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Current Perspectives

Severe acute respiratory syndrome coronavirus 2 vaccination for patients with solid cancer: review and point of view of a French oncology intergroup (CGO, TNCD, UNICANCER).

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Abstract

The impacts of SARS-CoV-2 pandemic on cancer care are multiple, entailing a high risk of death from COVID-19 in cancer patients treated by chemotherapy. SARS-CoV-2 vaccines represent an opportunity to decrease the rate of severe COVID-19 cases in cancer patients and also to restore normal cancer care.

Cancer patients to be targeted for vaccination are difficult to define due to the limited contribution of these patients in the phase III trials testing the different vaccines. It seems appropriate to vaccinate not only cancer patients with ongoing treatment or with a treatment having been completed less than 3 years ago, but also household and close contacts. High-risk cancer patients who are candidates for priority access to vaccination are those treated by chemotherapy. The very high-priority population includes patients with curative treatment and palliative first or second-line chemotherapy, as well as patients requiring surgery or radiotherapy involving a large volume of lung, lymph nodes and/or hematopoietic tissue.

When possible, vaccination should be done before cancer treatment begins. SARS-CoV-2 vaccination can be performed during chemotherapy while avoiding periods of neutropenia and lymphopenia. For organisational reasons, vaccination should be performed in cancer care centers and may use mRNA vaccines or non-replicating adenoviral vaccines in non-immunocompromised patients under 65 years old.

Considering the current state of knowledge, the benefit-risk ratio strongly favours SARS-CoV-2 vaccination of all cancer patients. In order to obtain more data concerning the safety and effectiveness of vaccines, it is necessary to implement cohorts of vaccinated cancer patients.

Keywords: COVID-19, SARS-CoV-2, vaccination, coronavirus, solid cancers, chemotherapy, radiotherapy

1. Introduction

COrona VIRus Disease 2019 (COVID-19) due to SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2) is an exceptional pandemic with a high impact on cancer care pathways. Morbidity and mortality from COVID-19 in patients treated for solid tumor is high with approximately 35% of severe diseases and 20% to 30% of deaths [1, 2]. Severity and mortality from COVID-19 are mostly due to patients' comorbidities, with a low impact of cancer treatments [1-3]. COVID-19 is also associated with delay in treatment and loss of chances in terms of cancer treatment and quality of life (postponement of chemotherapy, radiotherapy and/or surgery, limited access to supportive care...).

Immunocompromised patients have longer viral clearance due to late and low humoral immunity [4]. Moreover, anti-SARS-COV-2 humoral and T-cell immune response is less effective in cancer patients, raising questions about the effectiveness of vaccination. Indeed, cancer patients do not develop as much humoral immunity as noncancer subjects, and may remain contagious and able to spread the SARS-CoV-2 for two months or more [5]. Consequently, it seems appropriate to vaccinate all cancer patients who are frequently treated in cancer care centers.

In addition to the morbidity and mortality associated with COVID-19, the impact on the health care system for cancer care from cancer screening to palliative care is major [6]. While the prognostic impacts of diagnosis and treatment delays are not yet known, existing modelling analyses are worrisome [7]. Several recommendations for treatment strategy during the SARS-CoV-2 pandemic have been proposed [8-13].

No drug treatment, except corticosteroid and tocilizumab, has been shown with a high level of evidence to achieve a decreased rate of severe COVID-19. SARS-CoV-2 vaccine consequently represents a major hope for cancer patients, by not only limiting severe COVID-19 infection, but also by maintaining "normal" cancer care.

2. Methodology

The current perspective is focused on SARS-CoV-2 vaccination of adult patients with solid tumours (excluding vaccination of physicians and patients with hematologic malignancies). Our proposals are based on the scientific data concerning SARS-CoV-2 vaccines available on February 19, 2021, recommendations from the European Society of Medical Oncology (ESMO) [14], the American Association for Cancer Research (AACR) [15], the American Society of Clinical Oncology (ASCO) [16], the Society for Immunotherapy of Cancer (SITC) [17], and the French National Cancer Institute (INCa), and collaborative reflection of a French oncology inter-group (Thésaurus National de Cancérologie Digestive (TNCD), réseau de Groupes Coopérateurs en Oncologie (GCO) and Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER)) enriched by the expertise of immunologists and infectious disease specialists. In many respects, the available data are sparse, with a low level of evidence (expert agreement or expert opinion).

3. Immune response to SARS-Cov-2 infection in cancer patients

In about 80% of symptomatic cases of COVID-19, patients do not require special monitoring. In less than 20% of cases, COVID-19 progress to severe symptoms including an acute respiratory syndrome with a cytokine storm partially related to an insufficient type I and II interferon response [18]. The interferon response decreases not only with age, but also in cancer patients [19]. More specifically, severe COVID-19 in cancer patients is due to the cancer itself, treatments, and the severe comorbidities that are frequently present in these patients.

4. The different SARS-CoV-2 vaccines and data on cancer patients

According to country, different SARS-CoV-2 vaccines are available, and several have been approved or are in development (Table 1). The Spike protein is the “key” that allows SARS-CoV-2 to enter into our cells and is the target of vaccines. The first two vaccines approved by the European Medicines Agency (EMA) and the United States Food Drug Administration (US FDA) are two messenger RNA (mRNA) vaccines (BNT162b2 (Comirnaty[®]) from Pfizer/BioNTech and mRNA-1273 (COVID-19[®]) from Moderna) [20, 21]. Both vaccines have demonstrated an interferon increase after injection associated with a specific CD4+ and CD8+ T-cell response and neutralizing antibodies directed against the Spike protein (humoral and cellular immune response). In some phase III trials with these vaccines, cancer patients could be included; unfortunately, no results in this subgroup of patients have been reported to date (Table 1).

Three first non-replicating viral vectors (human and non-human adenoviruses) have been developed by the University of Oxford/AstraZeneca (non-replicating chimpanzee adenovirus AZD1222 vaccine), by the Russia/Gamaleya Research Institute (Gam-COVID-Vac (Sputnik V[®])) and by Johnson & Johnson/Janssen (JNJ-78436735) (two non-replicating human adenovirus vaccines). The first of these, which is 60-70% effective, was recently been approved by the EMA but remains restricted to the population under 65 years of age, pending ongoing studies in elderly patients [22]. Recently the Russian Sputnik V[®] vaccine showed 91.6% efficacy in a phase 3 study [23]. To date, while there exist no specific data on cancer patients, it bears mentioning that these viral vectors, which are non-replicating, are not contraindicated in immunocompromised patients.

Vaccines based on inactivated whole-virus, or on part of the virus, most often combined with an adjuvant to enhance immune response, are currently under development (Sinopharm[®],

China). While they do not seem to be particularly immunogenic, they may be of use in cancer patients.

5. Immunogenicity and safety of SARS-CoV-2 vaccines in immunocompromised patients

While most immunosuppressive agents may negatively impact vaccine efficacy and duration of humoral (antibody) and cellular (T-cell) vaccine immune responses, there are few specific data currently available on SARS-CoV-2 vaccines. Preliminary data suggest that anti-SARS-CoV-2 IgG concentrations after vaccination are not different between healthy patients and those with cancer. However, these results do not necessarily imply optimal protection for this population [24].

Immunosuppressive treatments lead to a decrease in immunogenicity (decrease in the number and functionality of CD4+ T-cells, IgM and IgA) and potentially in the efficacy of vaccines. Indeed, while immunocompromised patients have presented a lower seroconversion rate after influenza vaccine, clinical efficacy is preserved (78% decrease of mortality) [25].

Research on mRNA vaccines started 20 years ago, especially on anti-cancer vaccines with no safety issues [26]. In Phase II/III trials with the Pfizer/BioNTech BNT162b2 vaccine, 4% of patients had previous HIV infection or cancer [20]. Results in this group are not available, but vaccine safety in the overall population was excellent. There is no reason that immunosuppression can lead to adverse events following mRNA vaccines.

Regarding non-replicating viral vector, in the phase III trial with Astra Zeneca/University of Oxford AZD1222 vaccine, immunosuppression was an exclusion criterion [22]. By contrast, it is not an exclusion criterion for the Johnson & Johnson/Jansen adenoviral vaccine, for which the first results are expected in March/April 2021.

6. Contraindications and adverse events of SARS-COV-2 mRNA vaccines

The single definitive contraindication to mRNA vaccines is a history of severe allergy to a component of the vaccine (in particular polyethylene glycol (PEG) or polysorbate) or an immediate severe reaction (generalized urticaria, bronchospasm and/or anaphylaxis) to first vaccine dose. Other relative and temporary contraindications are ongoing infectious disease, flare of inflammatory or autoimmune disease, symptomatic COVID-19 less than 3 months previous and an influenza vaccination less than 3 weeks previous or with another vaccine less than 2 weeks previous.

Immunosuppression and autoimmune diseases (excluding flare-up period) are not contraindications. An allergy not qualified as anaphylaxis (for example to pets, venom, pollen, latex, or drugs) does not contraindicate vaccination. A history of immediate severe reaction (generalized urticaria, bronchospasm and/or anaphylaxis) to another vaccine or to an unidentified drug requires an allergist's opinion before vaccination and longer follow-up after SARS-COV-2 vaccination.

With mRNA SARS-COV-2 vaccines, anaphylactic reactions are exceptional with a rate of 11.3 cases per million people vaccinated with the Pfizer-BioNTech BNT162b2 vaccine and 2.5 cases per million people vaccinated with the Moderna mRNA-1273 vaccine [27]. Therefore, vaccinated people should be monitored for at least 15 minutes after injection and 30 minutes if there is a history of anaphylaxis. The other known side effects are expected and nonspecific [20-22].

7. Vaccination of patients treated with immune checkpoint inhibitors

Immune checkpoint inhibitors, anti-CTLA-4 (T-lymphocyte associated antigen 4) and PD-1/PDL1 (programmed death 1/ligand 1) do not increase the risk of viral infection, but can induce autoimmune adverse events to be treated with immunosuppressive agents. Despite the

lack of data on mRNA vaccines in patients treated with immune checkpoint inhibitors, SARS-COV-2 vaccination is not expected to have an impact on autoimmune adverse events. Influenza vaccination is safe (no increased risk of immune-induced adverse events) and effective in patients treated with immune checkpoint inhibitors [28]. All SARS-COV-2 vaccine is possible in cancer patients treated with immune checkpoint inhibitors (Table 2) [17]. Nevertheless, it seems reasonable to postpone vaccination in patients with an ongoing severe autoimmune side effect.

8. Which cancer target population for SARS-COV-2 vaccination?

On January 8, 2021, ESMO launched a triple call towards the European states: to vaccinate all patients with cancer, especially those on active anticancer treatment; to monitor effects of vaccine; and to instill confidence among patients and the public (Table 2) [14].

The target cancer population is determined on the basis of available scientific data. The availability of vaccines and national priorities will impact this target population. Scientific evidence suggests that immunosuppression after cancer treatment, especially chemotherapy, persists for several months. Therefore, all cancer patients with an ongoing treatment or treatment completed for less than 3 years previous should be vaccinated, as should people living in the same household. This target population represents millions of persons, approximately 5 to 10% of the population in European countries. Patients with planned major cancer surgery should also be vaccinated a few weeks before surgery to limit the risk of developing severe COVID-19 after surgery or surgery postponement [29]. In addition, other risk factors for severe COVID-19 should be taken into account: male gender, poor general condition and/or severe co-morbidities (heart disease, diabetes, chronic pulmonary disease, chronic renal failure, cirrhosis, body mass index $> 40 \text{ kg/m}^2$, complicated high blood pressure, and transplantation) [1]. In addition, the doctor-patient relationship is important in the

vaccination decision-making process, especially in the context of short-term life expectancy due to cancer progression (Table 2).

People around an immunocompromised patient are a potential source of SARS-COV-2 transmission. Due to the potential lower immunogenicity of the vaccination in patients treated by chemotherapy, it seems appropriate to vaccinate household/close contacts (wife, nurse, home help...). In addition, cancer patients vaccinated must continue to follow SARS-COV-2 protection since vaccine protection is not immediate, not 100%, of uncertain duration and possibly less effective in patients under chemotherapy and of varying efficacy depending on the variants of SARS-COV-2.

Three vaccines are now approved in most European countries (Pfizer/BioNtech BNT 162b2, Moderna/NIH mRNA-1273 and AstraZeneca AZD1222) but limited availability has led health authorities to prioritize populations at high risk of severe COVID-19. In France, INCa defined "ultra-priority" cancer patients for vaccination against SARS-COV-2 as: 1/ patients with curative intent treatment excluding basal cell skin carcinoma, 2/ patients on palliative first or second-line chemotherapy and 3/ patients receiving radiotherapy for a primary thoracic tumor with a large lung volume, radiotherapy on large lymph node areas and/or a large volume of hematopoietic tissue. Patients over 75 years or with a severe co-morbidity should also be vaccinated regardless of cancer history. Patients treated only by hormone therapy, as well as recent COVID-19, are not in the "ultra-priority" population. In addition, for patients with short life expectancy due to cancer progression, vaccination should be discussed on a case-by-case basis, especially in case of best supportive care. While vaccine strategy is identical for patients participating in clinical trials, specific recommendations have been proposed for phase I cancer trials [30]. Finally, mRNA vaccines are recommended in most European countries and the adenoviral vaccine (AstraZeneca AZD1222) is limited for patients younger than 65 years.

9. Conclusion

Indications for SARS-COV-2 vaccination, based on available scientific data, are patients with solid cancer under treatment or patients with treatment less than 3 years previous and household and close contacts. However, due to limitations in vaccine doses, 'ultra-priority' cancer patients are those under chemotherapy and/or with other curative intent treatment. It is essential to set up specific clinical studies or cohorts dedicated to cancer patients, the objective being to determine the safety and effectiveness of SARS-COV-2 vaccines in this population.

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Table 1. Main vaccines available or in ongoing phase II-III

Vaccines

Journal Pre-proof

BBIBPCorV
Beijing Institute
of Biological
Products /
Sinopharm

Inactivated
SARS-
CoV-2

Journal Pre-proof

Table 2. Summary of recommendations (expert agreement)

1) Indications of SARS-COV-2 vaccination

- ☐ Indication for patients with cancer under treatment or treatment ended less than 3 years previous
- ☐ Priority for cancer patients treated with chemotherapy
- ☐ Ultra-priority for 1/ patients with curative intent treatment (including surgery) excluding basal cell skin carcinoma, 2/ patients on palliative first or second-line chemotherapy and 3/ patients receiving radiotherapy for a primary thoracic tumor with a large lung volume, radiotherapy on large lymph node areas and/or a large volume of hematopoietic tissue
- ☐ Patients treated only by hormone therapy and recent COVID-19 patients are not "ultra-priority"
- ☐ Vaccination of the immediate entourage of cancer patients (person living in the same house and in frequent contact (home help, nurse, etc.)) (expert opinion)

2) SARS-COV-2 vaccination in cancer patients treated by immune checkpoint inhibitors

- SARS-COV-2 vaccination is recommended in cancer patients treated by immune checkpoint inhibitors
- In case of severe immune-related adverse events due to immune checkpoint inhibitors, it seems reasonable to postpone SARS-COV-2 vaccination

3) Strategy of SARS-COV-2 vaccination

- Vaccination could be done by mRNA vaccines (or by a non-replicating adenoviral vaccine in non-immunocompromised patients under 65 years of age)
- If possible, vaccination is recommended at least 10 days before the start of chemotherapy

- For cancer patients already on chemotherapy, vaccination can be done during chemotherapy, avoiding periods of bone marrow aplasia
- There is no need to postpone chemotherapy course for SARS-COV-2 vaccination
- If a chemotherapy holiday is planned soon, the SARS-COV-2 vaccination can be postponed for a few days and carried out during this chemotherapy holiday
- Serological monitoring after vaccination could be useful (if possible in specific cohort) (expert opinion)
- Cancer patients vaccinated must continue to follow SARS-COV-2 protection

4) Contraindications of SARS-COV-2 vaccination

- No "oncological" contraindication
- Definitive contraindications to mRNA vaccines are history of allergy to one of the vaccine components (in particular PEG or polysorbate) or anaphylactic reaction during the first dose
- Temporary contraindications requiring postponement of vaccination:
 - pregnancy or breastfeeding
 - ongoing infectious disease
 - flare of inflammatory or autoimmune disease
 - symptomatic COVID-19 less than 3 months previous
 - influenza vaccination less than 3 weeks previous or with another vaccine less than 2 weeks previous
 - history of severe reaction to another vaccine or to an unidentified drug requires an allergist's opinion before vaccination and longer follow-up after SARS-COV-2 vaccination (30 minutes)

5) SARS-CoV-2 vaccination and cancer clinical trials

☐ The vaccine strategy is identical for patients participating in clinical trials but specific recommendations have been proposed for phase I [30]:

- Not started phase I trial: avoid starting trial investigational medicinal product until 2–4 weeks after the second dose of SARS-CoV-2 vaccine and administered safely for trial with risk of cytokine release syndrome.

- Already in phase I trial: administer SARS-CoV-2 vaccine during the phase I trial but avoid vaccination on days of parenteral investigational medicinal product dosing and the dose-limiting toxicity period.

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Highlights

- Ultra-priority for SARS-CoV-2 vaccination in patients with curative intent treatment
- Priority for cancer patients treated with chemotherapy
- Vaccination can be done during chemotherapy avoiding periods of bone marrow aplasia
- Contraindications to vaccines if history of allergy to vaccine components

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Analysis and interpretation of data: all authors

Draft manuscript preparation: DT, MH, BSP, TA, JYB and OB

All authors reviewed the manuscript and approved the final version.

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