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Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate

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Summary

The practice of treating candidates for liver transplantation (LT) for hepatocellular carcinoma (HCC), with locoregional therapies, is common in most transplant centers. However, for T1 tumors and expected waiting times to LT <6 months, there is no evidence that these treatments are beneficial. For T2 tumors and for longer waiting times, neo-adjuvant treatments are usually performed with transarterial chemoembolization (TACE), ablation techniques and liver resection in selected cases. The treatment choice should be based on the BCLC staging system. At present, there is no evidence of the superiority of ablation/resection *vs.* TACE, but some studies showed better results of the former in achieving a complete response. The response to neo-adjuvant treatments should be evaluated through mRECIST criteria, but few studies adopted these criteria and properly analyzed factors affecting response. The simultaneous evaluation of the impact of neo-adjuvant therapies on dropout rate, post-LT HCC recurrence and patient survival is rarely reported. Tumor stage and volume, alpha-fetoprotein levels, response to treatments and liver function affect pre-LT outcomes. These same factors, together with vascular invasion and poor tumor differentiation, are major determinants of poor post-LT outcomes. Due to the low number of prospective studies with well-defined entry criteria and the variability of results, the role of downstaging is still to be defined. Novel molecular markers seem promising for the estimation of prognosis and/or response to treatments. With a persistent scarcity of organ donors, neo-adjuvant treatments can help identify patients with different probabilities of cancer progression, and consequently balance the priority of HCC and non-HCC-candidates through revised additional scores for HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the 5 most common malignancies worldwide, and its incidence is increasing in Western countries [1,2]. For patients with HCC and cirrhosis, liver transplantation (LT) represents the treatment of choice and provides excellent oncological results and a cure for cirrhosis. However, not all patients with HCC and cirrhosis can undergo transplantation because of the scarcity of liver donors.

HCC patients on the waiting list (WL) for transplantation can experience tumor growth beyond the accepted criteria for LT; the practice of treating HCC patients with hepatic resection or locoregional therapies before they are placed on the WL or while they are awaiting has thus gained favor and is now the standard of care in most transplant centers [3–6].

Radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transarterial chemoembolization (TACE) have considerably improved in the last decade, and they can have a positive impact on tumor growth control [3–7]. Similarly, the great improvements in diagnostic techniques and surveillance schedules have led to earlier diagnoses and better accuracy, and this has resulted in the increased curability of liver tumors.

Locoregional treatments can be used as neo-adjuvant therapies with two intents in the setting of LT. The first one is to prevent the dropout from the WL in patients meeting accepted criteria of transplantability; in this case, locoregional treatments are defined as bridging procedures. The second one is to treat patients initially outside criteria for LT in order to reach T2 stage HCC, to fulfill Milan criteria (MC) [8], University of California San Francisco criteria (UCSFC) [9], or other criteria, which allows entry to the WL for LT after an adequate period of follow-up, to verify the effectiveness of neo-adjuvant treatment. In this case, locoregional therapies are used as downstaging procedures.

Keywords: Hepatocellular carcinoma; Liver transplantation; Locoregional treatments.
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Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; WL, waiting list; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; MC, Milan criteria; UCSFC, University of California San Francisco criteria; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE-DEB, TACE with Drug-Eluting Beads; TARE, Trans-arterial radioembolization; MELD, Model for End-stage Liver Disease; HCV, hepatitis C virus; deMELD, dropout equivalent MELD.

Key Points

- Locoregional treatments are widely used in cirrhotic patients with hepatocellular carcinoma (HCC) listed for liver transplantation (LT) in order to prevent tumor progression, even though there is no strong evidence that neo-adjuvant treatments should be applied if the expected waiting time for LT is shorter than 6 months
- Neo-adjuvant treatments include transarterial chemoembolization (TACE), radiofrequency ablation, ethanol injection and liver resection, which should be selected according to the Barcelona Clinic Liver Cancer (BCLC) scoring system
- Other procedures, such as TACE with drug-eluting beads, transarterial radioembolization, radiotherapy, microwave ablation, cryoablation and irreversible electroporation, though promising, are still under investigation
- The efficacy of neo-adjuvant treatments should be evaluated by the rate of dropout from the WL and, methodologically, with a 3-month interval reassessment of modified Response Evaluation Criteria in Solid Tumors (mRECIST) and serum alpha-fetoprotein sampling
- Neo-adjuvant treatments have the 3 main purposes of controlling HCC progression for expected long waiting times, identifying patients with different probabilities of cancer progression and helping in balancing the priority of HCC and non-HCC candidates for LT

In order to assess the actual evidence of the impact of neo-adjuvant treatment in the management of potential candidates for LT, the following items will be discussed in the present paper:

(1) Are neo-adjuvant locoregional treatments indicated in patients considered for LT?
(2) How should response to locoregional treatments be evaluated, and what timing should be adopted for patient monitoring on the WL?
(3) Which types of locoregional treatment are available for patients considered for LT?
(4) Which is the best neo-adjuvant treatment in this setting?
(5) Which are the patient or tumor characteristics related to an unsuccessful neo-adjuvant therapy, a higher dropout rate, and a worse post-LT outcome?
(6) Can the effect of neo-adjuvant treatments be used to balance priority of HCC and non-HCC candidates?
(7) Are there new molecular markers for a better estimation of tumor biological behavior and/or response to treatment?

Are neo-adjuvant locoregional treatments indicated in patients listed for LT?

An international consensus conference was held in 2010 with the aim of reviewing current practice regarding LT in patients with HCC and to develop internationally accepted statements and guidelines [10]. Thirty-seven statements covering all issues of LT for HCC were produced; among these, 5 statements were focused on the management of patients on the WL. No recommendation could be made on bridging therapy in patients with United Network for Organ Sharing (UNOS) T1 HCC due to the absence of scientific evidence. In patients with UNOS T2 HCC and a likely waiting time longer than 6 months, locoregional therapy may be appropriate, but the low level of evidence for prognosis led to a weak recommendation. In fact, a cost-effective analysis based on Markov model and the review of cohort studies, indicate a benefit for bridging therapies if the waiting time is expected to be longer than 6 months [11–14]. However, in the clinical practice and given the often unpredictable waiting time for LT, there is a widespread attitude to treat most patients in the WL. In the following sections of this review, we will focus on the possible benefits derived from the routine adoption of neo-adjuvant treatments.

How should response to locoregional treatments be evaluated?

Whatever the type of locoregional therapy chosen, the response to neo-adjuvant treatments should be evaluated with the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [15,16]. The RECIST criteria were amended as mRECIST in 2008, based on the concept that the evaluation of the treatment response should take into account the induction of intratumoral necrotic areas in estimating the decrease in tumor load, and not just a reduction in overall tumor size [17].

Patients can be followed with either contrast-enhanced spiral computed tomography (CT), preferably with use of multislice scanners, or contrast-enhanced dynamic magnetic resonance imaging (MRI). The administration of intravenous contrast is recommended for CT and MRI, if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver [15,16].

According to mRECIST criteria, the following definitions should be applied for tumor response to treatment: (A) complete response: the disappearance of any intratumoral arterial enhancement in all target lesions; (B) partial response: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as the reference the baseline sum of the diameters of target lesions; (C) progressive disease: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as the reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started; (D) stable disease: any cases that do not qualify for either partial response or progressive disease [15,16].

Overall response is a result of the combined assessment of target lesions, non-target lesions, and new lesions.

Unfortunately, studies focusing on neo-adjuvant treatments before LT do not report the response to this therapy with uniform and/or well-defined parameters, and mRECIST, in particular, have rarely been used so far. Relationships between response to therapy and dropout from WL should represent the main aim of any dedicated study on this issue, and the capability of any proposed neo-adjuvant treatment should be assessed in the view of dropout due to tumor progression rather than response by itself.

Conversely, there is general agreement that monitoring of patients on the WL should be performed with the above reported