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EDITORIAL

Emerging issues related to COVID-19 vaccination in patients with cancer

Kamal S. Saini · Diogo Martins-Branco · Marco Tagliamento · Laura Vidal · Navneet Singh · Kevin Punie · Monika Lamba Saini · Isagani Chico · Giuseppe Curigliano · Evandro de Azambuja · Matteo Lambertini

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has resulted in millions of deaths globally. The pandemic has had a severe impact on oncology care and research. Patients with underlying cancer are more vulnerable to contracting COVID-19, and also have a more severe clinical course following the infection. The rollout of COVID-19 vaccines in many parts of the world has raised hopes of controlling the pandemic. In this editorial, the authors outline key characteristics of the currently approved COVID-19 vaccines, provide a brief overview of key emerging issues such as vaccine-induced immune thrombotic thrombocytopenia and SARS-CoV-2 variants of concern, and review the available data related to the efficacy and side effects of vaccinating patients with cancer.

K. S. Saini (✉) · L. Vidal · I. Chico
Covance Inc, Princeton, NJ, USA
e-mail: kamalveer.saini@covance.com; kamalsaini@gmail.com

D. Martins-Branco · E. de Azambuja
Institut Jules Bordet, Brussels, Belgium

M. Tagliamento · M. Lambertini
Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy

M. Tagliamento · M. Lambertini
Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy

N. Singh
Postgraduate Institute of Medical Education and Research, Chandigarh, India

K. Punie
Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium

K. Punie
Laboratory of Experimental Oncology, KU Leuven, Leuven, Belgium

M. L. Saini
CellCarta, Antwerp, Belgium

G. Curigliano
Istituto Europeo di Oncologia, IRCCS, Milan, Italy

G. Curigliano
University of Milano, Milan, Italy

E. de Azambuja
Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

K. S. Saini
77 Avenue Marcel Thiry, 1200 Brussels, Belgium

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Key Summary Points

Patients with underlying cancer who develop infection with SARS-CoV-2 have a high rate of mortality. They constitute a highly vulnerable population and must receive COVID-19 vaccination on priority.

Multiple vaccines have been approved by regulatory agencies around the world.

Patients with cancer were largely excluded from late-stage vaccine trials, leading to a paucity of data related to this population.

Based on the limited data available so far, there is no specific safety concern related to COVID-19 vaccination in patients with cancer.

A rare syndrome of thrombosis associated with thrombocytopenia, known variously as thrombosis with thrombocytopenia syndrome (TTS), vaccine-induced immune thrombotic thrombocytopenia (VITT), or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), has been reported in people, especially younger women, receiving AstraZeneca's ChAdOx1 nCoV-19 or Janssen's Ad.26.COV2.S vaccines. Currently, it is believed that the benefits of these vaccines outweigh the risks in the majority of people.

Patients with cancer may show a weaker immune response to COVID-19 vaccines, compared to the general population.

Results from the UK SOAP-02 study show that a prolonged prime-boost interval may leave patients with cancer vulnerable to COVID-19.

Current SARS-CoV-2 variants of concern (VoC) include B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), and B.1.617.2 (delta), which were first identified in the UK, South Africa, Brazil, and India, respectively. These VOCs may differ with respect to transmissibility, lethality, and response to vaccine.

"Mix-and-match" studies with heterologous prime-boost combinations and studies with three-dose schedules are ongoing, and results eagerly awaited.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14687430.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) [1], caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in about 3.5 million deaths globally as of 26 May 2021, including about 721,000 in the European Union, 590,000 in the USA, and 128,000 in the UK.

The pandemic has had a severe impact on oncology care and research [2–7]. While the majority of patients with COVID-19 remain pauci- or asymptomatic, about 10–15% have a more severe disease, with some developing a clinical syndrome that shares certain similarities with malignancy, including hyper-inflammation, immune dysfunction, and of most concern, widespread thrombosis [8], with microangiopathy being of particular concern [9].

Patients with underlying cancer who develop COVID-19 constitute a vulnerable population [10]. A meta-analysis of 33,879 patients with both COVID-19 and cancer showed that their probability of death was 25.4% (95% CI

22.9–28.2) [11]. Patients with lung cancer and hematological malignancies are at highest risk, as are recipients of stem cell transplants and adoptive cellular therapies [12–14]. Effective measures should be taken to protect patients with cancer from contracting COVID-19, including prioritization of vaccination against SARS-CoV-2 [15].

SARS-CoV-2 has a characteristic spike (S) protein which induces humoral and cellular immune responses against SARS-CoV-2, making it a potent target for vaccine development [16].

TYPES OF COVID-19 VACCINES

According to the World Health Organization (WHO), there were 101 COVID-19 vaccines in clinical development and 184 vaccine candidates in preclinical development as of 26 May 2021. Most of them aim to elicit an immune response against the S protein [17], and employ various COVID-19 vaccine platforms, such as nucleic acid, viral vector, protein subunit, inactivated or attenuated whole virus, and virus-like particle [16].

As of 26 May 2021, the US Food and Drug Administration (FDA) has authorized the emergency use of three vaccines (Pfizer-BioNTech's BNT162b2/tozinameran/Comirnaty, Moderna's mRNA-1273, and Johnson & Johnson/Janssen's Ad.26.COV2.S), while the European Medicines Agency (EMA) has approved the conditional use of AstraZeneca-University of Oxford's ChAdOx1 nCoV-19/Vaxzevria, in addition to the above three. Four other COVID-19 vaccines are currently under rolling review by EMA: Novavax's NVX-CoV2373, CureVac's CVnCoV, Gamaleya National Centre of Epidemiology and Microbiology's Sputnik V, and Sinovac Life Sciences' COVID-19 Vaccine (Vero Cell) Inactivated.

The BNT162b2 and mRNA-1273 mRNA nucleic acid vaccines contain the prefusion-stabilized S protein encapsulated within a lipid-nanoparticle complex [18]; Ad.26.COV2.S is a recombinant human adenovirus type 26 vector encoding the S protein; and ChAdOx1 nCoV-19 is a recombinant chimpanzee adenoviral vector encoding the S protein. The Ad.26.COV2.S is given as a single dose, but for the other approved vaccines the first (prime) dose is followed by a second (boost) dose a few weeks later.

Several other COVID-19 vaccines have been approved by regulatory agencies of specific countries, including Sputnik V, Sinovac's CoronaVac, and AstraZeneca-University of Oxford-Serum Institute of India's Covishield [19].

SAFETY OF COVID-19 VACCINES IN PATIENTS WITH CANCER

Most COVID-19 vaccine phase 3 studies have excluded the participation of patients with cancer. Hence, there are insufficient data regarding the safety or efficacy of these vaccines in this patient population. However, given the high mortality risk from SARS-CoV-2 infection among patients with cancer, the high efficacy of COVID-19 vaccines in preventing serious infection in the general population, and the low incidence of serious adverse effects, several professional oncology societies and other health organizations and agencies have advocated that the risk–benefit ratio is likely to be strongly in favor of vaccinating people with cancer [7, 20, 21]. A majority of patients with cancer, too, are supportive of getting vaccinated [22]. However, the global scenario is heterogeneous, with many low-income countries yet to prioritize vaccination of patients with cancer [23].

Immune checkpoint inhibitors (ICIs) have been approved for the treatment of a wide variety of malignancies [24, 25]. There is a theoretical concern that COVID-19 vaccines that induce a primarily T_H1-type response, or contain vaccine adjuvants such as Matrix-M1 [26], or toll-like receptor (TLR) 7/8 agonist molecule adsorbed to alum [27], could have an impact on the toxicity or efficacy of ICIs. However, the safety data available so far are reassuring, with no evidence of increased immune-related adverse events. In a study from Israel, 134 patients with cancer with ongoing ICI therapy were administered two doses of the BNT162b2 vaccine [28]. The commonest local side effects were injection site pain (63%) and local swelling (9%), whereas the most frequent systemic side

effects were muscle pain (34%), fatigue (34%), headache (16%), and fever, chills, and gastrointestinal complications (10% each). This toxicity profile was broadly similar between the cohort of ICI-treated patients with cancer and a matched cohort of healthy controls (HCs); no vaccine-related or ICI-related severe adverse events were observed.

In the UK SOAP-02 study, 95 patients with solid cancer, 56 patients with hematological cancer, and 54 healthy controls (HC) were enrolled [29]. Of these, 31 patients with cancer and 16 HCs were vaccinated with two doses of the BNT162b2 vaccine 21 days apart, while the others received only the prime dose of the vaccine at the time of reporting, and were scheduled to receive the boost dose 12 weeks later. In the overall cancer cohort, no toxicities were observed in 54% of the patients following the first dose, and in 71% of the patients following the second dose. In the HC cohort, no toxicities were reported in 38% after the first dose and in 31% after the second dose. Injection-site pain was the most common adverse event, and was recorded in 35% of the patients with cancer. No vaccine-related deaths were reported.

COVID-19 VACCINES, THROMBOSIS, AND LOW PLATELETS

Rare events of venous or arterial thrombosis associated with thrombocytopenia (clinically resembling heparin-induced thrombocytopenia [HIT]) have been reported in people receiving AstraZeneca's ChAdOx1 nCoV-19 or Janssen's Ad.26.COV2.S [30, 31]. This syndrome has recently been termed by the US Centers for Disease Control and Prevention (CDC) as thrombosis with thrombocytopenia syndrome (TTS) [32], and is also known as vaccine-induced immune thrombotic thrombocytopenia (VITT) [33] or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [34]. The thrombosis is often cerebral or abdominal in location and associated with platelet-activating antibodies against platelet factor 4 [33, 35], and younger women seem to be at higher risk [36]. Per current guidance, administration of the anticoagulant heparin should be avoided in patients with potential TTS, unless testing for HIT is negative [37].

As of 12 May 2021, 23.9 million first doses and 9.0 million doses of the of the ChAdOx1 nCoV-19 have been administered in the UK, following which the Medicines and Healthcare products Regulatory Agency (MHRA) received 309 reports (169 in females, 138 in males, 2 of unknown gender) of major thromboembolic events with low platelets, including 116 cases (mean age 46 years) of cerebral venous sinus thrombosis with thrombocytopenia [38]. With 56 reported deaths among these 309 cases to date, the overall case fatality rate is 18%.

In a large population-based study from Denmark and Norway involving 281,264 people who received the ChAdOx1 nCoV-19 vaccine, 59 cases of venous thromboembolic events were observed among the vaccine recipients, compared with 30 expected based on the incidence rates in the general population, corresponding to a standardized morbidity ratio of 1.97 (1.50–2.54) [39].

The MHRA has advised caution while using ChAdOx1 nCoV-19 in people of any age who are at higher risk of blood clots because of underlying medical conditions [40]. This guidance could impact patients with cancer, considering that malignancy itself is associated with an increased risk of thromboembolism [41]. Some countries have restricted the use of this vaccine to older age groups, even though the EMA and MHRA opine that based on data available on 26 May 2021, the benefits outweigh the risks in the majority of people.

According to the US FDA, 15 cases of thrombosis with thrombocytopenia have been reported up to 24 April 2021 among recipients of the Ad.26.COV2.S vaccine [42]. All of these cases occurred in women between the ages of 18 and 59 (median 37 years), with the onset of symptoms between 6 and 15 days after vaccination.

Thrombocytopenia following administration of mRNA vaccines BNT162b2 and mRNA-1273 has been reported in 20 patients (median age 41 years; 11 female) [43]. Of these, 17 had no pre-existing thrombocytopenia, while 14

reported bleeding symptoms prior to hospitalization.

EFFICACY OF COVID-19 VACCINES IN PATIENTS WITH CANCER

Currently, there are limited data about the efficacy of COVID-19 vaccines in patients with cancer.

In the SOAP-02 study described above, measurement of anti-S protein immunoglobulin levels 21 days following the first dose of the BNT162b2 vaccine showed that 97% (31/32) of HCs, 39% (21/54) of patients with solid cancer, and only 13% (5/39) of patients with hematological cancer had developed an adequate level of immune protection. However, some of these serological non-responders demonstrated an increase in T cells secreting IFN-γ and/or IL-2. Notably, among patients with solid cancers who received the boost dose at day 21, 95% (18/19) showed protective levels of anti-SARS-CoV-2 antibodies at week 5.

As a response to the current shortage of COVID-19 vaccine supply, some countries have adopted a policy of increasing the interval between vaccine doses. As an example, in the UK and British Columbia, Canada, the prime-boost gap is currently 8 and 16 weeks, respectively. Emerging data show that increased gap improves the immunogenicity and efficacy of the ChAdOx1 nCoV-19 vaccine [44]. While this approach may be suitable for the general population with an intact immune system, results from the SOAP-02 and other studies raise the concern that a prolonged prime-boost interval may leave patients with cancer vulnerable to COVID-19 [45].

While waiting for additional trial and real-world data to accrue, it may be prudent for policymakers to consider tailored time points for vaccinating patients with cancer or other causes of immunodeficiency.

Vulnerable patients with cancer could be further protected by vaccinating their caregivers and all care-home staff on priority.

EMERGING VARIANTS

Mutant variants of the wild-type (Wuhan) SARS-CoV-2 virus have been documented in most geographies of the world, and are tracked by online databases such as https://www.gisaid.org/hcov19-variants/. Knowledge regarding these variants is rapidly evolving. Currently, the variants of concern include B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), and B.1.617.2 (delta), which were first identified in the UK, South Africa, Brazil, and India, respectively. Such viral variants may differ with respect to transmissibility, lethality, and response to vaccines [46].

In a study of 2026 adults in South Africa, the ChAdOx1 nCoV-19 vaccine did not confer any significant protection against mild-to-moderate COVID-19 due to the B.1.351 variant [47]. A post hoc analysis found that efficacy against symptomatic COVID-19 of ChAdOx1 nCoV-19 was 70.4% for the B.1.1.7 variant and 81.5% for non-B.1.1.7 variants [48].

A population-scale study from Qatar showed that the effectiveness of the BNT162b2 vaccine was 89.5% (95% CI, 85.9–92.3) against the B.1.1.7 variant and 75.0% (95% CI, 70.5–78.9) against the B.1.351 variant [49].

There is rising concern that patients with an immunocompromised state, such as those with cancer, could develop long-lasting or persistent SARS-CoV-2 infection, which could accelerate viral evolution and emergence of variants [50]. Patients with cancer have been shown to carry significantly higher intra-host viral genetic diversity than their non-cancer counterparts [51]

The clinical impact of SARS-CoV-2 variants on patients with cancer is currently unknown.

COVID-19 VACCINATION IN PATIENTS WITH CANCER: PRACTICAL CLINICAL CONSIDERATIONS

- Patients with cancer should receive vaccination against COVID-19 on priority.
- Currently, there is a severe shortage of COVID-19 vaccines in many low and middle

income countries; global efforts should be made to mitigate this as quickly as possible.
- Per applicable guidance as on 26 May 2021, vaccines are not interchangeable, and the same vaccine that was used for the prime dose should be administered for the booster shot. However, "mix-and-match" studies are ongoing, including priming with ChAdOx1 nCoV-19 and boosting with BNT162b2 [52, 53], and such heterologous prime-boost combinations could be approved for use in the future.
- Even though COVID-19 vaccines currently have an emergency use authorization rather than full authorization, the US FDA has clarified that patients on clinical trials may receive COVID-19 vaccines, and this will not be considered a protocol deviation in studies that disallow the concurrent use of investigational agents [54].
- Optimal timing of the vaccination vis-à-vis the administration of anti-cancer therapy is an important clinical consideration; vaccines should ideally be administered at a time when the patient's immune system is least perturbed by therapy; operational guidance is emerging [55, 56].
- Transient axillary lymphadenopathy has been reported following COVID-19 vaccination. The Society of Breast Imaging has recommended that if feasible, women should consider scheduling their screening mammograms prior to the first dose or 4–6 weeks following the second dose of a COVID-19 vaccination [57]. Additionally, for patients with breast cancer, consider administering the vaccine in the thigh or the contralateral arm [58].
- The US CDC had previously suggested that any other vaccine should be given at least 14 days before or after the COVID-19 vaccine, partly to avoid incorrect attribution of potential adverse events. This guidance has been recently updated, and COVID-19 vaccines and other vaccines (including the influenza vaccine) may now be administered without regard to timing. The CDC advises that in the case of co-administration of multiple vaccines, the COVID-19 vaccines and vaccines such as tetanus toxoid-containing and adjuvanted vaccines that may be more likely to cause a local reaction should preferably be administered in different limbs [59].
- Live attenuated viral vaccines are generally avoided in patients with cancer; this should apply to future COVID-19 vaccines based on this technology platform as well.

FUTURE CONSIDERATIONS

Currently, most COVID-19 vaccines employ a two-dose schedule, a notable exception being Ad.26.COV2.S. which is given as a single dose. Some patients with cancer may have incomplete immune reconstitution following anti-cancer therapy, or may have an immunocompromised status as a result of their disease, and hence they may generate a suboptimal protective response following a two-dose schedule. Three-dose schedules of COVID-19 vaccines are currently in clinical trials (e.g., NCT04368728) in healthy volunteers, and similar trials are needed for patients with cancer as well.

The VOICE study (ClinicalTrials.gov identifier, NCT04715438, target sample size 873) aims to recruit patients with cancer being treated with chemotherapy, immunotherapy, or combination chemo-immunotherapy, and HCs, in order to assess side effects and the kinetics and strength of immune responses to COVID-19 vaccination. Results from this and similar studies from other countries will be valuable in designing future vaccination strategies for patients with cancer.

Several registries have been set up for collecting real-world COVID-19 data related to patients with cancer, and are generating valuable data and contributing to the scientific understanding of the ongoing pandemic [60].

Future late-phase COVID-19 vaccine trials should allow an adequate number of patients with cancer to participate as well [7].

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