

Peer Review File

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Reviewer A:

This is a monocenter case series (5 patients), focusing on patients with \geq cT3b RCC who were treated with presurgical combination therapy of IO/TKI and underwent nephrectomy. Of note, two of them were metastatic at diagnosis with a complete response on metastatic sites after systemic therapy. Two information are highlighted by the authors: firstly, they observed a reduction in the volume of thrombus in all cases, with 3 out of 5 experiencing a downstaging of the level, and in 2 cases allowing a less invasive surgery. Secondly, the potential challenges of this surgery, since adhesions, fibrosis and/or inflammatory changes were encountered at the operative sites during surgery in all cases. Finally, they conclude that this approach could provide favorable oncological outcomes and the opportunity to delay systemic treatment (even if the PFS is quite short).

I have three minor comments:

1. In the Material and Methods section, the authors defined Treatment-free survival (TFS) as the time from the first immunotherapy dose to the first dose of subsequent systemic therapy or death. This definition is not adequate and TFS must be defined from the last dose of immunotherapy or surgery (and therefore may be less than 10 months...)

Reply: Thank you for your comment. We mistook the beginning of the time of PFS and TFS. We changed the first day as the nephrectomy.

2. The authors specify that the thrombus level was defined according to the Novick classification. However, The Mayo classification is generally used. Please explain this choice, give the reference, and briefly detail this classification in the Material and Methods section.

Reply: We changed the definition of thrombus level from Novick classification to Mayo classification. The levels were not changed in each case.

3. In the abstract, the authors state that « adhesions were encountered at the operative sites during surgery in all cases ». But in the manuscript, the sentence « Surgeons reported the presence of fibrosis and inflammatory changes at the surgical sites » does not provide the information of « in all cases ». Please also include this important information in the manuscript.

Reply: Thank you for your comment. We added “in all cases” in the manuscript. (Page 8, Line 107 and Page 9, Line 140).

Reviewer B

In the present study, the authors concluded that the preoperative combination therapy using pembrolizumab or avelumab with axitinib is warranted in renal cancer patients with inferior

vena cava thrombus. There is no novelty in this study. Furthermore, it is impossible to draw their conclusion from the present results. My specific comments are as follows.

Comment 1. The authors' neoadjuvant therapy consisted of the two drugs are not approved. Did they obtain approval from any ethics committee? Did they obtain informed consent from the patients? These should be clearly stated in the text.

Reply: Thank you for your comment. We added the following sentence in Footnote. "Written informed consent was obtained from each subject." (Page 11, Line 167).

Comment 2: How did the authors know that their combination therapy is actually effective and meaningful? The authors should compare the survival and surgical complications etc. with those of the patients who were treated with nephrectomy only. Furthermore, to reach statistically significant results, the authors should analyze more patients.

Reply: Thank you for your comment. This is a case series, thus we summarized our patients who under IO/TKI as neoadjuvant therapy. As our future research topic, we would like to compare the oncological outcomes of IO/TKI neoadjuvant therapy with nephrectomy only.

3. LL. 79-81, "The regimens were pembrolizumab (every 3 weeks) with axitinib (n = 4) and avelumab (every 2 weeks) with axitinib (n = 1)": Two different regimens were used. I don't think this makes sense in the analysis of a small cohort consisted of only 5 patients. Furthermore, the authors did not show how they determined which regimen should be used.

Reply: Thank you for your comment. This is not original article but a case series. To summarize our experience, we drew KM curve. We added the following sentence in the manuscript "The regimens were selected at the discretion of the treating physicians". (Page 6, Line 85).

4. The authors did not show the dose of each drug concretely.

Reply: Thank you for your comment. We added the dose of each drug in the manuscript. (Page 6, Line 81-84).

5. Table 1: It is inappropriate to analyze the patients with metastasis and those without in the same cohort.

Reply: Thank you for your comment. This is case series thus, to summarize each case, we show the all cases in the same cohort.

6. Table 1: The cycles of the combination therapy considerably differ from patient to patient. The authors should show how they determined the cycles of the combination therapy.

Reply: Thank you for your comment. The cycles of the combination therapy was decided at the discretion of the treating physicians. We added the following sentence in the manuscript "The regimens and cycles were determined at the discretion of the treating physicians." (Page 6, Line 84-85).

7. Fig. 1: Incomprehensible. Unclear what the Y axis means

Reply: We added the following sentence in Y axis of Fig 1. "Relative change in primary tumor

and thrombus size (%)”.

8. LL. 102-103, “The PFS and TFS curves were estimated using the Kaplan-Meier method (Fig. 2)”: The curve for TFS is not shown.

Reply: We deleted TFS curve, because one patient who received IO within 1 month after surgery at the discretion of his physician. Thank you for your suggestion.

9. What is the novelty of this study?

Reply: In this case series, we summarized the experiences of neoadjuvant therapy for RCC using TKI-IO. The therapeutic courses of neoadjuvant TKI-IO were not fully investigated. Thus, although this is a case series, there is novelty to report these results.

Please define all the abbreviations used in the figures in their legends.

Reply: We added the abbreviations in the figure legends.

Reviewer C

- Figure 1 should contain the actual numbers for each graph. Instead of "relative changes", please present the actual data of thrombus height, tumor size and so forth. Please provide additional data on thrombus width.

Reply: Thank you for your suggestion. To clarify the size of ITT and primary tumor, we added supplementary Table 1. As shown in Supplementary Table 1, we added the size of ITT and primary tumor before and after neoadjuvant IO/TKI. Additionally, we added the following sentence to show how to calculate the tumor volumes “To assess tumor and thrombus volume, the calculation of major axis multiplied by minor axis and height was performed using CT images”. (Pages 85-86).

- Were there any patient who did not proceed with surgery because of toxicity or progression? Should be around 20% according to prospective series.

Reply: Luckily, we did not experience such a case in our institution.

- Please describe how thrombus size was measured. How about thrombi extending caudally?

Reply: Thank you for your comment. We measured the size of tumor and thrombus using enhanced CT images (major axis, minor axis, and height). No IVC thrombus was extended caudally.

- Was there a change in surgical approach i.e. laparoscopic instead of open surgery or avoidance of cardiopulmonary bypass (for example in patients 2 or 5)?

Reply: Thank you for your suggestion. It is an important point. We already described that case 3 was avoided laparoscopic surgery and case 5 was avoided open sternotomy.

- Please discuss the summary paper on presurgical therapy with TKI <https://doi.org/10.1111/bju.15966>. How do the authors see their current results in the light of

the outcomes with TKI alone?

Reply: Thank you for your suggestion. As the reviewer pointed, we did not compare with the results of neoadjuvant TKI or nephrectomy only. According to the reviewer's comment, we added the following sentence in the discussion part of our manuscript. "Furthermore, we did not juxtapose the outcomes with those of neoadjuvant TKI treatments. In a recent publication, Klatte et al (11). proposed a possible role for neoadjuvant TKI treatment in the management of RCC patients with ITT, whereas IO/TKI is a more modern systemic approach to RCC management. Thus, an imperative requirement exists for a prospective randomized trial to substantiate the survival benefits associated with neoadjuvant IO/TKI treatments for RCC patients with ITT." (Page 10, Line 147-152).

- Please describe dose reductions in IO/TKI treatments.

Reply: Thank you for your suggestion. We added the following sentence in the manuscript "During the neoadjuvant IO/TKI therapy, all patients received the IO drugs at the recommended dosage. However, in the cases of adverse events, the oral administration of axitinib was adjusted to 1 mg twice daily (case 4), 2 mg twice daily (case 5), and 3 mg twice daily (case 6)." (Page 7, Line 99-102).