Editorial

Radioembolization in the setting of liver transplantation: great expectations or hard times?

Quirino Lai, Gianluca Mennini

Hepato-bilio-pancreatic and Liver Transplant Unit, Department of Surgery, Sapienza University of Rome, Rome, Italy

Correspondence to: Quirino Lai, MD, PhD. Department of General Surgery and Organ Transplantation, Hepato-bilio-pancreatic and Liver Transplant Unit, Sapienza University of Rome, Umberto I Policlinic of Rome, Viale del Policlinico 155, 00161 Rome, Italy. Email: lai.quirino@libero.it.

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Trans-arterial radio-embolization (TARE) with yttrium-90 represents one of the most efficacious approaches for the treatment of selected patients with advanced hepatocellular cancer (HCC) (1). Recent studies have confirmed the superiority of TARE when compared with other intra-arterial treatments (2,3). A randomized phase II study comparing TARE and trans-arterial chemo-embolization (TACE) in HCC patients meeting Barcelona Clinic Liver Cancer stages A-B showed a longer median time-to-progression (>26 *vs.* 6.8 months; P value =0.001), and a better tumor control in post-TARE cases (2). Another study similarly compared TARE and TACE patients homogeneously selected using a propensity score matching: also in this case, TARE presented higher overall complete response rates (84% *vs.* 58%; P value <0.001), and longer median progression-free survivals (564 *vs.* 271 days; P value =0.002) (3).

In the specific setting of advanced HCC, TARE presents the undoubtful benefit of being the sole strategy, apart sorafenib, able to treat tumor-related portal vein thrombosis (PVT). A propensity score match analysis comparing TARE and sorafenib showed similar efficacy in terms of tumor control and progression (4). A systematic review based on 722 patients further confirmed that TARE is a safe and effective treatment for HCC patients with PVT (5). However, prospective randomized studies are still lacking in this specific setting (6).

It is clear that the opportunity to use TARE for efficaciously down-stage advanced and not-transplantable cases, even initially presenting macrovascular invasion, represents an attractive opportunity for liver transplantation (LT) physicians (7-9). A study comparing 172 HCC cases initially bridged/down-staged with different approaches (TARE =93; TACE =79) and then undergoing LT showed a trend towards better recurrence-free survivals in down-staged patients treated with TARE (7). Another study specifically investigating the ability of TARE *vs.* TACE to down-stage HCC cases from a Milan Criteria (MC)-OUT to a MC-IN status, showed that TARE was superior in terms of partial response rates (61% *vs.* 37%) and down-staging achievement (58% *vs.* 31%) (8).

In a recent study by Levi Sandri *et al.*, four cases even presenting initial tumor-related PVT were first down-staged and then efficaciously transplanted (9). Interestingly enough, these four cases corresponded to approximately 20% of all the cases down-staged using TARE, further suggesting that the systematic use of TARE should present a non-marginal role in improving the number of potentially transplantable patients. Another interesting aspect to underline was the very long waiting time reported from TARE to LT, with a mean time of approximately 16 months. As a matter of fact, in absence of available intention-to-treat analyses, it sounds acceptable that the proof of time should be retained necessary with the intent to select post-TARE good-responders.

However, some concerns may also be addressed with regard to the liberal use of TARE. Obviously, the high costs of the procedure should be at least balanced by a congruous number of patients efficaciously down-staged. A risk of radiological overestimation of post-TARE response exists.

A study comparing radiological and pathological response after TARE showed that different radiological criteria like the modified response evaluation criteria in solid tumors were not able to reliably predict complete pathological necrosis (10). Another study confirmed such an evidence, however reporting that post-TARE imaging findings of response were somehow predictive of the degree of pathologic necrosis (11).

This evidence further corroborates the attitude of Levi Sandri *et al.* to await for at least 6 months before LT, with the intent to confirm the effective validity of the radiological findings. In light of this, we should like to underline the role of biological markers like the alpha-fetoprotein (AFP) slope, as an important tool for selecting patients with HCC progression. In the series reported by Levi Sandri *et al.*, all the cases showed an AFP slope reduction, thus confirming the efficacy of the treatment.

Another important aspect to consider is the risk of post-TARE toxicity. Such an aspect is important mainly for patients waiting for LT, due to the possible risk of drop-out after liver decompensation. As a matter of fact, TARE should be considered only in case of patients at low-risk of being jeopardized by its use.

A systematic review based on 31 observational studies reported different complications (i.e., gastric ulcers, hepatic encephalopathy, cholecystitis, hepatic failure, pleural effusion, ascites, nausea) (12).

It is however clear that TARE represents an extraordinary opportunity for HCC patients, mainly in case of PVT. Recent studies comparing TARE and sorafenib (13) or hypothesizing their combinative role (14) showed very interesting preliminary results.

A recent study by Salem *et al.* further confirmed the great expectations for TARE: after a 15-year long experience and a series of 1,000 patients treated with TARE, the centre of Chicago has recently decided to adopt TARE as the first-line trans-arterial loco-regional treatment for all the patients with HCC (15).

In conclusion, TARE represents an excellent therapy for advanced HCC patients, mainly in presence of PVT. Only a very limited number of article exists investigating the opportunity to transplant patients initially presenting macrovascular invasion and efficaciously down-staged with TARE. It looks clear that intention-to-treat analyses are required, mainly with the intent to understand how many patients will be able to be down-staged to criteria of transplantability. A mandatory waiting-time of at least 6 months looks to be another important strategy in this specific setting. Our opinion is that in the next future hard times may be unfortunately postulated for non-responders, mainly in terms of tumor progression, toxicity and liver decompensation. However, also great expectations may exist for patients efficaciously treated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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