Neoadjuvant Therapy for Hepatocellular Carcinoma: Is There An Optimal Approach?

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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.

Primary hepatocellular carcinoma (HCC) is the eighth most common cancer, and is responsible for up to 1 million deaths worldwide every year. The incidence of HCC varies widely according to geographic location, with the highest incidence in sub-Saharan Africa, China, Hong Kong, and Taiwan. Distribution of HCC also differs among ethnic groups and between regions within the same country.[1]

The incidence of HCC in the United States is on the rise, with around 19,000 new cases and more than 16,000 estimated deaths expected in 2007. This rise is thought to be, at least in part, secondary to hepatitis B and hepatitis C infection.[2] It is expected that the number of patients with HCC will continue to increase over the next 2 decades. With the limited success of currently available screening strategies, most patients will present with advanced disease.

Treatment Background
HCC is usually diagnosed late in its course, with a median survival of 8 months following diagnosis.[3] While resection is the preferred treatment option, this is not always feasible because of the tumor extent or underlying liver dysfunction. After resection, the rate of recurrence is high. Recurrence occurs mostly in the remaining liver and is rarely extrahepatic.

Treatment of advanced HCC had remained stagnant following the initial pioneering work that led to an understanding of the link between cirrhosis and HCC. Recently, further headway has been achieved with the refining of criteria for orthotopic liver transplantation (OLT), which is a potential curative treatment. The purpose of OLT is to treat the underlying liver disease and eradicate the tumor. There is a worldwide shortage of liver donors, and liver transplant waiting time is a major prognostic factor, as many patients will drop off the transplant list because of disease progression. Historical data suggest that the median tumor doubling time in HCC is 3 to 6 months,[4] but the waiting time for liver transplantation continues to increase and is up to 24 months in the United States.

Neoadjuvant Therapy
Practitioners have shown increasing interest in "bridging" or neoadjuvant modalities in the management of HCC, devised in an effort to delay tumor progression and decrease the rate of dropouts from the transplant list. This strategy represents an intriguing clinical challenge, since it is not clear that any of these interventions improve overall outcome. The most common strategies used to prevent dropout of HCC patients on the waiting list for transplantation are systemic chemotherapy, chemoembolization, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and hepatic resection.

Many centers in the United States and around the world pursue some form of bridging therapy while...
patients are on the transplant list, even though no prospective randomized trials are being conducted. In this article, we will review the various neoadjuvant modalities and their effects on dropout rate, disease recurrence, and survival.

Radiofrequency Ablation

RFA involves the local application of radiofrequency thermal energy to the tumor. The movement of ions within the tissue heats the area, resulting in an area of necrosis surrounding the electrode. RFA is a safe and effective local treatment option, particularly for cirrhotic patients with small, unresectable hepatocellular carcinomas.[5,6]

RFA safety and efficacy, when used alone prior to liver transplant, has been evaluated in few studies (Table 1). These investigations were mostly small prospective or retrospective trials, including heterogeneous populations and using different tumor size criteria for treatment and varying types of radiofrequency generators. Johnson et al showed in a small pilot study that patients who underwent RFA were able to remain on the waiting list longer compared to those who received no neoadjuvant therapy (median: 484 vs 253 days, \( P = .03 \)), thus improving their chance to receive a new liver.[7] Lu et al presented retrospective data on 53 patients who received RFA prior to OLT. The dropout rate was only 5.8%, and 1- and 3-year post-OLT survival rates were 85% and 76%, respectively.[8]

One small prospective study in 33 patients used RFA as a bridging therapy that showed promising results.[9] In this study, despite a radiologic response rate of 66%, 54% experienced progression of disease post-RFA. However, 15 of 23 candidates were successfully bridged to liver transplantation. The 3-year posttransplantation survival rate was 85%. Another prospective study in 50 patients came to a similar conclusion.[10] In this study the post-RFA complete response rate was 55% and the posttransplant 3-year survival rate was 83%. The RFA procedure was well tolerated with no mortality. Most importantly, no dropouts were reported in patients who met the Milan criteria—ie, no evidence of extrahepatic tumor, unifocal tumor mass < 5 cm in diameter or fewer than four multifocal tumors, each < 3 cm in diameter.

In summary, the lack of controlled clinical trials notwithstanding, few uncontrolled studies support the use of RFA as a neoadjuvant therapy in patients who meet the Milan criteria. In numerous small series, RFA has been shown to control tumor progression and decrease the dropout rate, but for larger tumors, the role of RFA is uncertain.

Percutaneous Ethanol Injection

Before the advent of RFA, PEI had been the most widely accepted, minimally invasive method of treating small HCC tumors. The procedure is inexpensive, requires a minimal amount of equipment, and can induce tumor necrosis and shrinkage. Histopathologic studies have shown that PEI may lead to complete ablation of about 70% of tumors smaller than 3 cm in diameter.[11] Data suggest that PEI may be equivalent to surgical resection in HCC.[12,13]

Although PEI has been replaced by RFA in many centers, it has been proposed as a neoadjuvant therapy for HCC in patients awaiting transplantation. In one small retrospective study, PEI was found to be a safe neoadjuvant therapy for HCC in patient on the liver transplant waiting list.[14] The investigators found no evidence of tumor seeding in the needle track. Pain and self-limited fever were the most frequent complications.

Another retrospective analysis looked at both PEI and RFA as methods of bridging therapy prior to OLT.[15] In this study, RFA, PEI, or a combination of both treatments produced a complete response/necrosis in 75% of patients, with the treatment proving most effective in nodules smaller than 3 cm. However, the data regarding dropout and overall survival were not available.
Tumor Resection

Primary tumor resection is a potentially curative treatment for HCC, producing a 3-year survival rate of up to 70% in selected patients.[9] Ideal candidates should have a solitary liver lesion with no vascular invasion, well-preserved hepatic function, and no evidence of portal hypertension.[16] Unfortunately, tumor resection is associated with a high recurrence rate, and liver transplantation results in a better long-term survival.

Tumor resection, followed by salvage transplantation in case of tumor recurrence or when an organ becomes available, has been studied in many centers (Table 2). The feasibility of this approach was shown in a prospective study of 473 patients with Child-Pugh class A cirrhosis who underwent resection.[17] The study showed that in patients with small HCCs and good liver function, hepatic resection is a reasonable first-line treatment, as it was associated with a favorable 5-year overall survival rate of 70%. Ultimately, 67 patients developed a recurrence, and 53 (79%) were still considered eligible for salvage OLT.

In another retrospective study, Belghiti et al found that patients who underwent primary resection can also be salvaged with OLT for positive margins, recurrent disease, or deterioration of hepatic function.[18] Primary liver transplantation was comparable to liver transplantation after resection in terms of median operative time (551 vs 530 minutes), blood loss (1,191 vs 1,282 mL), transfusion (3 vs 2 units), intensive care unit stay (9 vs 10 days), hospital stay (32 vs 31 days), morbidity (51% vs 56%), or 30-day mortality (5.7% vs 5.6%). The 3- and 5-year overall survival rates after primary and secondary transplantation were 82% vs 82%, and 59% vs 61%. The authors concluded that liver resection prior to transplantation is a feasible treatment strategy for HCC.

In an outcome-oriented decision analysis, Majno et al found that primary liver resection followed by salvage transplantation is a rational way to deal with lengthy waiting lists, especially for patients with tumors close to the limit for transplantation criteria.[19] However, the observational series by Adam et al came to a different conclusion.[20] In this study, the authors found that liver transplantation after liver resection, compared to primary transplantation, was associated with higher operative mortality (28% vs 2%), a higher recurrence rate (54% vs 18%) and poorer posttransplant 5-year survival (41% vs 61%) and disease-free survival (29% vs 58%). In the intent-to-treat analysis of resected patients, only 23% of patients underwent OLT in cases of tumor reoccurrence. The author concluded that primary transplantation should remain the ideal choice of treatment when available. Nevertheless, 30% of patients who received initial hepatic resection in this study were in Child Pugh class B or C, which could explain the increased rate of complications. Another study, by Llovet et al, showed that the 1-, 3-, and 5-year intention-to-treat survival rates were 85%, 62%, and 51% for resection and 84%, 69%, and 69% for transplantation, favoring the primary transplantation arm.[21] Bilirubin and clinically relevant portal hypertension were independent survival predictors after resection. Similar to the data presented by Adam et al, however, only 10% of the patients with disease recurrence were bridged to OLT.

In conclusion, hepatic resection may be appropriate for small lesions in noncirrhotic patients or possibly in cirrhotic patients with well-preserved liver function, as 5-year survival rates above 50% are expected in those selected cases.[22] But with conflicting data as stated above, the role of hepatic resection prior to transplantation remains uncertain. This approach needs to be validated in well designed, randomized trials using intent-to-treat analyses, before it is widely adopted in clinical care.

Transarterial Chemoembolization

The blood supply for hepatocellular tumors is derived from the hepatic artery. In contrast, normal
liver tissue receives about 80% of its blood supply from the portal vein. This observation was used to selectively infuse embolization materials with or without chemotherapy into the left, right, or common hepatic artery, to eliminate the tumor's blood supply and administer cytotoxic chemotherapy directly to the tumor.

Transarterial chemoembolization (TACE), alone or with other modalities, is usually used for the treatment of large unresectable HCCs. Experience with TACE in the neoadjuvant setting prior to transplantation has been derived mostly from case series (Table 3). No large randomized controlled trials have evaluated TACE as a bridging therapy, and the available case series have demonstrated conflicting results. However, many centers routinely perform TACE on HCC patients with preserved liver function at the time of their initial listing, despite the lack of data.

The effectiveness of TACE in preventing dropout from the waiting list was evaluated in a retrospective study where 54 patients with HCC underwent chemoembolization prior to OLT. Neoadjuvant TACE for patients with HCC was associated with dropout rates of 15% and 25% over 6 and 12 months, respectively.[23] The 5-year overall survival for patients undergoing OLT with HCC was 77%, and survival on an intent-to-treat basis was 61% at 5 years. Graziadei et al obtained further encouraging data using TACE in a prospective study of 48 patients. All patients received chemoembolization followed by OLT. No patients required withdrawal from the transplant list because of tumor progression despite a mean waiting time of 178 days.[24] The 1-, 2-, and 5-year intention-to-treat survival rates were 98%, 98% and 94%, and the outcome after OLT was impressive, with a 5-year survival rate of 93%.

A pilot study from Mayo Clinic had similar results in a group of 27 highly selected patients with no extrahepatic metastasis, less than three tumor nodules of less than 5 cm each, and no vascular invasion.[25] Three patients dropped out secondary to disease progression, and 24 patients underwent chemoembolization followed by OLT. The procedure was well tolerated, and the mean waiting time for OLT was 167 days, leading to 1- and 2-year disease-free survival rates of 91% and 84%, respectively. The 2-year disease-free survival rate was similar to survival rates associated with OLT for cirrhosis. In this study, patients who underwent OLT also received adjuvant chemotherapy with fluorouracil (5-FU) plus levamisole, but this was associated with an unacceptable risk for cholestatic hepatitis.

In another small study, Troisi et al compared patients who underwent pretransplant TACE and PEI to those who received no therapy prior to OLT. After 48 months of follow-up, disease-free survival was 82% in 14 patients who underwent pretransplant TACE and PEI, compared to 65% in 6 patients who did not receive pretransplant therapy. [26] The authors concluded that a combination of TACE and PEI very effectively induces necrosis of tumor nodules, leading to improved disease-free survival. On the other hand, Oldhafer et al found that although preoperative TACE induced tumor necrosis, it did not translate into a survival benefit in a case control study. The study compared 21 HCC patients who received pretransplant TACE to 21 historical controls. The 3-year overall survival was 48% vs 53% in the TACE vs control patients, respectively. More importantly, the pretransplant TACE group had a higher risk of immediate postoperative infectious complications such as pneumonia.[27] With
an evidence-based analysis, Lesurtel et al similarly concluded that as a bridge to OLT, pretransplant TACE does not improve long-term survival, expand the current selection criteria for OLT, or decrease dropout rates on the waiting list.[28]

In conclusion, promising data support the role of TACE as a neoadjuvant therapy prior to liver transplant. TACE can induce significant tumor necrosis, but the outcome in terms of a survival benefit is not convincing. Small numbers of patients, cohorts with highly selected patients, and lack of randomization may have influenced the results of these studies. A prospective randomized study with intent-to-treat analysis would be required to assess a true long-term survival benefit of TACE.

Systemic Chemotherapy

HCC in general is a chemotherapy-refractory tumor secondary to a high rate of drug-resistant gene expression.[31] The most active chemotherapy in HCC is doxorubicin, which produces a response rate of under 20%.[32] Despite the modest effect in objective response, doxorubicin was associated with only a small survival advantage compared to best supportive care alone in advanced unresectable disease, with a median survival of 10.6 vs 7.5 weeks, respectively.[33]

Based on these data, doxorubicin was studied as a neoadjuvant therapy prior to liver transplantation. In a pilot study, Stone et al treated 20 HCC patients (more than half of them had stage IV disease) with doxorubicin. The chemotherapy was administered preoperatively, intraoperatorically, and postoperatorically at a dose of 10 mg/m² weekly, totaling 200 mg/m². For the 17 patients with tumors larger than 5 cm, overall survival was 63% and tumor-free survival was 49% at 3 years. The authors concluded that neoadjuvant doxorubicin chemotherapy favorably alters the posttransplant survival of patients with hepatocellular carcinoma.[34]

Other studies have mostly used chemotherapy in the adjuvant setting following transplantation. These studies suggested that adjuvant therapy after transplantation for HCC can provide some long-term survival benefits. However, the studies were not randomized, had small numbers of patients, and were hard to duplicate.[35,36]

The rapid development of targeted therapies and the lack of effective chemotherapy have made the evaluation of novel therapies with signal transduction modulation a natural alternative approach. Innovative modern techniques have provided further insight into the intracellular pathways that result in sensitivity and resistance of the neoplastic cells to drug treatment. This acquisition of new knowledge is occurring at a breakneck pace, resulting in a change in the understanding of the biology of the disease, a stage shift in clinical presentation, and the development of highly accurate prognostic models.

A recent phase II study found sorafenib (Nexavar) to have modest activities in patients with advanced HCC.[37] Phase III data using sorafenib in advanced HCC were presented at the American Society of Clinical Oncology (ASCO) meeting in 2007. Generally, chemotherapy as a neoadjuvant therapy is not used because of its toxicity, but further trials with targeted therapy for HCC in the neoadjuvant setting are warranted.

Multimodality Treatment

Many studies have used multimodality therapy for patients with HCC waiting for liver transplant. Multimodality therapy indicates the use of any combination of the treatments listed above. These studies have aimed to evaluate the effects of an aggressive "bridging" ablation therapy on decreasing dropout rate and improving overall and disease-free survival. Several retrospective studies using multimodality therapy have found it to be safe and effective in reducing tumor size and progression in cirrhotic patients, but without affecting cancer-free survival rates.[38,39]

Fisher et al evaluated 31 patients with HCC in an intent-to-treat analysis using multimodality therapy prior to OLT. The dropout rate was 12%, and the overall survival rate was 79% at 32 months.[40]

Predictors of dropout included high alpha-fetoprotein levels and T3 HCC stage. Roayaie et al used multimodality therapy as a bridging intervention for 80 patients who did not fit the Milan criteria. All patients received TACE as a neoadjuvant therapy and received systemic chemotherapy as an adjuvant therapy after the liver transplant. A total of 43 patients received a transplant, but 37 patients (46%) dropped out because of tumor progression—a higher dropout rate compared to other studies. Median overall survival in transplanted patients was 49.9 months, compared to 6.83 months among patients who were excluded. The study concluded that a significant proportion of patients with large HCCs can achieve a long survival after liver transplant in the context of aggressive multimodality adjuvant therapy.[41]

In a retrospective analysis, Bharat et al compared outcomes between 51 OLT patients with no previous locoregional control to 46 patients who underwent multimodality locoregional interventions while on the transplant waiting list. Patients who underwent locoregional treatment had notable tumor downstaging and a better 5-year survival rate (82% vs 51%). A total of 16 patients who
received therapy revealed complete tumor necrosis with no viable tumor cells on pathology, and these patients had no recurrence in long-term follow-up.[42]

In conclusion, multimodality neoadjuvant treatment for HCC can substantially downstage the primary tumor and decrease dropout rates, and may improve survival.

Conclusions

Liver transplantation in patients with HCC can lead to long-term survival. Dropout from the waiting list is the main limitation to successful liver transplantation for patients with HCC. Therefore, the lack of donors for all transplantation candidates requires a search of all possible alternatives to further obtain long-term survival. Neoadjuvant therapy is a feasible option while the patient is on the waiting list in order to prevent tumor progression, decrease the risk of dropout, and improve overall survival. Despite promising results, the most appropriate treatment protocol has not yet been defined. Only a few prospective studies have assessed the effects of treatment, and some of the results are contradictory.

Many of the trials reviewed in this article suffer from similar deficiencies secondary to small numbers, heterogeneous patient populations, and nonstandardized endpoints, which limit the conclusions that can be drawn. Analysis of outcomes data from contemporary clinical trials is further confounded by the stage migration caused by earlier detection of HCC in patients with viral hepatitis. Therefore, no data clearly indicate that neoadjuvant therapy lowers the dropout rate, decreases recurrence, or improves overall survival. We also have no good data as to which modality should be used in the neoadjuvant setting. Today, the choice of a modality depends on the expertise within the institution.

Randomized trials are desperately needed, with primary endpoints including dropout rate, disease recurrence, and overall survival. Ideally, these studies should compare active treatment against conservative treatment. Such studies will be difficult to conduct, given the institutional biases already present among the different transplantation centers. Stratification based on an ideal prognostic system before randomization will be crucial to the success of these studies. They will also require a large number of patients and the support of multiple institutions across the continents. Improvements in survival with the addition of currently available local ablative approaches to transplantation have been modest at best. However, the current era of drug development will likely lead to a treatment paradigm shift. Enhancements in our understanding of molecular pathways have resulted in an expanding portfolio of newer targeted agents, which can be combined with classic cytotoxic agents, and have lent themselves to testing in this setting. Recognizing the multifactorial nature of drug resistance and inherent survival mechanisms has made us realize that collateral and downstream pathways can circumvent targeting single mechanisms of drug resistance.

While none of the newer treatment modalities have yet been shown to be more effective than standard treatments, the potential armamentarium is steadily growing, triggering cautious optimism. The combination of local ablative approaches with newer targeted agents raises the appealing possibility of parallel, or even complementary, therapeutic effects. Efficient trial design, appropriate selection of correlative markers, and greater cooperation among hepatologists, surgeons, and medical oncologists, along with close toxicity monitoring, will propel this field further and improve our management of this disease.

Disclosures:
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