COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials

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Abstract | Emerging efficacy data have led to the emergency use authorization or approval of COVID-19 vaccines in several countries worldwide. Most trials of COVID-19 vaccines excluded patients with active malignancies, and thus data on the safety, tolerability and efficacy of the vaccines in patients with cancer are currently limited. Given the risk posed by the COVID-19 pandemic, decisions regarding the use of vaccines against COVID-19 in patients participating in trials of investigational anticancer therapies need to be addressed promptly. Patients should not have to choose between enrolling on oncology clinical trials and receiving a COVID-19 vaccine. Clinical trial sponsors, investigators and treating physicians need operational guidance on COVID-19 vaccination for patients with cancer who are currently enrolled or might seek to enrol in clinical trials. Considering the high morbidity and mortality from COVID-19 in patients with cancer, the benefits of vaccination are likely to far outweigh the risks of vaccine-related adverse events. Herein, we provide operational COVID-19 vaccine guidance for patients participating in oncology clinical trials. In our perspective, 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.

As 2020 ended, we saw a glimmer of hope against the coronavirus disease 2019 (COVID-19) pandemic, with promising safety and efficacy data emerging from clinical trials of several vaccines targeting the COVID-19 causative virus, SARS-CoV-2 (REFS[1–5]). As a result, the FDA has granted emergency use authorization (EUA) to BNT162b2 and to mRNA-1273, two lipid nanoparticle-formulated, nucleoside-modified mRNA-based vaccines encoding the prefusion spike glycoprotein of SARS-CoV-2, and to Ad26.COV2.S, a replication-incompetent adenovirus type 26 (Ad26) vector vaccine encoding a stabilized variant of the SARS-CoV-2 spike protein[1,2]. In addition, the UK Medicines and Healthcare products Regulatory Agency has approved the ChAdOx1 nCoV-19 vaccine, comprising a recombinant, replication-deficient chimpanzee adenovirus vector also encoding the SARS-CoV-2 spike glycoprotein[5]. Encouraging preliminary safety and efficacy results have also been reported with the rAd26 and rAd5 heterologous prime–boost recombinant adenovirus vector COVID-19 vaccine developed in Russia and with the CoronaVac inactivated SARS-CoV-2 vaccine developed in China[3,4], both of which have been authorized for use in their country of origin. Currently, more than 60 different COVID-19 vaccines are at different stages of clinical development. Limited data are available, however, on the safety, tolerability and efficacy of COVID-19 vaccines in patients with cancer, owing to the exclusion of patients with active malignancies from most of the vaccination trials[6]. For example, among the 43,540 participants enrolled in the trial of BNT162b2, only 3.7% were reported to have cancer. Overall, only ten patients had developed severe COVID-19 at the time of reporting of initial results from this trial, one in the vaccine arm and nine in the placebo arm (whether any of these patients had cancer was not reported)[2]. Thus, generating more data on the efficacy of COVID-19 vaccines in patients with cancer, especially in the setting of active cancer therapy, is a priority.

Multiple studies have revealed that patients with cancer have an increased risk of complications and mortality from COVID-19, including 30-day mortality of 30% in hospitalized patients with COVID-19 and cancer compared with 21% in those without cancer[7–14]. Given the greater severity of the disease and higher risk of death, patients with cancer are considered a high-priority subgroup for COVID-19 vaccination. In the USA, multiple organizations, including the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO) and the Association of American Cancer Institutes (AACI), have urged the Centres for Disease Control and Prevention (CDC) to prioritize patients with cancer for COVID-19 vaccination[15,16]. The European Society for Medical Oncology (ESMO), the Society for Immunotherapy of Cancer (SITC), the Spanish Medical Oncology Society (SEOM) and the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee have released their preliminary recommendations supporting vaccination in all patients with cancer, including those receiving active therapy[17–20]. Exception from vaccination would apply to patients undergoing transplantation or adoptive cell therapy, for whom immunization should be delayed for at least 3 months to maximize vaccine efficacy, in line with

the general recommendations of delaying vaccinations following such highly immunosuppressive therapies[18]. The NCCN committee also called for the inclusion of patients with cancer in the CDC priority group for phase Ib/Ic of COVID-19 vaccine distribution[18], which includes essential workers (such as those involved in law enforcement, teachers and firefighters), adults ≥65 years of age and individuals 16–64 years of age with high-risk medical conditions[21]. However, the NCCN guidelines encourage discussions between clinical trial leads and patients enrolled on their trials to prevent protocol violations or exclusions[18], and most of the other guidelines are silent on the language regarding patients enrolled in cancer clinical trials.

Given that the current vaccines are 'authorized' and not 'approved' in many countries, a question remains as to whether they are considered investigational. Recognition of this issue is important because the protocols of many trials include criteria prohibiting the concomitant use of other investigational agents, although usually such criteria are meant to apply to other anticancer therapies, specifically. In January 2021, the FDA provided clarification that receipt of a COVID-19 vaccine under an EUA is not considered to constitute treatment with an investigational product[22]. Similarly, other regulatory authorities should consider providing such clarification and guidance. Furthermore, no data are available on the safety or efficacy of COVID-19 vaccines in patients enrolled on oncology clinical trials, especially of novel investigational agents; therefore, rapidly generating data in this subset of patients is crucial. Indeed, several questions remain unanswered, including the time needed for immunity to develop, the duration of immunity, the effects of different systemic treatments on immunity and the optimal time points and posology of vaccine administration in patients with cancer. Given the experience with prior vaccines, such as those against influenza[23], no serious safety concerns are expected in patients with cancer. Moreover, the currently available vaccines do not contain functional coronavirus and are, therefore, hypothesized to have no possibility of causing an active infection, even in immunosuppressed patients.

Given the risk posed by the COVID-19 pandemic, prompt decisions need to be made regarding the use of any vaccine, including those approved and/or authorized for use against SARS-CoV-2, in patients treated with investigational agents on clinical trials. Patients with cancer should not have to choose between enrolling on an oncology clinical trial and receiving a COVID-19 vaccine. On this background, clinical trial sponsors, investigators and treating physicians need operational guidance on COVID-19 vaccination for patients with cancer who are currently participating in oncology clinical trials or might be considering or seeking trial enrolment.

Clinical trials are integral to high-quality oncological care and are crucial for improvements in the management of cancer. During the COVID-19 pandemic, patient enrolment has decreased across oncology trials of all phases (from trials of screening and/or prevention strategies to phase I, II and III trials)[24,25], which will likely hinder scientific and medical progress. For many patients with rare diseases or specific biomarker-driven cancers, trials testing novel investigational treatments might be the best therapeutic option — or sometimes the only option — following receipt of standard-of-care therapies. Although oncology trials are often complex, with mandated protocol schedules (including laboratory tests, scans, biopsies and clinical visits) at specific time points, both the FDA and the EMA have recognized that protocol deviations might be unavoidable and protocol modifications might also be required to maximize patient safety during the COVID-19 pandemic[26,27]. This timely regulatory guidance has facilitated investigators, industry partners and academic centres in working with their institutional review boards to navigate the pandemic and has made the clinical trials more patient-centric[28]. We believe that COVID-19 vaccination provides another such opportunity to focus on 'patient safety first and then protocols later' in the context of clinical trials. Depriving eligible and vulnerable patients with cancer of COVID-19 vaccination would fall below the standard of care; therefore, recruiting any patient with cancer to any trial that prevented or discouraged them from receiving a vaccine with at least EUA would be unethical. Herein, we outline COVID-19 vaccine guidance for patients participating in oncology clinical trials.

Recommendations

Classification of vaccines. A COVID-19 vaccine that has been authorized by the appropriate regulatory authorities in the respective countries should not be considered as an investigational agent for the purposes of oncology clinical trials. An approved and/or authorized vaccine should be considered as a concomitant medication and entered as such in the electronic record. The dates of first and second vaccinations, the doses used and any adverse effects should also be recorded. This information might be helpful in the future to evaluate the effects of COVID-19 vaccination on the safety and efficacy of anticancer therapies, in particular, immunotherapies.

Patient prioritization. COVID-19 vaccines should be offered to all patients with cancer, including those participating in clinical studies. Indeed, we recommend that immunization against COVID-19 be the norm, not an exception, for patients participating in trials of cancer treatments. Moreover, eligible patients who have received COVID-19 vaccines should be accepted on all phases of clinical trials.

We further recommend that patients with cancer in general, including those enrolled on clinical trials, should be prioritized for COVID-19 vaccination. Patients participating in clinical trials often have progressive advanced-stage cancer, are undergoing active treatment and usually make several visits to clinics and hospitals for study-related procedures, which potentially increases their exposure to SARS-CoV-2 infection at multiple points. Thus, prioritization for vaccination is imperative, particularly considering that patients with cancer also seem to have an increased risk of severe COVID-19 and complications and mortality from the disease[7–14]. Due consideration should also be given to other well-recognized risk factors for severe COVID-19, such as advanced age (≥65 years), comorbidities (for example, chronic pulmonary, cardiovascular or renal disease) and other sociodemographic factors (such as overcrowded housing, single-parent households and ethnicity)[29], when prioritizing patients with cancer for vaccination, with priority given to those at most risk.

In addition to patients with cancer, we also suggest that caregivers, household members and/or close contacts of these patients (adults regardless of age) should be vaccinated as early as possible based on the local guidelines for public vaccinations. This strategy will enable further reductions in risk of SARS-CoV-2 transmission from close contacts for high-risk patients with cancer.

Preference should be given to approved and/or authorized vaccines for use in patients enrolled on oncology clinical trials. In situations in which an authorized

vaccine is unavailable, if a specific trial of a COVID-19 vaccine is available to patients with cancer (for example, the vaccination against COVID in cancer (VOICE) study (NCT04715438), a prospective, national, multicentre, longitudinal, multi-cohort study in patients with solid malignancies undergoing active anticancer treatment[30], or any studies testing booster doses or revaccination schedules in immunocompromised patients that become available in the future)[31], patients who are participating in an oncology clinical trial should not be excluded from the vaccine trial. Moreover, loosening the eligibility criteria of all trials of COVID-19 vaccines to permit enrolment of patients with cancer, including those receiving investigational therapies, would be prudent.

Timing of vaccination. For patients currently enrolled on phase I trials, the timing of vaccination should be based on the type of anticancer treatment and the stage of the trial (dose escalation versus dose expansion) (TABLE 1). Due consideration should be given to any confounding variables relating to the expected adverse effects of the investigational drugs and vaccines, especially during the dose-limiting toxicity (DLT) window[32], to avoid overlapping toxicities that might compromise the safety and tolerability of either treatment. Patients entering clinical trials, especially phase I trials, could receive the first dose of a COVID-19 vaccine while undergoing screening procedures for trial eligibility. If clinical trial sponsors have specific, mechanism-based concerns regarding the timing of vaccination relative to the investigational agents (for example, agents with cytokine-release syndrome potential or anti-CD20 antibodies), they should issue immediate guidance on vaccination of patients who enrol on the trial.

Some adverse events seen with COVID-19 vaccines might manifest similarly to those of novel anticancer agents in early phase trials, especially hypersensitivity reactions. To minimize the need to determine whether a patient is experiencing hypersensitivity to an investigational product or an adverse event related to vaccine administration, consideration should be given to the timing of vaccination based on the mechanism of action of the anticancer agents. Most hypersensitivity reactions to novel agents are observed within the first one or two doses of monoclonal antibodies or within the first 1–2 weeks after initiation of therapy with tyrosine kinase inhibitors[33]. This pattern might be helpful when determining whether the causality of an adverse event is related to the study treatment or the vaccine. If possible, we recommend avoiding administration of an investigational agent within 48–72 h of vaccination to minimize confusion and/or inaccurate attribution of adverse event causation.

The currently available vaccines should not be a contraindication in patients with controlled HIV infection (or other immunocompromised states) and cancer. However, such patients should be counselled regarding the lack of data on the safety and particularly the efficacy of COVID-19 vaccination, especially with novel mRNA-based vaccines, in this setting.

In general, we recommend that patients with solid tumours or haematological malignancies who are receiving cytotoxic therapies, targeted therapies, hormone therapies and/or immunotherapies on a clinical trial should be vaccinated against COVID-19 at the earliest available opportunity. The suggested vaccination schedules for such patients can vary according to the type of trial, disease and cancer treatment (TABLE 1). The only exception to this rule relates to patients on clinical trials involving transplantation or adoptive cell therapies: vaccine administration might need to be delayed for ≥3 months to enable these patients to regain adequate immune function, given that potential graft versus host disease and the immunosuppressive regimens used are expected to blunt immune responses to any vaccine. Other considerations in patients with haematological malignancies include the timing of vaccine administration around infusions required for various chemotherapy regimens and decreased blood counts, particularly neutropenia, lymphopenia and thrombocytopenia, according to local practices at each hospital and the treating physician's judgement in the patient's best interest.

For patients receiving cytotoxic chemotherapy, given the lack of data on the optimal timing of vaccination, we recommend COVID-19 vaccination whenever a vaccine is available (TABLE 1). Data from a study on the optimal timing of influenza vaccination during 3-week chemotherapy cycles indicate that antibody responses to the vaccine are similar in patients inoculated concurrently with chemotherapy administration and in those inoculated during the cytopenic period of the chemotherapy cycle[34]. Extrapolating from the findings of this study, we recommend that COVID-19 vaccines should be administered whenever available, until more data on optimal timing become available. This recommendation might be updated when further data on COVID-19 vaccination emerge.

According to the CDC[35], at this time, revaccination is not recommended after immune competence is regained in persons who received one of the authorized mRNA-based COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs. However, recommendations on revaccination or additional doses of COVID-19 vaccines might be updated as additional information becomes available.

For patients undergoing elective surgery, the work-up time should enable COVID-19 vaccination before surgery. In the case of urgent or emergent surgery, patients can be vaccinated postoperatively, after patient recovery.

For participants in breast cancer screening trials, consideration should be given to the fact that COVID-19 vaccination can cause transient lymphadenopathy[36,37]. Therefore, if possible and if patient management will not be unjustifiably interrupted, screening examinations should be conducted either before the first dose of a COVID-19 vaccine or 4–6 weeks after the second dose, as recommended previously by other groups[36,37].

Importantly, long-term pharmacovigilance is required for all patients who receive any COVID-19 vaccine. Any emerging concerns regarding the safety or efficacy of COVID-19 vaccines should be recorded appropriately.

Clinical trial reporting. We encourage, when possible, the inclusion of the vaccination status of oncology clinical trial participants in the data record. This practice will enable accurate assessment and attribution of adverse events, which could be sub-stratified for the vaccinated and unvaccinated subgroups, wherever feasible, for further analysis. COVID-19 vaccination details (including vaccine name, batch and manufacturer, dose, date of administration and whether the right or left arm was injected) should be captured as a concomitant medication to enable better assessment of the overall effect of COVID-19 vaccination on oncology trial results.

Additional considerations

Other reasons for delaying COVID-19 vaccination of participants in oncology clinical trials, such as recent exposure to COVID-19 or previous allergic or anaphylactic reactions to vaccine components, should be consistent with the

Table 1 | **COVID-19 vaccine guidance for patients participating in oncology clinical trials**

Trial, treatment and/or disease setting	Vaccination strategy and timing
Type of study	
Screening and/or prevention, quality of life, supportive care and/or palliative care, or natural history studies	On vaccine availability: for breast cancer screening trials, if possible, and when it does not unjustifiably interrupt management, screening exams should be conducted before the first dose of a COVID-19 vaccine or 4–6 weeks after the second dose of a COVID-19 vaccine
Phase I trials	For most novel investigational agents, the timing of vaccination should be mechanism-based
	Dose-escalation phase: with most anticancer agents, including TKIs, avoid vaccination on cycle 1 day 1. In general, defer initiation of the first cycle of investigational therapy until after all vaccine adverse effects have improved to grade ≤1 and for at least until 72 h after vaccination
	For immunotherapy agents with no known potential for cytokine-release syndrome, avoid vaccination on the day of infusions of intravenous immunotherapy, at least in the DLT period
	For immunotherapy agents associated with a potential risk of cytokine-release syndrome, defer vaccination until after the DLT window or delay administration of the investigational agent for 2 weeks after vaccine administration
	For first-in-human agents with an unknown adverse effect profile, delay administration until all adverse effects of the vaccine should have resolved to grade ≤1
	Dose-expansion phase: on vaccine availability, with timing based on mechanism of action
Phase II and phase III trials (including placebo-controlled randomized trials)	On vaccine availability, with timing based on mechanism of action
Type of treatment	
Surgery clinical trials	Administer at discharge after recovery from post-operative complications or 1 week before surgery, whichever is most feasible
Radiation oncology clinical trials	On vaccine availability (the exception is total body radiation, after which vaccination might need to be delayed to provide time for immune reconstitution)
Solid tumours	
Cytotoxic chemotherapies	On vaccine availability (1–2 weeks before or 1–2 weeks after drug dose, when possible, to increase the potential for the immune system to mount a response)
Targeted therapy (e.g. TKIs)	On vaccine availability
Hormone therapy (e.g. anti-androgens or anti-oestrogen therapy)	On vaccine availability
Immunotherapy (e.g. immune-checkpoint inhibitors)	On vaccine availability
Epigenetic therapy	On vaccine availability
Haematological malignancies	
Intensive cytotoxic chemotherapies expected to result in profound and prolonged immunosuppression (e.g. anthracycline-based and/or cytarabine-based induction regimens)	Delay until absolute neutrophil count recovery
Epigenetic therapy	On vaccine availability
Targeted therapy (e.g. TKIs)	On vaccine availability
Immunotherapy (e.g. anti-CD20 antibodies)	On vaccine availability
Haematopoietic stem cell transplantation (allogenic or autologous)	>3 months after treatment
Adoptive cell therapies (for example, CAR T cells)	>3 months after treatment

Recommendations on primary vaccination and schedules, and guidance on revaccination or additional doses of mRNA-based COVID-19 vaccines and other COVID-19 vaccines should be viewed as preliminary in patients with cancer, including those participating in clinical trials, and might be updated as additional information becomes available[35]. It should be noted that some of these recommendations are based on those made for patients with cancer in general by other organizations, such as the NCCN, ASCO, ESMO or SITC[17–20,41]. This table provides operational guidance and is a panel summary. This guidance is for informational use only in the rapidly evolving COVID-19 pandemic. This information does not constitute medical or legal or regulatory advice, does not endorse any specific products or therapies, does not recommend or mandate any particular course of medical care, and is not a statement of the standard of care. CAR, chimeric antigen receptor; COVID-19, coronavirus disease 2019; DLT, dose-limiting toxicity; TKI, tyrosine kinase inhibitor.

general CDC or WHO guidelines[38,39]. We hope that additional large-cohort trials and real-world data on COVID-19 vaccines with longer follow-up durations will provide timely information on the effectiveness of the vaccines in patients receiving different cancer treatments; however, the current situation requires swift action to prevent the potential harm of delaying COVID-19 vaccination for this vulnerable subgroup.

To gain a deeper understanding of patients' experiences when receiving treatment on a specific trial, the systematic integration of patient-reported outcomes and other quality-of-life assessments

longitudinally throughout the course of therapy is suggested when possible. This awareness of both therapy-related and cancer-related symptom burden over time while patients are on a trial will provide crucial information for the frontline clinical teams as well as patients and their families to guide decision-making and the selection of therapies that are in line with their overall goals and values.

Mobilization efforts from local and state governments and increased flexibility from protocol administrators are required to bring widespread COVID-19 vaccination of patients with cancer to fruition. At the level of investigational centres, ethics committees should be more understanding in cases of protocol deviations, especially if the language in specific protocols is not clear or updated with regard to COVID-19 vaccinations. Allowances for COVID-19 vaccination should ideally be documented in the protocol. Any protocol deviations should be documented, however, considering that such deviations are generally made in the interest of patient safety.

Clinical trial sponsors have begun to roll out guidance on COVID-19 vaccination to investigators, even providing appropriate timing of when study medications should be taken (for example, at least 2 h before or after administration of the vaccine). The sponsors might also request that the electronic data capture systems be updated to reflect this vaccination and to document any associated adverse events. Importantly, major research networks such as the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP), the Experimental Therapeutics Clinical Trials Network (ETCTN) and the SWOG Cancer Research Network[40] have granted broad permission for, and indeed encouraged, COVID-19 vaccination of participants on their respective trials. Their guidance includes capturing receipt of the vaccine in the medical history, if received before trial enrolment, or as a concomitant medication if administered after enrolment. This kind of clear precedent is welcome and gives individual investigators the freedom to encourage vaccination of their trial patients without trepidation. Furthermore, nationwide coordinated research efforts, such as the NCI Serological Sciences Network for COVID-19 (SeroNet), are studying the immune response to COVID-19, with the aim of combating the pandemic by accelerating the development of treatments and vaccines.

Lastly, advocacy for patients with cancer, including those involved in clinical trials, by their caregivers, physicians and other health-care professionals is imperative to convince stakeholders to consider this group as a high priority. Guidance from the FDA, EMA, NCI and other cancer-focused organizations worldwide might also be needed[41]. Meanwhile, all close contacts of such patients should continue to wear masks, adhere to social distancing guidelines and follow other recommendations, including avoiding unnecessary travel, in order to reduce the risk of SARS-CoV-2 infection and, thus, COVID-19. Given the need to generate data on the immunogenicity of vaccines during systemic cancer therapy, we encourage patient participation in such studies if available locally.

Conclusions

In summary, COVID-19 vaccination, where authorized or approved, should be considered a standard of care for patients with cancer who are currently enrolled on investigational trials. Uncommon exceptions might occur when the principal investigator or treating physician considers use of the vaccine not to be safe or in the patient's best interest. Current knowledge of the safety and efficacy of the authorized COVID-19 vaccines in patients with cancer and particularly those receiving active treatment is limited, although the benefits likely outweigh the risks of vaccine-related adverse effects, considering the high risk of morbidity and mortality from COVID-19 in patients with cancer. Moreover, equitable access to cancer clinical trials and COVID-19 vaccines is imperative. Indeed, continued quality oncological care requires that patients on clinical trials be prioritized for COVID-19 vaccination, which, in and of itself, should not affect clinical trial eligibility.

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