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The Impact of Immune Checkpoint Inhibitors on COVID-19 Severity and Decision Making Continuing or Interrupting Therapy

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Abstract

COVID-19 may cause lymphocytopenia; increased levels of the inflammatory cytokines secreted by monocytes and neutrophils including IL-6 and TNF-α as well as increased expression of programmed death-1/ligand-1 (PD-1 and PD-L1). The net result is T cell anergy and impairment of functional memory. The effect of blockade of these critical pathways with immune checkpoint inhibitors (ICIs) in COVID-19 infected cancer patients is unknown. ICIs could theoretically either alleviate or exacerbate COVID-19 severity. Caution with the use of ICIs treatment in cancer patients during COVID infection is suggested. Early data regarding the effects of PD-1/PD-L1 inhibitors on other viruses have been mixed.

Abbreviations: ICI: Immune Checkpoint Inhibitor; PD-1/PDL1: Programmed Death-1/Ligand-1; irAEs: Immune-related Adverse Events; MSKCC: Memorial Sloan Kettering Cancer Center; CRS: Cytokine-Release Syndrome

Introduction

Immune checkpoints are regulatory molecules that are present on the surface of the immune cells. Their immunosuppressive function is crucial to provide the balance between coinhibitory and co-stimulatory signals in the process of T-cell's primary and secondary activation. Cancer cells induce checkpoint molecules upregulation leading to further augmentation of their inhibitory signals. This results in T cells exhaustion and target cells' escape from immune surveillance. There is tremendous improvement in immune checkpoint inhibition (ICI) in the field of cancer treatment in the recent years. Cancer patients with chronic viral infections were usually excluded from ICI treatment [1]. An important challenge is to continue or discontinue treatment of cancer patients with ICI during the period of COVID-19 infection? [1].

ICI specifically those targeting programmed death-1/ligand-1 (PD-1/PDL1) causes an array of immune-related toxicities distinct from those of standard anticancer treatment. Immune-related adverse events (irAEs) of ICI may affect any organ. Rarely, irAEs cause life-threatening or fatal complications, particularly myocarditis or pneumonitis [2]. Uncontrolled immune and cytokine activation are common physiological similarities between irAEs induced by ICIs and COVID-19-induced cytokine-release syndrome (CRS) or cytokine storm, suggesting that ICIs could impact the course of COVID-19 [2]. There is controversy on whether the immune checkpoint therapy acts as a risk or protective factor in cancer patients with COVID-19 infection [1]. The performance of the modified immune system in cancer patients treated with ICI during the COVID-19 pandemic has not been thoroughly studied yet [1].

The impact of ICIs on COVID-19 outcomes is emerging and remains unknown because of small cohorts and limited data collected early in the pandemic [3]. Real world studies have yielded conflicting results. ICIs were found to be risk factors for severe COVID-19 outcomes by some researchers. For example, the collected data on multiple types of cancer from Memorial Sloan Kettering Cancer Center (MSKCC) from March 2020 to April 2020 revealed an association between ICI treatment and higher frequencies of hospitalizations and severe respiratory illness [3]. Perhaps, ICI administration may reactivate the exhausted T cells and potentiate immune hyperactivation in some patients [1] triggering CRS or ICI-related pneumonitis resulting in poorer outcomes. Some of these concerns arise from preclinical data

which showed that PD-L1/PD-1 blockade is associated with an exacerbation of inflammation during acute viral infection [3].

In contrast, some studies do not find such association and support the safety of ICI treatment during the pandemic [3]. Studies on lung cancer patients at MSKCC found that disease severity was not affected by prior administration of programmed death-ligand 1 (PD-L1) blockade (with or without chemotherapy) [3]. The mortality risk in those receiving ICI was 8%. "This is similar to the mortality rate of the general cancer population [with COVID-19], which was in the range of 7.6% to 12%" [4]. Others suggested that cancer patients infected with SARS-CoV-2 could theoretically benefit from the enhanced T-cell activity induced by ICIs treatment [3]. COVID-19 may cause T-cell exhaustion by inducing both membrane-bound and soluble checkpoint molecules over-expression which results in the induction of T-cells apoptosis, T-cell depletion, and lymphopenia [1]. ICI may allow greater immunologic control of viral infection [3] by inhibiting the engagement of checkpoint receptors and ligands, thus lowering T cells death rate, increasing the anti-viral T cell function, and subsequently boosting viral load clearance [1].

An important issue is how to manage patients with immune checkpoint inhibitors during the period of COVID-19 infection

The following questions need to be answered (on a case-by-case basis).

Should cancer patients initiate ICIs during COVID-19 infection high-risk period

It is suggested to hold treatment in those who are tested for COVID-19 infection. Initiation of therapy may be delayed safely in patients with low-volume and indolent malignancies. ICIs should not be withheld in patients with metastatic disease without COVID-19 infection [2].

When should ICI be started or resumed in patients recovered from COVID-19 infection

Avoid treatment of infected patients. Wait for 2 weeks following symptoms resolution to (re) start treatment and consider two consecutive negative PCR tests before restarting therapy when feasible [2].

What are the diagnostic measures in patients receiving ICI who develop symptoms consistent with either ICI toxicity or COVID-19

COVID-19 respiratory symptoms can mimic the commonly seen clinical presentations of ICI–pneumonitis in cancer patients. Dry cough and dyspnea without fever in cancer patients could point to either ICI–pneumonitis or respiratory viral infection (including COVID-19). Furthermore, radiological appearance including diffuse ground-glass opacities may be similar in both COVID-19 and ICI pneumonitis. Indeterminate cases may be distinguished by bronchoscopy with bronchoalveolar lavage (done with great caution) [2].

What are the considerations in patients with respiratory failure and known/suspected COVID-19 infection and history of ICI treatment

Corticosteroids are often considered in cancer patients with ICI–pneumonitis or myocarditis. Extreme caution must be considered with steroids use in other coronaviruses since its use may blunt viral clearance. Alternative agents including anti-IL-6 or JAK2 inhibitors which mitigate inflammation should be used [2]. Tocilizumab and other anti-inflammatory agents inhibit cytokines function during CRS preventing tissue damage and organ failure [1].

Should ICI be discontinued early in some cancer patients

Early pausing, or discontinuation of ICI therapy, might be highly considered in patients with (near) complete responses particularly in older patients. At-home infusions through home-healthcare services should also considered, although this approach is still not yet widely available [2].

Conclusion

We are in need to characterize the impact of ICI and different cancer treatments on the outcomes of COVID-19 infected cancer patients to guide treatment decision-making.

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