

Jin-Lei Wang

Company Editor-in-Chief

World Journal of Transplantation

Re: Manuscript #78241 (Review); Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation

Dear Editor,

Thank you for your time to review our submission to your journal. Your suggestions and the reviewers' comments have been extremely helpful for the final development of our manuscript. Please find below (underlined) the changes that we have made to our initial submission in response to your suggestions and the reviewers' comments.

Company editor-in-chief comments:

Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 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 PowerPoint (PPT): Copyright ©The Author(s) 2022.

Thank you for this important comment. Attached, please find a PowerPoint (PPT) file that contains the Figure accompanying the Review. All the necessary arrangements have been made, and the arrows and text portions can be

reprocessed by the editor. Also, the copyright information has been added to the bottom right-hand side of the picture, as requested.

Reviewer #1 comments:

I have 2 suggestions that I hope the author can consider: 1. Immunotherapy for liver cancer patients generally requires specific dosage regimens, including drug doses and drug varieties, which may be one of the reasons why immunotherapy cannot be promoted on a large scale, especially in smaller hospitals. 2. Although liver transplantation is one of the treatments for liver cancer, the paucity of donors substantially limits the popularization of this treatment. Is it possible to do autologous liver transplantation following immunotherapy?

Thank you for these important comments.

We added the following paragraph to address your first suggestion (*Immunotherapy for liver cancer patients generally requires specific dosage regimens, including drug doses and drug varieties, which may be one of the reasons why immunotherapy cannot be promoted on a large scale, especially in smaller hospitals*) just before the chapter “Immunotherapy as a downstaging therapy prior to liver transplantation”.

Although combination immunotherapy is a superior approach than single-agent immunotherapy for the treatment of HCC, there are a few remarks that need to be pointed out. The need of combining various immunotherapeutic drugs in specific dosages may come as a challenge for smaller hospitals that are neither readily equipped, nor familiar with the specific combination regimens used to treat HCC. The lack of availability of highly efficacious drugs in resource-limited hospitals prevents the widespread application of immunotherapy, leaving healthcare providers with a restricted panel of drug options, mainly systemic chemotherapeutic agents, that, although effective, do not demonstrate the superiority of immunotherapy in treating HCC. Unfortunately, this hurdle inevitably affects pre-transplant ICI use for the same reasons mentioned above.

We added the following paragraph to address your second suggestion (*Although liver transplantation is one of the treatments for liver cancer, the paucity of donors substantially limits the popularization of this treatment. Is it possible to do autologous liver transplantation following immunotherapy?*) just before the chapter “ c. Clinical trials and case reports assessing the use of immunotherapy as a downstaging technique prior to LT in patients with HCC”.

As already mentioned before, the paucity of available donors for LT substantially limits this treatment approach for the management of HCC. Although currently not employed in the armamentarium of HCC management, autologous LT is a theoretically promising approach that could increase the number of patients receiving curative treatment. Data regarding autologous LT following immunotherapy are not yet available, but a hypothetical explanation of the mechanism behind this approach could ignite future discussions around this topic. Liver regeneration capabilities are well studied in the literature. The effects of immunotherapy in the TME have been extensively discussed above and generally promote an antitumoral immune response that aims to halt tumor progression and decrease tumor burden. As such, more liver parenchyma can be restored to its physiologic architecture. Such an occurrence can aid in the autologous LT process by increasing the available tissue for extraction and reimplantation following diseased liver removal. As ideal as this approach may sound, challenges along the way, such as remaining unidentified tumor burden, metastatic disease and recurrence of malignancy are all topics of concern that need further investigation. For the time being, autologous LT following immunotherapy requires more research in order to delineate the exact mechanisms that could result in positive outcomes.

Reviewer #2 comments:

The theme is interesting and appealing to readers. The content is reasonable, the structure is clear, and the language is appropriate and easy to understand.

Thank you for your comments and your time to review our work.

We hope that the above mentioned changes satisfactorily address your comments and that our revised manuscript will now be approved for publication in your journal.

Sincerely,

Emmanouil Sinakos