Considerations for cancer immunotherapy during the COVID-19 pandemic

Cancer immunotherapy during the COVID-19 pandemic presents management challenges related to immune-related toxicities, requiring careful patient selection

The coronavirus disease 2019 (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 option in diseases such as melanoma, lung, urothelial, renal, and head and neck cancers. Immune checkpoint inhibitor (ICI) therapy, namely anti-programmed cell death protein 1 (anti-PD-1), anti-programmed cell death ligand 1 (anti-PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibodies, halt the negative regulatory checks of T lymphocytes, thus activating the immune response against tumours. Patients with cancer 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 has been raised during the current outbreak. In particular, an overlap in the physiological insult from immunotherapy-mediated pneumonitis and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related interstitial pneumonia is hypothesised.[1] Both conditions may present with lung parenchymal changes, and their coexistence may potentially aggravate 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 patients with lung cancer and smokers.[2] Whether prior thoracic radiation may have an impact on outcomes from COVID-19 pneumonia is unknown.

Parallels have been drawn between the cytokine storm driving COVID-19-associated acute respiratory distress syndrome and cytokine release syndrome as a complication following T cell-engaging therapies, such as chimeric antigen receptor T cell and CD3-based bispecific T cell engager therapies. It is known that interleukin (IL)-6, IL-10 and interferon (IFN)-γ are key drivers behind cytokine release syndrome. Elevated circulating IL-6 levels have been observed in patients with COVID-19-associated pneumonia.[3] Patients with severe COVID-19 have significantly higher circulating levels of pro-inflammatory cytokines, including IL-1B, IL-6, IL-8 and IL-10, compared with milder cases of COVID-19;[3] and elevated IL-6 has been 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-α-2, IL-1a, IL-1B, IL-2 and IL-12,[4] with some but incomplete overlap with the cytokine milieu seen in severe COVID-19 cases.[3]

The outcomes of COVID-19 in patients with cancer treated with immunotherapy remain under investigation, with some[2,5] but not all[6] studies suggesting a more severe outcome. In a multicentre study from China involving 105 patients with cancer infected with SARS-CoV-2, 6% received anti-PD-1 therapy within 40 days of COVID-19 symptom onset and experienced increased risk of death and critical symptoms.[2] Another series of 423 cancer patients with SARS-CoV-2 infection from New York City also reported that treatment with ICI therapy within 90 days was a predictor for admission to hospital and for severe respiratory illness, defined as the requirement for high flow oxygen supplementation or mechanical ventilation.[5] Of interest, even after exclusion of patients with lung cancer, the ICI group experienced worse outcomes, inferring that the ICI therapy itself conferred inferior COVID-19 outcomes 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 Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry of patients with thoracic malignancies did not observe a worse outcome among the 37% of patients receiving ICI 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,[7,8] but is associated with greater incidence and severity of treatment-related toxicity compared with monotherapy.[7] 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 cases of COVID-19[9] reduces concerns for its empirical use in cases where immune-mediated pneumonitis is a differential diagnosis. Secondly, patients with severe irAEs, such as immune-mediated pneumonitis requiring intensive care support may 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

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Practice points for cancer immunotherapy during the coronavirus disease 2019 (COVID-19) pandemic

- Judicious use of combination anti-CTLA-4 and anti-PD-1/anti-PD-L1 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 (eg, pneumonitis), which may potentially have an adverse impact on outcomes in patients with COVID-19
- Use of approved dosing schedule with longer duration between treatments (eg, nivolumab every 4 weeks, pembrolizumab every 6 weeks)
- Individualised assessment for pausing or cessation of immunotherapy in patients with controlled low disease burden
- Rapid assessment and COVID-19 testing for patients receiving cancer immunotherapy who have clinical presentations with overlapping features for COVID-19 and immune-related adverse events
- Prevention of co-infections: seasonal influenza vaccination for patients taking single-agent immune checkpoint inhibitor (the use in combination checkpoint recipients should be individualised). *Pneumocystis jirovecii* prophylaxis for patients receiving prolonged corticosteroid therapy for immune-mediated toxicities
- Maintain current knowledge through professional journals, dynamic resource links (examples below) and webinars sharing clinical knowledge and experience internationally:
  - ▶ Clinical Oncology Society of Australia (https://www.cosa.org.au/publications/covid-19-updates/articles/)
  - ▶ American Society of Clinical Oncology (https://www.asco.org/asco-coronavirus-information)
  - ▶ European Society for Medical Oncology (https://www.esmo.org/covid-19-and-cancer/covid-19-full-coverage)
  - ▶ *Journal of Thoracic Oncology* (https://www.jto.org/content/covid19)

anti-CTLA-4 = anti-cytotoxic T-lymphocyte-associated protein 4; anti-PD-1 = anti-programmed cell death protein 1; anti-PD-L1 = anti-programmed cell death ligand 1. ◆

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nosocomial infections.[10,11] This has the potential to add further burden to the health care system.

The impact of cancer immunotherapy on microbial infection in general is not fully understood. A retrospective study of patients with metastatic melanoma 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.[10] Nonetheless, the study of this interaction is complex, with the receipt of corticosteroids for irAEs and having diabetes as a comorbidity[10,12] associated with an increased risk of infection in patients with cancer receiving ICI therapy. Furthermore, immune checkpoint blockade can reactivate tuberculosis and viral infections. There are case reports of acute tuberculosis developing in patients with cancer receiving immunotherapy, without concurrent corticosteroid therapy.[13] At least three of five cases were suspected to represent reactivation of latent tuberculosis, which may be directly mediated through PD-1 inhibition driving an exaggerated immune response to tuberculosis infection.

Another consideration for patients with cancer receiving immunotherapy 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 nations approaching winter facing the seasonal influenza period. Controversy surrounds whether influenza vaccination in patients receiving cancer immunotherapy heightens the risk of irAEs.[14] Numerous retrospective series support the safety of inactivated influenza vaccine in recipients of anti-PD-1 monotherapy, with no increase in irAEs observed.[15] Reassuringly, influenza vaccination had no adverse impact on the anticancer effect of ICI therapy.[14,15] However, there may be heightened concerns for influenza vaccination in combination immunotherapy (anti-PD-1 with anti-CTLA-4) recipients, as they are more prone to irAEs, including rarer, but potentially fatal, complications such as immune-mediated myocarditis. This potential concern for influenza vaccination in recipients of combination ICI can leave this patient population more vulnerable from influenza infection. For patients taking monotherapy ICI, current evidence supports the safety and efficacy for influenza vaccination.

There are guidelines addressing the use of cancer immunotherapy in the COVID-19 era.[16,17] 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 demand.[16] On a practical note, this requires individual patient risk–benefit assessment. Patient factors such as age, smoking and comorbidities (eg, diabetes and chronic obstructive pulmonary disease) may affect their recovery from irAEs and affect the outcomes from concomitant COVID-19. Tumour factors for consideration include the burden and biology of disease. Combination immunotherapy may be justified, for example, in a young patient with metastatic melanoma with high disease burden and/or intracranial metastases. This is in contrast to a patient with underlying comorbidities who has low volume disease and/or disease characteristics, such as underlying B-Raf proto-oncogene (*BRAF*) V600K mutation or desmoplastic melanoma subtype, associated with higher likelihood of response to single-agent anti-PD-1/anti-PD-L1 therapy.

Current guidelines recommend ICI monotherapy to be delivered at increased dosing intervals, such as nivolumab four times per week and pembrolizumab six times per week.[16] These approved alternate schedules have been shown to maintain therapeutic efficacy, while advantageous in reducing patient attendance at health care facilities, potentially reducing exposure and community transmission of COVID-19. The timing of immunotherapy cessation in patients is another consideration. A number of trials in metastatic non-small cell lung cancer had a 2-year treatment duration for immunotherapy in responding patients.[18] Data on metastatic melanoma support that cessation of anti-PD-1 after at least 6 months of therapy in patients

achieving complete response can be feasible without adversely affecting outcome.[19] Selection of patients with cancer suitable to stop immunotherapy may further reduce these patients' hospital visits and may potentially reduce the chance of acquiring COVID-19.

There are international efforts to collate the clinical experience of COVID-19 in patients receiving 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. The data will also improve our understanding of the outcomes 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 maintain current knowledge through regularly updated resources (Box).

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 may cause diagnostic difficulties at initial presentation. Severe irAEs requiring corticosteroids and prolonged immunosuppression may predispose patients to opportunistic infections. Furthermore, there is a possibility of worse outcomes in the setting of COVID-19 with underlying immune-mediated pneumonitis and damaging inflammatory response from immune checkpoint blockade. Practical measures, namely prolonging treatment interval and careful patient selection for combination ICI therapy, may help minimise harm.

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