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## Coronavirus Disease 2019 or Lung Cancer: What Should We Treat?



### To the Editor:

Management of patients with lung cancer in the era of coronavirus disease 2019 (COVID-19) has become a global concern. We read with great interest the article written by Zhang et al.,<sup>1</sup> who first reported the treatment and outcome of a patient with lung cancer infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A 57-year-old Chinese man affected by advanced lung adenocarcinoma harboring *EGFR L858R* mutation continued targeted therapy with osimertinib despite development of COVID-19 pneumonia. The patient achieved stable cancer control and recovered from pneumonia after antiviral therapy. As the authors have admitted, the patient continued osimertinib treatment because his overall situation permitted.

Nevertheless, the scenarios we might face in clinical practice may be quite different. First of all, both lung cancer and SARS-CoV-2 infection can manifest heterogeneously, ranging from an asymptomatic condition to severe respiratory distress requiring urgent treatment or intensive care. Furthermore, tumors harboring driver mutations, such as *EGFR* and treated with targeted therapy, usually affect young and never-smoker patients who represent a minority of cases. More frequently, patients with lung cancer are older people with a smoking habit and have no targetable mutations. Then, in most cases, treatments are chemotherapy, immunotherapy, or combination strategies.

Therefore, COVID-19 can occur in patients who are frail not only by tumor but also by age and comorbidity. In this context, patients have a higher risk of developing severe or lethal SARS-CoV-2 complications. In addition, there is an increasing debate on potential interactions between coronavirus and anticancer therapies.<sup>2</sup> Chemotherapy can cause immunosuppression and favor infectious complications. Conversely, patients receiving immunotherapy should be more immune reactive. Nonetheless, anti-programmed cell death-

protein 1/programmed death ligand-1 or anti-CTLA4 immune checkpoint inhibitors (ICIs) may have a harmful effect on coexisting COVID-19 too.

Accumulating evidence suggests that the lung injury in COVID-19 is mainly owing to an aberrant inflammation process mediated by a cytokine storm.<sup>3</sup> Interestingly, increasing levels of cytokines are considered possible mechanisms underlying the immune-related events,<sup>4</sup> and cytokine release syndrome has been described as a rare complication of ICI treatment. In addition, SARS-CoV-2 can also affect T cells and macrophages. So, it may cause an immunologic dysregulation that might interfere with the response to immunotherapy. These processes could also motivate a possible overlap between COVID-19 pneumonia and immune-related pneumonitis. These two events have similar clinical and radiologic features that make their differential diagnosis and management more difficult. Moreover, serious, immune-related pneumonitis requires high-dose intravenous corticosteroids, which have a controversial role in the treatment of COVID-19 pneumonia.<sup>5</sup>

There is no clear evidence supporting the interactions between SARS-CoV-2 and ICIs. Nevertheless, on the basis of the limited data available, a mutual and detrimental effect cannot be excluded.

For all these reasons, stopping or continuing anticancer treatment in patients with COVID-19 may be a very difficult decision. Clinicians must consider several variables in the risk/benefit assessment. Continuation of targeted therapies in patients with COVID-19 could be safe if clinical conditions permit. Contrariwise, temporary suspension of anticancer treatment pending recovery from SARS-CoV-2 may be reasonable in patients who have had long-term control of the disease with maintenance chemotherapy or ICIs. Pending further evidence, the dramatic COVID-19 outbreak requires extreme caution while making therapeutic decisions for patients with lung cancer.

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## The Management of Patients With Lung Cancer During the Outbreak of Coronavirus Disease 2019



### To the Editor:

We thank Russano et al.<sup>1</sup> for their thoughtful comments on our report. To date, accumulating evidence suggests that patients with cancer are at higher risks of severe acute respiratory syndrome coronavirus 2 infections and more likely to have higher mortality than the general population.<sup>2,3</sup> Lung cancer is one of the most common malignancies worldwide, the clinical manifestations and signs of which overlap with novel coronavirus disease 2019 (COVID-19). Therefore, the management of patients with lung cancer during the COVID-19 outbreak is raising concerns. We previously reported a case of a patient with *EGFR T790M* mutant lung cancer who continued osimertinib therapy despite the development of COVID-19,<sup>4</sup> indicating the feasibility and safety of maintaining targeted treatment in patients with good condition. Russano et al.<sup>1</sup> pointed out that patients harboring driver mutations just represent a minority of cases. Nevertheless, in contrast to the white population, patients with driver mutations account for approximately 50% to 60% of the east Asian population with nonsquamous NSCLC.<sup>5</sup> In addition, some noncytotoxic drugs, such as antiangiogenesis agents, are also indicated for wild-type lung cancer. Therefore, our experience still benefits a considerable number of patients with lung cancer during the COVID-19 outbreak.

Admittedly, we are facing complicated scenarios in clinical practice as stated by Russano et al.<sup>1</sup> Potential interactions between coronavirus and anticancer therapies may exist. Chemotherapy and radiotherapy are

immunosuppressive and favor infectious complications, and immunotherapy might lead to immune-related events, the mechanisms of which overlap with lung injury in COVID-19. Therefore, it is reasonable to temporarily interrupt the abovementioned treatments pending recovery from COVID-19. On the basis of our single-institute data,<sup>3</sup> six patients with lung cancer without *EGFR* mutations were interrupted in anticancer treatment pending recovery from COVID-19. As of February 23, 2020, two had died from COVID-19. The other four discharged patients did not report cancer-related symptoms. The median hospitalization duration of the six patients with lung cancer for COVID-19 was 13 days, which indicated that the interruption of anticancer treatment was short.

In addition, owing to concerns about potential severe acute respiratory syndrome coronavirus 2 infection, patients with cancer were suggested to reduce hospital visits during the epidemic episodes. The delay or interruption of anticancer treatment in patients without COVID-19 was controversial. We further investigated the impact based on our single-institute data.<sup>3</sup> Of the 288 hospitalized patients with lung cancer, 276 patients without COVID-19 have ongoing anticancer treatment. A total of 197 patients experienced treatment interruption, in which 50 might develop progression (Table 1). Compared with the patients continuing targeted therapy, a considerable proportion of cases were suspected to have progression owing to the delay of radiotherapy (10.7%) or periodic chemotherapy and immunotherapy (26.0%). Therefore, we suggested that life-saving chemotherapy and radiotherapy with curative intent should be reserved and prioritized under strict quarantine measures.

Collectively, there is no easy, universal solution to oncologic care during this outbreak. Clinicians can make decisions on the basis of several variables, including the extent of the epidemic, capacity of local health care institutions, stage of cancer, intent of the treatment, and patients' comorbidities and age. In these trying times, it is important to weigh comprehensively and individually these variables rather than to rely on a routine.

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