Editorial

Targeting intra-tumoral lactic acidosis in hepatocellular carcinoma: a long way to go

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Hepatocellular carcinoma (HCC) is the sixth commonest cancer worldwide and at first presentation more than 80% of patients are beyond surgical resection and cure (1). The Barcelona Clinic Liver Cancer (BCLC) staging system, which links the disease stage to a specific treatment strategy, is used to inform treatment decisions. According to this algorithm, transarterial chemoembolization (TACE) is offered in patients with intermediate stage HCC, who do not have a curative potential (2). TACE consists of the selective injection of a chemotherapy agent in the hepatic artery branch that feeds the tumor, followed by the administration of an embolizing agent (3). HCC demonstrates neo-angiogenic activity and meta-analysis have shown that bland embolization (TAE) or TACE confer a survival benefit, improving the median survival from 16 to 20 months (2).

The study by Chao *et al.* (4) studied the local infusion of bicarbonate solution simultaneous to TACE treatment (TILA-TACE) in order to improve tumor response as compared to standard TACE. The primary outcome of the study was the number of viable tumor residues (VTR), while tumor response using the EASL criteria and overall survival were secondary outcomes.

The rational for this study is based on the observation that lactic acidosis is common in solid tumors as a consequence of the Warburg effect, during which aerobic glycolysis converts glucose into excessive amounts of lactate despite adequate oxygenation. Lactic acidosis protects solid tumors from a potentially detrimental glucose deprived state through creating a microenvironment that facilitates tumor cell resistance to glucose-deprivation (5). A study by Xie *et al.* using culture medium described that removing this protective microenvironment through the manipulation of the tumor pH demonstrated a potential method of controlling tumor growth (5). Tumor cell survival, in the presence of glucose deprivation, is facilitated by acidosis through both the efficient utilization of glucose as well as the transformation of the cell into the (protective) dormant state when it becomes glucose deprived (5). The authors of this study have therefore proposed that by inhibiting this process using a bicarbonate infusion and thereby removing the protective micro-environment of the tumors one could enhance the effect of the TACE procedure, increasing its effectiveness.

The study was conducted in two stages; initially a case control study of 57 patients, comparing TILA-TACE with historical patients who underwent TACE. This data was then used to calculate a sample size of 20 patients for the randomized controlled trial to further evaluate the same intervention.

The TILA-TACE procedure consisted of the selective infusion of bicarbonate 5% in the tumor artery, the amount of which depended on the size of the tumor. This was infused alternatively with the chemotherapy regimens of doxorubicin-lipiodol emulsion and oxaliplatin-homocamptothecin and was subsequently followed by the use of polyvinyl alcohol (PVA) to complete the embolization. The method remained the same for both the case-control and randomized cohorts. Given the heterogeneity between studies looking at the efficacy of TACE, there remains

debate concerning the most efficacious regimens and timing of administration to use. However, the authors used widely accepted chemotherapeutic and embolizing agents for the TACE procedure.

In the non-randomized cohort, Chao *et al.* reported an improvement of VTR in the TILA-TACE group of 7.1% as compared to 45.1% in the TACE group (P<0.001), while the VTR improvement in the randomized arm in the TILA-TACE group was 80% (P=0.008). The results remained the same after adjustment for BCLC stage, age and extra-hepatic metastases.

When examining the results according to the EASL criteria they additionally reported significant improvements in complete or partial responses. In the non-randomized cohort results of complete response (CR), partial response (PR), stable disease (SD) or progression of disease (PD) were 23%, 77%, 0%, and 0% respectively in the TILA-TACE group as compared to 0%, 44%, 33%, and 22% in patients treated with TACE (P<0.0001). Similarly in the randomized group the CR, PR, SD and PD improved from 9%, 55%, 18% and 18% respectively in the cTACE cohort to 33%, 66%, 0% and 0% in those treated with TILA-TACE (P=0.003). In regards to overall survival, although there was a numerical improvement, this was not statistically significant.

There are various points worth commenting on in this study. Firstly, although there is a theoretical benefit of TILA-TACE, there is no published evidence that lactic acidosis is present or has a protective effect in HCC. Data on the effects of lactic acidosis in cancer cell survival are only available from cell lines, therefore it is unknown if this effect is significant *in vivo*. Moreover, there is no data on the effects of high lactate levels on survival in clinical cohorts of HCC. Therefore, one would expect experimental data with the effect of various doses of bicarbonate in cancer cells and animal models to precede the use of this method in a clinical setting.

Secondly, viable tumor residue, which was the primary outcome of the study, is an unvalidated measure of tumor response with questionable relevance. To the best of our knowledge, VTR has not been tested before in patients with HCC and there are no data on its correlation with disease progression, treatment response or survival. It would make much more sense to use the EASL (or even better the mRECIST) response criteria in order to inform the sample size calculation for the randomized trial. It seems that the selection of this endpoint was based on convenience (in order to justify an RCT with small number of patients) rather than clinical relevance.

Thirdly, a number of patients were inappropriately allocated to TACE. When utilizing TACE, there is much emphasis on patient selection in order to maximize benefit and also prevent the induction of liver failure secondary to treatment. As such it is advocated that macroscopic vascular invasion or extrahepatic spread are major contraindications to its use. Therefore only patients at a BCLC B staging, i.e., asymptomatic multinodular disease, should be considered for treatment (2). When reviewing the patient selection group in this paper it is evident that a significant number of the patients lie outside these inclusion criteria and were thus inappropriately selected. In the non-randomized study, 20 of 57 patients were staged BCLC C, with 9 demonstrating macrovascular invasion and 16 known to have extrahepatic metastases. Similarly when looking at the RCT, 5 of 20 patients were BCLC C with evidence of both macrovascular invasion and extrahepatic metastases.

TACE as a local treatment is an independent prognostic factor in BCLC B patients, however it is difficult to extrapolate this for patients who already have distant metastasis and therefore despite the improvement demonstrated in VTR in these patients it is questionable if this is translated in to clinical benefit or if it could actually confer harm.

In conclusion, the use of bicarbonate as an infusion in this study has shown some promising results that warrant further investigation into its use. What is needed first however is a signal that HCC is associated with increased lactic acidosis and that this can be reversed with bicarbonate infusion. This would most likely require an experimental HCC model to start with. If there is an effect, then a phase IIa RCT using the mRECIST criteria in eligible BCLC B patients should be conducted. Ultimately, an adequately powered phase III RCT in BCLC B stage HCC with hard primary endpoints such as survival would be required. Until such trials are performed, the results of this study can only be regarded as preliminary and TILA-TACE should not be used in routine clinical practice.

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