COVID-19 Vaccine Effectiveness in Oncology Patients

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Abstract
Oncology patients are at greater risk of morbidity and mortality from coronavirus disease 2019 (COVID-19) infection than the general population. Patients with malignancies were prioritized in vaccine distribution to confer protection to a vulnerable population. However, immunocompromised patients were not included in the initial COVID-19 vaccine trials. Will patients with cancer mount an adequate serologic response to vaccination to be protected from COVID-19 infection? Overall, oncology patients had diminished antibody response to the COVID-19 vaccines compared with healthy patients. The patients with the lowest seroconversion rates were those who received anti-CD20 monoclonal antibody therapy, Bruton tyrosine kinase inhibitor therapy, stem cell transplantation, and chimeric antigen receptor T-cell therapy. Although the response may not be robust, expert organizations strongly recommend that oncology patients should pursue COVID-19 vaccination and booster to ensure some degree of protection from infection. Immunocompromised patients should continue to practice mask wearing, social distancing, and proper hand hygiene to minimize the risk of contracting COVID-19.

In 2019, a global pandemic emerged from a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), now a ubiquitous household term. COVID-19 has caused significant morbidity and mortality, resulting in nearly 1 million deaths in the United States and over 6 million deaths worldwide (The New York Times, 2022). Immunocompromised patients, including patients with cancer, are particularly at risk for severe infection and death from COVID-19 (Liang et al., 2020).

COVID-19 VACCINES
Development of a COVID-19 vaccine began swiftly. COVID-19 vaccines induce immunity by exposing the immune system to the SARS-CoV-2 spike protein without infecting the individual. Comirnaty (BNT162b2), a vaccine from Pfizer-BioNTech, and Spikevax (mRNA-1273), a vaccine from Moderna, use messenger ribonucleic acid (mRNA) technology to deliver 95% (Polack et al., 2020)
and 94% (Baden et al., 2021) efficacy, respectively, against wild-type COVID-19 infection, in two immunizations. Ad26.COV2.S is single-dose adenovirus vector vaccine from Johnson & Johnson/Janssen (JJJ). The JJJ vaccine provides up to 90% efficacy against wild-type SARS-CoV-2 infection under Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA; Sadoff et al., 2021). Vaxzevria (AZD1222) is an adenovirus-based vaccine by Oxford/AstraZeneca (AZ) and has received emergency approval in several countries (Voysey et al., 2021). Vaxzevria confers up to 74% efficacy against symptomatic COVID-19 infection in two doses (Voysey et al., 2021).

ONCOLOGY PATIENTS

Given their increased susceptibility to infection, patients with cancer were given priority in the COVID-19 vaccine rollout. However, immune suppression in this patient population could compromise their serologic response to COVID-19 vaccination. Immunocompromised patients were excluded from COVID-19 vaccine trials, making it difficult to extrapolate the original trial data onto the oncology patient population. Oncology patients are a diverse cohort based upon type of malignancy and type of cancer-directed therapy, with varying degrees of immunosuppression.

Subsequent international studies have demonstrated that patients with cancer produced an inferior serologic response to COVID-19 vaccination compared with healthy controls. This was most notable in patients with hematologic malignancies and patients undergoing stem cell transplantation (SCT) and chimeric antigen receptor (CAR) T-cell therapy. A summary of studies demonstrating oncology patients’ responses to COVID-19 vaccination is included in Table 1.

Solid Tumors

Among patients with cancer, those with solid tumors demonstrated the most favorable antibody response to COVID-19 vaccination (Addeo et al., 2021; Goshen-Lago et al., 2021; Palich et al., 2021; Thakkar et al., 2021). Some patients with solid tumors seroconverted as well as healthy controls (Addeo et al., 2021). Patients on active surveillance (not currently receiving therapy) or those receiving endocrine/hormonal or immune checkpoint inhibitor therapy demonstrated seroconversion rates near 100% (Addeo et al., 2021). Patients actively receiving chemotherapy, however, had lower titers after vaccination (Palich et al., 2021). Metastatic disease and advanced age negatively impacted vaccine response (Palich et al., 2021).

Patients with solid tumors undergo diverse treatments, including myelosuppressive chemotherapy, targeted therapy, immunotherapy, surgery, and/or radiation therapy. The patient’s underlying malignancy and type of therapy contribute to their ability to mount an immune response to COVID-19 vaccination.

Hematologic Malignancies

Patients with hematologic malignancies had lower seroconversion rates (39%–85%) and lower antibody titers compared with patients with solid tumors or healthy controls (Addeo et al., 2021; Agha et al., 2021; Herishanu et al., 2021; Maneikis et al., 2021; Roeker et al., 2021; Thakkar et al., 2021). Several therapies predicted poor serologic response. These include anti-CD20 monoclonal antibodies, Bruton tyrosine kinase (BTK) inhibitors, venetoclax (Venclexta), immunomodulators, proteasome inhibitors, and hydroxyurea (Maneikis et al., 2021).

Patients with hematologic malignancies often require intensive, myelosuppressive chemotherapy to adequately control their disease. Hematologic malignancies impair the very leukocytes that generate one’s immune response to vaccination. The therapies used to treat these malignancies attack these same immunologic cells, blunting seroconversion following vaccination.

ANTI-CD20 MONOCLONAL ANTIBODY THERAPY

Patients receiving anti-CD20 therapy had a nearly negligible serologic response to the COVID-19 vaccines (Addeo et al., 2021; Maneikis et al., 2021; Thakkar et al., 2021). In studies by Addeo and colleagues (2021) and Herishanu and colleagues (2021), zero patients developed antibodies if treated with anti-CD20 therapies within the past 6 to 12 months. Patients greater than 12 months post anti-CD20 therapy had improved seroconversion rates and titers compared with patients actively receiving anti-CD20 therapy (Herishanu et al., 2021; Maneikis et al., 2021).
Anti-CD20 therapy specifically targets the CD20 antigen on the surface of B cells, causing cell lysis and depleting normal B-cell and antibody production for 6 to 12 months (Addeo et al., 2021; Genentech, 2021).

**CHRONIC LYMPHOCYTIC LEUKEMIA**
Patients with chronic lymphocytic leukemia (CLL) demonstrated particularly poor response to vaccination, with low seroconversion rates (23%–52%) and low antibody titers (Agha et al., 2021; Herishanu et al., 2021; Roeker et al., 2021). Treatment-naive patients had higher rates of seroconversion than treated patients (Herishanu et al., 2021; Roeker et al., 2021). Patients receiving several common CLL therapies, including anti-CD20 therapy, BTK inhibitors, and venetoclax, had poor seroconversion rates (Herishanu et al., 2021; Roeker et al., 2021). Patients with higher serum immunoglobulin levels—likely a surrogate marker for B-cell function—had better seroconversion rates than patients with hypogammaglobulinemia (Eichhorst, 2021; Herishanu et al., 2021).

Chronic lymphocytic leukemia impairs normal B lymphocytes, causing hypogammaglobulinemia and often requiring intravenous immunoglobulin (IVIG) replacement. Patients with CLL cannot typically produce normal immunoglobulin levels; it is not surprising that their serologic response to COVID-19 vaccination is also inadequate. This leaves CLL patients more vulnerable to COVID-19 infection despite full immunization.

**STEM CELL TRANSPLANTATION AND CELLULAR THERAPY**
Patients who have undergone SCT had poor seroconversion rates, but higher titers were seen in patients status post autologous SCT compared...
with allogeneic SCT (Easdale et al., 2021; Maneikis et al., 2021; Redjoul et al., 2021; Thakkar et al., 2021). Patients status post CAR T-cell therapy also had poor serologic response to COVID-19 vaccination. Thakkar and colleagues (2021) demonstrated zero CAR T-cell therapy patients seroconverted; Dhakal and colleagues (2021) noted seroconversion rates of 11%. Seroconversion rates and titers were higher with greater time post SCT or CAR T-cell therapy, and particularly improved 12 months after these therapies (Dhakal et al., 2021; Easdale et al., 2021; Maneikis et al., 2021; Redjoul et al., 2021). Active immunosuppression for graft-vs.-host disease (GVHD) predicted poor seroconversion and titers (Dhakal et al., 2021; Easdale et al., 2021; Redjoul et al., 2021).

High-dose conditioning for SCT and lymphodepleting regimens for CAR T-cell therapy cause profound myelosuppression. Patients receiving CAR T-cell therapy are expected to have prolonged B-cell aplasia and require chronic IVIG replacement following CAR T-cell therapy. Following SCT and CAR T-cell therapy, the immune system gains improved function—and improved response to COVID-19 vaccination—over time.

RECOMMENDATIONS
The American Society of Hematology, American Society for Transplantation and Cellular Therapy, Memorial Sloan Kettering Cancer Center (MSKCC), and the National Comprehensive Cancer Network (NCCN) have provided recommendations for the optimal vaccination approach for patients with cancer. COVID-19 vaccines are safe for patients with cancer, and oncology patients should be vaccinated, even though their serologic response may not be robust (MSKCC, 2021; NCCN, 2022). Live, attenuated vaccines should certainly be avoided in immunocompromised patients, but as of yet, none of the COVID-19 vaccines in the US are live viral vaccines (Auletta et al., 2022; NCCN, 2021). Vaccination recommendations for specific patient populations based on guidelines provided by these expert organizations are included in the following section. Clinicians should be mindful that during times of high viral transmission, it may be appropriate to vaccinate as soon as possible, depending on the patient’s individual risk for COVID-19 infection and mortality (MSKCC, 2021).

Prior to Vaccination
Providers should consider standard laboratory evaluations, such as complete blood count with differential and quantitative immunoglobulin levels prior to vaccine administration (Auletta et al., 2022). For patients who will receive intensive, cytotoxic chemotherapy, it is suggested to wait until neutrophil and platelet recovery to vaccinate (MSKCC, 2021; NCCN, 2022). Neutrophil recovery is a surrogate marker of immune cell restoration following count nadir. Intramuscular injections carry a risk of bleeding in patients with thrombocytopenia; waiting until platelets recover minimizes this risk.

For patients enrolled on clinical trials, contact the study sponsor to ensure that vaccine administration is not a contraindication to study participation (NCCN, 2022). However, COVID-19 vaccination should not be delayed in order to enroll the patient on a clinical trial (NCCN, 2022).

Hematologic Malignancies
For patients who will receive therapies that affect B-cell function (e.g., anti-CD20 monoclonal antibodies, BTK inhibitors) but are currently asymptomatic from their malignancy, consider prioritization of COVID-19 vaccination first, and then wait 1 month after vaccination to begin therapy (Addeo et al., 2021; Khawaja et al., 2021; MSKCC, 2021). To maximize seroconversion, clinicians can consider postponing COVID-19 vaccination until at least 6 months after completion of anti-CD20 therapy, if appropriate (MSKCC, 2021). For patients on long-term or continuous therapy, clinicians should not hold therapy; vaccination should still be encouraged, knowing that the B-cell response may not be optimal (MSKCC, 2021). For patients with newly diagnosed acute leukemia or high-grade lymphomas, clinicians should not delay induction chemotherapy to vaccinate and should wait for a period of count recovery (e.g., consolidation or maintenance phase) prior to administering COVID-19 vaccines (MSKCC, 2021).

Stem Cell Transplantation
Patients who receive an allogeneic SCT typically begin standard revaccination protocols starting 3 to 6 months after transplant, upon restoration of
B- and T-cell function (NCCN, 2021). Expert organizations concur that COVID-19 vaccination in autologous and allogeneic SCT patients should follow the same schedule, beginning 3 to 6 months after transplant, prioritizing the COVID-19 vaccines over other vaccines (Khawaja et al., 2021; MSKCC, 2021; NCCN, 2022). COVID-19 vaccines can be administered simultaneously with other vaccines (Khawaja et al., 2021). Vaccination should be postponed for patients with grade 3 to 4 GVHD (Khawaja et al., 2021; MSKCC, 2021).

**CAR T-Cell Therapy**

For patients who received CAR T-cell therapy, consider their current immunoglobulin levels and IVIG replacement needs. Plan COVID-19 vaccination at least 3 months after CAR T-cell infusion and once no longer IVIG dependent (MSKCC, 2021).

**COVID-19 Booster Vaccine**

To extend the duration of vaccine-induced immunity against COVID-19 infection, the Centers for Disease Control and Prevention (CDC) recommend a booster vaccine for all adults (Auletta et al., 2022; CDC, 2022a). However, moderately and severely immunocompromised patients should receive a further augmented immunization regimen. This includes patients with hematologic malignancies, patients who received a SCT, patients on immunosuppressive medications (including high-dose corticosteroids), as well as patients with other immunocompromising disease states (CDC, 2022b).

Following the initial two-dose mRNA vaccine series, these patients should receive a third mRNA vaccine at least 4 weeks after the second dose to complete their modified primary vaccine series. Subsequently, the CDC recommends a fourth mRNA vaccine as a booster, to be given at least 3 months after the third vaccination.

For the moderately and severely immunocompromised patients who initially received the JJJ vaccine, they should complete the primary series with a dose of mRNA vaccine at least 4 weeks after the JJJ vaccination. Then, 2 months after the second immunization, the CDC recommends a booster dose of mRNA vaccine for enhanced immunity.

**Vaccine Equity**

Equity in vaccine access should be prioritized for patients with diverse racial and ethnic backgrounds, language proficiency, and persons with disabilities (NCCN, 2022). Black, Hispanic/Latinx, Native American, Alaska Native, Pacific Islander, and indigenous persons experience a disproportionately higher rate of mortality from COVID-19 (Mackey et al., 2021). This risk is magnified when simultaneously facing a cancer diagnosis. Vaccination can mitigate these risks, yet many factors may impact vaccine uptake: access, transportation, education, safety concerns, misinformation, and distrust due to racism in medicine (CDC, 2021; Momplaisir et al., 2021).

Recommendations from trusted health-care providers hold significant weight in the patient’s decision to pursue or defer vaccination (Momplaisir et al., 2021). Oncology providers foster trust and rapport as they help patients to navigate their cancer diagnosis and therapy. Patients will likely seek vaccination advice from their oncology team. Clinicians should utilize the opportunity for education and discussion within this safe space, in which patients can voice their concerns and fears. In addition, clinicians should identify potential language and communication barriers and provide vaccine information in the patient’s native language (NCCN, 2022). These efforts towards vaccine equity can help to narrow COVID-19 health disparities.

**Pre-Exposure Prophylaxis**

An additional protective measure for the profoundly immunocompromised is tixagevimab and cilgavimab (Evusheld), a monoclonal antibody injection. Evusheld has received EUA from the FDA for pre-exposure prophylaxis of COVID-19 in moderately and severely immunocompromised individuals (AstraZeneca, 2022). Evusheld is not a replacement for vaccination; the monoclonal antibodies bind to the SARS-CoV-2 spike protein to prevent viral attachment to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells (AstraZeneca, 2022). Presently, a single-dose administration of Evusheld is suggested for immunocompromised patients, given the uncertain effectiveness of the drug with future viral variants (AstraZeneca, 2022; NCCN, 2022).
Final Recommendations
Following COVID-19 vaccination and booster, immunocompromised patients should remain vigilant and continue to practice safety measures to prevent COVID-19 exposure. This includes masking indoors, social distancing, practicing hand hygiene, and avoiding poorly ventilated indoor spaces. An additional strategy to protect the immunocompromised is the “cocoon” approach. All household contacts, caregivers, family members, close contacts, and health-care workers should be vaccinated to minimize the spread of COVID-19 to the patient (Auletta et al., 2022; Khawaja et al., 2021; NCCN, 2022). These nonpharmacologic measures of viral mitigation remain prudent practice for those at high risk of severe COVID-19 infection.

CONCLUSION
Patients with a cancer diagnosis face an increased risk of COVID-19 infection given their underlying malignancy and myelosuppression from chemotherapy. However, they also receive objectively less protection from COVID-19 vaccines given their immunocompromised state. Patients with solid tumors undergoing endocrine or checkpoint inhibitor therapy alone had comparable seroconversion rates to healthy controls, so should have similar protection from severe illness, hospitalization, and death from COVID-19. Yet, patients with hematologic malignancies, particularly those undergoing anti-CD20 therapy, BTK inhibitor therapy, SCT, and CAR T-cell therapy had poor antibody responses to vaccination, and must use caution to protect themselves from COVID-19 infection.

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