

Peer Review File

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Reviewer A

In the manuscript entitled “Tumor lysis syndrome associated with the use of gemcitabine and pazopanib in a patient with high-grade sarcoma of the left lower limb: A case report” the authors present a case report on a rare occurrence of Tumor lysis syndrome in a patient with solid tumor (Sarcoma).

The subject is relevant. The manuscript is well written, and the results are clearly presented and discussed.

Thus, this reviewer RECOMMENDS this manuscript for publication in Chinese Clinical Oncology

It is a good quality paper. No English review needed.

Reply 1: We are grateful for the comments and time spent reading the manuscript.

Reviewer B

The authors present an interesting and informative case report of TLS with the combination of gemcitabine and pazopanib. There are however several formatting errors that need to be corrected:

1) Please correct the figure 1: there are 9 values listed for each of the labs but headings for only 7 days are present (ie, the first and last lab values do not have any heading: not sure what days they represent). Also, there is "," at a lot of places instead of decimal.

It might be worth illustrating these labs in the form of a graph to make it more visually appealing

Also please use arrows to show the mass in the radiological images.

Reply 1: Table 1, corresponding to laboratory parameters, was corrected to give clarity to the behaviour of these parameters on key days: admission, start of chemotherapy, haemodialysis, complications.

The decimal units were also corrected with dots.

White arrows were added to the graphs to indicate the tumour lesion.

2) There are some English language/grammatical errors: for ex line 85 of the manuscript contains the word "hiporexia". Line 109-111 is not grammatically sound. Similarly, the abstract lines 39-40 need restructuring.

Reply 2: Spelling and grammatical corrections were made to clarify the idea of the paragraph, and the summary was restructured.

Reviewer C

In this clinically interesting manuscript, the authors report a case of tumor lysis syndrome after third-line systemic therapy with gemcitabine and pazopanib. However, the major concern locates in the lack of the detailed information about THIRD-LINE systemic therapy with gemcitabine and pazopanib and the in-depth analysis for such clinical problem. Authors are invited to add the vital information to answer the concerns in below.

Title

Please provide a more rigorous title for the case report. The current title “Tumor lysis syndrome associated with the use of gemcitabine and pazopanib” would be inappropriate. This result can’t be obtained from the case just as the authors stated in the Conclusion “Any of the drugs used in our case possess the capacity to trigger TLS”. The related opinions and statements about “TLS after third-line systemic therapy with gemcitabine and pazopanib” should be check and revised in the full-text.

Reply 1: According to the recommendations, the grammatical restructuring of the title of the manuscript should be carried out.

Abstract

The abstract does not convey the value and the whole story of the case. The current abstract would need to be rearrange especially following the suggestions as below.

1- The abstract is a key section for the writing of a scientific work. The authors must highlight the unique of the case in the Abstract-Background. Is this the first description of TLS after initiation of gemcitabine and pazopanib in progressive sarcomas?

Reply 1: According to the recommendation, the abstract was adjusted, describing the particularity of our case, not previously described, lines 31-33.

2- Case Description: What is the dosage and duration of pazopanib and gemcitabine therapy? What the meaning of “therapies established”? The detailed and clearer information should be added to answer those problems. And the follow-up information should be provided in the subsection. “They later...” should be revise to “He later...”.

Reply 2: The therapies used during her hospital stay were clarified, as well as the patient's follow-up and outcome. Lines 41-48

3- Conclusions: Please re-consider the content in the Conclusions. I failed to get the information about how to “prevent the appearance of this type of complications in the short and long term” in the manuscript.

Reply 3: The final conclusion of the manuscript was reorganised

Introduction

Among the antecedents of this work, those similar publications on the subject should be mentioned. Several examples for the authors’ reference: PMID: 34511623; PMID: 23599770; PMID: 8318370; PMID: 8342564; PMID: 20360879; PMID: 20517638. The authors MUST clearly analyze and clarify the internal clinical importance and highlight the unique point of

this manuscript in the Introduction. This should be supported by evidence based on comparison with those similar cases.

Reply 1: The literature describing the clinical event is mentioned, however none of them were related to the chemotherapy described in our case. Lines 74-77

Case Presentation

1- The detailed date of admission and the date of related therapeutic interventions received in your hospital (Date, Month, Year) should also be provided.

Reply 1: Important dates and events in the patient's evolution were described in detail. Lines 86-94

2- The diagnostic criteria of TLS should be specified in the Case presentation. The authors should also clearly indicate the diagnostic index on the basis of which the patient was diagnosed with TLS.

Reply 2: Clinical and laboratory changes are described, correlated with the time of initiation of therapies to make the diagnostic approach. Lines 125, 131-134

3- The authors should provide detailed information of different complicated therapies, especially the THIRD-LINE systemic therapy with gemcitabine and pazopanib for the clinicians' reference. Detailed information includes dosage, strength, duration and so on.

Reply 3: Information on the chemotherapy used, as well as subsequent changes for restarting chemotherapy, was supplemented. Lines 119-121, 141-143

4- It's great the authors present relevant events in the patient's history in chronological order in Table 1. However, all key core elements of the case should be provided, such as, the surgery, second-line oncological therapy, antibiotic therapy, and the dose change of gemcitabine. Here are some examples from the journals you can reference:

<https://jgo.amegroups.com/article/view/50913/html> ;

<https://tlcr.amegroups.com/article/view/35939/24197>

Reply 4: Following the recommendations, a timeline was drawn up, which is detailed in figure 1.

5- Authors should provide the related diagnostic results not just state "We monitored the progress of the patient". And provide the exact data in the sentence "the dose of gemcitabine was reduced by 20%".

Reply 5: The complications are described, as well as the improvement of laboratory parameters, which can be verified in table 1, and the gemcitabine dose adjustment is specified. Lines 138- 145.6- How long was the follow-up? Was the patient always in good outcome in the follow-up? Whether there are any unanticipated events after leaving the hospital?

Reply 6: It specifies the indication to restart chemotherapy, adjustments, good tolerance and outpatient follow-up, describing the final outcome. 141-148

Discussion

1- Para 3: The reference of the diagnostic criteria made by Cairo and Bishop also should be cited (PMID 15384972).

Reply 1: As suggested the respective referencing is done. Line 275

2- Para 4: In 2011 Howard et al. proposed a refinement of the Cairo and Bisshop classification of TLS. However, they suggested that a 25% change from baseline after initiation of treatment should not be considered a criterion, since such increases are rarely clinically important unless the initial value is already outside the normal range. The sentence “or 25% increase from baseline” needs to be revised.

Reply 2: The criteria describing the reported event are reviewed and a respective citation is made. Lines 164-169

3- Due to the rare of TLS, the authors should provide in-depth analysis between the current case with the 11 cases reported in the published references. Table on the difference in clinical characteristic between the cases would be helpful for clinicians.

Reply 3: The analysis and description that makes our clinical case unique, especially in relation to risk factors and type of therapy, is carried out. 173-196

4- To consistent with the Title, a scientific discussion part about the underlying reason of TLS from initiation of gemcitabine and pazopanib for ST is needed for this report. In addition, what did the role of the dose of gemcitabine and pazopanib in the case of TLS?

Reply 4: A description of the importance of the therapy used is given, with the respective citation. Lines 192-199

5- Para 7: What’s the definition of low dose in the sentence “even more so at low doses”?

Reply 5: Described and referenced as described in the literature. Line 196

6- The contents of the first and second paragraphs of the current Discussion section are not for discussion, but like the introduction. And excluding them, the current discussion part is not sufficient to prove the clinical value of the case. In this part, the authors could discuss how to prevent, diagnose and effectively treat similar cases of TLS at the early stage, which is the core part of the case report.

Reply 6: In accordance with their recommendations, the discussion was rewritten to reinforce the importance of the description in the literature of this case. Lines 154-203

7- The authors should point out the strengths AND limitations of the case report in a separate paragraph.

Reply 7: A paragraph was added recognising weaknesses and strengths of this case clinic. Lines 204-208

The authors should use the arrows to indicate the mass in the Figures.

Reply 1: White arrows were added to the graphs to indicate the tumour lesion.

Table

Just by way of example: the data “13,5” of BUN should be revised to “13.5”. The similar problems in the Table 1 should be revised. And “AU (mg/dL)” should be revised to “UA (mg/dL)”.

Reply 1: Translation, spelling and grammatical errors were adjusted. Table 1

Author instruction for the case report

The authors should organize the structure of the manuscript according to the author instruction of CCO (<https://cco.amegroups.com/pages/view/guidelines-for-authors#content-2-5>).

Reply 1: The requested forms were filled in.