Juefeng Wan

Fudan University Shanghai Cancer Center (FUSCC)

270 Dong'an Road, Shanghai 200032, PR China

wjf62313172@163.com

April 1st, 2023

Dear editors,

Thank you and reviewers for evaluating our manuscript and providing useful comments. We have carefully addressed the comments and improved the quality of this manuscript accordingly. Please find below our detailed response point by point.

Reviewer Comments:

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Summary: A valuable case report on a dramatic response of a deadly, advanced gastric cancer to a combination of chemotherapy, immunotherapy, and radiotherapy. General evaluation: Valuable in terms of clinical implication.

Comments to improve:

1. Abstract-Case summary: Please name the chemotherapy and immunotherapy agents. Besides, please mention the radiotherapy regimen (including dose, fraction numbers, clinical target volume, and schedule).

A modification has been made in the abstract of the revised manuscript: The patient received mFOLFOX6 regimen chemotherapy, Nivolumab and a short course of hypofractionated radiotherapy (4Gy * 6 fractions) targeting the primary lesion.

2. Abstract-Case summary: It is recommended to update the pathological response per the standard

iRECIST criteria. This comment also include the main text.

RECIST 1.1 remains the primary evaluation standard in our clinical practice, and iRECIST is applicable after the occurrence of PD according to the RECIST 1.1 and serves as an exploratory evaluation standard. This patient did not experience PD, so evaluation based on RECIST 1.1 is appropriate. Moreover, for this patient, the evaluation results of RECIST 1.1 and iRECIST are the same, both of which are PR (or iPR).

3. Abstract-Case summary: Please mention the interval duration (in months) of recurrence-free survival.

A modification has been made in the abstract of the revised manuscript: Chemoimmunotherapy started four weeks after surgery and examination was performed every three months.

4. Please explain the acronyms for their first presentation in either Abstract and Main text.

Thank you for your valuable suggestions. In the revised manuscript, all the acronyms have been explained in their first presentation.

5. Page 3-line 12: please mention the cut-off point of high tumor mutation burden in gastric cancer. Is 5.98 muts/MB high-TMB or low-TMB?

TMB-H refers to at least 10 mutations per Mb. Therefore, 5.98 muts/MB is determined as TMB-low.

A modification has been made in the revised manuscript: Next-generation sequencing showed that the tumor mutation burden (TMB) was 5.98 muts/MB and was determined as TMB-low as TMB-high refers to at least 10 mutations per Mb in GC.

6. Page 4-line 2: Please mention the interval between treatment and the follow-up PET-CT scan.

For this patient, the follow-up PET-CT was performed one month after treatment.

A modification has been made in the revised manuscript: One month after these treatments, whole-body FDG PET/CT and enhanced abdominal CT were performed to evaluate the treatment effect.

7. Discussion: Case reports are clues for clinical and research studies. The presented case experienced dramatic response to chemoimmunotherapy in combination with radiotherapy. It is expected the Discussion section explains the putative mechanisms involved in this dramatic response. Recent evidence has put forward the importance of cancer mitochondrial metabolism in response to either radiotherapy and immunotherapy. Recently, Houshyari et al. noted that enhanced mitochondrial metabolism can enhance the response to anti-PD1 agents by downregulating the PD-1 expression on immune cells and providing prerequisite for the prolonged anti-tumor response (https://pubmed.ncbi.nlm.nih.gov/36469835/). Another study highlighted the importance of mitochondria biogenesis in response to radiotherapy (https://pubmed.ncbi.nlm.nih.gov/36719474/). This study noted that enhanced mitochondrial metabolism can improve tumor response through activating the 6th R of radiobiology, the Reactivation. It is recommended the authors mention this correlation using the noted references.

A modification has been made in the discussion of the revised manuscript: Besides, enhanced mitochondrial metabolism also plays an important role in the better treatment response to anti-PD1 agents[11] and radiotherapy[12].

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors presented in the manuscript a very interesting clinical case of successful treatment of stage 4 gastric cancer since May 12, 2023. They used an innovative combined treatment method of chemotherapy, radiation therapy, immunotherapy and gastrectomy. The manuscript meets the requirements of evidence-based medicine. The positive dynamics of the patient as a result of treatment has been convincingly confirmed. This combination therapy is worthy of further exploration, and also needs long-term follow-up of patients. Recommended for publication in the World

Journal of Gastrointestinal Oncology or the World Journal of Clinical Cases.

Thank you for your comments and valuable suggestions.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in

1) According to the editor's request, we have visited the RCA database to obtain more information.
2) Uniform presentation has been added to the figure legends.
3) Decomposable figures have been organized into a single PowerPoint file.

We have uploaded the clean version of the revised manuscript, figures and tables according to the above-mentioned requirements.

The revisions in the manuscript have been done. We would be glad to respond to any further questions and comments that you may have.

Thank you for your help in revising the manuscript.

Sincerely,

Juefeng Wan, M.D.

Associate Professor, Department of Radiation Oncology

Fudan University Shanghai Cancer Center