COVID-19 Treatment Guidelines

Summary Recommendations

- COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible (AI), including patients with active cancer and patients who are receiving treatment for cancer (AIII).

- Because vaccine response rates may be lower in people with cancer, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices. The Panel recommends following the most current COVID-19 vaccination schedule for people with cancer.

- Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible (AIII).

- 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 as pre-exposure prophylaxis (PrEP).

- The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute COVID-19 (AIII). The Panel also recommends performing diagnostic molecular testing 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 overlapping toxicities and drug-drug interactions between drugs that are used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], dexamethasone) and cancer-directed therapies, prophylactic antimicrobials, 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 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 (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 had a lower risk of death from COVID-19 than those who were receiving active treatment. It is unclear whether cancer survivors have an 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
- American Society of Clinical Oncology
- Society of Surgical Oncology
- American Society for Radiation Oncology
- International Lymphoma Radiation Oncology Group

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.

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

The clinical trials that evaluated the COVID-19 vaccines that have received Emergency Use Authorizations (EUAs) and/or approvals from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices notes that the COVID-19 vaccines that are authorized for use in the United States are not live vaccines; therefore, they can be safely administered to immunocompromised people.

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 and patients who are receiving treatment for cancer (AIII). Observational data suggest that the serological responses to vaccines may be blunted in immunocompromised patients; however, vaccination is still recommended for these patients, because it may provide partial protection, including protection from vaccine-induced, cell-mediated immunity. See the CDC website COVID-19 Vaccines for People who are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for these individuals. Given the effectiveness of COVID-19 vaccines, the Panel recommends COVID-19 vaccination as soon as possible for everyone who is eligible (AI), including individuals who have immunodeficiency or are on immunosuppressive medications (AIII).

Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible (AIII). There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. For patients who experience severe anaphylactic reactions 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.

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.\textsuperscript{18,19} • 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.\textsuperscript{20} • Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.\textsuperscript{19,20}

It is unknown whether the immune response to COVID-19 vaccination can increase the risk of graft-versus-host disease. No immune-related adverse events were reported after COVID-19 vaccination in two studies of patients with cancer who received immune checkpoint inhibitors.\textsuperscript{21,22}

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.\textsuperscript{9,23} 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).\textsuperscript{23} In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.\textsuperscript{9,24,25} Several observational studies support the use of a third vaccine dose in patients with cancer, even though vaccine failure may still occur.\textsuperscript{26-28} See the CDC website COVID-19 Vaccines for People who are Moderately or Severely Immunocompromised for guidance on vaccine dosing.

**Pre-Exposure Prophylaxis**

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some patients with cancer, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

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

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute COVID-19 (A\textsuperscript{III}).

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.\textsuperscript{29} A retrospective study suggests that patients with cancer and neutropenia have a higher mortality rate if they develop COVID-19.\textsuperscript{30} 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.\textsuperscript{31,32} Because of this, the Panel recommends performing diagnostic molecular testing for SARS-CoV-2 in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (B\textsuperscript{III}).

**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. 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.\textsuperscript{33-35} Health care providers and patients should take precautions to reduce the risk of SARS-CoV-2 exposure and infection, including wearing a mask, maintaining a distance of 6 feet from others, and practicing good hand hygiene.\textsuperscript{36}

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, avoid treatment delays 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.\textsuperscript{37}
- 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{38}
- Preventing neutropenia can decrease the risk of febrile 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{39}
- 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{40}
- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.\textsuperscript{41,42}

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{43} In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered. At this time, there is no evidence that COVID-19 can be transmitted through blood products.\textsuperscript{44}

### Febrile Neutropenia

Patients with cancer and febrile neutropenia should undergo diagnostic molecular or antigen 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{45} 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{45} 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{46,47}
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. Patients with cancer are at high risk of progressing to severe COVID-19, and they may be eligible to receive anti-SARS-CoV-2 therapies in the outpatient setting if they develop mild to moderate COVID-19.

The use of dexamethasone has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or 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.

Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults With COVID-19). The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in patients with cancer who recently received chemotherapy is unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for patients with cancer who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/µL should not receive therapeutic anticoagulation to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The NCCN recommends against using G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute COVID-19 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 (BIII). The optimal time to initiate or restart cancer-directed therapies after the infection has resolved is unclear. If possible, clinicians should withhold treatment until COVID-19 symptoms have resolved. Prolonged viral shedding 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 (AIII).

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

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating
mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong cytochrome P450 (CYP) 3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase concentrations of certain concomitant medications, including certain chemotherapeutic agents and immunotherapies that are used to treat cancer. Significant increases in the concentrations of these drugs may lead to serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient’s concomitant medications. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used.

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 CYP3A4 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.56-58 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.59 Two publications provide guidance on managing specific malignancies and supportive care and a summary of web links from groups of experts that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.59,60 Special considerations for using antiviral drugs in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.61

References


