

Peer Review File

Article information: <http://dx.doi.org/10.21037/tcr-22-1162>

Reviewer Comments

The authors report successful treatment with infliximab for immune checkpoint inhibitor-related pneumonia in a patient with small-cell lung cancer.

The reviewers have several concerns explained below.

i) What is the standard treatment for the limited stage-SCLC? The reviewers think concurrent chemoradiotherapy is the gold standard; however, chemotherapy plus PD-1 inhibitor followed by radiotherapy is the recommended treatment? Please add the references for clinical trials.

Reply i):

We thanked the Reviewer for this professional comment.

The standard treatment for limited-stage small cell lung cancer has always been concurrent chemoradiotherapy. But in some areas of China, radiotherapy was not started in the first cycle of chemotherapy, delayed due to the patient's physical condition and acceptance. At the same time, the first-line PD-1 (Tislelizumab) combined with chemotherapy in this patient we reported was just an attempt and was not supported by evidence-based medicine, clinical trials are underway. Our primary objective in reporting this case was to accumulate experience with Infliximab in the treatment of immune-related pneumonia.

References: Arrell MJ, Yahya JB, Degin C, et al. Timing of Thoracic Radiation Therapy With Chemotherapy in Limited-stage Small-cell Lung Cancer: Survey of US Radiation Oncologists on Current Practice Patterns. *Clin Lung Cancer*. 2018 Nov;19(6):e815-e821.

ii) Discussion (page 3, lines 102-103). The authors described that "Sever CIP (grade 4) was considered, and confirmed by later examination and treatment response". The reviewers think it is challenging to distinguish radiation pneumonitis and irAE in the presented figures. What is the critical examination supporting irAE, not radiation pneumonitis?

Reply ii):

We thanked the Reviewer for this professional comment and strongly agree with the comments made by the reviewers.

There are obvious differences in imaging between immune-related pneumonia and radiation pneumonia. The typical CT imaging manifestations of radiation pneumonia are strip-like consolidation shadows consistent with the radiation field, with neat edges, showing the "knife cut sign", the bronchi in the lesion are mainly dilated, and there are traction changes in the adjacent pleura and mediastinal organs. Immune-related pneumonia can manifest with various interstitial pneumonia changes, including AIP, NSIP, OP, etc. as detailed in the second paragraph of the Discussion section of the manuscript.

Among the patients we reported, The key point for us to consider irAEs is through our

dynamic follow-up thoracic imaging in this patient with lung lesions involving all lobes of both lungs, with a multifocal distribution that is not limited to the radiation field, followed by a rapidly progressive ground-glass pattern in both lungs Shading and consolidation. Radiation pneumonitis is usually not exacerbated within a short period of time after treatment with glucocorticoids, and in the case we reported, we were treated with oral glucocorticoids and the lung lesions were hyperprogressive.

We have also made modification on this topic in the revised Manuscript. You can also see it on Page 3, line 102 to 112.

iii) Discussion (page 4, lines 141-143). Please add the references on clinical or preclinical data regarding the role of TNF- α levels on infliximab treatment.

Reply iii):

We thanked the Reviewer for this valuable comment.

References:

(1)Ye C, Zhu S, Yuan J. Characterization of Two TNF-Related Subtypes Predicting Infliximab Therapy Responses in Crohn's Disease. *Front Immunol.* 2022 Apr 22;13:871312.

(2)Song YJ, Choi IA, Meylan F, et al. Circulating TNF-like protein 1A (TL1A) is elevated early in rheumatoid arthritis and depends on TNF. *Arthritis Res Ther.* 2020 May 7;22(1):106.

Two references have been added and they have been properly cited in the revised Manuscript.

iv) There are many errors in the manuscript. The text should be revised to correct English grammar, spelling and space. Below are the examples.

(page 1, lines 23-24) ...considered 24when...in 25sever CIP.

(page 1, line 26) (CTLA-4), via disrupting the interactions.

(page 1, lines 31-32) A series of ... (irAE) (1).

(page 2, line 36) ...lung cancer(SCLC) suffered from...

Reply iv):

We thanked the Reviewer for this valuable comment.

We have checked the full Manuscript and found errors such as Page 1 Lines 25-26, Page 2 Line 28-32 and Page 2 Line 33-36.

We have adapted the corresponding modifications in the revised Manuscript.

v) Please explain the following abbreviations: ICPs, DT, G test, GM test.

Reply v):

We thanked the Reviewer for this constructive comment.

Specifically, the full name of ICPs is Immune checkpoint inhibitors.

DT is tumour does.

G test is 1,3- β -D glucan test. The detection is the fungal cell wall component 1,3- β -D glucan. Plasma 1,3- β -D glucan is a polysaccharide component with high content in the fungal cell wall, while other microorganisms, animals and humans Neither the cellular components nor the extracellular fluid contain this component. After phagocytizing fungi, human phagocytes can continuously release the substance, which increases the content in blood and body fluids. 1,3- β -D glucan can specifically activate factor G in the lysate of *Limulus* amoebocytes, causing the lysate to coagulate, so it is called the G test.

GM test is galactomannan test. Serum galactomannan is a specific polysaccharide antigen on the cell wall of *Aspergillus*, which is released into the blood during invasive infection. The content of this antigen in blood and body fluids can increase in the early stage of infection, so it can be used for the early diagnosis of *Aspergillus* infection.

We have also added the full name of these abbreviation at where they first appeared in the revised Manuscript.

v) Figure legends (Figure 1). There are several errors, and the explanation is very difficult to understand.

Reply vi):

We thanked the Reviewer for this valuable comment.

We have renewed Figure 1 for a good understanding in the revised Manuscript.

vii) Figure (Figure 2). What does the red colour indicate?

Reply vii):

We thanked the Reviewer for this valuable comment.

The first red indicates the oxygenation index of the patient when he was admitted to the department, the second red color indicates that the patient's oxygenation index did not change after hormone combined with immunoglobulin treatment before, oxygenation index increased on day 2 after the addition of infliximab, which is a breaking point for the improvement of the disease.

We have also renewed Figure 2 for a good understanding in the revised Manuscript.