Special Considerations in Adults and Children With Cancer

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**Summary Recommendations**

- Given the effectiveness of the COVID-19 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for patients with active cancer or patients who are receiving treatment for cancer (AIII).

- Patients who are receiving active cancer therapy may have suboptimal responses to the current two-dose vaccine series. Because of this, the Centers for Disease Control and Prevention recommends a third dose of an mRNA vaccine for these patients. See the text below for additional information on the criteria for receiving a third dose and the appropriate timing for COVID-19 vaccination in these patients.

- Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies for treatment or as post-exposure prophylaxis (PEP).

- The Panel recommends performing molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest COVID-19 (AIII) and in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (BIII).

- The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population (AIII). See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information.

- Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications (AIII).

- Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications (AIII).

- Decisions about administering cancer-directed therapy during SARS-CoV-2 infection should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient’s history of tolerance to the treatment (BIII).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Weak

**Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

People who are being treated for cancer may be at increased risk of severe COVID-19, and clinical outcomes of COVID-19 are generally worse in people with cancer than in people without cancer.°-°° A meta-analysis of 46,499 patients with COVID-19 showed that all-cause mortality (risk ratio 1.66; 95% CI, 1.33–2.07) was higher in patients with cancer, and that patients with cancer were more likely to be admitted to intensive care units (risk ratio 1.56; 95% CI, 1.31–1.87).° A patient’s risk of immunosuppression and susceptibility to SARS-CoV-2 infection depend on the type of cancer, the treatments administered, and the stage of disease (e.g., patients who are actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, patients with cancer who were in remission or who had no evidence of disease were at lower risk of death from COVID-19 than those who were receiving active treatment.° It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

Many organizations have outlined recommendations for treating patients with cancer during the COVID-19 pandemic, such as:

- National Comprehensive Cancer Network (NCCN)
- American Society of Hematology (ASH)
This section of the COVID-19 Treatment Guidelines complements these sources and focuses on testing for SARS-CoV-2, managing COVID-19 in patients with cancer, and managing cancer-directed therapies during the COVID-19 pandemic. The optimal management and therapeutic approach to COVID-19 in this population has not yet been defined.

**Vaccination for COVID-19 in Patients With Cancer**

The clinical trials that evaluated the COVID-19 vaccines that have received Emergency Use Authorizations and/or approval from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The Advisory Committee on Immunization Practices notes that the authorized COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.7 Given the effectiveness of the COVID-19 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for patients with active cancer or patients who are receiving treatment for cancer (AIII). The Centers for Disease Control and Prevention (CDC) recommends a third dose of an mRNA vaccine for patients who are receiving active cancer therapy; this third dose should be administered at least 28 days after the completion of the initial two-dose mRNA COVID-19 vaccine series.8 ASH and NCCN have provided additional recommendations for administering a third vaccine dose in patients with cancer based on the patient’s tumor type and therapy.9,10

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. In patients who experience a severe anaphylactic reaction to PEG-asparaginase, consider performing allergy testing for PEG prior to vaccination with either of the mRNA vaccines, or consider using the J&J/Janssen vaccine with precautions.11-13

When determining the timing of COVID-19 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should complete vaccination for COVID-19 at least 2 weeks before starting chemotherapy.9,14
- In patients with hematologic malignancy who are undergoing intensive chemotherapy (e.g., induction chemotherapy for acute myelogenous leukemia), vaccination should be delayed until neutrophil recovery.15
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.14

It is unknown whether the immune response to COVID-19 vaccination can increase the risk of graft-versus-host disease. Studies of patients who received immune checkpoint inhibitors did not report immune-related adverse events in these patients after vaccination.16,17

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.18,19 The type of therapy has been shown to influence the patient’s response to vaccination. For example, people with chronic lymphocytic leukemia who were treated with Bruton’s tyrosine kinase inhibitors or venetoclax with...
or without anti-CD20 antibodies had extremely low response rates (16.0% and 13.6%, respectively). In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses. Currently, it is not known how a third dose of an mRNA vaccine affects response rates in patients with cancer.

Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) as post-exposure prophylaxis (PEP).

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated.

**Testing for SARS-CoV-2 in Patients With Cancer**

The Panel recommends molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms of COVID-19 (AIII).

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The NCCN Guidelines for Hematopoietic Growth Factors categorizes cancer treatment regimens based on the patient’s risk of developing neutropenia. A retrospective study suggests that patients with cancer and neutropenia have a higher mortality rate if they develop COVID-19. Studies have reported an increased risk of poor clinical outcomes for patients with COVID-19 in the setting of neutropenia and/or during the perioperative period. Because of this, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (BIII).

**General Guidance on Medical Care for Patients With Cancer During the COVID-19 Pandemic**

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer and/or treatment-related complications. Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. CDC has published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient’s community. Telemedicine may improve access to providers for medically or socially vulnerable populations, but it could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported. Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on a case-by-case basis, and clinicians should consider the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Additional factors that should be considered include the following:

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD-1 inhibitors)
must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.\textsuperscript{32}

- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department evaluation and hospitalization. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10\% to 20\%) or high (>20\%) risks of febrile neutropenia.\textsuperscript{33}

- Cancer treatment regimens that do not affect the outcomes of COVID-19 in patients with cancer may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among patients with cancer and COVID-19.\textsuperscript{34} A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and found that 114 of 37,161 patients (0.3\%) who were treated with therapies other than androgen deprivation therapy became infected, compared to 4 of 5,273 patients (0.08\%) who were treated with androgen deprivation therapy (OR 4.05; 95\% CI, 1.55–10.59).\textsuperscript{35} A small cohort study of patients from Finland with prostate cancer did not find an association between androgen deprivation and the incidence of SARS-CoV-2 infection.\textsuperscript{36} The viral spike proteins that SARS-CoV-2 uses to enter cells are primed by transmembrane serine protease 2 (TMPRSS2), an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts or clinical trials.\textsuperscript{35}

- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.\textsuperscript{37,38}

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. The FDA has proposed revising the donor criteria to increase the number of eligible donors.\textsuperscript{39} In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.\textsuperscript{8} At this time, there is no evidence that COVID-19 can be transmitted through blood products.\textsuperscript{40,41}

**Febrile Neutropenia**

Patients with cancer and febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.\textsuperscript{42} Low-risk febrile neutropenia patients should be treated at home with oral antibiotics or intravenous infusions of antibiotics to limit nosocomial exposure to SARS-CoV-2. Patients with high-risk febrile neutropenia should be hospitalized per standard of care.\textsuperscript{42} Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continuously evaluate neutropenic patients for emergent infections.

**Treating COVID-19 and Managing Chemotherapy in Patients With Cancer and COVID-19**

Retrospective studies suggest that patients with cancer who were admitted to the hospital with SARS-CoV-2 infection have a high case-fatality rate, with higher rates observed in patients with hematologic malignancies than in those with solid tumors.\textsuperscript{43,44}

The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population (AIII). See \textit{Therapeutic Management of Nonhospitalized Adults With COVID-19} and \textit{Therapeutic Management of Hospitalized Adults With COVID-19} for more information. Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 mAbs as treatment if they develop mild to moderate COVID-19.
Dexamethasone treatment has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation. In patients with cancer, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of dexamethasone are expected to be the same in patients with cancer as in those without cancer. If possible, treatments that are not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well-defined in patients with cancer.

The NCCN recommends against using G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokine levels and pulmonary inflammation. Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient’s history of tolerance to the treatment. The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in patients with cancer, although it is unknown how this relates to infectious virus and how it impacts outcomes. Therefore, there is no role for repeat testing in those recovering from COVID-19, and the decision to restart cancer treatments in this setting should be made on a case-by-case basis. Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications.

**Medication Interactions**

The use of antiviral or immune-based therapies to treat COVID-19 can present additional challenges in patients with cancer. Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications.

Several antineoplastic medications may interact with therapies that are being investigated for COVID-19. For example, tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients who are being treated with venetoclax, gilteritinib, or tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for patients with cancer and is recommended for the treatment of certain patients with COVID-19 (see Therapeutic Management of Hospitalized Adults With COVID-19). Dexamethasone is a weak to moderate cytochrome P450 (CYP) 3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered.

**Special Considerations in Children**

Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed. Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group that received input from the International Society of Paediatric Oncology, the Children’s Oncology Group, St. Jude Global, and Childhood Cancer International. Two publications include guidance for managing specific malignancies, guidance for supportive care, and a summary of web links from expert groups that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.
Special considerations for using antivirals in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.57

References


