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Relationship between Corona Virus Infection and Immune Checkpoint Inhibitors

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Abstract

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) causes infectious disease, COVID-19, and the relationship between COVID-19 and cancer immunotherapy such as immune checkpoint inhibitors (ICIs) is not fully understood. Recent rapid progress in ICI therapy has reported their immune response-related reaction, which demonstrates the importance of studies on the relationship between ICIs and COVID-19. In this Editorial, the application of ICIs in COVID-19 is focused on.

Introduction

Immune checkpoint inhibitors (ICIs)

Recent advances in ICIs have great impacts on clinical application in many fields including cancer therapeutics and the toxicities [1-8]. The patients treated with ICIs alone or in combination with chemotherapy have some side effects, which demands the needs for the prognostic and predictive markers for ICI therapy [1]. ICIs have a variety of target antigens, where nivolumab, pembrolizumab, and cemiplimab target programmed death-1 (PD-1), whereas durvalumab, avelumab, and atezolizumab target PD-ligand 1 (PD-L1), and ipilimumab targets cytotoxic T lymphocyte-associated protein 4 (CTLA-4)[2]. Nivolumab-related pulmonary toxicity includes interstitial lung disease, pneumonitis, organizing pneumonia, pulmonary sarcoidosis, pulmonary infection reactivation, and asthma [2]. A pharmacovigilance cohort of ICI therapy revealed that the median time to onset of immune-related adverse events varies from 28 days in myocarditis to 112 days in diabetes [3]. Adverse drug reactions included myocarditis, myositis, neurologic, hepatitis, vasculitis, pneumonitis, colitis, thyroiditis, hematologic, uveitis, skin, mucositis, arthritis, nephritis, hypophysitis, pancreatitis, adrenal and diabetes [3]. ICI-associated myocarditis is characterized by arrhythmias/conduction disturbances, concomitant skeletal myositis and myasthenia gravis, and high mortality [4]. Pneumonitis is relatively uncommon but fatal in adverse effects of ICI treatment [5].

ICIs and COVID-19

Several recent studies have suggested the relationship between ICIs and COVID-19[9-18].A melanoma patient treated with nivolumab, an ICI, and bempegaldesleukin, PEGylated interleukin-2 (IL-2), developed COVID-19 pneumonia with no serious adverse outcome [9], however, modification of the immune response to COVID-19 by treatment with ICIs and bempegaldesleukin has been suggested [9]. Treatment with ICIs, tocilizumab plus pembrolizumab showed decreased time to clinical improvement in COVID-19 patients [10,11].Patients with lung cancer treated with ICIs demonstrated no increased incidence of immune-related adverse events associated with mRNA vaccines, while the vaccine immunogenicity was lower [12]. Pulmonary toxicity secondary to treatment of ICIs was similar to that of infectious pneumonia of COVID-19 [13]. Some similarities in neurotoxicity in cancer immunotherapy such as chimeric antigen receptor (CAR) T-cell therapy or ICIs and neurological manifestations of cytokine storms such as COVID-19-related encephalopathy have been suggested[14]. Serious adverse neurological events of ICIs include meningitis, encephalitis, demyelinating syndromes, central nervous system vasculitis, neuropathy, neuromuscular junction disorders, and myopathy [14]. Antibody and T-cell responses after COVID-19 vaccinations in a majority of solid tumor patients were equivalent to those of healthy donors [15]. A case report of a diabetic patient with refractory invasive fungal diseases after SARS-CoV-2 infection demonstrated that treatment with ICI and interferon reversed T cell exhaustion and enhance leukocytes activation, whereas careful consideration in immune-mediated adverse events is needed [16]. A cohort study in cancer patients demonstrated that the immune response to COVID vaccination is independent of the anti-cancer immune response in ICI treatment [17]. While the efficacy of mRNA vaccines for SARS-CoV-2 was not affected by the immunosuppression in cancer patients, the relationship between ICI and humoral response to mRNA vaccines in cancer patients needs to be investigated [18]. The lymphopenia occurs in treatment with temozolomide, ICIs, or other anti-cancer

drugs, which may negatively affect the mortality with COVID-19[19]. As COVID-19 affects global concern, many cancer drugs including monoclonal antibodies, antibody-drug conjugates, CAR-T cell therapies, and ICIs have been approved in the COVID-19 pandemic [20]. Immune response and adverse effects of ICIs in COVID-19 need to be carefully monitored.

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