Hepatocellular Carcinoma Patients Awaiting Transplant: General Guidelines for Management

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Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. The incidence of hepatocellular carcinoma is increasing in the United States and worldwide. Orthotopic liver transplantation (OLT) is a viable and potentially curative option for selected patients with HCC. Locoregional therapy has been used to control HCC before transplantation because of the limited number of donor organs, to prevent tumor progression, and to decrease the incidence of dropouts from the transplant waiting list. Traditionally, multiple investigational locoregional modalities such as tumor resection, radiofrequency ablation, transarterial chemoembolization, and systemic chemotherapy have been used as "bridging" therapies. While the investigation of novel neoadjuvant treatments is justified in an effort to prevent tumor progression, the absence of randomized controlled trials leaves uncertainty about the utility of these maneuvers in improving outcome. This review summarizes the current data on the different modalities used worldwide in the neoadjuvant treatment of hepatocellular carcinoma, the rationale for these approaches, efficacy, potential complications, and future prospects.

Liver transplantation is frequently the preferred treatment of hepatocellular carcinoma (HCC). Transplantation extirpates both the underlying malignancy and the nontumorous cirrhotic parenchyma, which is at risk of developing de novo tumors. While liver transplantation is currently the accepted best treatment for HCC in the cirrhotic patient, only patients with HCC tumors that meet strict morphologic criteria (Milan or University of California, San Francisco [UCSF]) are generally offered transplantation. In addition, as demand for liver transplantation increases, patients are confronted with longer waiting times. As such, there is considerable interest in preventing progression of disease in patients on the waiting list. In the accompanying article, Dr. Almhanna and colleagues review the current state of the literature and attempt to answer the question: "Is there an optimal neoadjuvant therapy for patients with HCC awaiting transplantation?" While providing a helpful overview of several pertinent studies, Dr. Almhanna and colleagues fail to offer even a preliminary answer to this query. Although the preponderance of data on bridging therapy for HCC is clearly suboptimal—coming largely from retrospective, single-institution series—and prospective clinical trials are obviously necessary, current data do provide clinicians with an informed, rational approach to patients with HCC who are awaiting transplantation.

'Bridge,' 'Salvage,' or 'Destination' Therapy?

Although mentioned in the accompanying article, neither hepatic resection nor systemic chemotherapy should truly be considered as "bridge" therapy for patients awaiting transplantation. Rather, in discussing hepatic resection, the authors conflate the concepts of "bridge" and "salvage" therapy. While the role of hepatic resection vs transplantation for early-stage HCC in the well-compensated cirrhotic remains somewhat ill-defined, both therapies should be considered "destination" therapies. That is, resection[]even if associated with increased rates of recurrence and possible subsequent hepatic failure[]should only be undertaken with curative intent. Unlike transarterial chemoembolization (TACE) or radiofrequency ablation (RFA), which are utilized explicitly in the bridging paradigm to "buy time" while a patient awaits liver transplantation, hepatic resection[]in general]is employed as an alternative (albeit sometimes temporary) choice to liver transplantation. As noted in the article, the ability to salvage patients who do develop recurrence postresection remains controversial and has yet to be defined.[1,2] Similarly, there is currently no role for systemic chemotherapy as a bridge to liver transplantation. The one article cited by the authors by Stone et al[3] represented an attempt by the investigators to improve outcomes following transplantation at a time predating the adoption of more stringent morphologic criteria. Given response rates of only about 20% for HCC using systemic chemotherapy, as well as the driving concern that local intrahepatic tumor disease will progress outside established transplantation criteria (Milan or UCSF), modalities to bridge patients to liver transplantation have appropriately focused on locoregional therapies. Whether novel agents such as sorafenib (Nexavar) will have a role...
in the treatment of pre- (or post?)-transplantation patients will need to be determined in future clinical trials.

TACE vs RFA
TACE and RFA are the most commonly employed bridge therapy approaches, whereas percutaneous ethanol injection (PEI) has not been as widely used in Western centers. As Dr. Almhanna and colleagues note, data evaluating TACE and RFA as bridge therapies largely come from single-institution series that employ one or the other technique, making direct comparisons between the efficacy of TACE vs RFA difficult, if not impossible. Although the authors comment on several studies that purportedly used multimodality neoadjuvant therapy, only the study by Fisher et al[4] truly investigated combined-modality bridge therapy. (For example, in the study by Bharat et al,[5] only 8.7% of patients received multimodality locoregional therapy.) In the more recent update of the Fisher series,[6] these investigators reported a 76% 5-year survival rate for patients treated with multimodality therapy, with the mean number of pretransplantation procedures being 2.9. Whether TACE or RFA is a more efficacious bridge to liver transplantation is difficult to determine based on the currently available data. However, most series report an overall dropout rate between 0% and 15% regardless of which modality is employed. As such, the choice of TACE vs RFA should not be dogmatic. Rather, the decision to use TACE vs RFA should depend on local institutional expertise, as well as tumor size, number, and distribution throughout the liver. One theoretical benefit of TACE is that the relative response to pretransplantation therapy may be easier to assess with chemoembolization vs RFA. Specifically, following TACE the degree of viable tissue can be somewhat quantified based on computed tomography or magnetic resonance imaging. Perhaps more importantly, some investigators have reported that assessment of response to pretransplantation TACE may correlate with posttransplantation outcome.[7]

Dropout Rate
Although the general dropout rate for patients awaiting transplantation may vary significantly, most centers cite a 20% to 25% dropout rate. However, a more in-depth look at the pattern and predictors of dropout is informative in helping to determine which patients may benefit most from bridge therapy.

In the study by Millonig et al,[7] only 2.9% of patients who initially met the Milan criteria had to be removed from the waiting list during a median waiting time of 9 months, compared to 12.1% of patients who met the UCSF expanded criteria. In a separate study by Yao et al,[8] patients with a solitary tumor > 3 cm or those with two or three lesions at the time of initial presentation were about five times as likely to drop out, compared with patients who had a solitary tumor < 3 cm. As others have noted,[8] based on the natural history of untreated, small HCC,[9] it is unlikely that a small (< 3 cm) lesion will increase in size to more than 5 cm in less than 6 months. Tumor size at presentation, therefore, must be considered in light of anticipated time on the waiting list. For example, Yao et al[8] reported that patients with two or three tumor nodules or a single lesion > 3 cm had cumulative probabilities of dropout at 6, 12, and 18 months of 12%, 56.2%, and 89.1%, respectively. In comparison, patients with a solitary lesion < 3 cm had dropout rates of 0%, 10%, and 21.3%, respectively. In aggregate, these and other data, suggest that initial tumor stage and waiting time are the most important factors influencing outcome of patients with HCC awaiting transplantation.

Clinical Guidelines
While future prospective clinical trials are desperately needed, clinicians must make current decisions based on the available data. Therapeutic planning should be individualized to the specific clinical situation; nonetheless, some general guidelines regarding bridge therapy for liver transplantation can be postulated.

Patients with solitary HCC lesions < 3 cm and an anticipated waiting period of less than 6 months probably do not benefit from bridge therapy, as significant tumor progression is unlikely. However, patients with larger (> 3 cm) or multiple tumors[especially those with anticipated waiting periods of greater than 6 months][may benefit from bridge therapy. Specifically, patients with tumors approaching institutional transplant criteria (Milan or UCSF) should particularly be considered for bridge therapy when the anticipated wait time is 6 months or greater. Although limited, data do suggest that patients who receive bridge therapy and subsequently undergo liver transplantation have survival rates comparable to early-stage HCC patients who did not require bridge therapy.[10,11] As such, clinicians should selectively employ bridge therapy to ensure that patients who may potentially benefit from transplantation do not have disease progression that would subsequently preclude them from transplant consideration. Every effort should be made to accrue this cohort of patients to prospective clinical trials and/or registries to better elucidate and define the
true role of bridge therapy prior to liver transplantation.

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References:

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