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

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To the Editor:

We read with great interest the article by Kim et al. entitled "Impact of ABO-incompatibility on hepatocellular carcinoma recurrence after living donor liver transplantation" [1] recently published on European Journal of Surgical Oncology.

ABO-incompatible living donors liver transplantation (ABO-I LDLT) is associated with a high risk of antibody-mediated rejection (AMR), lower patient and graft survival and a high risk of vascular thrombosis and ischemic bile duct complications if compared to ABO-compatible LT. Despite this, it represents a precious opportunity for patients affected by hepatocellular carcinoma (HCC), shortening the waiting time for surgery and minimizing disease progression that might occur waiting for an ABO-compatible living or deceased donor.

A concern may arise that additional immunosuppression required for ABO-I LDLT may increase the likelihood of HCC recurrence after LDLT, because high-dose immunosuppressive treatment may inhibit tumour surveillance properties of the immune system. Basic science findings together with several clinical experiences indicate that not only the type or schemes of immunosuppressive regimen but, even, the total immunosuppressive load plays a role in cancer recurrence [2] advocating for a "minimization" of immunosuppressive protocols.

Rituximab, a murine/human monoclonal chimeric antibody against CD20 depleting B-lymphocytes, has traditionally been used to treat haematological malignancies and autoimmune diseases. More recently, it has been gained interest as an immunomodulatory agent in solid organ transplantations [3]. The main finding of the study by Kim et al. is that Rituximab was shown to be effective in preventing antibody-mediated rejection (AMR) as a desensitizing regimen and not associated with HCC recurrence in ABO-I LDLT. Current literature is more and more supporting the finding about the effectiveness of Rituximab in AMR prevention, but the conclusions of Kim et al. on HCC recurrence need discussion. Firstly, the limited sample size and short follow-up period cannot be considered adequate to assess the HCC recurrence rate, especially considering the concomitant immunosuppressant therapy. It is also important to note that patients with HCC beyond the Milan criteria showed really poor outcomes, with 2-, 3- and 4-years recurrence free survival rates of 52%, 39% and 18% for ABO-compatible LDLT and of 26%, 16% and 5% for ABO-I LDLT respectively. These numbers should raise the ethical issue whether a living donor should be considered for Milan-out recipients.

Moreover, different modalities of Rituximab free immunosuppressive regimens to prevent AMR have been successfully reported in literature, such as the use of high-dose polyclonal intravenous immunoglobulin associated with plasmapheresis without the use of steroid pulses or monoclonal antibodies, or even of everolimus-based immunosuppressive regimen under a strict monitoring of anti-A/B antibodies titres [4,5].

Furthermore, no data have been reported on subtypes of A donors (e.g. A2 → 0) which should require a tailored modulation of immunosuppressive regimen [6].

In conclusion, we strongly believe that more and more efforts should be make to minimize the immunosuppressive regimen in ABO-I LDLT in order to reduce HCC recurrence rates and improve long term graft survival. Longer follow up is required to validate ABO-I LDLT experience.

Conflict of interest statement

Dr Desirée Gianardi, Dr Davide Ghinolfi, Dr Simone Guadagni and Prof. Luca Morelli have no conflicts of interest or financial ties to disclose.

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