

Considerations for the Management of Oncology Patients During the COVID-19 Pandemic

Julie Huang, DO*; Abhinav Rohatgi, MD*; Jeffrey Schneider, MD; and Marc Braunstein, MD, PhD

*Authors contributed equally to this manuscript

ABSTRACT: Worldwide incidence and mortality due to the coronavirus disease 2019 (COVID-19) pandemic is greatest in the United States, with the initial epicenter in New York. In Nassau County, New York, where we practice, our institution has had more than 2500 cases and has discharged from the hospital more than 1000 patients. As many academic and private institutions have swiftly shifted their clinical and research priorities to address the pandemic, data are emerging regarding both the impact of malignancy on COVID-19 outcomes as well as the challenges faced in assuring that cancer care remains unimpeded. Of concern, recent studies of cancer patients primarily in China and Italy have suggested that advanced malignancy is associated with increased susceptibility to severe COVID-19 infection. At present, more than 500 clinical trials are underway investigating the pathogenesis and treatment of COVID-19, including expanded use of oncology drugs, such as small molecular inhibitors of cytokine pathways. Here, we begin by reviewing the latest understanding of COVID-19 pathophysiology and then focus our attention on the impact of this virus on hematologic and oncologic practice. Finally, we highlight ongoing investigational treatment approaches that are so relevant to the care of oncology patients during this extraordinary pandemic.

Introduction

The 2019 novel coronavirus severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus that was first reported in Wuhan, China, in December 2019,¹ and it is responsible for coronavirus disease 2019 (COVID-19). COVID-19 is highly contagious, spreading by droplets, respiratory secretions, and direct contact. Its symptoms can include bilateral interstitial pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and, ultimately, multiorgan failure.^{2,3}

The virus has since rapidly spread to more than 100 countries and was declared a pandemic on March 11, 2020, by the World Health Organization.⁴

As of September 9, 2020, there were 27,699,974 confirmed cases of COVID-19 with 18,636,426 recovered and 900,239 deaths worldwide. In the United States, there were 6,358,983 confirmed COVID-19 cases; New York was a major epicenter, reporting 441,154 cases and 33,013 deaths.⁵ The numbers of new cases are still increasing across the United States, but they have

declined dramatically in New York, likely consequent to the adoption of social distancing measures.

While many therapeutic strategies are currently being evaluated as possible COVID-19 treatments, there are currently no highly effective antiviral therapies or vaccines available to combat this virus, and mortality in severe disease remains high.⁶ Risk factors for severe illness resulting from COVID-19 are age greater than 65 years, diabetes, chronic lung disease, and obesity,⁷ and cancer patients who contract COVID-19, in

TABLE 1. Review of Published Literature on Cancer Patients and COVID-19

PubMed ID	Journal	Country	Cancer and COVID-19 population (% of total population studied)	Major finding(s)
32066541	<i>Lancet Onc</i>	China	18 (1%) PWC; 28% lung	Composite ICU/death rate: 39% in PWC vs 8% in general population (P = .0003)
32211820	<i>JAMA Onc</i>	China	12 (0.8%) PWC	Most PWC studied had non–small cell lung cancer
32224151	<i>Ann Oncol</i>	China	28 PWC; 25% lung	54% of PWC had severe events; mortality rate, 29%. Chemotherapy within 14 days had a hazard ratio of 4.1 for severe COVID-19
32332856	<i>Leukemia</i>	China	13 (10%) patients with hematological malignancies	Hematological cancer patients had more severe COVID-19 and more deaths (62%) than health care providers with COVID-19 (0%)
32345594	<i>Ca Discov</i>	China	105 PWC vs 536 controls, all with COVID-19	Patients with hematologic or lung cancers, or with stage IV cancers, had the highest frequency of severe COVID-19
32460829	<i>Breast Ca Res</i>	France	59 patients with early or metastatic breast cancer	COVID-19 mortality rate in breast cancer depended more on comorbidities than prior radiation or current anticancer therapy
32203977	<i>JAMA</i>	Italy	87 (25%) PWC who died	24% (87) of these were cancer patients
32250659	<i>JCO Global Onc</i>	Meta-analysis	11 studies; 3661 total PWC	Incidence of all PWC with COVID-19 was 2%-3%
32511470	<i>medRxiv</i>	Meta-analysis	31 studies; 23,736 PWC	Mortality was highest in hematological malignancies (OR, 2.43) followed by lung cancer (OR, 1.8)
32449128	<i>Clin Tran Onc</i>	Spain	45 PWC	Mortality 42% in PWC vs 13% in general population
32505076	<i>Lung Ca</i>	Spain	17 (0.9%) PWC, all lung	Lung cancer patients with COVID-19 had higher mortality than the general population
32473682	<i>Lancet Onc</i>	United Kingdom	800 PWC with COVID-19	226 (28%) of PWC died, with risk of death increased with advancing age, male sex, comorbidities such as hypertension, and receiving cytotoxic chemotherapy within 4 weeks of COVID-19 positivity
32330541	<i>Ann Oncol</i>	US	334 patients (6%); 40% with breast, lung, or prostate cancer	Relative risk of intubation in PWC was 1.9, but there was no difference in death compared with general population
32357994	<i>Cancer Discov</i>	US	218 PWC	37% patients with hematologic malignancies had higher mortality compared with 25% with solid tumors
32561401	<i>Ann Oncol</i>	US	102 PWC, all lung	COVID-19 was severe in patients with lung cancer (62% hospitalized; 25% died)

COVID-19, coronavirus disease 2019; ICU, intensive care unit; OR, odds ratio; PWC, patients with cancer.

particular, have been shown to have worse outcomes.⁸

In the initial experience reported from Wuhan, China, 1% of cancer patients were noted to contract COVID-19, compared with just 0.29% incidence in the general population.⁸ This may be attributed to greater detection rates in more closely surveilled cancer patients, but it could also be associated with nosocomial exposures and diminished im-

mune defenses.⁸ Cancer patients were also observed to be at higher risk for the development of severe COVID-19, which may be due to generally advanced age, increased prevalence of tobacco use, and higher incidence of comorbid pulmonary disease.⁹ Liang et al also demonstrated that cancer patients were more likely to require intensive care or experience mortality as compared with other COVID-19 patients (39%

vs 8%).⁹ Cancer treatment may also increase COVID-19 susceptibility. In a small subset of patients reported by the National Health Commissions of the People’s Republic of China, those cancer patients who had undergone recent chemotherapy or surgery were observed to have a 75% likelihood of developing COVID-19 illness as compared with a 43% incidence in other cancer patients.⁹ However, this study by Liang et al

included only 18 patients (1%) of 1590 COVID-19 cases had a history of cancer, making it difficult to make meaningful conclusions based on the small proportion of cancer patients included. Other studies, while also underpowered, have similarly suggested that patients with cancer are at greater risk for severe COVID-19.¹⁰

Patients with lung cancer and those with hematologic malignancies appear to be most vulnerable to COVID-19, presumably due to diminished pulmonary reserve in the former and immunodeficiency in the latter.¹¹ In a report of 28 patients with cancer infected with SARS-CoV-2 in 3 Wuhan hospitals, 7 (25%) were noted to have lung cancer, 4 (14%) had esophageal cancer, and 3 (10.7%) had breast cancer.¹⁰ Severe hypoxia and devastating viral infection in lung cancer patients has been attributed to compromised baseline pulmonary function. Patients with stage IV cancers were also noted to experience severe COVID-19 infection (70%) more often than earlier-stage patients (44%).¹⁰ While cancer patients with COVID-19 infection often presented with typical symptoms of fever, dry cough, fatigue, and dyspnea, they were also noted to have atypical presentations, notably including anemia and hypoproteinemia. This may be secondary to nutritional deficiency associated with their cancer, which affects their immunocompetency to combat respiratory pathogens.¹⁰ As summarized in **Table 1**, available data suggest that cancer patients have poorer outcomes from COVID-19 illness, prompting the publication of specific guidelines on how to manage cancer patients during this crisis.^{11,12}

COVID-19 has also been associated with increased incidence of thromboembolic disease attributed to clinical hypercoagulability. For example, a study conducted in Tongji Hospital in Wuhan, China, evaluated 183 patients from January to February 2020 and showed that of the 21 who died from COVID-19, 15

(71.4%) met criteria for overt disseminated intravascular coagulation (DIC) (≥ 5 points based on the International Society on Thrombosis and Hemostasis criteria),¹³ had significantly higher D-dimer and fibrinogen degradation product levels, and longer prothrombin times on admission, compared with survivors.¹⁴ Another study at Union Hospital in Wuhan reported a 25% incidence of lower extremity deep venous thrombosis in patients with severe COVID-19 pneumonia in ICU, with high (40%) subsequent mortality. This same report also suggested that since COVID-19 can decrease lymphocyte count, this may lead to immune dysfunction and a higher risk of venous thromboembolism due to poor immunity and DIC.¹⁵ Hypercoagulability in COVID-19 may also be due to the dysfunction of endothelial cells caused by infection that promotes thrombin formation and inhibits fibrinolysis.¹³ Some patients who died from COVID-19 were reported to have ischemic changes, with ecchymosis of their fingers and toes due to hypercoagulability from DIC and the development of microthrombi.¹⁶

Li et al proposed that early anticoagulation with low-molecular-weight heparin (LMWH) and intravenous immunoglobulins (Igs) would block the clotting formation seen in DIC and inhibit cytokine release storm (CRS), respectively.¹⁶ They recommend empiric anticoagulation for patients with D-dimers greater than 4 times the upper limit of normal range in the absence of contraindications. Lin et al recommend LMWH at 100 U/kg every 12 hours for at least 3 to 5 days.⁸ In addition, a study performed in Tongji Hospital in Wuhan reviewed 449 patients with severe COVID-19, with 94 patients receiving LMWH (40-60 mg/day) and 5 receiving unfractionated heparin (1000-15,000 U/day) for 7 days or longer; the results showed that the 28-day mortality for LMWH or unfractionated heparin users with a sepsis-induced coagulopathy score of ≥ 4

and D-dimers >6 times the upper limit of normal was lower than that of non-LMWH or unfractionated heparin users.¹⁴ This has led several institutions, including our own, to institute anticoagulation protocols based on various parameters such as D-dimer levels.¹⁷

Pathophysiology of COVID-19

Coronaviruses are large, single-stranded, positive-sense RNA strand that encapsulate within a membrane envelope surrounded by glycoprotein spikes, forming a crown-like appearance.¹⁸ Less-pathogenic endemic human coronaviruses such as OC43, HKU1, NL63, and 229E exist, causing seasonally, self-limited upper respiratory symptoms.¹⁹ In contrast, more severe respiratory symptoms are caused by zoonotic human coronaviruses, including severe acute respiratory distress syndrome coronavirus (SARS-CoV) discovered in November 2002 in Guangdong, China; Middle Eastern respiratory syndrome-related coronavirus (MERS-CoV) identified in 2012 in Saudi Arabia; and COVID-19.¹⁸ The subfamily, Coronavirinae, is divided into 4 classes of coronaviruses: α , β , δ , and γ . Sequencing data from SARS-CoV-2 share high degrees of homology—87.9% and 87.2%—with β coronavirus from Chinese bats, bat-SL-CoVZC45 and bat-SL-CoVZXC21, respectively.¹⁸ In comparison, SARS-CoV-2 is less genetically similar to its zoonotic human coronavirus counterparts, with 79% homologous to SARS-CoV and 50% homologous to MERS-CoV.¹⁸

SARS-CoV and SARS-CoV-2 contain structural proteins, including glycosylated spike (S) protein, that targets angiotensin-converting-enzyme 2 (ACE2) on the surface of host cells. Upon entry into the membrane, the viral genome is released as a single-stranded, positive-sense RNA and is translated into viral polyproteins (pp1a and pp1ab) and cleaved by effector proteins, (viral proteinases 3CLpro and PLpro).^{2,18} Type II pneumocytes and the apical surface of ciliated airway epithelial cells within lungs express ACE2, which

is a negative regulator in the renin-angiotensin system. ACE2 has been shown to promote anti-inflammatory and anti-fibrotic effects, and it protects these cells from ARDS.¹⁹ In SARS-CoV-2, ACE2 ectodomain can shed as a result of spikes

from the viral glycoprotein, reducing the catalytic function of ACE2 and promoting ARDS.¹⁹ In addition, SARS-CoV-2 has been shown to reduce synthesis of interferon- α and interferon- β and to increase inflammatory cytokines and

chemokines.²⁰ In lung adenocarcinomas, ACE2 gene expression has been higher in malignant as compared with normal lung tissue, especially in the proximal proliferative subtype. On the other hand, most squamous lung cancers exhibit

TABLE 2. Cancer-Directed Therapies Observed in the Past to Be Efficacious Against SARS-CoV and MERS-CoV

Name of drug	Class of drug	Drug used in type of cancer	Mechanism of action	Adverse effects	Potential action against coronavirus
Carfilzomib ²⁹	Protease inhibitor	Multiple myeloma	Inhibits protease to cause cell destruction	Peripheral neuropathy	Potential inhibitor of COVID-19 protease
Gemcitabine hydrochloride ³⁰	DNA metabolism inhibitor	Pancreatic cancer, bladder cancer	Inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, cell cycle-specific for the S-phase of the cycle	GI distress, peripheral edema, anemia, neutropenia, thrombocytopenia.	Inhibition of viral replication
Imatinib ²⁷	TKI	CML, GIST, Ph+ ALL	Targets Abl kinase portion of BCR-Abl protein	Pancytopenia, nausea, diarrhea, skin rash and fevers	Reduces SARS-CoV and MERS-CoV viral titers and prevents its entry by HIV SARS S and MERS S pseudotyped virions
Nivolumab ³² Ipilimumab ³²	PD-1 inhibitor CTLA-4 inhibitor	Lung cancer; renal cancer; bladder cancer; melanoma	Inhibits immune inhibitory PD-1 pathway and CTLA-4	Autoimmune hypophysitis, thyroiditis, colitis, hepatitis, nephritis; fatigue and rashes, diarrhea	Checkpoint blockade would potentially increase the threshold of CD8+ T cell activation by immunogenic viral peptides thus improved early immune response
Ruxolitinib ²⁵ Baricitinib ²⁵	JAK inhibitor	Myelofibrosis; polycythemia vera; chronic neutrophilic leukemia; acute GVHD	Inhibition of JAK 1 and JAK 2 proteins	Diarrhea; anemia; thrombocytopenia; neutropenia	Anti-JAK1 inhibitory action to reduce pro-inflammatory cytokines such as IL-2, IL-6, and TNF- α ; reduce receptor mediated endocytosis
Saracatinib ²⁸	TKI	Discontinued in phase 2 trial in breast cancer due to lack of efficacy	Inhibitor of Src-family of tyrosine kinases	Fatigue, elevated liver enzymes, nausea, hyponatremia	Inhibits MERS-CoV at early stages in Huh-7 cells through suppression of SFK signaling pathway
Sunitinib ²⁶ Erlotinib Fedratinib	TKIs EGFR inhibitor JAK inhibitor	Renal cancer Lung cancer Myelofibrosis	Prevents tyrosine kinase signaling, resulting in cell death	Fatigue, rashes, GI upset	Inhibits AP2-associated protein kinase 1 (AAK1) which is a regulator of endocytosis in AT2 lung cells thus preventing viral entry ²⁶
Tamoxifen ³⁰	Estrogen receptor inhibitor	Breast cancer	Selective estrogen receptor modulator that competitively binds to estrogen receptors on tumors and other tissue targets	Fatigue, hot flashes, risk of venous thrombosis and ischemic heart disease	Inhibition of viral replication, off target effects
Tocilizumab ⁴¹ Sarilumab ⁴¹ Siltuximab ⁴¹	IL-6 receptor antagonist	CRS from CAR T-cell therapy or BiTE therapy	Antagonist of the IL-6 receptor	Increased LFTs, cholesterol, infusion-related reaction	Decrease COVID-19induced hyperinflammation by reducing endogenous IL-6

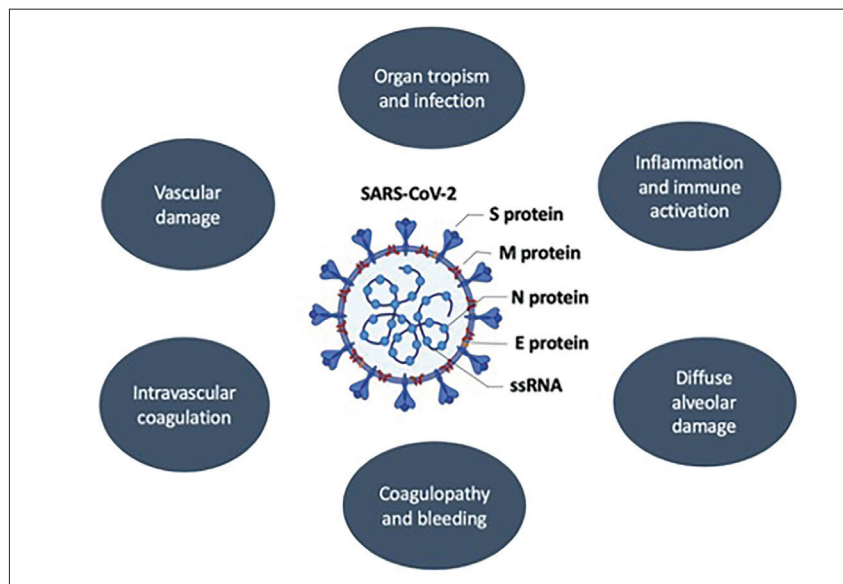
BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CML, chronic myeloid leukemia; CRS, cytokine release storm; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; GVHD, graft-versus-host disease; IL, interleukin; LFT, liver function tests; MERS-CoV, Middle Eastern respiratory syndrome-related coronavirus; Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukemia; S, glycosylated spike; SARS-CoV, severe acute respiratory distress syndrome coronavirus; TKI, tyrosine kinase inhibitor.

similar ACE2 expression in both normal and malignant cells. One exception is the primitive subtype of squamous cell lung cancer, in which ACE2 expression has been shown to be higher in normal cells as compared with their adjacent malignant counterpart cells, which has been associated with increased susceptibility to SARS-CoV-2 infection in this particular subpopulation.²¹ A summary of the pathophysiologic mechanisms of SARS-CoV-2 is shown in **Figure 1**.

Investigational Agents for COVID-19

Treatment approaches for COVID-19 are continually evolving and there is currently no consensus therapeutic approach. Severe infection in COVID-19 is characterized by a CRS, rich in highly proinflammatory cytokines such as interleukin (IL)-1 and IL-6. Critically ill patients infected with COVID-19 often suffer from multiorgan dysfunction, including respiratory failure, renal failure, and eventually cardiovascular collapse, leading to death. Oncology patients are especially vulnerable to this disease due to their overall frailty and immunocompromised state. A large number of antiviral therapies, including remdesivir, are under investigation, and as described below, several oncology drugs are also being repurposed to target COVID-19.

Anticytokine strategies. Because critically ill patients may be most challenged by endogenous cytokine release, even after viral eradication a large focus of attention has been focused upon the use of an agent to directly neutralize the CRS. Tocilizumab, an anti-IL-6 monoclonal antibody used to manage CRS associated with chimeric antigen receptor T-cell therapy, has been studied to suppress the toxic proinflammatory response in COVID-19. IL-6 may be a particularly important target, because increased IL-6 levels are released from the injured pulmonary bronchial and alveolar epithelial cells seen in ARDS²² and IL-6 levels were directly associated



■ **Figure 1.** Summary of Pathophysiologic Mechanisms of SARS-CoV-2. Viral components involved in pathogenesis of coronavirus disease 2019 include the spike proteins (S) S1 and S2, which adhere to the ACE2 receptor; the matrix protein (M), which allows for bud release; and nucleocapsid (N) and envelope (E), which surround the viral single-stranded RNA (ssRNA) genome and modulate immune evasion.

with the severity of SARS infections. Other cytokines—including IL-2, IL-6, IL-7, IL-10, granulocyte colony stimulating factor, 10 kD interferon γ -induced protein, monocyte chemoattractant protein-1, macrophage inflammatory protein 1- α (MIP-1 α), and tumor necrosis factor (TNF)- α —have all been observed at elevated levels in COVID-19 patients requiring intensive care support.^{2,3} This suggests that steroids or other broad spectrum anti-inflammatory agents may play an important role in the management of catastrophic COVID-19 illness.

Convalescent plasma. Convalescent plasma is theorized to transfer neutralizing antiviral antibodies from patients who have recovered from COVID-19 infection to those who have been more recently infected.²³ Unlike anticytokine strategies, convalescent plasma and other purely antiviral therapies must be given early in the course of COVID-19 illness, and certainly prior to viral eradication. The early experience with convalescent plasma at the Huoshenshan Hospital in Wuhan reported clinical

and radiographic improvement in all 6 selected cases. However, convalescent plasma was administered late in the disease course of all these patients; prior to treatment, 4 of 6 had tested negative for residual virus and 5 of 5 had already tested positive for their own endogenous antiviral antibodies. The authors hypothesized that plasma might promote anti-inflammatory properties to prevent CRS,²³ but it is also possible that these patients might have recovered just as well without plasma therapy. Similarly, Shen et al reported clinical improvement in 5 critically ill COVID-19 patients on ventilators in Shenzhen Third People's Hospital, including extubation and ultimate discharge in 3 of these patients. But again, none of these patients were treated in the first 14 days after viral infection, which is when the introduction of antiviral antibodies is predicted to be most strategic.²⁴ Most recently, the results of a small randomized clinical trial of convalescent plasma versus standard management failed to demonstrate protocol-defined clinical improvement

TABLE 3. Ongoing Clinical Trials Repurposing Cancer-Directed Therapies to Combat SARS-CoV-2⁴⁶

Study identifier	Investigational agent(s)	Hematology/oncology diseases	Mechanism of action	COVID-19 disease hypothesis	Study site(s)
Best-RCT (NCT04305106) CORIMMU-NO-BEVA (NCT04344782)	Bevacizumab in PWCov	Metastatic colorectal cancer, recurrent glioblastoma, NSCLC, ovarian cancer, RCC	Recombinant, humanized mAb, anti-VEGF	Targets VEGF, which has been seen in higher levels in COVID-19 patients, causing hypoxia, severe inflammation, and up-regulation of respiratory epithelium	China France
CALAVI (NCT04346199)	Acalabrutinib in PWCov	CLL, mantle cell lymphoma	Selective, irreversible second-generation Bruton TKI	Decrease in inflammation by Bruton TKI inhibition reduces severity of COVID-19-induced respiratory distress ⁴²	Spain
Copernico (NCT04335305)	Tocilizumab + pembrolizumab in PWCov	Tocilizumab: CRS-related CAR T-cell therapy or BiTE therapy Pembrolizumab: NSCLC, SCLC, urothelial carcinoma	Tocilizumab: anti-IL-6 inhibitor Pembrolizumab: anti-PD-1 humanized mAb	Evaluate recovery of T cell functionality and regulate CRS in COVID-19 pneumonia	Spain
CORIMU-NO19-ECU (NCT04346797) SOLID-C19 (NCT04288713)	Efficacy and safety of eculizumab in PWCov	PNH, atypical HUS	Humanized, monoclonal IgG antibody targets C5	Modulate activity of distal complement, preventing formation of membrane attack complex, allowing for patient recovery	France USA
IMMUNONCOVID (NCT04333914)	Chloroquine vs nivolumab vs tocilizumab in patients with metastatic cancer	Nivolumab: metastatic colorectal cancer, metastatic head and neck, HCC, melanoma, Hodgkin's lymphoma, RCC, NSCLC, urothelial carcinoma Tocilizumab: CRS-related CAR T-cell therapy or BiTE therapy	Nivolumab: anti-PD-1 human IgG4 mAb Tocilizumab: anti-IL-6 inhibitor	Checkpoint blockade would potentially increase the threshold of CD8+ T-cell activation by immunogenic viral peptides, thus improve early immune response ³²	France
NCT04273529 NCT04273581	Efficacy and safety of thalidomide in adjuvant treatment vs placebo in PWCov Efficacy and safety of thalidomide with low-dose hormones vs placebo in PWCov	Multiple myeloma	Increases natural killer cells and IL-2 and INF- γ	Anti-inflammatory action to degrade mRNA in blood cells, reduce TNF- α , increase secretion of ILs, and activate natural killer cells ⁴³	China
NCT04329650 NCT04345445 NCT04330638	Siltuximab vs corticosteroids in patients with COVID-19 pneumonia Tocilizumab vs corticosteroids in PWCov with high risk of progression Anakinra vs siltuximab vs tocilizumab vs standard care in PWCov	Siltuximab: multicentric Castleman disease, multiple myeloma, prostate cancer, ovarian cancer, lung cancer ⁴⁴ Corticosteroids: antiemetic, lymphoma, ITP, multiple myeloma Tocilizumab: CRS-related CAR T-cell therapy or BiTE therapy	Siltuximab: anti-IL-6 Corticosteroids: suppress normal immune response Tocilizumab: anti-IL-6 inhibitor	Use of anti-inflammatory drugs, including siltuximab, at time of hyperinflammation episodes could improve prognosis of PWCov Steroids have been observed to be beneficial in SARS-CoV and prolongs survival time of clinical cases ⁴³ Tocilizumab decreases COVID-19-induced hyperinflammation by reducing endogenous IL-6 ⁴¹	Spain Malaysia Belgium
NCT04331665	Ruxolitinib in PWCov	GVHD, myelofibrosis, polycythemia vera	JAK inhibitor	Ruxolitinib, when given early in the disease, may prevent overproduction of cytokines and thus prevent lung damage	Canada
NCT04349098	Safety and efficacy of selinexor in PWCov	Multiple myeloma	Inhibition of exportin 1	Selective inhibitor of nuclear exportin compounds have the potential to interfere with key host protein interactions with SARS-CoV-2 ⁴⁵	USA

BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; CRS, cytokine release storm; GVHD, graft versus host disease; HCC, hepatocellular carcinoma; HUS, hemolytic uremic syndrome; Ig, immunoglobulin; IL, interleukin; INF, interferon; ITP, immune thrombocytopenic purpura; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PNH, paroxysmal nocturnal hemoglobinuria; PWCov, patients with COVID-19; RCC, renal cell carcinoma; SARS-CoV, severe acute respiratory distress syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

or overall survival improvement at 28 days, but the trial was underpowered, including <10% patients with disease diagnosed within 14 days of randomization. It did demonstrate significantly enhanced viral clearance (90% vs 41% at 72 hours) in the subset of patients who tested positive for active virus at study entry.³

Repurposed antineoplastic agents. Many medications commonly used to treat cancer or cancer therapy–related adverse effects have also been explored for their potential beneficial effects in the treatment of SARS-CoV and MERS-CoV infections. **Table 2** includes commonly used targeted oncology therapies which have mechanisms of actions as well as prior evidence of possible effectiveness in viral inhibition. Ruxolitinib, a JAK1/2 inhibitor, is associated with a decrease in proinflammatory cytokines downstream of JAK1/2 signaling and thereby leads to improved symptoms and quality of life in patients with myelofibrosis. Ruxolitinib also modulates the activity of natural killer cells, dendritic cells, T helper cells, and regulatory T cells, and was shown to be involved in the signaling pathway of proinflammatory cytokines such as IL-2, IL-6, and TNF- α .²⁵ By reducing proinflammatory cytokines, ruxolitinib could be effective in decreasing the CRS in COVID-19 and is being evaluated in clinical trials. Tyrosine kinase inhibitors (TKIs) such as sunitinib, erlotinib, and fedratinib have been found as targets of the AAK1 protein, which is responsible for receptor-mediated endocytosis, the mechanism by which COVID-19 enters lung AT2 cells.²⁶ Imatinib, another TKI, reduces SARS-CoV and MERS-CoV viral titers and prevents cellular entry by HIV SARS S and MERS S pseudotyped virions.²⁷ Saracatinib, a TKI that was discontinued in a phase 2 study in breast cancer, has been observed to inhibit MERS-CoV at early stages in Huh-7 cells, via suppression of the SFK signaling pathway.²⁸ Carfilzomib, a pro-

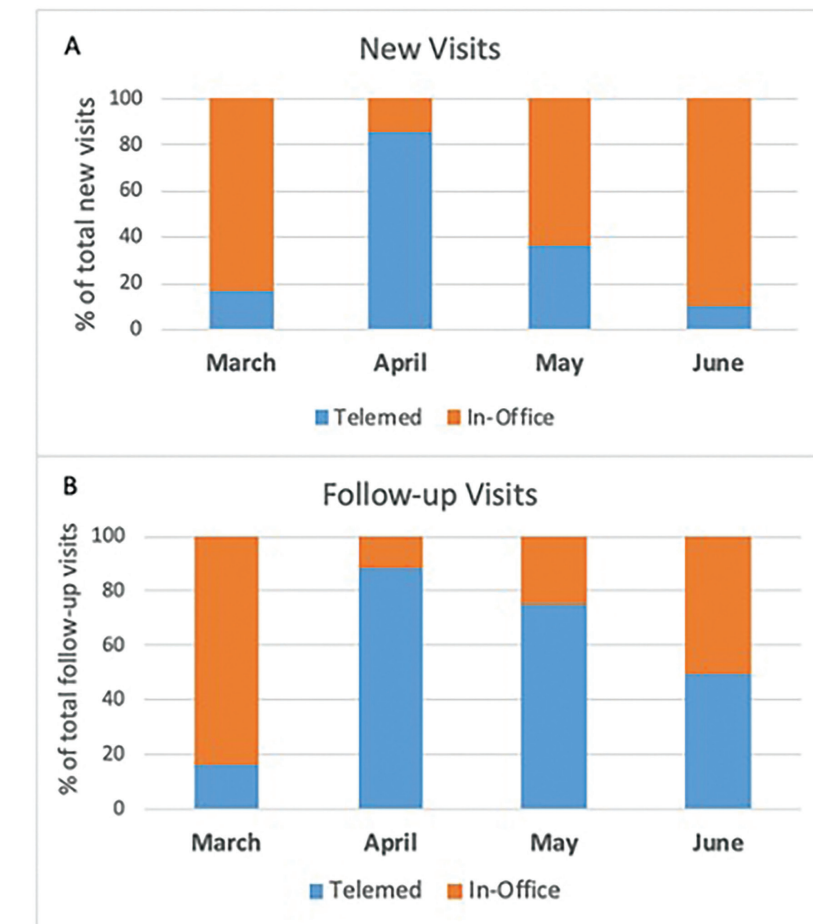


Figure 2. Trend Toward Increased Use of Telemedicine. This trend applied for both new patient and follow-up visits at our institution during the peak of the coronavirus disease 2019 epidemic in New York in April 2020.

tease inhibitor commonly used to treat multiple myeloma, is being evaluated in COVID-19 illness for its potential ability to inhibit viral proteases.²⁹

Estrogen receptor modulators such as tamoxifen represent another class of FDA-approved anticancer drugs that have shown potential activity in both MERS and SARS-CoV. Tamoxifen was identified in a drug screen to have significant antiviral activity; this is likely secondary to off-target effects, as the estrogen signaling pathway doesn't play a role in viral entry. Gemcitabine hydrochloride is a deoxycytidine analogue that inhibits DNA synthesis and repair, and it was found in a drug screen to in-

hibit both MERS-CoV and SARS-CoV, although the mechanism is unclear as these are RNA viruses.³⁰

Many global clinical trials are underway to repurpose existing medications and evaluate the ways in which COVID-19 can be targeted to reduce viral entry or replication, or the excess inflammatory response and CRS (Table 3).³¹ The role of the PD-1/PD-L1 axis, which plays a fundamental role in the evasion of tumor cells from humoral immunity, has been well described in many solid malignancies such as lung cancer, renal cancer, bladder cancer, and melanoma. Viral infections such as HIV, hepatitis C, and hepatitis B also upreg-

TABLE 4. Ongoing Clinical Trials Recruiting Cancer Patients Related to Cancer Management During COVID-19 Pandemic⁴⁶

Study identifier	Cancer	Study investigation	Location
CBP-COVID	Lung cancer	Review consequences of restrictive measures to SARS-CoV-2 in patients with lung cancer in 2020 during COVID-19 from a control, pre-COVID time in 2019	France
CORO-NA-SHIELD (NCT04357574)	Cancer (unspecified)	Assess radiation oncology providers' implementation and perception of tele-medicine for on-treatment PWC	USA
COVIPACT (NCT04366154)	Cancer (unspecified)	Assess coronavirus impact on PWC who are undergoing treatment for cancer	France
EVIDENCE (NCT04367870)	Cancer (unspecified)	Review SARS-CoV-2 testing in PWC	France
GRAVID (NCT04344002)	Lung cancer	Information on clinical features, clinical course, management, and outcomes will be collected for both thoracic cancers and COVID-19 infection.	Spain
NCT04330521	Cancer (unspecified)	Impact of COVID-19 on PWC through a survey	USA
NCT04341012	Hepatocellular cancer	Collect and analyze breath samples in healthy patients, and patients with documented liver disease, an organ transplant, or positivity for COVID-19	USA
NCT04341480	Gynecological cancer	Safety of chemotherapy with gynecological malignancy	China
NCT04345315	Cancer (unspecified)	Testing of COVID-19 in PWC and health care professionals	Italy
NCT04351139	Gynecological cancer	Review modification of gynecological treatment	France
NCT04352556	Hematologic malignancies	Evaluate mortality and predictors for increased mortality of hematological malignancies with COVID-19	Italy
NCT04354701	Cancer (unspecified)	Registry of PWC infected with COVID-19	USA
NCT04369365	Cancer (unspecified)	Prophylactic azithromycin vs placebo in PWC undergoing cancer treatment during COVID-19 pandemic	Austria
NCT04373005	Cancer (unspecified)	Review asymptomatic COVID-19 infection in PWC receiving cancer therapy, as well as immune response and outcome	Canada
ONCOVID (NCT04340219)	Cancer (unspecified)	Review anxiety, mood, and quality of life in PWC during COVID-19 pandemic	Belgium
ONCOVID (NCT04341207)	Locally advanced or metastatic malignancy	Evaluate prevalence and 3-month incidence of SARS-CoV-2 in PWC, and evaluate mortality in PWC treated by hydroxychloroquine and azithromycin	France

COVID-19, coronavirus disease 2019; PWC, patients with cancer; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

ulate PD-1 and PD-L1 during acute and chronic infection, suggesting a potential role for PD-1/PD-L1 antagonists in the treatment of COVID-19 infection.³² However, concern has also been raised regarding the potential for these and other immunostimulatory agents to worsen disease by promoting CRS. The Bruton TKI ibrutinib, which modulates B-cell function, has shown potential to provide protection against COVID-19–induced lung injury in a small subset of patients with lymphoplasmacytic lymphoma.³³ Other drugs approved for the

treatment of hematologic and oncologic conditions that are being actively investigated for their potential benefits in COVID-19 illness include bevacizumab, an anti-VEGF used in multiple cancer therapies; eculizumab, an IgG antibody targeting C5 for paroxysmal nocturnal hemoglobinuria; and selinexor, an inhibitor of exportin 1 used in refractory multiple myeloma.

Logistical Modifications to Cancer Care During the COVID-19 Pandemic

Outpatient visits. At the peak of the pandemic between March and April 2020, upward of 97% of inpatient admissions at our institution were patients with confirmed or suspected COVID-19. Several adaptations were required to protect both patients and staff, while assuring continuity of cancer care; many of these adaptations continue.^{11,34} Our clinic remained open, but more stringent personal protection provisions and infusion center policies were instituted, including screening all patients with temperature checks, symptom/risk ques-

tionnaires at facility entrances, and strict limitations on entry by nonpatient chaperones. Systemwide policies were instituted to convert most visits to billable virtual telemedicine visits. Patients were able to schedule video telehealth visits directly through their smartphones or tablets through our hospital's secure app, and an increase in these visits was noted (**Figure 2**). Where possible, those patients who could not access the app were followed via telephone visits without a video component.

For cancer patients who required in-person evaluation, such as those requiring a physical exam to survey cancer growth, temperatures were checked before entry. They were asked screening questions, including those regarding the presence of muscle aches; unusual fatigue; flulike symptoms or fever within the past 5 days; cough or shortness of breath; sick contact; and travel or contact with those who have traveled. Either an affirmation to any of these questions or an infrared temperature of 99.5 °F or greater warranted a separate physician evaluation in a designated screening area. Patients with concerning signs or symptoms were directed to urgent care or the emergency department for SARS-CoV-2 nasal swab testing. For patients who were actively on cancer treatment who tested positive for SARS-CoV-2, policies were instituted describing when they could resume treatment. To restart treatment after testing positive, patients were required to be self-quarantined for 14 days and to be afebrile for at least 72 hours. If a staff member had been potentially exposed to COVID-19, a hotline was provided to discuss starting post-exposure prophylaxis empirically with hydroxychloroquine when these studies were still ongoing.

Supportive medications. Several modifications to cancer care were implemented at our center to enhance safety during the pandemic, in line with guidelines for best practice.³⁵ Most supportive care treatments, such as

bone-modifying agents (eg, denosumab or zoledronic acid) or maintenance intravenous iron infusions for iron-deficient patients, were delayed so long as they were deemed nonessential. In addition, routine cancer screening tests, such as mammograms and colonoscopies, and bone density tests and restaging CT scans were also temporarily delayed. Genetic screenings for hereditary cancer syndromes like Lynch syndrome or *BRCA* mutations were done with telehealth visits and swabs sent to patients' homes. The long-term consequences of these measures during the pandemic on cancer detection and prevention remain to be determined.

Cancer-specific modifications. The decision to treat an individual patient with myelosuppressive/immunosuppressive cancer therapies seemingly conflicts with strategies to improve infection control and decrease patient and staff exposure to SARS-CoV-2. Therefore, we have had to assess whether treatment plans be initiated on the usual schedules or delayed. For new patients with cancer at low risk of acute progression, such as asymptomatic low-grade lymphomas, treatment was generally delayed based on the diagnosis, cancer stage and presentation, goals of treatment, and an informed conversation with patients about the potential risks of cancer treatment during the pandemic. At our institution, new enrollments into clinical trials were temporarily halted to limit exposure to infections, and also as a consequence of allocation of ancillary research staff to other COVID-19-related responsibilities, such as screening patients at entrances to various clinical centers. Similarly, new stem cell transplants were delayed when possible due to the need for inpatient beds. European Society for Blood and Marrow Transplantation guidelines recommended freezing a secured stem cell product until it becomes appropriate for conditioning.¹¹ Diagnostic procedures such as biopsies were permitted; however, most elective proce-

dures, such as embolizations, ablations, staging endoscopies and laparoscopies, and indwelling catheters, as well as invasive pain management measures, such as epidural pain pumps, were temporarily delayed.

Elective surgeries posed a challenge due to limited staffing and operating room space. Such procedures were placed on hold unless absolutely necessary due to acute symptoms. For those essential procedures, patients were tested for SARS-CoV-2 three days prior to surgery and, if positive, the surgery was delayed for 14 days and then conducted in an operating room designated for additional COVID-19 precautions such as airborne protections. As surgeries were deferred due to resource allocation, lower-stage cancers that are typically managed with resection, such as breast and lung cancers, were temporarily treated with neoadjuvant treatment in certain instances until surgery could be instituted. For example, neoadjuvant systemic therapy was recommended for early-stage gastric and esophageal cancer patients in accordance with management guidelines published in the *Annals of Surgical Oncology*.³⁶ Similarly, for patients with newly diagnosed early-stage colon cancer who were unable to go immediately for surgery, neoadjuvant chemotherapy was used following guidelines published by the National Comprehensive Cancer Network.³⁷ For hormone-positive DCIS or breast cancer, we often treated patients with endocrine therapy upfront, as was also suggested by several societies.³⁸ Our proposed approach for triple-negative and HER2+ invasive breast cancers was to treat with neoadjuvant chemotherapy for all lower-stage disease in an effort to delay surgery for up to 4 to 8 weeks in resource-deprived settings, according to guidelines published in the *Annals of Surgical Oncology*.³⁶ Similarly, for some lower-risk prostate cancers, hormonal therapy was recommended until surgery could be safely pursued.

Management of patients on immu-

notherapies was taken on a case-by-case basis. Immune checkpoint inhibitor (ICI)-related pneumonitis occurs in 2.5% to 5% of patients receiving anti-PD-1/PD-L1 monotherapy and in 7% to 10% of those on anti-CTLA-4/anti-PD-1 combination therapy, and it is the most common fatal adverse event in patients receiving these therapies.³⁹ Given the extent of lung damage that is caused by COVID-19, and the possibility of pneumonitis associated with ICIs, we recognized a major clinical challenge in the timing of resumption of ICI therapies following recovery from COVID-19 illness.⁴⁰ At a minimum, all patients resuming ICIs were required to demonstrate, on CT, stabilization or improvement in COVID-19–related chest findings, as well as declining inflammatory markers associated with CRS. At our institution, we did not withhold immunotherapy from cancer patients who were deemed to be benefiting and were without evidence of active or recent prior SARS-CoV-2 infection.

Lifesaving surgeries—such as those for intestinal perforation secondary to cancer, bowel obstruction from cancer, or acute hemorrhage from cancer with transfusion dependence—have been uninterrupted. Similarly, radiation therapy for emergent situations such as spinal cord compression, symptomatic brain metastasis, bleeding, airway compromise, or uncontrollable pain were not delayed during the pandemic. Patients with active SARS-CoV-2 infection requiring radiation therapy under such

circumstances were scheduled as “last case of the day” followed by terminal facility cleaning prior to next-day operations.

It was and remains vital that we help patients make treatment decisions that are in line with their goals of care for themselves, while setting realistic expectations regarding prognosis with mechanical ventilation or with prolonged delays in treatment. We also communicated to patients that a prolonged delay to seeking care due to a fear of hospitalization could paradoxically lead to prolonged hospitalizations and have detrimental effects on their cancer care.

Given the major impact that COVID-19 has had on our oncology patients, clinical trials are underway to assess the changes that have occurred within this particular population (**Table 4**). Sixteen clinical trials were either actively recruiting cancer patients or planning imminent recruitment to address specific concerns related to cancer management during the COVID-19 pandemic: 3 are designed to evaluate unique psychosocial issues of cancer patients during COVID-19; 3 are related to patient testing for COVID-19; 3 address specific changes to standard cancer treatment in recognition of COVID-19 concerns; 2 are designed to create a registry for cancer patients infected with COVID-19; 1 reviews the use of telemedicine visits for patients receiving radiation therapy; and the last looks at azithromycin prophylaxis for cancer patients on active therapy.

Conclusions

Many challenges exist in caring for oncology patients during the COVID-19 pandemic, including balancing the benefits of oncology-directed treatment with the implicit increased risks of severe COVID-19 infection. Encouragingly, the rapid sequencing of the SARS-CoV-2 virus, development of a quantitative polymerase chain reaction test to detect infected individuals, evidence-based intensive care measures, and more than 500 clinical trials examining potential strategies to treat COVID-19 will all likely decrease harm to cancer patients and the general population during this pandemic. As more data come to light on the pathophysiology of the novel coronavirus, we will be able to better modify cancer care and treatment protocols to minimize risks to our patients. Until then, best practice in oncology care mandates strict infection control processes and informed conversations with our patients in which we discuss the risks and benefits of modifying standard approaches in order to decrease the risk of COVID-19 infection and its complications. We hope that our experience and perspective from relatively early in this pandemic will help to inform others for whom the worst may still lie ahead. ■

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➤ For full reference list, visit cancernetwork.com/NYU_COVID-19



Rohatgi

is a hematology and medical oncology fellow at NYU Winthrop Hospital.



Schneider

is chief, Division of Oncology-Hematology and director, Thoracic Lung Cancer Program at NYU Winthrop Hospital.



Huang

is a hematology and medical oncology fellow at NYU Winthrop Hospital.



Braunstein

is assistant professor of medicine, program director, Hematology/Oncology Fellowship, NYU Long Island School of Medicine and NYU Winthrop Hospital.