Editorial

Bridging to liver transplantation patients with a hepatocellular carcinoma within Milan criteria: how worth is it?

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The American Association for the Study of the Liver has recently provided conditional recommendations for locoregional ablative therapy to consolidate listing to liver transplantation of patients with a hepatocellular carcinoma (HCC) fulfilling the Milan criteria (MC, OPTN T2), an approach aiming at preventing tumor progression and patients to be delisted accordingly (1). The European association for the Study of the Liver released the same recommendation, however focusing on the subset of patients within MC with a projected waiting time of at least 6 months (2). This notwithstanding, the success of a bridge therapy is often challenged by a number of factors inherent with tumor biology, like development of micro and macrovascular invasion by tumor cells, occult spread of tumor cells and enhanced tumor proliferation, that are difficult to identify and only occasionally are captured by such surrogate markers as serum kinetics of alpha fetoprotein (AFP) and tumor cell grading. In the end, a maintained radiological response to bridge therapy over a reasonably long waiting time stands as the most comprehensive predictor of tumor control, granting for a successful listing even though such an approach lacks standardization with respect to the choice of ablative technique (radiofrequency versus transarterial embolization or other techniques), end-points of treatment (tumor eradication versus tumor downstaging) and radiological criteria to assess a response (RECIST versus modified RECIST) (1,3). Transarterial (chemo) embolization, TA(C)E, has extensively been employed to bridge both patients outside and within MC, the latter group reaching delisting rates of 8.6% in 116 patients in Austria, that was accompanied by 14% rates of HCC recurrence (4). In this cohort, the 5-year survival from listing was as high as 85% in the subset of patients who achieved a complete response versus 64% in those with partial response and 51% in non-responders (4). Though a few studies have reported a good response to TACE (>60% tumor necrosis) leading to improved long-term survival after transplantation and lower rates of recurrence (5), the survival benefits provided by this form of bridge therapy are not universally recognized, yet TACE remains a widely used technique in clinical practice. No doubts that radiofrequency ablation (RFA) and microwave ablation (MWA) are perceived as stronger options for bridging treatment than TACE, in some studies resulting in a significant reduction of the dropout rates from the waiting list, with the obvious caveat that the success in achieving a complete necrosis was driven by the initial size of the target lesion. Indeed, the nodules with a diameter of 2.5 cm or less were prone to achieve higher rate of complete necrosis, up to 90% of cases, as compared to larger nodules

of 5 cm in diameter or greater, that might better benefit from treatment with MWA. This latter approach causes, in fact, larger areas of necrosis being more performant than RFA in multifocal tumors and nodules located near large vessels, mainly because of the lack of 'heat sink' effect. However, despite reports of high response rates with MWA (6,7), yet a clear advantage of this approach over RFA has not been demonstrated in appropriate trials whereas no data are available on RFA applied to patients with a HCC within MC. Importantly, as randomized controlled studies are lacking to evaluate the cost-effectiveness of bridge therapy in patients within MC, the only insights we may have are distilled from large cohort studies, even though in these studies the risk of biased evaluation of the clinical benefits provided by interventions, is not fully abrogated as well.

In one such large retrospective study by Agopian and colleagues, pre-transplant bridge therapy with a variety of locoablative techniques was delivered to more than 2,700 patients with a HCC within MC treated in 20 academic centers in the US, without resulting in any survival and tumor recurrence benefit (8). Interestingly enough, while any modality of locoregional therapy was not decisive in driving patient outcome, the delivery of increasing number of treatments associated with an increased risk of recurrence following liver transplantation, all in all determining a worse prognosis. As expected, a complete pathological tumor response and a reduction in serum levels of AFP after treatment of HCC were both associated with reduced recurrence rates and extended survival, thus confirming previous observations in patients beyond MC (9-11). By the same token, patients who failed to achieve a complete pathological response to bridge therapy faced a higher risk of recurrence compared to patients who did not receive any local therapy for their HCC, with deleterious clinical consequences. While this was the larger cohort in which efficacy of bridge therapy in patients with a HCC within MC was assessed, outcome assessment is clouded by significant methodological inconsistencies that are not unexpected in studies based on retrospectively recruited cohorts of patients and leave many questions unanswered. One major query relates to the lack of identification of those patients who initially were within MC and subsequently dropped from the wait list, making therefore impossible to assess whether the clinical benefits provided by locoregional therapies to this special population included also prevention of delisting due to tumor progression. Such a benefit, instead, was demonstrated in a small retrospective study in Italy, where DEB-TACE was delivered "a la demande" to 55 patients with 79 tumors within MC until complete tumor devascularization or progression beyond MC was reached (12). In that study, a complete radiological response was achieved in 32 (58%), and was maintained up to 4 months in 21 (38%) and up to 7 months in 17 (31%), respectively, leading to the accumulation of progressive tumors beyond MC at 12 and 24 months in 30%, and 54% of the patients, respectively and causing MC to be preserved for a median of 19 (range, 2–63) months, on average. Another important information overlooked by the report by Agopian and colleagues, is the length of waiting time elapsed between achievement of a radiological response to locoablative therapy and transplantation, which is known to predict how safe is listing to liver transplantation in terms of risk of recurrence (3). To some extent, the correlation between increased recurrence and higher number of local ablative procedures observed by Agopian and colleagues may be misleading as it underscores the presence of multiple or difficult to cure tumors that in the end are more than prone to recur. The reassuring message of Dr. Agopian and associates report is to confirm that achieving a complete radiological response after a limited number of TACE associates to a better outcome after transplantation (13) whereas a complete radiological response to the first TACE in one study was the strongest independent predictor of MC maintenance (12). Needless to say, these findings contrast with experiences in patients with an intermediate stage of HCC where a progressively better response to serial TACE courses was the strong predictor of patient survival (14). In the study by Agopian, it would be worth clarifying whether transplant outcome differed by the number of locoregional treatments in the subgroup who achieved a complete pathological response, an uncertainty reflecting the lack of a predefined algorithm administered to all participating centers that might have resulted in an impactful referral bias across the patients in study. Along this line, it might be worth knowing whether a correlation exists between explant pathology and radiological response after each procedure, as this data might help refining the management of patients enrolled into bridge therapy protocols. This information might also help building prediction of recurrence-free survival, disease-specific survival, and cumulative incidence of recurrence after controlling for the competing risk of non-HCC mortality in patients achieving a complete radiological response. Worth to be annotated is that in the present study an AFP decline after bridge therapy did predict an attenuated risk of recurrence and mortality, a finding that aligns with a recent report from the group of

Yao and Colleagues (15), where 390 patients in the United Network for Organ Sharing (UNOS) registry underwent transplantation having AFP >1,000 ng/mL at least once prior to liver transplantation with tumor burden initially within MC or within University of California San Francisco (UCSF) criteria downstaged. The 5-year post-transplant survival for those with AFP >1,000 ng/mL at transplant was much shorter (48.8%, versus 67.0% and 88.4%) compared to those with AFP between 101–499 and <100 ng/mL, respectively (P<0.0001). The probability of HCC recurrence at 5 years was 35% with AFP >1,000 ng/mL versus 13.3% for AFP between 101–499 ng/mL (P=0.0006) and 7.2% for AFP <100 ng/mL (P<0.0001). In that study, the kinetic of AFP decline, i.e., the median time for AFP decline from >1,000 to 101–499 and to <100 ng/mL was of strategic importance, being in fact 88 and 181 days, respectively.

Taken together, these data and those by Agopian and colleagues suggest that even in patients with a HCC within MC achieving a complete radiological response must be the real objective of bridge therapy as it maximizes the clinical benefits, whereas caution should be exercised not to take straightforward the increasing number of bridge treatments as a negative predictor of outcome: a complete pathological response in difficult to cure tumors might take many courses of therapy that ultimately may still result in a reduced risk of tumor recurrence and improved survival compared to untreated patients.

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Footnote

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

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