Considerations in treating patients with advance lung cancer during the epidemic outbreak of novel coronavirus (SARS-CoV-2)

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Abstract

The outbreak of pneumonia caused by novel coronavirus (SARS-CoV-2) in Wuhan, China, at the end of 2019 quickly escalated into a global health emergency. Since its outbreak until the 29th of April 2020, the pandemic has affected more than 3 million of people and caused 207,973 deaths globally. SARS-CoV-2 belongs to the β -coronavirus genus of the Coronavirus family, and it shares the same subfamily with severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East respiratory syndrome-associated coronavirus (MERS-CoV), all of which lead to severe pneumonia. For cancer patients, especially those with lung cancers, their immune systems are compromised due to the disease itself as well as the treatment for cancer. The weakened immunity of these patients puts them at a higher risk of not only developing diseases but severe diseases. In this study, through a literature review and data collection, we focus on the selection and consideration of antitumor treatment strategies for advanced lung cancer during the coronavirus disease 2019 (COVID-19) epidemic.

Keywords COVID-19 · SARS-CoV-2 · Lung cancer · Coronavirus

Introduction

Coronaviruses belong to the genus Coronavirus of the family Coronaviridae in the order Nidovirales. They are viruses with single-stranded RNA enclosed within an envelope structure. Along with Middle East respiratory syndrome-associated coronavirus (MERS-CoV) and the severe acute respiratory syndrome-associated coronavirus (SARS-CoV), SARS-CoV-2 is the seventh coronavirus thus far that has been found to infect humans. Viral infections by MERS-CoV, SARS-CoV and SARS-CoV-2 in human have high incidence rates of developing into acute respiratory distress syndrome (ARDS), for which the mortality rates are high [1, 2]. The outbreak of SARS-CoV infections among humans between 2002 and 2003 led to a global epidemic that rapidly spread to more than 30 countries and killed approximately 800 people [1]. The mortality rate among all

patients infected with SARS-CoV was approximately 10%. In 2012, a decade later, the first MERS-CoV infection was reported in Saudi Arabia [3]. The mortality rate for MERS-CoV infection in the population was approximately 30% [2]. The transmission capacity of SARS-CoV-2 is considered relatively strong by the World Health Organization (WHO). During the novel coronavirus disease 2019 (COVID-19) outbreak, one population of patients who cannot be ignored is cancer patients. Based on a report by the Chinese Center for Disease Control and Prevention (CCDCP), in which the epidemiological characteristics of 72,314 COVID-19 cases (including confirmed cases and suspected positive cases) on mainland China as of February 11, 2020, were described and analyzed, 107 (0.5%) of the patients had preexisting cancers. Six of them died; therefore, the mortality rate was 5.6%, higher than the overall mortality rate for the general population [4].

In the past 10 years, as the lives of cancer patients have extended due to improved treatment options, the number of cancer patients with compromised immune function has also expanded. Because respiratory viruses mainly attack lung tissues, patients with advanced lung cancers who already have impaired pulmonary function and a weakened immune system are more susceptible to SARS-CoV-2 infections,

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often with a poor prognosis [5]. Therefore, many of these cancer patients chose to suspend their treatment during the epidemic, not only to avoid possible infections from contact with the external environment but also to allow immune function to be properly restored so as to have some resistance to viral infections. However, because the duration of the epidemic could become extensive, long-term interruption of treatment will inevitably lead to tumor progression and an elevated risk of recurrence and metastasis. However, if a lung cancer patient is infected with SARS-CoV-2 but is only experiencing mild symptoms, how should the situation be handled appropriately to achieve effective control of the viral infection while preventing cancer recurrence in the lungs? Hence, proper management of the treatment for this special population of patients during the outbreak has become a top priority for oncologists. The current treatment for patients with advanced lung cancer consists of a comprehensive approach that includes chemotherapy, targeted therapy, and immunotherapy. In this article, after reviewing the literature and collecting relevant information on lung cancer treatment and viral infections, the advantages and disadvantages of treating advanced pulmonary tumors during the COVID-19 epidemic were analyzed from multiple different perspectives, with the aim of providing a theoretical basis for lung cancer treatment strategies during the outbreak.

Chemotherapy

Lung cancer has long been ranked as the malignant tumor with the highest incidence and mortality rate. Eighty-five percent of cancers in the lung are non-small cell lung cancer (NSCLC), and most NSCLC patients are already at advanced stage when seeking treatment [6, 7]. As the most basic treatment for cancer treatment, chemotherapy has a broad scope of application and high intensity of action, and doctors have substantial experience using the treatment drugs. Chemotherapy is considered as the base treatment option for most advanced lung cancers without apparent driver genes. Cell cycle-specific drugs plus platinum-based reagents are the most frequent chemotherapeutic drug combinations. Once the drugs are administered, either through intravenous injection or oral consumption, they enter the body and act directly on the cell cycle to kill rapidly growing tumor cells. Many chemotherapeutic drugs are bone marrow inhibitors that inhibit blood cell production in the bone marrow; thus, they can lead to anemia and reductions in the numbers of platelets and absolute white blood cells and lymphocytes [8, 9]. Increased risk for infections after chemotherapy has also been confirmed [10–12]. Additionally, patients may experience fatigue and adverse gastrointestinal reactions such as nausea and vomiting, which can cause difficulty in food intake and malnutrition. Such reactions can worsen a

patient's situation and lead to further weakening of immunity, rendering patients undergoing chemotherapy as a susceptible population for SARS-CoV-2 infection. The first study of SARS-CoV-2 infections in cancer patients by Liang et al. analyzed the detailed medical records (ending on January 31, 2020) of 1590 COVID-19 patients and found that 18 patients (1%) had a history of cancer, of whom 5 were lung cancer patients (5/18, 28%). Compared with patients with no cancer history, cancer patients exhibited a higher incidence of developing critical illness (38.9% vs. 7.9%, $P=0.0003$). Moreover, patients who underwent chemotherapy/surgery in the past month (6/14, 42.9%) displayed an elevated risk for severe illness compared with those who did not receive treatment during the same period (1/3, 75.0%) [5]. Because of the already declined immune function in cancer patients, further chemotherapy-introduced damage to the functions of immune cells, such as granulocytes and lymphocytes, will not only raise patients' risk of COVID-19 but also increase the chance of developing critical illness once infected. Therefore, in regions of the COVID-19 outbreak where the viral load of SARS-CoV-2 are high and the risk of infection are greater, for patients whose cancer is in stable condition, delaying adjuvant chemotherapy to reduce the risk of viral infections is recommended. For lung cancer patients who have received chemotherapy and have SARS-CoV-2 infection, close attention should be paid to the condition of those patients, being aware of the risk of severe pneumonia. Timely interventions should be carried out to avoid irreversible damage. In areas where there is no significant outbreak of COVID-19 and the viral load and number of infected individuals is low and under control, chemotherapy should continue to be carried out at local clinics for patients with advanced lung cancer who meet the following criteria: (1) not infected with SARS-CoV-2; (2) in good health with all immunity markers falling within the normal range; and (3) well-tolerated current chemotherapy regimen. Special protective measures ought to be taken during treatment to minimize the chance of cross infections. For advanced lung cancer patients who have SARS-CoV-2 infection, regardless of whether the patients have mild symptoms or are asymptomatic carriers of the virus, the chemotherapy should be temporarily suspended to avoid the possibility of further progression of the viral infection because of the impaired patient immune function caused by chemotherapy treatment. Specific cancer treatment strategies should be developed as appropriate based on the clinical outcome of viral infections.

Molecular targeted therapy

Molecular targeted therapy is one of the breakthrough treatment options developed based on genetics. Because certain drugs have direct inhibitory effects on the pathway of

cancer driver genes, they can directly block tumor growth and achieve better treatment outcomes while minimizing adverse reactions. In non-small-cell lung cancer (NSCLC), the most frequent mutation occurs in *EGFR*, with a rate of mutation of approximately 50%, followed by *ALK* fusion, with a positive rate of approximately 10%. Some additional rare lung cancer driver genes include the fusion genes *ROS1*, *RET*, *NTRK* and *BRAF* [13, 14]. Epidermal growth factor receptor (EGFR), a member of the ERBB family of tyrosine kinase receptors, is a transmembrane glycoprotein encoded by the p12 loci on chromosome 7. It forms a dimer with its ligand, which then binds the activated protein kinase to initiate the critical downstream signaling pathways (such as RAS-RAF-MEK-MAPK and PI3K-AKT-mTOR) that promote cell proliferation and angiogenesis and reduce metastasis and apoptosis [15]. Currently, the most frequently used drugs targeting EGFR in clinical practice are small molecule receptor tyrosine kinase inhibitors (TKIs). There are currently several types of EGFR-TKIs, including erlotinib, gefitinib, afatinib, and osimertinib. It was suggested in clinical studies that NSCLC patients treated with EGFR-TKIs showed an increased risk of interstitial lung disease (ILD), which is a prognostic indication for pulmonary fibrosis [16]. If a patient already exhibits detrimental signs of ILD after receiving EGFR-TKIs treatment and is then infected with SARS-CoV-2, the viral infection will undoubtedly aggravate the lung damage and likely lead to severe pneumonia. Therefore, it is necessary to immediately stop TKIs drug therapy and begin active anti-viral treatment in these patients. An appropriate treatment strategy for targeted therapy should be selected once treatment for the viral infection is completed.

It has been suggested that SARS-CoV-2 infects pulmonary cells through angiotensin-converting enzyme 2 (ACE2), a receptor that is abundantly expressed in type II alveolar epithelial cells (AT2 cells), kidney cells and gastrointestinal tract epithelial cells. AT2 cells are particularly vulnerable to viral infections [17, 18]. AP2-related protein kinase 1 (AAK1) and cyclin G-related kinase (GAK) regulate receptor-mediated endocytosis and trans-Golgi network (TGN) transport [19–22]. Sunitinib and erlotinib are effective, non-selective inhibitors of AAK1 and GAK, respectively. A variety of viruses, such as Dengue virus (DENV) and Ebola virus, enter cells and produce infectious viral particles through AAK1- and GAK-mediated processes. In DENV- and Ebola-infected mice, the sunitinib-erlotinib combination treatment has prevented disease onset and reduced mortality [23]. An additional benefit of sunitinib and erlotinib treatment for patients is that it can alter the body's cytokine response (shifting the balance from pathogenesis to viral clearance) [24]. From that perspective, erlotinib may have an antiviral effect in treating COVID-19. If EGFR-TKI treatment was well tolerated by lung cancer patients and did not cause significant damage to pulmonary

tissues, continued treatment with EGFR-TKIs under mild SARS-CoV-2 infections should still be an option, as long as the lungs do not display detectable changes in imaging features. However, changes in pulmonary tissues should be frequently monitored using imaging technologies.

In summary, we believe that patients with advanced lung cancer who do not have SARS-CoV-2 infections should continue their treatment with EGFR-TKIs. For lung cancer patients infected with SARS-CoV-2, if their lungs are fully functioning and without significant interstitial inflammation, the continued use of EGFR-TKIs is recommended, as these drugs may also have inhibitory effects on the viral infection. However, each patient's lungs should be closely monitored through imaging examinations during and after anti-viral treatment to detect interstitial pneumonia. If the chest computed tomography (CT) of lung cancer patients with COVID-19 shows apparent indications of interstitial changes, the use of EGFR-TKIs should be immediately suspended to prevent irreversible lung damage caused by the combinational effects of the drug and viral infection. However, no situation is absolutely static; thus, any treatment plan must be made based on each patient's specific situation.

Immunotherapy

Immunotherapy for lung cancer mainly refers to treatment through programmed death receptor 1 (PD-1)/programmed death receptor-ligand 1 (PD-L1). These monoclonal antibodies target programmed necrosis factors, removing the “brake” effect of tumors on the immune system and thereby rejuvenating the body's immunity to attack and kill tumor cells and suppress tumor growth. Xu et al. [25] performed the first pathological autopsy on a patient who died of COVID-19. According to the report, the patient's lungs showed signs consistent with ARDS, including diffuse alveolar damage and pulmonary hyaline membrane formation, of which the overall pathological manifestations in the lungs were similar to those of SARS and MERS. When the researchers analyzed the peripheral blood using flow cytometry, they discovered that although the numbers of CD4⁺ and CD8⁺ T cells in the blood were significantly reduced, the cells were in an over-activated state; i.e. Th17 cells were elevated, and CD8⁺ T cells exhibited high cytotoxicity. These results suggest, to a certain extent, that the patient's immune system was severely damaged. Leukopenia and lymphocytopenia were both observed in the peripheral blood of patients in the acute phase of infection with SARS-CoV, MERS-CoV and SARS-CoV-2 [26–28]. The extent of T cell reduction was correlated with the severity of acute phase SARS-CoV-2 infection in patients [28–30]. CD8⁺ cytotoxic T lymphocytes (CTLs) are the major immune cell type that clears respiratory viral infections. CTL deficiency in mice

results in delayed clearance of viruses, while individuals with T cell deficiency associated with aging, immunosuppression, or cancer tend to have more severe infections and poor prognostic outcomes [31, 32]. However, the effects of killing invaded pathogens via the immune system can also simultaneously causes damage to normal cells in tissues [33, 34]. Therefore, the balance between immune protection and immunopathology is critical for host defense against respiratory viruses.

PD-1 and PD-L1 inhibitors, which are immune checkpoint inhibitors, are commonly used for lung cancer immunotherapy. Viral infection can lead to the increased expression of PD-1 and PD-L1 on the surface of antigen-specific T cells [35, 36], inhibit the proliferation of CD4+ and CD8+ T cells, reduce the secretion or spread of the cytokines interleukin-2 (IL-2) and interferon- γ (IFN- γ), reduce the immune function of specific T lymphocytes, and even lead to organ failure. The above effects of viral infection can weaken the host's antiviral immune response, cause damage to target organs, and eventually lead to diseases associated with persistent viral infection. Although blocking the PD-1-mediated signaling pathway can enhance the abilities of CD8+ T cells to proliferate, secrete cytokines and kill infected cells, thereby reducing the viral load theoretically [37–39], it will make activated CD8+ T cells further exhausted, and immune system will be damaged in another way. Patients who contract common respiratory viral infections while under immunotherapy may bear a higher risk for pneumonia [40], which is also very likely to progress into a critical condition due to a disrupted immune status. Hence, if a patient becomes infected with SARS-CoV-2, treatment with immune checkpoint inhibitors should be discontinued regardless of how mild or severe the symptoms may appear.

We believe that during the COVID-19 epidemic, advanced lung cancer patients who have not been infected with SARS-CoV-2 should continue immunotherapy treatment if their immune function is still normal. However, proper precautions and protection must be taken to avoid possible infections. In advanced lung cancer patients who have SARS-CoV-2 infection, taking into account of the impact of the viral infection on immune cells and the disrupted status of their immune system, suspending treatment with immune checkpoint inhibitors is an appropriate consideration. The patient should first undergo antiviral treatment to control the infection; immunotherapy can then be resumed as appropriate.

Conclusions

In summary, during the COVID-19 epidemic, cancer patients, especially lung cancer patients, represent one of the focal points of epidemic prevention due to their weakened

immunity, severe symptoms and high fatality rate. When lung cancer patients who are receiving anticancer therapies exhibit symptoms such as fever or cough, suggesting possible infection, COVID-19 differential diagnosis should be carefully performed, and the risk of COVID-19 should be assessed for appropriate early intervention. For patients with advanced lung cancer who have contracted SARS-CoV-2, continued chemotherapy and immunotherapy can generate a greater risk of progressing into severe viral infection. Therefore, we recommend temporarily suspending the use of drugs; however, for targeted therapies such as EGFR-TKIs, decisions should be made based on the presence or absence of lung damage. Briefly, in clinical settings, situations always change, and each case requires careful review to make decisions based on the specific status of each patient.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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