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Reply to: Considerations on "Impact of ABO-incompatibility on hepatocellular carcinoma recurrence after living donor liver transplantation"

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We appreciate Luca Morelli and colleagues for reading and commenting on our study entitled "Impact of ABO-incompatibility on hepatocellular carcinoma recurrence after living donor liver transplantation" [1]. The issues they brought up need to be addressed.

The main issue raised in their letter regarding our manuscript is whether or not Rituximab is closely linked with HCC recurrence in ABO-incompatible (ABO-I) living donor liver transplantation (LDLT). Rituximab was recently reported to be effective in preventing antibody-mediated rejection (AMR) as a desensitizing regimen so that it has brought about acceptable outcomes in LDLT [2,3]. However, there has been limited evidence on the effects of Rituximab from the standpoint of the oncologic outcomes of ABO-I LDLT for hepatocellular carcinoma (HCC). This lack of data was the starting point for our research. In this study, Rituximab was given to all ABO-I LDLT patients with plasmapheresis performed only in the early period. Otherwise patients from both groups were on the same immunosuppression protocol. So the only difference in the matter of immunosuppression was the use of rituximab. Accordingly, from the comparable outcomes between the two groups, it could be deduced that depletion of B cells by Rituximab doesn't affect HCC recurrence after LDLT. However, some of the most important limitations of our study include the small sample size, a relatively short follow-up period of a median 40.2 months (interquartile range, 28.3–48.8), and its retrospective, non-randomized design from a single institution. Although reasonable attempts were made to overcome the effects of confounders other than ABO incompatibility through propensity score matching, these preliminary results should undoubtedly be corroborated by larger multicenter trials before being established as an advisable clinical practice.

Abbreviations: ABO-I, ABO-incompatible; AMR, Antibody-mediated rejection; HCC, Hepatocellular carcinoma; LDLT, Living donor liver transplantation.

Another point at issue is that LDLT can be considered for patients with HCC beyond the Milan criteria. The similar but poor outcomes of both groups in this study can surely raise an ethical issue accompanied by professional skepticism.

The Milan criteria were initially proposed for deceased donor liver transplantation in which the donor grafts were allocated by the public organ sharing system. However, in LDLT, living donor grafts are dedicated only to their respective recipients. Therefore, a lower expected survival rate could be tolerated in LDLT on the condition of shared treatment decision making by which the physicians informed patients of research information about available HCC treatments including LDLT and their benefits and risks while the patients brought personal information about their illness, lifestyle and values. This close interaction can lead to an agreement on LDLT as the best treatment option.

Actually, in this study, all ABO-I LDLTs were performed as the only option for curative treatment in patients who had no ABO-compatible living or deceased donor. At the authors' institution, deceased donor liver transplantation is performed in less than 5% of all patients undergoing liver transplantation while most patients undergo LDLT. Furthermore, lots of expanded criteria have already been suggested and are currently being used to transplant patient beyond the Milan criteria although they still remain to get widespread acceptance.

The impact of immunosuppression in patients with HCC warrants further investigation for the time being. So, various modalities of Rituximab free immunosuppressive regimens or a tailored modulation of immunosuppressive regimen that were also mentioned in their letter will hopefully be good topics for further research on ABO-I LDLT for HCC.

In conclusion, ABO-I LDLT can be considered a feasible option of treatment for HCC in patients with no compatible donor. However, further studies are needed for the exact mechanism for rituximab-induced immune system impairment and its relationship with HCC recurrence.

Conflict of interest statement

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