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REVIEW ARTICLE

Vaccination of cancer patients against COVID-19: towards the end of a dilemma

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Abstract

With the emergence of second wave of COVID-19 infection globally, particularly in India in March–April 2021, protection by massive vaccination drive has become the need of the hour. Vaccines have been proved to reduce the risk of developing severe illness and are emerging as vital tools in the battle against COVID-19. As per the GLOBOCAN database, nearly 19.3 million new cancer cases have been reported in 2020 globally, which posed a significant challenge to health care providers to protect such large number of 'vulnerable' patients from COVID-19. Nevertheless, a considerable degree of doubt, hesitancy and misconceptions are noted regarding the administration of vaccines particularly during active immuno-suppressant treatment. This review article highlights the added vulnerability of cancer patients to the COVID-19 infection and has explored the immunological challenges associated with malignancy, anticancer treatment and COVID-19 vaccination.

Keywords COVID-19 · SARS-CoV-2 · COVID-19 vaccines · Cancer patients · Anticancer treatment

Introduction

World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) outbreak as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and subsequently declared COVID-19 a pandemic on 11 March 2020. The entire world has experienced massive disruption in public health, economy and almost every aspect of human lives. With the emergence of second wave of COVID-19 infection globally, particularly in India in March–April 2021, protection by vaccination of priority groups such as cancer patients has become the need of the hour. Various countries on global collaboration have already developed ambitious vaccination programme which serves the herculean task of vaccine production, maintaining safety and efficacy norms, distribution of vaccines, maintaining cold chain and to implement the vaccination strategy in their respective countries.

To date, at least 10 major different vaccines have been rolled out across the world and the vulnerable populations and frontline workers in the countries are the highest priority for vaccination (Table1). More than 200 additional vaccines are in the process of roll-out, to cater to the unprecedented requirement of global coverage. Vaccines have been proved to reduce the risk of developing severe illness and are emerging as vital tools in the battle against COVID-19. However, large-scale data are lacking about the degree to which the vaccines can protect not only against COVID-19 but also against transmission of the infection.

As per the GLOBOCAN database, nearly 19.3 million new cancer cases have been reported in 2020 globally, which posed a significant challenge to health care providers to protect such large number of 'vulnerable' patients from COVID-19.[1] The pandemic and the associated lockdown in various countries also led to an inevitable drop in the new diagnosis of cancer and multidisciplinary oncological care [1]. Nevertheless, a substantial degree of doubt, hesitancy and misconceptions are noted regarding the administration

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[1] GLOBOCAN 2020: New Global Cancer Data | UICC. Available from: https://www.uicc.org/news/globocan-2020-new-global-cancer-data. (Accessed May 15, 2021).

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Table 1 COVID-19 vaccine platforms, their mechanisms of action and recommended dosages

Type of vaccine	Vaccine platform	Mechanism	Company	Trial Phase	Dosage & Route
Nucleic acid vaccines	Lipid nanoparticle RNA vaccine	mRNA template for spike protein of SARS-CoV-2 enclosed in lipid nanoparticle	Pfizer/BioNTech, Moderna	Phase III	2 (0, 21d), IM
	DNA vaccine	DNA encoding spike protein of SARS-CoV-2 attached to a plasmid	Inovio	Phase II	2 (0, 28d), ID
	Viral vector (non-replicating)	Recombinant replication defective adenovirus expressing SARS-CoV-2 spike surface glycoprotein	Oxford/AstraZeneca Janssen (J & J) Gamaleya-Sputnik Cansino BBV154 (Bharat Biotech)	Phase III Phase III Phase III Phase III Phase I	2 (0, 90d), IM 1, IM 2 (0, 21d), IM 1, IM 1, intranasal
	Viral vector (replicating)	Recombinant replication-competent attenuated strains of H1N1, H3N2 and B-expressing SARS-CoV-2 spike surface glycoprotein	Wantai-Xiamen	Phase I	1, intranasal
Protein vaccines	Viral subunit vaccines	Full-length, prefusion spike protein of SARS-CoV-2 combined with adjuvant	Novavax, SCB-2019	Phase II/III	2, (0, 28d), IM
	Virus-like particle (VLP) vaccine	Nanostructures that mimic viral capsid protein but lack genomic material. They trigger strong humoral and cellular immune response due to their repetitive structures	AdaptVac	Phase I/II	Not scheduled
Viral vaccines	Live attenuated vaccines	Mutated live strain of SARS-CoV-2 having all structural components but reduced ability to replicate inside human cells	Codagenix	Phase I	1, intranasal
	Inactivated vaccines	Whole virion-inactivated SARS-CoV-2 with alum adjuvant, incapable of replication but able to induce a memory response	Bharat Biotech SinoVac SinoPharm	Phase III Phase III Phase III	2 (0, 28d), IM

IM intramuscular, *ID* intradermal

of vaccines particularly during active immuno-suppressant treatment.

'Vaccine hesitancy' and 'vaccine eagerness'

One of the barriers to the successful vaccination programme is the public hesitancy to get vaccinated because of the various misconceptions and apprehensions about vaccine safety and efficacy[2]. Multidose vaccine regimen and logistic hurdles to maintain proper cold chain are the additional obstacles of mass vaccination. In a survey conducted in USA, investigators found that 44% of adults believed that the vaccines provide strong protection against COVID-19 by one to two weeks after the second dose, whereas 20% believed strong protection occurs even before the second dose and 36% were unsure about the efficacy of the vaccine [2]. The lengthy phase-wise vaccination programme in some countries or any delay in the process may create potential disappointment or '**eagerness**' amongst the people for their unmet demands. So, to generate awareness and to provide correct, consistent and timely information to any intended priority group is extremely important upon the arrival of different vaccines against COVID-19.

[2] COVID-19 Vaccine Communication Strategy: 2 Gaj Ki Doori. www.mohfw.gov.in. (Accessed May 4, 2021).

Should the patients with malignancy be treated as a 'priority group'?

The susceptibility of immunocompromised cancer patients to get infected with influenza virus was well known before the emergence of severe acute respiratory syndrome CoV-2 (SARS-CoV-2) [3]. Influenza increases the risk of hospital admission with severe respiratory distress by fourfold, and the risk of death by tenfold when compared with patients without malignancy [4]. Data of cancer patients with COVID-19 from 14 different hospitals in Hubei province, China (epicentre of COVID-19 outbreak) revealed nearly threefold higher death rate than that of COVID-19 patients without cancer [5]. Patients with haematological malignancy, lung cancer and stage IV malignancy had the highest severity.

Review of published studies on epidemiological and clinical features of cancer patients with COVID-19

Demography and clinical manifestations of COVID-19 amongst cancer patients compared to the general population are remarkably different across the world given to the complex biology of cancer, difference in the performance status of the patient and diverse anticancer treatment. Codacci-Pisanelli et al. lucidly elaborated these differences in a review of published case studies and showed alarming drop in cancer screening and follow-up visits as well [6]. Prospectively, The COVID-19 and Cancer Consortium (CCC19) registry is collecting data on the factors which are associated with short- and long-term outcomes of COVID-19, its severity and fatality in patients with cancer.[3] An initial analysis of 928 patients from this database revealed that the patients with cancer are at increased risk of severe illness and mortality [7]. Till date, this largest cohort of cancer patients with COVID-19 positivity has found moderate or poor Eastern Cooperative Oncology Group performance status and active or measurable cancer to be significantly associated with increased 30-day all-cause mortality. Increasing age, male sex, former history of smoking, presence of comorbidities and receipt of azithromycin plus hydroxychloroquine are noted as the general factors associated with increased mortality.

UK Coronavirus Cancer Monitoring Project (UKCCMP) is another large database that analysed 800 patients with cancer and COVID-19 coinfection [8]. Twenty eight per cent of patients were reported to succumb and the risk of death was significantly associated with similar general factors such as increasing age, male gender, presence of comorbidities like hypertension and cardiovascular diseases.

Patients with thoracic malignancies are likely to be more susceptible to severe illness with COVID-19 given to their older age, smoking habits and pre-existing comorbidities. The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry from eight countries including Italy, Spain, France, Switzerland, the Netherlands, the USA, the UK and China found death rate as high as 33% amongst the patients with thoracic malignancy [9].

In a more vulnerable cohort of haematopoietic stem cell transplantation (HSCT) recipients, poor overall survival (OS) is observed after diagnosis of COVID-19 [10]. Fourteen per cent of such patients required mechanical ventilation and at 30 days after detection of SARS-CoV-2, OS was reported as 68% for recipients of allogeneic HSCT and 67% for autologous HSCT. Vijenthira et al. conducted a systematic review and meta-analysis of 3377 patients with haematological malignancies with COVID-19 from Asia, Europe and North America and observed that patients aged ≥ 60 years had a significantly higher risk of mortality, whereas paediatric population was relatively spared [11]. Active treatment did not appear to influence the risk of death.

These data whatsoever available till now suggest the need for proactive strategies to reduce chance of infection in cancer patients especially for older age and to build up protection against developing severe illness. We have summarised the available, published data of treatment status, disease severity and mortality amongst cancer patients with COVID-19 in (Table 2) which highlights the added vulnerability of cancer patients in this pandemic.

Association between recent treatment and severity of disease

Initially in this pandemic, patients with cancer and specifically those receiving active treatment were advised for delayed or suspended therapy, which is not a sustainable measure in longer term. But emerging evidences show that increased mortality in cancer patients with COVID-19 is mainly because of older age and comorbidities and less likely from drug-induced therapeutic immunosuppression. Most of the studies did not find any significant association of mortality with either cytotoxic chemotherapy or non-cytotoxic treatment such as radiotherapy, surgery or hormonal therapy. Hence, withholding or discontinuing treatment for cancer, out of apprehension of severe COVID-19-related symptoms might not be warranted.

However, the use of immune checkpoint inhibitor (ICI) is an established risk factor for severe outcomes in COVID-19, independent of age, type of malignancy and other comorbid conditions. ICI may trigger immune dysregulation by

[3] COVID-19 and Cancer Consortium Registry—Full Text View—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04354701. (Accessed May 6, 2021).

Table 2 Published data on treatment status, disease severity and mortality amongst cancer patients with COVID-19

Study	Country	No. of cancer patients with COVID	Patients receiving treatment for cancer (%)	Severe illness (%)	Mortality (%)
Kuderer et al. [5]	USA, Canada, Spain and Cancer Consortium (CCC19) database	928	39% on active treatment	7%	13%
Lee et al. (Mar 18–Apr 26, 2020) [6]	UK Coronavirus Cancer Monitoring Project (UKCCMP)	800	17% on chemotherapy, 22% on non-cytotoxic therapy, 60% off treatment at least last 4 weeks	Not reported	28%
Robilotti et al. (Mar 10–Apr 7, 2020) [11]	MSKCC	423	Not reported	20% had severe respiratory illness, 9% required MV	12%
Goudsmit et al (Mar 10–May 18, 2020) [35]	Institut Jules Bordet, Belgium	45	45.6% received anti-cancer treatments within 14 days, and 24.4% between 14 and 30 days from PCR-test day	35% developed severe disease, 20% required ICU	15%
Zambelli et al Apr 2020 [36]	Papa Giovanni XXIII Hospital, Italy	172	All patients were on active treatment	21% required hospitalisation on 8 weeks follow-up	3%
Garassino et al. (Mar 26–Apr 12, 2020) [7]	The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, 8 countries	200	74% on active treatment	76% patients got hospitalised and 10% required ICU	33%
Assaad et al. (Mar 1–Apr 25, 2020) [37]	France (PRE-ONCOVID-19 study)	55	64.2% had recent anti-cancer treatments	29.5% had severe COVID-19 pneumonia as detected by CT scan	9.9% (survival of cancer patients with COVID-19 symptoms and/or pneumonia was worse than other patients)
Moiseev et al. [38]	Russia	31	1.5% patients had active tumours or treatment in the past 3 months	Patients in intensive care unit were only included	Not reported
Ma et al. (Jan 1–Mar 30, 2020) [39]	Renmin Hospital, Wuhan University, China	37	Not reported	54.1% of cancer patients had severe disease (significantly higher than general population	13.5%

T-cell hyperactivation and may exacerbate lung injury [12]. Robilotti et al. similarly found treatment with ICI as one of the predictors for hospitalisation and severe COVID-19-related illness at Memorial Sloan Kettering Cancer Center [13].

Immunological challenges for cancer patients with COVID-19, treatment and vaccination

Severe illness in patients with COVID-19 is frequently linked to an inflammatory flare up resulting into the cytokine storm and lymphopenia. Secondary haemophagocytic lymphohistiocytosis (sHLH) is a less recognised hyperinflammatory condition in viral infection which is characterised by the fulminant and fatal hypercytokinaemia with multiorgan dysfunction [14]. A deranged cytokine profile with elevated interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein 1-α, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1 and tumour necrosis factor-α are found to be associated with poor outcome in COVID-19 as well. However, it could be hypothesized that, immunosuppression is likely to be beneficial in hyper inflammatory conditions [15]. Approval of tocilizumab, which blocks IL-6 receptor in 'cytokine storm' reiterates the beneficial role of immunosuppression in severe COVID-19.

There are complex, multiple, inter-connected mechanisms by which malignancy, anti-cancer therapies and various immunomodulators act. Haematological malignancies can harbour specific defects in lymphoid and myeloid lineages. Similarly, patients with advanced, solid malignancies can have persistent hyperinflammatory state with elevated cytokines. Cytotoxic chemotherapy and surgery may further add on lymphopenia in the landscape of generalised immunosuppression. The extent to which these events impact immune responses in COVID-19 (innate or adaptive) is still not clearly established [16].

In a prospective, longitudinal cohort study of cancer patients with COVID-19 and health care workers (CAPTURE) by Royal Marsden NHS Foundation, S1-reactive and neutralising antibodies to SARS-CoV-2 were detected even five months post-infection and $CD4^+$ T-cell responses correlated well with S1 antibody levels [17]. Patients with haematological malignancies were found to have impaired but partially compensated immune responses. Furthermore, investigators found that the stage of the malignancy and ongoing therapies do not correlate with the immune responses.

Lower seroconversion rate with malignancy

SARS-CoV-2 infection results in antibody response to major antigens (spike and nucleocapsid proteins) as well as a neutralising antibody response. The magnitude of the response appears to be dependent on disease severity and may persist up to 6 months [18, 19]. $CD4^+$ T-cells play a critical role for inducing antibody response and maintaining B-cell memory to SARS-CoV-2 infection even beyond six months [20]. Patients with cancer might have sustained immune dysregulation resulting into lower seroconversion rate, and viral shedding for prolonged duration after SARS-CoV-2 infection. Solodky et al. intriguingly reported lower detection rates of SARS-CoV-2 antibodies in cancer patients as compared with otherwise healthy HCW [21]. Although the cohort size was small, the finding pointed out the possibility of delayed or failed seroconversion in some patients with underlying malignancy.

Another virological phenomenon that has direct impact on the disease spread in the community is the prolonged shedding of replication-competent SARS-CoV-2 virus from the immunocompromised patients. Aydillo et al. investigated 20 patients who underwent HSCT or chimeric antigen receptor (CAR) T-cell therapy and detected viral RNA in respiratory samples for up to 78 days after symptom onset [22]. Henceforth, the current practice for isolation of COVID-19 patients may need to be prolonged for immunocompromised patients.

Effect of treatment with androgen-deprivation therapies (ADT)

Cellular entry of SARS-CoV-2 depends on the binding of virus spike protein (S), with angiotensin-converting enzyme 2 (ACE2) receptor on the surface of target host cells, and the priming by transmembrane serine protease 2 (TMPRSS2) [23, 24]. Aberrant expression of TMPRSS2 is a hallmark of several cancers and respiratory viruses could also exploit this serine protease to promote their spread inside human host [25]. Hence, TMPRSS2 is implicated in both cancer and viral infections and could be a potential target for intervention. TMPRSS2 is found upregulated in prostate cancer being an androgen-regulated gene and ADT strikingly decrease the levels of TMPRSS2 [26]. In a population-based study in Italy, investigators found significantly lower risk of SARS-CoV-2 infection with prostate cancer patients who received ADT [27].

Low-dose radiotherapy

Similarly, low-dose radiation (0.3–1 Gy) can induce polarisation shifts of lung macrophages from M1 pro-inflammatory to M2 anti-inflammatory phenotype and activates a cascade towards reduction of several pro-inflammatory cytokines and reduces the severity of lung injury caused by SARS-CoV-2 [28, 29].

Safety and efficacy of vaccines for cancer patients

Large scale prospective evaluation on neutralising antibody or T-cell responses in COVID-19 is lacking for cancer patients. Similarly data on immunological responses induced by SARS-CoV-2 vaccines and their effectiveness are absolutely inadequate for this subgroup. A short-term safety report of Pfizer BNT162b2 mRNA COVID-19 vaccine in 137 patients with cancer in Israel, treated with immune checkpoint inhibitors, has observed no new immune-related side effects or exacerbation of existing immune-related complications [30]. The side-effect profile was mostly similar in the healthy control and the observation can be noted as a reassuring safety signal for vaccines for such patients.

In an interim analysis, Monin et al. reported that a single dose of the BNT162b2 Pfizer–BioNTech COVID-19 vaccine is poorly immunogenic in patients with malignancy, as measured by seroconversion rates, viral neutralisation capacity and T-cell responses at three weeks and five weeks following the first inoculum [31]. Immunogenicity was found markedly improved at two weeks after the second dose given at 21-day interval. Hereby, this study supports the prioritisation of cancer patients for an early (day 21) second dose, although this view requires validation by larger studies and might be confounded by the use of different types of vaccines.

Based on such small cohort studies and available safety data regarding other routinely used vaccines such as influenza vaccine, expert panels believe that vaccination will not hamper the safety and efficacy of treatment for cancer, whereas cancer treatment may reduce the robustness of immunological response after vaccination, although the extent of such interaction is not clearly understood [32].

Accepted recommendations

Centers for Disease Control and Prevention (CDC) interim clinical guidance has noted the pitfall of limited safety and efficacy data but has continued recommendations in favour of vaccines for patients with cancer, as it will confer some benefits and will reduce the risk or severity of COVID-19. Similarly, CDC has also recommended COVID-19 vaccines for immunocompromising conditions other than cancer, autoimmune diseases, and history of Guillain-Barré syndrome and Bell's palsy since no extra safety hazards have been reported so far.[4] The American Society of Clinical Oncology and The National Comprehensive Cancer Network have reiterated this view and have put no contraindication for vaccines in the clinical scenario including "marrow failure from disease and/or therapy expected to have limited or no recovery" and "long term maintenance therapy" in haematological malignancies. Similarly patients receiving any active treatment with cytotoxic chemotherapy, immunotherapy, targeted agents, and/or radiotherapy can be vaccinated, whenever available[5]. [33] The Society for Immunotherapy of Cancer has also advocated SARS-CoV-2 vaccination for the patients receiving approved or any investigational immunotherapy with a caveat that those receiving corticosteroids or TNF blockers or patients with B-cell deficiency, may not mount a robust immune response and they may need additional booster dose[6].

Optimal timing of vaccination in relation to cycles of chemotherapy requires more in-depth analysis. Because of variability of chemotherapy regimens and intervals between cycles, it is difficult to recognise the most effective timing of vaccination during chemotherapy cycle. [34] Strategies such as vaccination in between cycles of chemotherapy can be explored to reduce the unknown risks whilst maintaining the efficacy.

Contraindications and precautions for vaccines

Based on limited efficacy data, it is advocated that patients who have underwent HSCT or chimeric antigen receptor (CAR) T-cell therapy should delay COVID-19 vaccination until at least 3 months after the completion of treatment. The data is also not clear for the patients who are getting aggressive chemotherapy, such as intensive treatment regimen in leukaemia. It would be prudent to delay vaccination until the white blood cell counts recover after such therapies[7].

In addition, cancer patients who are planned for elective surgeries should preferably wait for a week after completion of surgery. This approach is formulated to prevent any potential side effects from the vaccine to defer the plan of surgical intervention. Apart from these oncological reasons, general

[4] Centers for Disease Control and Prevention (CDC). Summary Document for Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States—FactSheet. Available from: https://www.cdc.gov/vaccines/covid-19/downloads/summary-interim-clinical-considerations.pdf.

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[6] SITC Statement on SARS-CoV-2 Vaccination and Cancer Immunotherapy. Available. from:https://www.prweb.com/releases/sitc_statement_on_sars_cov_2_vaccination_and_cancer_immunotherapy/prweb17633616.htm. (Accessed May 17, 2021).

[7] Coronavirus Vaccines and People with Cancer—National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2021/people-with-cancercoronavirus-vaccine. (Accessed May 13, 2021).

contraindications such as allergic reactions to any component of the intended vaccine and the age criteria would apply for the vaccination of cancer patients as well.

CDC has clearly stated that, COVID-19 vaccines can be given safely to people with prior SARS-CoV-2 infection but should be deferred until recovery from acute illness. But persons treated with convalescent plasma or any SARS-CoV-2-specific monoclonal antibody should wait for at least 90 days till such therapies[8].

Post-vaccination, patients may develop enlarged lymph nodes, particularly in axilla due to a robust immune response and imaging scans may show enhancement/uptakes of such lymph nodes. These findings might be misleading towards unnecessary fear of malignant lymphadenopathy and should be interpreted with caution. Patients having lymphoedema due to the surgery for breast cancer should receive vaccine on the opposite arm or on thigh, alternatively. All people who are vaccinated should continue adequate preventive measures including wearing masks, physical distancing, hand hygiene and avoiding large crowds as general precautions.

Conclusion

Most of the registry trials of COVID-19 vaccines excluded patients with active malignancies, or those receiving systemic anticancer therapies and thus, data on the safety and efficacy of the vaccines in such patients are currently limited. Moreover, initial analysis of patients with cancer and COVID-19 infection are limited by small sample size, geographical restriction and confounding factors like different performance status of the cancer patients and different modalities of anticancer treatment. But emerging evidences and international guidelines are now clearly in favour of vaccination whenever available for most of the cancer patients, except certain immediate contraindications such as HSCT and CAR T-cell therapy.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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