarations

Ethics Approval
Not applicable, no patient data presented.

Consent to Participate
Not applicable.

Consent for Publication
Not applicable.

Conflict of Interest
Manit K. Gundavda declares that he has no conflict of interest. Kaival K. Gundavda declares that he has no conflict of interest.

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•• Of major importance

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Continued quality oncological care requires that patients with cancer, including those involved in trials, be prioritized for COVID-19 vaccination, which should not affect trial eligibility.

Publisher's Note