Special Considerations in Adults and Children With Cancer

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Summary Recommendations
• COVID-19 vaccination remains the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible, including patients with active cancer and patients receiving treatment for cancer, according to the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices **(AI)**. • See the CDC webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule. • Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. Clinicians should strongly encourage all household members and close contacts of patients with cancer to be vaccinated against COVID-19 **(AI)**. • The Panel defers to CDC recommendations for diagnostic molecular or antigen testing for SARS-CoV-2 infection in patients with cancer who develop signs and symptoms that suggest acute COVID-19. The Panel also defers to CDC recommendations for testing of asymptomatic patients before procedures and hospital admissions. • For patients with cancer and COVID-19, clinicians should follow COVID-19 evaluation and management guidelines for patients who do not have cancer. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information. • 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 cancer treatment **(BIII)**. • Clinicians should consult with a hematologist or oncologist when making decisions about stopping or adjusting the doses of cancer-directed medications in patients with cancer and COVID-19. • Clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], dexamethasone) and cancer-directed therapies, prophylactic antimicrobials, and other medications **(AIII)**.
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

People 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.[1-4] A meta-analysis of 46,499 patients with COVID-19 showed that all-cause mortality was higher in patients with cancer (risk ratio 1.66; 95% CI, 1.33–2.07), 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).[5] 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 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.[6] Cancer survivors may also have an increased risk of severe COVID-19.[7]

This section of the COVID-19 Treatment Guidelines focuses on testing for SARS-CoV-2 and managing COVID-19 and cancer-directed therapies in people with cancer and COVID-19.

COVID-19 Vaccination

The clinical trials that evaluated the COVID-19 vaccines that received Emergency Use Authorizations or approvals from the Food and Drug Administration excluded patients who were severely immunocompromised. The COVID-19 vaccines authorized for use in the United States are not live vaccines; therefore, they can be safely administered to people who are immunocompromised.

COVID-19 vaccination remains the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible, including patients with active cancer and patients receiving treatment for cancer, according to the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices **(AI)**. See the CDC webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule.

Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.[8,9] However, vaccination is still recommended for these patients because it may provide partial protection, including protection from vaccine-induced, cell-mediated immunity.

Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. Clinicians should strongly encourage all household members and close contacts of patients with cancer to be vaccinated against COVID-19 **(AI)**. There is evidence that vaccinated individuals infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals[10,11] and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[12-14]

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

- If possible, patients planning to receive chemotherapy should receive vaccinations for COVID-19 at least 2 weeks before starting chemotherapy.[15,16]
- COVID-19 vaccines can be offered as early as 3 months after a patient receives hematopoietic cell or chimeric antigen receptor T cell therapy.[16]
- Graft-versus-host disease symptoms may flare after COVID-19 vaccination.[17] No immune-related adverse events were reported after COVID-19 vaccination in 2 studies of patients with cancer who received immune checkpoint inhibitors.[18,19]

Decreased immunologic responses to COVID-19 vaccination have been reported in patients receiving treatment for solid tumors and hematologic malignancies.[9,20] 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).[20] In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.[9,21,22] Several observational studies support the use of a third vaccine dose in patients with cancer, even though vaccine failure may still occur.[23-25] See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for guidance on vaccine dosing.

Polyethylene Glycol Allergies

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) mRNA vaccines contain polyethylene glycol (PEG), whereas the NVX-CoV2373 (Novavax) vaccine contains polysorbate 80.[26] PEG and polysorbate are used in many products, including in agents used for cancer chemotherapy (e.g., PEG-

asparaginase). PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds might occur.[27]

The detection of PEG antibodies after vaccination was not associated with increased adverse reactions (such as delayed-onset reactions, including injection site rashes, or severe allergic reactions) to the mRNA vaccines.[27] Therefore, testing for anti-PEG antibodies should not be used as a screening tool to assess the risk of allergic reactions[28] and should not replace an assessment by a specialist in those rare individuals with a history of anaphylaxis.[29] The CDC has issued guidance on triaging people with a history of allergies or allergic reactions to the components of COVID-19 vaccines.

Testing for SARS-CoV-2

The Panel defers to CDC recommendations for diagnostic molecular or antigen testing for SARS-CoV-2 infection in patients with cancer who develop signs and symptoms that suggest acute COVID-19. The Panel also defers to CDC recommendations for testing of asymptomatic patients before procedures and hospital admissions.

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The National Comprehensive Cancer Network Guidelines for Hematopoietic Growth Factors categorize cancer treatment regimens based on the patient's risk of developing neutropenia.[30] A retrospective study suggests that patients with cancer and neutropenia have an increased risk of mortality if they develop COVID-19.[31] Studies have reported an increased risk of poor clinical outcomes for patients with COVID-19 in the setting of neutropenia and during the perioperative period.[32,33]

General Guidance for Patients With Cancer

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer or treatment-related complications. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.[34-36] Health care providers and patients should take precautions to reduce the risk of SARS-CoV-2 exposure and infection, including wearing a mask and practicing good hand hygiene.[37] Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. For people who have difficulty accessing health care, telemedicine may improve access to providers, but it could worsen disparities if these populations have limited access to technology.

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. 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.[38]

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 antimicrobial therapy per the standard of care.[39]

Treating COVID-19 and Managing Chemotherapy

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.[40,41]

For patients with cancer and COVID-19, clinicians should follow COVID-19 evaluation and management guidelines for patients who do not have cancer. Patients with cancer are at high risk of progressing to severe COVID-19 and are eligible to receive anti-SARS-CoV-2 therapies in the outpatient setting if they develop mild to moderate COVID-19. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for details.

The Panel also provides recommendations for treating COVID-19 in hospitalized patients. See Therapeutic Management of Hospitalized Adults With COVID-19 for more information. In patients with COVID-19 who required supplemental oxygen or mechanical ventilation, the use of dexamethasone has been associated with lower mortality than standard of care treatment alone.[42] 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.

The immunomodulators baricitinib, tocilizumab, abatacept, or inflixamab used in combination with dexamethasone are recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults With COVID-19).[43-46] The risks and benefits of using dexamethasone in combination with another immunomodulator in patients with cancer who recently received chemotherapy is unknown. Because dexamethasone and the other immunomodulators 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 for COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

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 cancer 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,[2] although it is unknown how this relates to infectious virus or outcomes. The decision to restart cancer treatments in this setting should be made on a case-by-case basis. Clinicians should consult with a hematologist or oncologist when making decisions about stopping or adjusting the doses of cancer-directed medications in patients with cancer and COVID-19.

Drug-Drug 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 used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], dexamethasone) and cancer-directed therapies, prophylactic antimicrobials, and other medications **(AIII)**.

A 5-day course of ritonavir-boosted nirmatrelvir 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 some chemotherapeutic agents and immunotherapies used to treat cancer. Significant increases in the concentrations of these drugs may lead to serious or life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications, including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions. 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 Food and Drug Administration's prescribing information 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 antiviral treatment option should be used (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

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.[47-49] Guidance on managing children with cancer and COVID-19 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.[50] Guidance on managing specific malignancies and supportive care and weblinks relevant to the care of children with cancer and COVID-19 are available in 2 publications authored by groups of experts.[50,51] Special considerations for the treatment of children with COVID-19, including those who are immunocompromised, can be found in Therapeutic Management of Hospitalized Children With COVID-19 and Therapeutic Management of Nonhospitalized Children With COVID-19.

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