Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-23-634

Reviewer A

Comment 1: Authors showed 5 case reports about systemic therapies as the neoadjuvant setting for liver transplant recipients with unresectable HCC. As authors mentioned, neoadjuvant therapy in liver transplantation is expected because systemic therapies, especially combined immunotherapy, have been developing. Combined immunotherapy is effective but concerns about rejection are found. In present study, various treatments were performed before liver transplantation. The timing of systemic therapies was varied. Clinical course after liver transplant was also varied. Therefore, the significance as case series for neo-adjuvant setting was lacking.

Reply 1: The term “neoadjuvant” has now been now removed from the manuscript. We refer to systemic therapies with ICI in the pre-transplant setting instead.

Changes in the text: All throughout.

Comment 2: MRI and MR abdomen were found. The presence of contrast enhance should be described.

Reply 2: We have specified the presence of contrast enhancement.

Changes in the text: 123, 235, 277

Comment 3: Trade name should change to common name or show with trademark.

Reply 3: We have changed the trade name into a common name

Changes in text: 217ß

Comment 4: Abbreviation should be shown with full spelling at the first appearance.

Reply 4: Immune checkpoint inhibitors were described and then abbreviated for the remainder of the manuscript.

Changes in text: 29

Comment 5: Detailed date was unnecessary.

Reply 5: All dates have been removed.

Changes in text: 121-285

Reviewer B

The authors report on a case series of patients who received preoperative adjuvant chemotherapy prior to liver transplantation. This is a very interesting report, but there are a few points to consider.

Comment 1: All in all when describing the progress of a case in a case report, it may not be desirable from the viewpoint of protection of personal information to include the date of the case.

Reply 1: All dates have been removed.
Changes in text: 121-285

Comment 2: Neoadjuvant systemic therapy may be safe, but it would be an oversimplification to say that neoadjuvant systemic treatment can help control disease progression and extend patient eligibility for a liver transplant as far as cases are concerned.
Reply 2: I have reworded to stated that immunotherapy "may be associated with disease control or downstaging of disease".
Changes in text: Highlight Box. 291-292, 357-358.

Comment 3: What is the rationale for assuming that hepatic reserve improved with treatment with atezolizumab and bevacizumab despite a larger tumor? Is there a reason, such as a portal vein thrombus that has disappeared? Did he abstain from alcohol, or was he given diuretics or branched-chain amino acids? There is scant evidence to suggest that the neoadjuvant improved the hepatic reserve.
Reply 3: You are correct, there had been a change in diuretic from amiloride to spironolactone. Thus, his clinical improvement cannot be attributed to immunotherapy alone.
Changes in text: Removed discussion paragraph 2. 223.

Comment 4: Line 78~82 should be written in the conclusion section, not in the methods section. Also, since reduction was not obtained in all of the five cases, "as neoadjuvant treatment to reduce disease burden such that patients can receive definitive treatment with liver transplantation."should be phrased differently.
Reply 4: These lines have now been removed entirely.

Comment 5: In the discussion section, we think it is necessary to discuss whether neoadjuvanting could have led to liver transplantation or whether there were cases that could have gone to transplantation without neoadjuvanting. I think you can say enough about the safety of doing neoadjuvanting, but you should have more discussion about the significance.
Reply 5: Agree. This was added to the discussion.
Changes to text: 287-358

Comment 6: Table 1- It is strange that lenvatinib is included in the ICI section. The heading should be changed. It would be clearer to add to this list whether reduction or downstaging was obtained with neoadjuvant.
Reply 6: I have removed lenvatinib cases.
Changes to text: 524

Reviewer C

Authors reported five patients received systemic chemotherapy prior to liver transplantation for unresectable hepatocellular carcinoma. Some queries were raised in the present report.

Comment 1: First of all, lenvatinib and immunotherapy were not neoadjuvant therapy for HCC.

Atezo/bev achieved approximately 30% of CR/PR. In case of treatment change, evaluation of prior therapy is necessary. Authors should revise the word 'neoadjuvant therapy' and add the assessment of systematic therapy before liver transplantation.
Reply 2: The term neoadjuvant has completely been removed. We now state systemic therapy prior to liver transplant.
Changes to text: All throughout.

Comment 2: Next, TKIs was totally different from immunocheck point inhibitors in effect and adverse effect. Authors had better select patients treated with one of them.
Reply 2: TKI patients have been completely removed.

Comment 3: Drug information recommends that surgical therapy should be postponed for 1 or 2 weeks from the end of Lenvatinib and Bevacizmab administration. These drugs might prolong wound healing through inhibiting neovascularization. How about any effects in surgical wound healing in five patients? Did authors explain patients the irregular use of drugs and surgical therapy?
Reply 2: No issues with wound healing were seen. We do dedicate a paragraph in the discussion section about the complications associated with bevacizumab as well (please see 369-378).
Changes to text: 360

Reviewer D
Comment 1: Ohm. et al found the clinical significance of adopting neoadjuvant systemic therapy before liver transplantation for patients with unresectable hepatocellular carcinoma. They vividly described five clinical cases that patients received either multi-kinase inhibitors or immunotherapy to downstage or decrease the size of tumor pior to transplant, which may aid them to gain the transplantation eligibility or prevent disease progression. These results led the authors to conclude that the neoadjuvant therapy pior to liver transplantation brings benefits to patients.
Although some of these observations are well documented and convincing, there are numerous weaknesses in this study. Although the clinical cases are well described, there is no statistical analysis for the data and the results should be quantified. Thus, it is quite difficult to convince the readers how much benefit can this treatment bring to the patient. Meanwhile, if more cases are added, it would made the conclusion more significant, while similar articles normally include more cases. There are some other major concerns listed below. To represent a significant contribution, these comments should be substantially addressed.
Comment 1: We lack the ability for statistical analysis at this time due to the small number of cases. However, much more quantifiable data was included in the form of reporting liver enzymes, function tests, and hemoglobin post-transplant. Unfortunately, no other similar cases with ICI use prior to transplant have occurred at our site.
Changes to text: 531

Comment 2: Page 4, 25: There should be a period between "post-operatively" and "Although".
Reply 2: Noted and changed.

Comment 3: I suggest that there are some grammatical errors that need to be corrected. For example, page 2, 30: “are safe and do not” should be changed into “is safe and does not”, because the subject of clause is “therapy”. The grammatical errors are quite common in the manuscript, please check all the grammars.
Reply 3: Submitted through app to check grammar.

Comment 4: Some sentences do not read smoothly. For example, page 5, 94: there shold be a “that” after “optioin”. Thus, polishing may be needed.
Reply 4: The text has been heavily revised in this version.

Comment 5: I suggest that the patient's neoadjuvant therapy and transplantation could be divided into different paragraphs, so that the different stages of each case can be more clearly found.
Reply 5: With the removal of the TKI cases, there is not much post-transplant course that needs to be documented. Therefore, we have not made any changes with regards to this comment.

Comment 6: Page 8, 189: There is no explanation or description of the abbreviation TARE. And the HIMALAYA at page 9, 210.
Reply 6: The paragraph with TARE is now removed from the manuscript. HIMALAYA is the name for an RCT and cannot be fully spelled out.

Comment 7: At present, the indicators after liver transplantation only include survival time, while other indicators can be introduced such as blood cell, hemoglobin and platelet trends in a patient with graft versus host disease.
Reply 7: We inserted a new table 2 that details the last blood work of these patients at followup.
Changes to text: 531

Comment 8: I recommended that the inclusion and exclusion criteria should be described more clearly.
Reply 8: The inclusion criteria were HCC patients who received ICI prior to liver transplant. No exclusion criteria as the pool of eligible patients are quite small.
Changes to text: 113

Comment 9: Some papers have conducted in-depth research on this topic, such as the following two articles. I think adding these two articles to the introduction or discussion part can make the argument more complete.
PMID: 35284509
PMID: 34159158
Reply 9: These studies have been incorporated to the introduction and discussion.
Changes to text: 90-93, 408-409