Adjuvant Treatment After Orthotopic Liver Transplantation: Is It Really Necessary?

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This review summarizes the current data on efficacy and rationale of adjuvant treatment for hepatocellular cancer after orthotopic liver transplantation, as well as future prospects. No adjuvant treatment is currently advocated.

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, accounting for about 90% of primary malignant liver tumors in adults. It is the sixth most common cancer and the third most common cause of cancer-related death worldwide.[1] While HCC is more prevalent in Asia and Africa, its incidence has been growing in the United States and Europe, secondary to discovery of hepatitis C infection in patients who have remained asymptomatic for many years since the diagnosis.[2]

Surgical resection and orthotopic liver transplantation (OLT) offer the only potentially curative treatment options. Surgical resection of HCC is usually reserved for patients with well preserved hepatic function, intact hepatic vasculature, and no evidence of portal hypertension. However since surgical resection usually leaves a diseased liver in place, patients treated with these methods have recurrence rates of 50% at 3 years and 70% at 5 years, and this complication still represents the main cause of death.[3,4] The most recent meta-analysis addressing adjuvant treatment after hepatic resection showed no benefit from either systemic or local therapy in terms of preventing recurrences.[5]

On the other hand, OLT is a more viable option for curative treatment as it addresses both the underlying liver pathology and HCC. The fairness of organ distribution among non-HCC and HCC patients continues to be a matter of debate.

Early experience with OLT in HCC was disappointing due to high recurrence rates and poor overall survival.[6] But a landmark study by Mazzaferro et al showed that patients with single tumor ≤ 5 cm, or up to three separate lesions with none larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases, (now known as the Milan criteria) had a 4-year survival of 85%. [7] The current system allows extra MELD (Model for End-stage Liver Disease) score points in patients with HCC who are within Milan criteria. With such criteria, however, few HCC patients were eligible for OLT. Yao et al from the University of California, San Francisco (UCSF) tried to overcome this issue with their own expansion of the Milan criteria (Table 1). In a retrospective study, authors showed that outcomes using UCSF criteria were comparable to those based on the Milan criteria, with an overall survival of 90% and 75.2% at 1 and 5 years, respectively.[8]

More recently, Silva et al suggested different criteria (Table 1) and showed that 5-year survival and recurrence rates were also comparable to those using the Milan criteria.[9] However, these patients are still at risk for recurrence for many reasons including intraoperative dissemination of tumor caused by extensive manipulation of the native liver, undetected micrometastases prior to surgery, and acceleration of tumor growth by immunosuppression. A recent study looking at salvaged blood during surgery showed that up to 50% of salvaged samples were contaminated with tumor cells and responded to leukocyte depletion filters. This suggests a possible role in recurrence secondary to manipulation of the native liver, although this needs to be studied in more depth.[10]

There are no standard adjuvant treatments after OLT. But with the recent approval of sorafenib (Nexavar) in advanced HCC, there has been a renewed interest in adjuvant treatment for HCC. A large global study is currently underway (the Sorafenib as Adjuvant Treatment in the Prevention of...
Recurrence of Hepatocellular Carcinoma [STORM] trial), looking into sorafenib therapy after potentially curative treatment with liver resection or radiofrequency ablation. This review will discuss adjuvant treatment in patients with HCC who have undergone OLT and possible future directions for management in this setting.

**Prognostic Factors for Disease Recurrence After OLT**

Patients who meet the Milan criteria and undergo OLT tend to have a favorable outcome, as actuarial 4-year survival and recurrence-free survival rates of 85% and 92% are achieved. However, those beyond the Milan criteria can present with both intra- and extrahepatic posttransplant recurrence, accounting for reduced survival. Therefore, it is important to identify prognostic factors that can predict high risk of tumor recurrence.

Registry review of 800 HCC patients who underwent OLT showed that nodal metastasis, tumor size > 5 cm, and histologic grade (G3 and G4) were significant predictors of a decreased probability of patient survival. Recurrence-free survival was influenced by node status, bilobar spread, tumor size > 5 cm in diameter, and vascular invasion.[11] Other studies indicate that alpha-fetoprotein levels > 1,000 ng/mL, poorly differentiated histology, age ≥ 55 years, and tumor diameter > 8 cm were associated with a reduced 1-year survival of 50%.[8] A study by Kirimlioglu et al showed that vascular invasion was the strongest predictor of disease recurrence after OLT.[12] In the absence of macroscopic or large-vessel invasion, they showed that the largest tumor size, apoptosis/mitosis ratio, and number of tumors were independent predictors of disease-free survival. Since HCC is a highly angiogenic tumor, some data suggest that vascular endothelial growth factor receptor 2 (VEGFR-2) expression was associated with poor differentiation and tumor progression.[13]

Unfortunately, there are currently no effective methods to diagnose pretransplant microvascular tumor spread, despite the advances in imaging studies, and even though small studies have tried to use positron-emission tomography (PET) scan to predict tumor recurrence. In other studies, VEGF expression in HCC have been shown to correlate with shorter overall survival.[14] A group from Pittsburg developed a molecular predictive marker using a fractional allelic imbalance (FAI) rate index. The FAI rate index is defined as the number of mutated markers divided by the total number of informative markers. This retrospective study concluded that FAI was the strongest predictor of HCC recurrence currently available, surpassing all components of the tumor-node-metastasis classification system for staging of malignant tumors, and vascular invasion.[15] A caveat about FAI, however, is that this requires liver biopsy prior to OLT.

**Adjuvant Therapy After Liver Transplantation**

**Systemic Chemotherapy**

Various chemotherapy agents have been tested in the adjuvant setting after liver transplantation. The rationale behind this approach is to eliminate micrometastasis that may be present at the time of transplant.

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<th>Adjuvant Therapies After Liver Transplantation</th>
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<td>Doxorubicin is one of the older chemotherapy drugs that have been frequently studied. The benefit of doxorubicin has been suggested in several uncontrolled small series but with modest results. Stone et al conducted a pilot study in 20 patients with unresectable advanced-stage HCC who underwent OLT and received doxorubicin preoperatively, intraoperatively, and postoperatively.[16] A total of 17 patients (85%) had tumors &gt; 5 cm. Actuarial survival and tumor-free survival rates were 59% and 54%, respectively, at 3 years. The authors concluded that doxorubicin given in this protocol had a favorable impact on posttransplant survival in patients with HCC. However, an updated series of 43 patients revealed a 66% 1-year survival, 52% 2-year survival, and a disappointing 37% 5-year survival, suggesting that adjuvant treatment with doxorubicin delayed recurrence but did not</td>
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significantly alter overall long-term survival compared to historical controls.[17] Other small studies using perioperative doxorubicin reached similar conclusions in that the drug did not improve either survival or recurrence-free survival in patients with HCC undergoing OLT (Table 2).[18,19] The combination of doxorubicin with other chemotherapy agents has been investigated as an adjuvant treatment after OLT, but no improvement in outcome was noted compared to single-agent doxorubicin. Oltöff at al reported a 3-year overall survival rate of 46% in a small study of 25 patients with doxorubicin, cisplatin, and fluorouracil (5-FU).[20] Bernal et al studied 43 patients with HCC who underwent OLT based on the Milan criteria. Twelve patients were considered to have a high risk for recurrence and were treated with adjuvant chemotherapy consisting of cisplatin and doxorubicin monthly for up to seven cycles. Recurrences occurred in seven patients, six of whom died within the first 3 years.[21] Newer agents are being explored to improve outcomes of patients after liver transplantation. Gemcitabine (Gemzar) was shown to have activity against HCC by Graziadei et al.[22] Hsieh et al later studied the combination of gemcitabine and cisplatin in 17 patients who did not satisfy the Milan criteria and found better 2-year disease-free survival and 3-year disease-specific survival rates of 78% and 56%, respectively, compared to controls (32% and 38%, respectively). Thirteen patients had tumors > 5 cm in diameter. Overall survival data were not reported, and follow-up was short.[23]

Intra-arterial Approaches With or Without Systemic Chemotherapy

In contrast to normal liver parenchyma, the majority of the blood supply to HCC is derived from the hepatic artery rather than the portal vein. Techniques designed to cut off the tumor’s blood supply by particle embolization with or without cytotoxic chemotherapy into branches of the hepatic artery supplying tumor masses have been shown to be effective. Various methods of intra-arterial approaches include bland embolization, transarterial chemoembolization (TACE) with or without lipiodol (an oily contrast agent thought to promote intratumoral retention of chemotherapy), and transarterial infusion of chemotherapy. Several studies have shown promising preliminary results when combining transplant with preoperative locoregional control with or without adjuvant systemic chemotherapy in the treatment of unresectable advanced HCC. The rationale for neoadjuvant therapy of HCC is to control tumor growth during the waiting period for liver transplantation and to induce tumor necrosis, which may reduce the risk of tumor dissemination during surgery, while adjuvant systemic chemotherapy after surgery targets undetected distant metastases. Carr et al reported the use of preoperative intra-arterial doxorubicin and cisplatin and subcutaneous alpha-interferon followed by 12 months of postoperative doxorubicin in 11 patients. Results were promising with a 1-year disease-free survival of 82%, but follow-up is too short to draw any real conclusions.[24]

• **TACE Chemotherapy**—A pilot study was conducted by Cherqui et al in nine patients undergoing liver transplantation who were treated in a multimodality approach consisting of preoperative TACE (using iodized oil, doxorubicin, and gelatin sponge), radiotherapy (5 Gy in one fraction immediately before surgery), and postoperative systemic chemotherapy with mitoxantrone. Seven patients had stage IVA tumors. The 3-year actuarial survival was 64%. Updated results in 14 patients revealed 1-, 3-, and 5-year survival rates of 85%, 62%, and 54%, respectively.[25] Outcome was likely worse due to advanced-stage HCC at the time of transplant.

Similarly Bismuth et al looked at 20 patients who underwent preoperative TACE and postoperative chemotherapy using 5-FU and doxorubicin, which showed 50% tumor necrosis. Long-term survival was not available (Table 2).[26] Roayaie et al evaluated 43 patients with localized unresectable HCC with tumors greater than 5 cm treated using a combined multimodality protocol that included selective TACE with mitomycin, doxorubicin, and cisplatin at the time of diagnosis, followed by liver transplantation and intra- and postoperative systemic doxorubicin.[27] TACE was repeated as often as needed every 3 months while patients were on the waiting list. Overall and recurrence-free survival at 5 years were reported to be 44% and 48%, respectively, which still falls considerably short of the 83% recurrence-free survival rate at 4 years reported by Mazaferro for patients with smaller tumors.[7] These results are relatively similar to survival rates for tumors beyond the Milan criteria, as also reported by Mazaferro’s group (for patients who did not receive adjuvant chemotherapy).[28]

TACE has some limitations. It is contraindicated in patients with severe liver failure (Child-Pugh class C), jaundice, and portal thrombosis. Because of the localized effect of TACE, it does not address potential extrahepatic disease. Major complications of TACE are uncommon but include acute liver failure, acute renal failure, encephalopathy, ascites, upper gastrointestinal bleeding, and hepatic or
There is also a concern that neoadjuvant TACE can increase serum VEGF expression, which is associated with the development of metastasis in HCC after TACE.[30]

New Agents

Sorafenib is a multitargeted small molecule tyrosine kinase inhibitor that inhibits tumor growth and angiogenesis by inhibiting intracellular RAF kinases (CRAF, BRAF, and mutant BRAF), and cell surface kinase receptors (VEGFR-2, VEGFR-3, PDGFR-beta, cKIT, and FLT-3). It is currently the standard treatment of advanced unresectable HCC based on the Sorafenib HCC Assessment Randomized Protocol (SHARP), a multicenter double-blind, placebo-controlled trial that showed a statistically significant overall survival of 10.7 months in the sorafenib group compared to 7.9 months in the placebo group.[31] A phase I trial by the National Cancer Institute (NCI) is currently recruiting patients to study the toxicity of sorafenib in patients with HCC after liver transplantation. Promising results were obtained with the intravenous radioimmunologic agent licartin (a 131I-radiolabeled murine monoclonal antibody that targets an HCC-specific molecule, HAb18G/CD147) in a small placebo-controlled randomized double-blind study from China.[32] Licartin specifically binds to HCC cells that express Hab18G/CD147 with a tumor/nontumor ratio > 1. The blood clearance fits a biphasic model, and its half-life is 63 to 90 hours. At 1-year follow-up, the HCC recurrence rate was significantly decreased by an absolute 30% (27% vs 57%), and the survival rate was increased from 62% to 83% in the treatment group compared to those in the control arm. Although results are promising, longer follow-up and further experience in a larger-scale study are needed to confirm these results and to establish the use of licartin in the adjuvant setting.

Immunotherapy

Patients who undergo liver transplantation are kept on lifelong immunosuppression. This poses an increased risk for recurrence with calcineurin inhibitors such as cyclosporine or tacrolimus (Prograf, FK506). Sirolimus (Rapamune)-based immunosuppressants have gained popularity and interest recently in the adjuvant setting after OLT. Sirolimus is an mTOR inhibitor, and in addition to its immunosuppressive actions, it was shown to possess antitumor effects through its antiangiogenic actions. Zhou et al retrospectively examined 73 patients exceeding the Milan criteria after OLT; 27 received sirolimus-based therapy and the rest received tacrolimus. Mean overall survival was 594 ± 35 days and 480 ± 42 days, respectively. There was no difference in disease-free survival.[33] Another study by Zimmerman et al included 97 patients, of which 45 received sirolimus-based therapy after OLT. Overall survival at 1 and 5 years was 95.5% and 78.8%, respectively, and for those receiving sirolimus was 83% and 62%, respectively. It is not clear how many patients were within the Milan criteria.[34] These studies have shown a possible survival advantage with sirolimus immunotherapy in the adjuvant setting without compromising engrafting.

Discussion

Hepatocellular carcinoma recurrence after OLT remains a problem. Even with the implementation of the Milan criteria, recurrence rates have been shown to be 8% to 15% in most studies and even higher in patients who are beyond the Milan criteria.[7] In this article, we have reviewed data on the role of systemic chemotherapy and combination of neoadjuvant local therapy and adjuvant systemic chemotherapy after OLT.

Since most recurrences after OLT are extrahepatic, systemic control of disease plays a vital role.[35] In all adjuvant chemotherapy studies, the main toxicity has been bone marrow suppression requiring interruption of treatment or the use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) to overcome this problem.[20] This complication is exacerbated by immunosuppressants used to reduce the risk of graft rejection after liver transplantation. Furthermore, the combined use of immunosuppressants and chemotherapy drugs can lead to drug interactions resulting in either decreased efficacy or increased toxicity.

Optimal timing of adjuvant systemic treatment has not been established. Theoretically, it seems reasonable to start systemic chemotherapy as early as possible after transplant at the time of maximal immunosuppression, during which micrometastases are most likely to grow.[17] However, this is often difficult due to overlapping toxicities of chemotherapy and immunosuppressive medications, the need to recover from surgery, and the need for adequate hepatic, renal, and hemodynamic functions prior to initiation of treatment. In addition, there is also a concern about causing injury to the newly implanted liver by chemotherapy agents. Increased risk of viral reactivation with adjuvant chemotherapy has also been reported.[36]
Many of the adjuvant trials reviewed in this article suffer from shared deficiencies. Most are uncontrolled studies with small numbers, heterogeneous inclusion criteria (eg, the Milan criteria were not used in older studies), and the omission of stratification by well-known prognostic factors. Furthermore some trials were not pure adjuvant trials, as some patients received local neoadjuvant therapy prior to liver transplantation. It is difficult to design a trial with an endpoint of overall survival after OLT in patients who meet Milan criteria as they have a very good prognosis. Similar to the situation with stage II colon cancer, a few thousand patients need to be enrolled in order show an absolute benefit of 2% to 3%. Also, given the large financial burden these agents will put on patients and the health-care system, cost-effectiveness and cost-benefit are issues as well. Instead, the focus of adjuvant trials should be on patients at a higher risk of recurrence, such as those with vascular invasion or tumor size beyond Milan or UCSF criteria, in order to match their survival with those who are within the criteria. Retrospective data by Mazzaferro et al showed that overall prognosis was worse in patients who did not meet the Milan criteria, with a 5-year overall survival of 53.6%, compared to 73.3% in patients who met those criteria.[28] If future adjuvant trials show an improvement in overall survival for those who are at high risk or beyond recognized transplantation criteria, then transplant communities may be more receptive to expanding criteria for OLT and allow more patients to become eligible for the waiting list. A possible drawback to this is that if more patients are listed, the wait for an organ in an organ-shortage era will be longer and perhaps allow for disease progression while awaiting transplantation, or possibly deny an organ to a patient who does not have HCC. It is important to develop a scoring system to predict recurrence that can be applied in adjuvant studies after OLT. Chan et al developed the Predicting Cancer Recurrence Score (PCRS) tool using multiple prognostic factors such as histology, tumor size, and vascular invasion. Patients are stratified into low, intermediate, or high risk of recurrence.[37] Molecular markers may play a bigger role in predicting reoccurrence in the future. As stated above, when FAI alone was compared to the Milan or UCSF criteria, it was found to be the stronger predictor of tumor-free survival.[15] Similarly, Mazzaferro et al came up with the “up-to-seven” criteria, by which seven was defined as the result of the sum of the largest tumor size (in cm) and number of tumors for any given hepatocellular carcinoma. Patients who are beyond these criteria have a 5-year survival rate of only 48%.[28] Therefore, it would be reasonable to conduct an adjuvant trial with patients who are beyond these criteria.

Data suggest that the presence and number of circulating tumor cells are associated with a worse survival.[38] Studies should be developed to examine circulating tumor cells after OLT. In the era of novel agents, drugs like sorafenib should be studied in the adjuvant setting, provided there are safety data in terms of interactions with other immunosuppressants. The NCI is currently conducting a phase I trial to answer this question. Once safety profiles are established, then larger studies randomizing patients to agents of interest vs placebo should be performed in those with intermediate or high risk of recurrence.

**Conclusions**

In conclusion, there is a paucity of data concerning adjuvant treatments after liver transplantation for hepatocellular carcinoma. Adjuvant therapy is not currently recommended for any patient undergoing liver transplantation for HCC except in the context of a clinical trial. Effective adjuvant treatment should be systemic to tackle the circulating tumor cell burden. Novel agents should be developed and tried in randomized trials, especially in patients with intermediate and high risk of disease recurrence. Sirolimus-based immunotherapy after OLT may offer improved outcomes and should be studied in a controlled setting. In the era of organ shortage, it is imperative that we design trials to properly select patients and possibly use new molecular biomarkers or nomograms to improve the prognostic accuracy selection criteria for OLT. This will allow us to capture the potential benefits while maximizing our current resources.

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