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Considerations for cancer immunotherapy during the COVID-19 pandemic

Introductory line

Cancer immunotherapy during COVID-19 pandemic present management challenges from immune-related toxicities requiring careful patient selection.

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Abstract

Immunotherapy is a major treatment modality for cancer, with specific considerations during the COVID-19 pandemic. Although immune checkpoint inhibitors (ICI) do not cause immunosuppression, they can cause immune-related adverse effects (irAEs) in a wide range of organ systems. Immune-mediated pneumonitis can complicate the diagnosis of and potentially aggravate COVID-19 pneumonia. Furthermore, severe irAEs require treatment with corticosteroids and sometimes additional immunosuppressive agents, which may predispose patients to opportunistic infections. The use of combination immune checkpoint blockade is associated with highest risk of irAEs, and possible vaccination-related complications, requiring careful patient selection. Clinicians should be aware of implications of ICI therapy complications during the COVID-19 outbreak, and follow updated guideline practices to minimise patient harm.

MAIN TEXT

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The COVID-19 pandemic has led to fundamental re-evaluation of the benefits versus risks of treatment in oncology. Immunotherapy has had an expanding presence in oncology, becoming a primary systemic treatment in diseases such as melanoma, lung, urothelial, renal and head and neck cancers. Immune checkpoint inhibitor (ICI) therapy, such as anti-programmed cell death protein 1 (PD-1), anti-programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) antibodies, halt the negative regulatory checks of T lymphocytes thus activating the immune response against tumours. Cancer patients receiving these treatments are faced with a unique set of treatment-related toxicities driven by an autoimmune mechanism.

An association between immune-related adverse events (irAEs) and severe COVID-19 infection has been raised during the current outbreak. In particular, an overlap in the physiological insult from immunotherapy-mediated pneumonitis and SARS-CoV-2 related interstitial pneumonia is hypothesized(1). Both conditions can present with lung parenchymal changes; and their co-existence can potentially aggregate the underlying interstitial inflammatory infiltrate and diffuse alveolar damage, leading to a common final pathway of respiratory failure. Pre-existing lung pathology is expected to be a risk factor for COVID-19 pneumonia, with higher incidence in lung cancer patients and smokers(2). Whether prior thoracic radiation may have an impact on outcome from COVID-19 pneumonia is unknown.

Parallels have been drawn between the cytokine storm driving COVID-19 associated acute respiratory distress syndrome (ARDS), and cytokine release syndrome (CRS) as a complication following T cell engaging therapies such as chimeric antigen receptor (CAR)- T cell and CD3-based bispecific T cell engager therapies. It is known that interleukin (IL)-6, IL-10 and interferon (IFN)-gamma are key drivers behind CRS. In patients with COVID-19 associated pneumonia, elevated circulating IL-6 levels have been observed(3). Severe COVID-19 cases have significantly higher circulating levels of pro-inflammatory cytokines including IL-1, 6, 8 and 10, compared with less milder COVID-19 infections(3); and elevated IL-6 is shown to be a predictor of mortality risk. Patients with immune-related toxicity have higher levels of 11 circulating cytokines, such as G-CSF, GM-CSF, IFN-alpha-2, IL-1a, 1B, 2, and 12(4); with some but incomplete overlap with the cytokine milieu seen in severe COVID-19 infection(3).

The outcome of COVID-19 infection in cancer patients treated with immunotherapy remains under investigation, with some(2, 5) but no all(6) studies suggesting a more severe outcome. In a multicentre study from China involving 105 cancer patients infected with SARS-CoV-2, 6% received anti-PD1 therapy within 40 days of COVID-19 symptom onset and experienced increased risk of death and critical symptoms(2). Another series of 423 SARS-CoV-2 positive cancer patients from New York City also reported that treatment with ICI within 90 days predicted for hospitalisation and severe respiratory illness, defined as the requirement for high-flow oxygen supplementation or mechanical ventilation(5). Of interest, even after exclusion of lung cancer patients, the ICI group experienced worse outcome; inferring that the ICI therapy itself conferred worse COVID-19 outcome without the confounding effect of lung cancer, which had been shown as an independent predictor of poor prognosis in COVID-19. However, an interim analysis of the first 200 patients from the TERAVOLT registry of patients with thoracic malignancies did not observe a worsen outcome among the 37% of patients receiving immune checkpoint inhibitor therapy (23% ICI alone and 14% ICI plus chemotherapy), with data collection ongoing(6).

Dual checkpoint inhibitor (anti-CTLA4 with anti-PD1 antibody) therapy has achieved high response rates in a number of cancer types, but are associated with greater incidence and severity of treatment-related toxicity compared with monotherapy. This has several implications. Firstly, differentiating between immune-mediated pneumonitis and COVID-19 associated pneumonia can be difficult due to similarities in clinical and radiological features. Earlier in the pandemic there were concerns that this may cause delays in initiation of corticosteroids, which is the standard management of irAEs. However, emerging evidence for potential benefit of dexamethasone in severe COVID-19 infection(7), reduces concerns for its

empirical usage in cases where immune-mediated pneumonitis is a differential diagnosis. Secondly, patients with severe irAEs, such as immune-mediated pneumonitis, requiring intensive care support can face a health system already strained by demand from COVID-19 cases. Finally, severe irAEs require treatment with high-dose corticosteroid, and at times additional immunosuppressive agents such as infliximab and mycophenolate. To avoid rebound of the irAEs corticosteroids are weaned over 6-8 weeks, subjecting patients to prolonged immunosuppression that can predispose them to opportunistic and nosocomial infections(8, 9). This has the potential to add further burden to the healthcare system.

The impact of cancer immunotherapy on microbial infection in general is not fully understood. A retrospective study of metastatic melanoma patients receiving immunotherapy (mainly ipilimumab, an anti-CTLA4 antibody) reported a 7.3% incidence of serious infections, due to a variety of bacterial, viral, fungal or parasitic infections requiring hospitalisation or parenteral antimicrobials(8). Nonetheless, the study of this interaction is complex, with the receipt of corticosteroids for immune-related adverse events (irAEs) and having diabetes as a comorbidity(8, 10) associated with an increased risk of infection in cancer patients on ICI therapy. Furthermore, immune checkpoint blockade can reactivate tuberculosis and viral infections. There are case reports of acute tuberculosis developing in cancer patients receiving immunotherapy, without concurrent corticosteroid therapy(11). At least three of five cases were suspected to represent reactivation of latent tuberculosis, which maybe directly mediated through PD-1 inhibition driving an exaggerated immune response to tuberculosis infection.

Another consideration for cancer immunotherapy patients is influenza vaccination during the COVID-19 pandemic. While there is currently no vaccine specifically against COVID-19, many health authorities encourage the uptake of influenza vaccination to reduce the concurrent burden from influenza illnesses, particularly for southern hemisphere nations approaching winter facing the seasonal influenza period. Controversy surrounds whether influenza vaccination in patients receiving cancer immunotherapy heightens the risk of irAEs(12). Numerous retrospective series support the safety of inactivated influenza vaccine in recipients of anti-PD-(L)1 monotherapy, with no increase in irAEs observed(13). Reassuringly, influenza vaccination had no adverse impact on the anticancer effect of ICI therapy(12, 13). However, there may be heightened concerns for influenza vaccination in combination immunotherapy (anti-PD-1 with anti-CTLA4) recipients, who are more prone to irAEs, including rarer, but potentially fatal complications such as immune-medicated myocarditis. This potential concern for influenza vaccination in recipients of combination ICI can leave this patient population more vulnerable from influenza infection. For patients on monotherapy ICI therapy, current evidence supports the safety and efficacy for influenza vaccination.

There are guidelines addressing the use of cancer immunotherapy in the COVID-19 era(14, 15). These call for careful considerations on the use of dual checkpoint inhibitor therapy depending on the local prevalence of community transmission and the capacity of the local health service to cope with demands on it(14). On a practical note, this requires individual patient risk-benefit assessment. Patient factors such as age, smoking, and comorbidities such as diabetes and COPD can affect their recovery from irAE and impact on outcome from concomitant COVID-19 infection. Tumour factors for consideration include the burden and biology of disease. Combination immunotherapy maybe justified, for example, in a young patient with metastatic melanoma with high disease burden and/or intracranial metastases; in contrast to a patient with underlying comorbidities who has low volume disease and/or disease characteristics such as underlying BRAF V600K mutation or desmoplastic melanoma subtype, associated with higher likelihood of response to single agent anti-PD-(L)1 therapy.

Current guidelines recommend ICI monotherapy to be delivered at increased dosing intervals such as 4-weekly nivolumab and 6-weekly pembrolizumab(14). These approved alternate schedules have been shown to maintain therapeutic efficacy, while advantageous in reducing patient attendance at healthcare facilities, potentially reducing exposure and community transmission of COVID-19 infection. The timing of immunotherapy cessation in patients is another consideration. A number of trials in metastatic non-small cell lung cancer had a two-year treatment duration for immunotherapy in responding patients(16). There is data in metastatic melanoma to support cessation of anti-PD1 after at least 6 months of therapy, in patients achieving complete response, can be feasible without adversely affecting outcome(17). Selection of cancer patients suitable to stop immunotherapy can further reduce these patient hospital visits and potentially, reduce the chance of COVID-19 infection.

There are international efforts to collate the clinical experience of COVID-19 infection in patients on cancer immunotherapy(6). These registries will provide a valuable resource for further areas of research, such as assessing the impact of irAEs on COVID-19 infection. The data will also improve our understanding of the outcome in this patient population, to aid management decisions and counsel patients. Research on potential biomarkers of disease severity may also assist in patient triage. In this rapidly evolving area, it is helpful for practising clinicians to keep maintain current knowledge through regularly updated resources (Table 1).

In summary, the increased role of ICI therapy in oncology calls for consideration of the impact of their use during the COVID-19 pandemic. While these agents are not directly immunosuppressive, as with cytotoxic chemotherapy, ICI-associated toxicities pose diagnostic and therapeutic challenges for management in the setting of a COVID-19 outbreak. Overlapping clinical and radiographic features in immune-mediated pneumonitis and COVID-19 associated pneumonia can cause diagnostic difficulties at initial presentation. Severe irAEs requiring corticosteroids and prolonged immunosuppression can predispose patients to opportunistic infections. Furthermore, there is a possibility of worse outcome in the setting of COVID-19 infection with underlying immune-mediate pneumonitis and damaging inflammatory response from immune checkpoint blockade. Practical measures, such as prolonging treatment interval and careful patient selection for combination ICI therapy, can help minimise harm.

Table 1: Practical practice points for cancer immunotherapy during COVID-19 pandemic
• Judicious use of combination anti-CTLA4/PD-(L)1 immunotherapy in patients requiring high tumour response rate with good organ functional reserve. Combination checkpoint therapy is associated with higher rate for immune-related toxicities (e.g. pneumonitis) which can potentially adversely impact outcome of COVID-19 infection.
• Use approved dosing schedule with longer duration between treatments (e.g. nivolumab 4-weekly, pembrolizumab 6-weekly)
• Individualised assessment for pausing or cessation of immunotherapy in patients with controlled low disease burden.
• Rapid assessment and COVID-19 testing for patients on cancer immunotherapy with clinical presentations with overlapping features for COVID-19 infection and immune-related adverse events.
• Prevention of co-infections: Seasonal influenza vaccination for patients on single-agent immune checkpoint inhibitor (use in combination checkpoint recipients should be individualised). *Pneumocystis jirovecii* prophylaxis for patients on prolonged corticosteroid therapy for immune-mediated toxicities.
• Maintain current knowledge through professional journals, dynamic resource links (examples below) and webinars sharing clinical knowledge/experience internationally. https://www.cosa.org.au/publications/covid-19-updates/articles/ https://www.asco.org/asco-coronavirus-information https://www.esmo.org/covid-19-and-cancer/covid-19-full-coverage https://www.jto.org/content/covid19

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