NARRATIVE REVIEW ARTICLE

COVID-19 in the Cancer Patient

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The novel Coronavirus Disease 2019 (COVID-19) was first reported in China in December 2019. Since then, it has spread across the world to become one of the most serious life-threatening pandemics since the influenza pandemic of 1918. This review article will focus on the specific risks and nuanced considerations of COVID-19 in the cancer patient. Important perioperative management recommendations during this outbreak are emphasized, in addition to discussion of current treatment techniques and strategies available in the battle against COVID-19. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

ACE2 = angiotensin-converting enzyme 2; **ACEI** = angiotensin-converting enzyme inhibitors; **AHA** = American Heart Association; **ALT** = alanine aminotransferase; **ARB** = angiotensin receptor blockers; **ARDS** = acute respiratory distress syndrome; **BTKi** = Bruton tyrosine kinase inhibitors; **CAR** = chimeric antigen receptor; **CBC** = complete blood count; **CDC** = Centers for Disease Control and Prevention; **CFR** = case fatality rate; **COVID-19** = Coronavirus Disease 2019; **CrCl** = creatinine clearance; **CT** = computed tomography; **EQUATOR** = Enhancing the Quality and Transparency of health Research; **ESAS** = Elective Surgery Acuity Scale; **GI** = gastrointestinal; **HMEF** = heat and moisture exchanging filter; **HSCT** = hematopoietic stem cell transplant; **ICU** = intensive care unit; **IL-6** = Interleukin 6; **JAKi** = Janus kinase inhibitors; **LFTs** = liver function tests; **MERS-CoV** = Middle East respiratory syndrome coronavirus; **OR** = operating rooms; **PACU** = postanesthesia care unit; **PAPR** = powered air-purifying respirator; **PPE** = personal protective equipment; **RSV** = human respiratory syncytial virus; **SARS** = severe acute respiratory syndrome; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **TIL** = tumor-infiltrating lymphocytes; **VEGF** = vascular endothelial growth factor

The novel Coronavirus Disease 2019 (COVID-19) first emerged as an outbreak in the province of Hubei, China, in December 2019, with its causative virion formally known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a beta coronavirus, like that with Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS), which is thought to have originated from an animal host with eventual spread to humans.[1] COVID-19 became a global pandemic in a matter of months, affecting over 100 countries and totaling 824,559 infections and 40,673 deaths worldwide as of March 31, 2020.[2]

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Coronaviruses constitute a large family of viruses known to infect both humans and animals. Bats have been implicated as vectors in the largest variety of coronaviruses. The human coronaviruses can be subclassified into alpha and beta coronaviruses. Clinical manifestations of coronavirus infections are typically respiratory and enteric, although some present with neurologic manifestations.[1]

At the time of publication of this article, COVID-19 is thought to have an incubation period of approximately 2 weeks, with most infected individuals becoming symptomatic 5 days after exposure. Illness severity ranges from mild to critical and fatal. Approximately 80% of cases are asymptomatic or have mild symptoms, 15% have severe illness, and 5% have critical illness. Due to testing availability and limitations, the true case fatality rate (CFR) with COVID-19 is difficult to determine, but it is believed to range from 1% to 2%–3% based on existing data from different countries.[1,2] Patients typically present with fever, cough, shortness of breath, gastrointestinal, musculoskeletal, and neurologic symptoms. When severe, these patients present with pneumonia and acute respiratory distress syndrome (ARDS), and 1%–3% progress to multiorgan failure and ultimately succumb to the viral syndrome.[3] This review adheres to applicable Enhancing the Quality and Transparency of health Research (EQUATOR) guidelines.

IMMUNOCOMPROMISED STATE OF THE CANCER PATIENT

Underlying health conditions that increase susceptibility to severe COVID-19 include hypertension, chronic obstructive pulmonary disease, diabetes mellitus, and cardiovascular disease.[4,5] An immunocompromised state, such as autoimmune disease, nonautoimmune inflammatory diseases; patients taking immunosuppressive agents with transplanted organs; and active cancer also increase susceptibility for severe COVID-19.

As the pandemic is evolving, incidence rates in cancer patients have suggested higher rates of severe and critical disease. One prospective cohort study of COVID-19 in cancer patients observed that patients with cancer had a higher risk of severe events compared with patients without cancer.[6] Patients who recently underwent chemotherapy or surgery had a higher risk of clinically severe events compared with patients who did not.[6] However, several limitations included a small sample size, different cancer types, variable disease courses, diverse treatment strategies, and contribution of age to the risk.[7] The Chinese Center for Disease Control and Prevention (CDC) has published the largest case series to date of COVID-19 in mainland China and reported a CFR of 5.6% among patients with cancer.[8] Insufficient data on the current COVID-19 in cancer patients require examining past studies for coronavirus disease in the immunocompromised population and extrapolating risk of susceptibility and/or development of severe COVID-19. Nevertheless, a nationwide analysis in China observed that patients with cancer had a higher risk of severe events compared with patients without cancer and that patients who underwent chemotherapy or surgery in the previous month had a higher risk of severe events.[6] They noted that cancer patients had a higher risk of COVID-19 and that these patients had poorer outcomes than patients without cancer.[6]

Immunocompromised patients remain vulnerable to respiratory viral infections. Viral pneumonia has been associated with a mortality rate of 19% in immunocompromised patients.[8] More specifically, conventional coronaviruses have been shown to be associated with higher rates of oxygen requirement and mortality in patients with hematologic malignancies and hematopoietic cell transplant.[9] In one study, coronavirus pneumonia had a 24% mortality in cancer patients compared to 3% in noncancer patients.[10] Furthermore, these patients tend to have frequent prolonged viral shedding.[11]

The immune system is altered in several ways in cancer patients, putting them at increased risk of infection. This can be the result of the specific cancer therapies, extent of disease, or location of primary disease origin. Lymphopenia has been observed in 20% of patients with advanced cancer disease and in 3% of patients with localized disease.[12] Lymphopenia can be seen in a variety of cancer types from pancreatic, melanoma, sarcoma, hepatocellular, non-Hodgkin lymphoma, and colon cancer.[12] In several studies of patients with hematologic malignancies with respiratory viral infections, lymphopenia independently predicted progression to pneumonia.[13–15] Laboratory findings in patients with COVID-19 have included lymphopenia in most hospitalized patients, with nonsurvivors developing more severe lymphopenia over time.[16–18] Platelets also play an important immune system role and have viricidal effects against some viruses.[19] Cancers that invade and displace normal bone marrow, such as leukemia or lymphoma, can lead to thrombocytopenia and an associated immunocompromised state.

An effective immune response against viral infections depends on the activation of T cells that help clear the infection. In a recent study of COVID-19 patients, over 70% nonintensive care unit (ICU) cases had decreased total T cells, whereas 95% of ICU patients had decreases in total T cells.[20,21]

THERAPIES CONTRIBUTING TO IMMUNOCOMPROMISED STATE

Chemotherapy

Use of corticosteroids and immunosuppressive therapy are risk factors for severe respiratory viral infections.[22] Chemotherapy damage to bone marrow cells can lead to thrombocytopenia and neutropenia, rendering patients more susceptible to infections. Patients are at greater risk during their nadir period when their neutrophil numbers are the lowest. This nadir occurs 7–12 days after completion of each dose of chemotherapy and can sometimes last up to 1 week.[23] Most chemotherapeutic agents can depress the immune system, but cytotoxic agents that cause bone marrow suppression, such as temozolomide, cyclophosphamide, paclitaxel, methotrexate, and alemtuzumab, can increase infection risks for cancer patients. Of the chemotherapy drugs, cyclophosphamide, cisplatin, methotrexate, fludarabine, and taxes are among the most potent agents that result in lymphopenia.[12]

Since limited data are available to estimate mortality risk in patients who undergo chemotherapy and become infected with SARS-CoV-2, 1 article used modeling to extrapolate this risk. They found that most cancer patients have a >5% mortality risk if infected with SARS-CoV-2 and that older patients with solid tumors have a greater risk, with harm likely to outweigh the benefit for most chemotherapy in most patients.[24] Recommendations have been made to postpone adjuvant chemotherapy for stable cancer in active pandemic

areas. Based on limited data, decisions about initiating or continuing cytotoxic chemotherapy will need to be considered individually and carefully.

Radiation Therapy

Radiation treatment can affect the immune system. High-dose body irradiation is a significant risk factor for progression to lower respiratory tract infection with respiratory syncytial virus (RSV) in hematopoietic cell transplant patients.[25] Lymphocytes are affected by external beam radiation, resulting in radiation-induced lymphopenia. Because lymphocytes are exposed through the irradiated field, there is a direct toxic effect. This phenomenon has been reported to occur in 40%–70% of patients undergoing conventional external beam radiation therapy.[12,26] This risk can be mitigated by using proton beam therapy, stereotactic body radiation, or a hypofractionated schedule.[12] There are no clear guidelines on continuing or initiating radiation therapy during the COVID-19 pandemic, and each case should be reviewed on an individual level with a risk-benefit analysis.

Immunotherapy

Immunotherapy to treat certain cancer types include immune checkpoint inhibitors, T-cell transfer therapy, vaccines, and immune-modulating agents.[27] There are no well-defined guidelines for continuing or initiating immunotherapy during the COVID-19 pandemic. However, some side effects of this therapy may serve as a guide in decision making. The basis of these side effects is due to hyperactivated T-cell response with reactivity directed against normal tissue.[27] Immune checkpoint inhibitors have rare side effects of thrombocytopenia and pneumonitis T-cell transfer therapy, consists of tumor-infiltrating lymphocytes (TIL) and chimeric antigen receptor (CAR) T-cell therapy. Side effects for TIL include prolonged lymphopenia, and CAR T-cell therapy can lead to cytokine release syndrome.[27–29] Cancer vaccines are associated with minimal toxicity.[27] Finally, certain immune-modulating agents can cause thrombocytopenia, anemia, leukopenia, and vascular permeability leading to pleural effusion or pulmonary edema.[27] Interestingly, some immune-modulating agents that diminish inflammation during infection have shown therapeutic promise in mice models infected with various influenza strains.[30]

Bone Marrow Transplant

Severity of viral respiratory disease, with the highest morbidity and mortality, has been observed in patients with hematopoietic stem cell transplant (HSCT).[15,31] This treatment essentially eliminates the host immune system and replaces it with a donor's. These patients are most vulnerable for infection during the first 3 months after transplant, with recovery to baseline extending up to 1 year in some cases.[32]

CANCER PATIENTS AND INFECTIOUS RISK

Specific cancer patients are at particularly high risk for infections due to their cancer type and treatment. Patients with blood malignancies involving immune system cells, such as lymphomas, aplastic anemia, myelomas, and most leukemias, are vulnerable to infection by virtue of their cancer. Janus kinase inhibitors (JAKi) and Bruton tyrosine kinase inhibitors (BTKi) used in the treatment of certain cancers, including leukemias and lymphomas, can also cause immunosuppression by inhibiting cytokine and growth factor signaling pathways and inhibition of B-cell maturation, respectively.

Nosocomial infections are more common in cancer patients who are at increased risk for viral, bacterial, and fungal pathogens.[33–35] While patients are hospitalized, they are susceptible to various respiratory infections such as human RSV, influenza A and B viruses, parainfluenza virus, and human metapneumovirus. Patients who have undergone HSCT and then acquired parainfluenza viruses with lower respiratory tract involvement had a 40% greater likelihood of respiratory failure and death.[34] In addition, HSCT patients who have community-acquired pulmonary viral infections can have severe lower respiratory tract involvement, late airway outflow obstruction, and multiple fungal and bacterial coinfections.[36]

Postsurgical infection is a common but often severe complication in cancer patients. Depending on the type, location, tumor size, lymph node involvement, and organ involvement, subsequent infectious complications can range from minor to moderate or severe.[37] Bevacizumab, an angiogenesis inhibitor that works by blocking vascular endothelial growth factor (VEGF), can cause significant delays in wound healing and obligates timed surgical resection for various cancers. Type of surgery and tumor location can also have significant effect on postoperative infection. Oral and maxillofacial tumor resection with complex reconstructions, radical neck dissections, prolonged length of surgery (>6 hours), and need for blood transfusion were associated with an infection rate of >12%.[38]

Younger cancer survivors often have more robust reconstituted immune systems compared to older survivors; however, survivors at any age have higher rates of infectious complications compared to their noncancer counterparts. Cancer survivors were more likely to be hospitalized for respiratory infections[39] with increasing particulate matter pollution;[40] were at least 2 times more likely to develop sepsis;[41] and had increased infectious-related mortality rates.[39]

Cancer patients with SARS-CoV-2 infection may have increased morbidity and mortality from COVID-19 than noncancer patients with SARS-CoV-2 infection. Liang et al[6] reported a Chinese nationwide analysis of cancer patients with SARS-CoV-2 infection. In their

analysis of 1590 COVID-19 cases, they included 12 patients with cancer history, 2 patients with unknown cancer treatment, and 4 patients with recent cancer treatment. These cancer patients were older with history of smoking, dyspnea, and more advanced computed tomography (CT) scan findings than those without cancer. They reported that 7 of these 18 patients had higher risk of severe events (ICU admission, mechanical ventilation, death); 3 of 4 patients who had recent cancer treatment experienced severe events; and patients with cancer exhibited faster clinical deterioration (13 vs 43 days). The small study sample size, age bias (63 years in cancer group versus 48 years noncancer group),[42] and higher rate of smoking in the cancer cohort[7] limited the external validity (generalizability) of the findings.

In a recent study, Williams et al[24] created models that estimated mortality risk of age-matched cancer patients with COVID-19 infection. The article was based on data from the Chinese CDC, Italian public health authorities, and the cohort on the Diamond Princess cruise ship. Williams et al[24] demonstrated a strong effect of age on mortality (>15% for those >70 years) and increased CFR due to cancer and chemotherapy. They conclude that cancer patients have >5% mortality compared to cancer-free patients and that this increase in mortality is greater than any purported aggregate benefit of solid tumor chemotherapy.

The malignancies with the most severe immune deficits are likely at greatest risk and include lymphomas, leukemias, and multiple myelomas. Severity of viral respiratory disease with the highest morbidity and mortality was found in patients with myelosuppression and hematopoietic cell transplant.[15,31] Risk factors for lower respiratory tract disease included age >50 years, graft versus host disease, corticosteroid use, neutropenia, lymphopenia, and hypoalbuminemia.[43,44] An effective immune response against viral infections depends on the activation of T cells that assist in clearing the infection.

Approximately 3.3 million cases of tobacco-associated cancer were reported in the United States during 2010–2014, with lung cancer accounting for about one-third of these cases. The majority are also diagnosed with chronic obstructive pulmonary disease.[45] One prospective cohort study determined the most frequent type of cancer among COVID-19 patients was lung cancer (28% of COVID-19 cases).[6]

Recent data demonstrated a significantly higher angiotensin-converting enzyme 2 (ACE2) gene expression in former smoker's lung compared to nonsmoker's lung.[46] SARS-CoV-2 binds to the host cell receptor, ACE2, which is a critical step for viral cell entry.[5,47] The ACE2 enzyme is an important regulator of the immune response, particularly in acute lung injury.[48] Murine studies have observed that overexpression of ACE2 leads to a protective effect against acute lung injury.[48,49] Possible mechanisms include a proliferation of receptors for virus binding, leading to greater risk, or perhaps that increased gene expression confers a protective immunologic mechanism. Further investigation is needed to determine whether smokers are at greater risk of acute lung injury after viral infection.

PERIOPERATIVE MANAGEMENT OF THE CANCER PATIENT WITH COVID-19

Perioperative management of the patient with suspected or confirmed COVID-19 focuses on several aspects, including regional and institution-specific factors; patient, community, and employee safety; and conservation of resources such as staff, hospital beds, equipment, and supplies.

As of March 2020, organizations such as the American College of Surgeons and the Ambulatory Surgery Center Association have provided guidance for the management of nonemergent surgical procedures in the setting of COVID-19. If a procedure can be safely postponed without significant risk to the patient, it should be delayed until after the pandemic.[50,51]

Cancer patients pose unique management dilemmas during viral pandemics like COVID-19 because cancer is a life-threatening disease process. While cancers vary in natural history, prognosis, and mortality rates, all patients regardless of cancer type struggle with feelings of anxiety and fear that can only be alleviated with the relief and hope that come from medical and surgical treatment. Hence, according to tools like the Elective Surgery Acuity Scale (ESAS) used for the triage of nonemergent operations, most cancer surgeries are considered of high acuity and should proceed as planned assuming resource availability.[50,51]

Certain procedures and surgeries (eg, otolaryngology, dental, pulmonary, and gastroenterology) are high risk for aerosolizing virus regardless of cancer status. Many professional societies have released statements on delaying, restricting, rescheduling nonurgent procedures.[52–55] Considerations should always be made to avoid high-risk aerosolizing procedures. If such cases must proceed due to life-threatening circumstances, all providers involved in care should be attired with appropriate personal protective equipment (PPE) such as N95 masks, eye protection, water-resistant gowns, and gloves, and furthermore, such procedures should be performed in negative pressure rooms when available.

Preoperative Phase

Care must be taken preoperatively to closely screen patients for influenza-like symptoms before their arrival to the hospital. This may be done with a telephone call before hospital arrival, in addition to screening on hospital admission. The number of caregivers having direct contact with each patient should

be limited to only those necessary throughout the perioperative period.

Intraoperative Phase

A patient with suspected or confirmed COVID-19 requiring emergency surgery should avoid a preoperative holding area and instead be transported directly to a designated operating room (OR), preferably in a mobile isolation unit. Signs should be posted on all OR entry points, and all attempts should be made to minimize health care staff exposure by ensuring that only required staff remain in the OR.[56]

PPE is essential for health care providers throughout the perioperative period to ensure airborne/droplet/contact isolation precautions can be achieved. Full PPE for airway manipulation includes a fit-tested, disposable N95 respirator or a powered air-purifying respirator (PAPRs), goggles, face shield, water-resistant gowns, double gloves, and protective footwear. Protocols for donning and doffing of PPE must be strictly adhered to.

The most experienced anesthesia provider should perform the intubation, especially if the patient is severely ill. Video laryngoscopy should be considered and adequate paralysis ensured before intubation to avoid aerosol generation through bucking and coughing.[56]

Postoperative Phase

Patients with suspected or confirmed COVID-19 should not be transferred to a postanesthesia care unit (PACU). These patients should be recovered in the OR or transferred directly to an airborne isolation infection room. To minimize contamination, heat and moisture exchanging filter (HMEF), which can remove airborne particles of 0.3 μm or greater, should be applied to the endotracheal tube during transfer.[56] After the patient has left the OR, as much time as possible should be allowed before subsequent patient care (for optimal decontamination of the OR).[57]

Visitor policy may be fluid, with restrictions ranging from limitations on number of visitors per patient to a strict no-visitor policy. These will be determined by federal and state mandates. Exceptions may be considered for special situations, such as end-of-life and pediatric care.

CURRENT TREATMENT OF THE CANCER PATIENT WITH COVID-19

To date, treatment of most patients with COVID-19 centers on supportive measures. Several treatment modalities are currently available for COVID-19 patients. While all existing therapies are still investigational, certain drugs have proven helpful.[1]

Overall, treatment is determined by infection severity and patient comorbidities. Patients with mild infections and self-limiting courses can recover uneventfully with home management. The focus for these patients should be isolation and prevention of spread to others.[1] Patients with moderate symptoms and pneumonia may require hydroxychloroquine and azithromycin in addition to supportive care (Table 1).

Table 1. Drug Therapies for Patients With COVID-19

	Treatment Recommendations	
Drug	**Description and Indication**	**Considerations**
Hydroxychloroquine (Plaquenil; Concordia Pharmaceuticals Inc, St Michael, Barbados) and chloroquine (Aralen; Sanofi-aventis US LLC, Bridgewater, NJ)	- First-line treatment antiviral agents - Treats moderate infection - Treats associated pneumonia - Treats critically ill awaiting Remdesivir (or those who do not qualify)	- Caution in patients with diabetes mellitus due to glucose fluctuation - Caution in patients at risk for QT prolongation

Remdesivir	- Second- line treatment antiviral agent
	- Investigational, requires approval
	- Treats severe infection
		- Inclusion criteria
		  - confirmed diagnosis
		  - hospitalization
		  - mechanical ventilation
		- Exclusion criteria:
		  - multiorgan failure
		  - pressor requirement
		  - ALT level >5× norm
		  - CrCl <30 mL/min or dialysis
		  - concurrent use with other antivirals

Hydroxychloroquine + azithromycin	- Combination shortens duration of infection - Potentially more effective than hydroxychloroquine alone	- Same as for hydroxychloroquine alone - Azithromycin has moderate drug- drug interactions - Azithromycin may pose extra risk to patients with preexisting cardiac disease - Caution in patient at risk for QT prolongation - Caution in patient with cardiac dysrhythmias
Lopinavir/ritonavir	- Supplementary antiviral agents - Treat moderate to severe infections	- Monitor LFTs - Monitor GI (diarrhea)

Abbreviations: ALT, alanine aminotransferase; COVID-19, Coronavirus Disease 2019; CrCl, creatinine clearance; GI, gastrointestinal; LFTs, liver function tests.

Table 2. Additional Drug Therapies for Patients With COVID-19

Drug	Treatment Recommendations: Description and Indication	Considerations
Tocilizumab	- Supplementary immunosuppressive - IL- 6 receptor antagonist - Treats severe infection with cytokine release syndrome	- Monitor CBC - Caution in immunosuppressed - Caution with concurrent fungal or bacterial infections
Interferon B-1a	- Supplementary anti- inflammatory immunomodulator - Treats severe, worsening, or refractory infection	- Monitor CBC - Caution in immunosuppressed - Caution with concurrent fungal or bacterial infections
Convalescent plasma	- Immunoglobulin suppresses viral load - Treats severe, refractory infection - Last resort drug to reduce mortality	- No specific adverse events - Same precautions as administering any blood product

Abbreviations: CBC, complete blood count; COVID-19, Coronavirus Disease 2019; IL-6, Interleukin 6.

While anecdotal, hydroxychloroquine and azithromycin have shown potential in both prophylaxis and treatment of patients with COVID-19. Of note, combination of drugs appears to reinforce the beneficial effect and significantly decreases viral load, thereby reducing the length of the infection.[58,59] If bronchodilators are needed for moderate infections, a metered dose inhaler is recommended instead of nebulizer treatments so as to limit viral spread. Remdesivir and lopinavir/ritonavir are currently recommended for patients with severe symptoms, including ARDS, and requiring mechanical ventilation (Table 1).[1,60] Patients with severe symptoms and cytokine release syndrome (ARDS with acute lung injury and high levels of inflammatory markers) should be started on tocilizumab.[1] In the most refractory severe infections with worsening symptoms, interferon B-1a and convalescent plasma should be considered (Table 2).[61–63]

As previously mentioned, the cancer patient with an immunocompromised state is more likely to present with more severe disease states like pneumonia and ARDS that may warrant intubation and mechanical ventilation with consideration of aforementioned drug therapies.[1] Special caution must be taken in immunosuppressed cancer patients when prescribing tocilizumab and interferon B-1a, and recommendations should be made on an individual basis.[1]

The US CDC recommends avoiding steroids during COVID-19 treatment, and the American Heart Association (AHA) recommends continuing angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for all patients already prescribed these medications.[1,64,65] Perioperatively, it is important to continue all prescribed treatment medications and understand associated considerations.

CONCLUSIONS

Our review on COVID-19 and the cancer patient is based on the latest information and knowledge available to the medical community at this time. As the COVID-19 pandemic continues to evolve and unfold, it is likely that the health care community will be faced with additional, yet unknown challenges.

It is imperative that we stay abreast of all developments with COVID-19 to protect ourselves as frontline health care providers and to provide our most vulnerable patients with the care needed for their best chance of survival and return to optimal health. ■

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