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COVID-19 and immune checkpoint inhibitors: initial considerations

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Abstract COVID-19 infections are characterized by inflammation of the lungs and other organs that ranges from mild and asymptomatic to fulminant and fatal. Patients who are immunocompromised and those with cardiopulmonary comorbidities appear to be particularly afflicted by this illness. During pandemic conditions, many aspects of cancer care have been impacted. One important clinical question is how to manage patients who need anticancer therapy, including immune checkpoint inhibitors (ICIs) during these conditions. Herein, we consider diagnostic and therapeutic implications of using ICI during this unprecedented period of COVID-19 infections. In particular, we consider the impact of ICI on COVID-19 severity, decisions surrounding continuing or interrupting therapy, diagnostic measures in patients with symptoms or manifestations potentially consistent with either COVID-19 or ICI toxicity, and resumption of therapy in infected patients. While more robust data are needed to guide clinicians on management of patients with cancer who may be affected by COVID-19, we hope this commentary provides useful insights for the clinical community.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes COVID-19, the fifth global pandemic of the 21st century. While often following a mild course, severe cases present with respiratory failure, cytokine release syndrome or myocarditis, often in older patients and those with underlying comorbidities. Patients who are immunosuppressed, including those receiving cytotoxic chemotherapy, may be vulnerable. The initial published series of COVID-19 in patients with cancer suggested more frequent complications.[1–3] One study even suggested higher death rates in patients with recent therapy, but the small numbers of patients on active therapy (<20) limit definitive conclusions.[2 4 5] Less clear are the effects of newer antineoplastic therapies, especially immune checkpoint inhibitors (ICIs), on COVID-19 severity.

ICI, specifically those targeting programmed death-1/ligand-1 (PD-1/PD-L1), causes an array of toxicities distinct from standard anticancer modalities.[6 7] These immune-related adverse events (irAEs) involve a robust immune-mediated response affecting any organ. Rarely, irAEs cause life-threatening or fatal complications, particularly myocarditis or pneumonitis.[8] Common pathological features between irAEs and COVID-19 include unrestrained immune and cytokine activation, suggesting that ICIs could impact the course of COVID-19.

Should ICI be given during these pandemic conditions? Limited evidence may help guide clinicians. Early data regarding the effects of PD-1/PD-L1 inhibitors on other viruses have been mixed. Most preclinical studies demonstrate that viral clearance is expedited with blockade of PD-1/PD-L1.[9] COVID-19 may cause T-cell exhaustion with increased expression of PD-1 and PD-L1.[10] In this setting, the effect of blockade of these critical pathways with ICIs is unknown. Pembrolizumab has shown efficacy in a small cohort of patients with progressive multifocal leukoencephalopathy caused by persistent John Cunningham (JC) virus infection.[11] However, in other preclinical models, inflammation and tissue damage may be exacerbated by anti-PD-1/PD-L1 and perhaps attenuated by restoring cytotoxic T lymphocyte antigen-4 (CTLA-4) signaling.[12 13] Moreover, we observed a link between Epstein-Barr virus and ICI–encephalitis.[14] In contrast, we have not observed increased toxicities in winter months, when respiratory viruses are more frequent.[15 16] On the other hand, overexuberant cytokine/chemokine production characterizes COVID-19; tocilizumab (anti-interleukin (IL)-6 receptor) has demonstrated early success and is being used in severe cases.[17] Chloroquine (and hydroxychloroquine) has demonstrated in vitro activity by reducing cytokine production and has been incorporated into treatment guidelines[18 19]; however, recent data suggest caution. Thus, ICI could theoretically either mitigate or exacerbate COVID-19 severity.

Several clinical scenarios may arise related to ICI and COVID-19. First, should patients initiate ICIs during this high-risk period? We suggest that given the lack of adverse data, ICIs

should not be withheld in patients with metastatic disease without COVID-19. However, discretion may be used in other cases. For example, nivolumab and pembrolizumab are approved in the adjuvant setting for patients with stage III resected melanoma, but delaying therapy until recurrence may have similar effects on overall survival. Physicians should weigh the advantages of relapse-free survival benefit against the novel disadvantages, namely, the risk of COVID-19 transmission between patient and infusion staff and the increasing use of healthcare resources. Thus, one could consider limiting anti-PD-1 therapy for this patient population. In addition, the initiation of therapy may be safely delayed in certain malignancies with low-volume, indolent disease.[20] Second, should ICI be discontinued early in some patients? This should be considered on a case-by-case basis, incorporating cancer-related risks and complications from COVID-19. Early discontinuation, or pausing therapy, might be strongly considered in patients with (near) complete responses.[21 22] This is particularly salient in older patients who wish to limit contact with the medical system. One could also consider at-home infusions through home-healthcare services, although this approach is not yet widely available. Third, what are diagnostic considerations in patients receiving ICI who develop symptoms possibly consistent with either irAEs or COVID-19? This represents a diagnostic dilemma as symptoms of COVID-19 can mimic commonly seen clinical presentations for patients with cancer. For example, COVID-19 may present with shortness of breath and cough (mimicking pneumonitis), elevated troponin or heart failure (myocarditis) and/or elevated liver function tests (hepatitis). Isolated fever could suggest fever from ICI or infectious causes, including COVID-19. Dry cough and dyspnea without fever could point toward ICI–pneumonitis, respiratory viral infection (including COVID-19), or other non-infectious etiologies common in patients with cancer. Furthermore, radiographical appearance of COVID-19 and ICI pneumonitis may be similar and include diffuse ground-glass opacities. Anecdotally, however, one patient at our center (Vanderbilt) was presumed to have pneumonitis (dyspnea without fever) but was found to have COVID-19 (PCR+ for SARS-CoV-2). Bronchoscopy with bronchoalveolar lavage may be helpful in distinguishing indeterminate cases, although this would require great caution to protect providers performing the procedure and should be discouraged in most cases. Fourth, what are considerations in critically ill patients with respiratory failure and history of ICI treatment with known/suspected COVID-19 infection? Corticosteroids are often considered in these patients when ICI–pneumonitis or myocarditis are diagnostic considerations. However, steroids appear to blunt viral clearing in patients with other coronaviruses, so extreme caution should be used.[23] Alternative agents to mitigate inflammation should be considered, including anti-IL-6 or JAK2 inhibitors.[24] Fifth, in patients on or considering starting ICI, when should ICI be started or resumed in patients recovering from COVID-19? We suggest holding treatment in those who are being tested for infection. We also suggest waiting 2 weeks following resolution of symptoms to (re)start treatment. Two consecutive negative PCR tests before restarting therapy could also be considered, when feasible, to avoid treating infected patients and to limit exposure to healthcare workers and other patients. Finally, should asymptomatic patients initiating ICI be screened for active COVID-19 infection prior to starting therapy? We (Vanderbilt) have begun screening patients treated with ICI and certain cytotoxic chemotherapy regimens prior to treatment, although there are no prospective data for this approach. This should only be considered after adequate testing capacities are in place for testing symptomatic patients.

To conclude, we plea for careful collection of clinical data in all patients with cancer with COVID-19. Multicenter retrospective studies will be required to provide more definitive guidance for clinicians. Sample collection, particularly of peripheral blood, although complicated by infectious precautions, will also help assess the role of immune checkpoints in COVID-19 infection. Clinical research, though difficult, may yield critical insights in this challenging period.

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