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Bridge Therapy in Hepatocellular Carcinoma Before Liver Transplantation: The Experience of Two Chilean Centers

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ABSTRACT

Background. Orthotopic liver transplantation (OLT) is currently an established therapy for small, early-stage hepatocellular carcinoma (HCC) within the Milan criteria. Long waiting times due to the shortage of donor organs can result in tumor progression and drop-out from OLT candidacy. Therefore a wide variety of procedures are necessary before OLT. The aim of this retrospective study was to review our experience in relation to bridge therapy prior to OLT for HCC.

Methods. This was a retrospective database review of all of the patient who underwent transplantation in our institutions between January 1993 and June 2009. We analyzed patients with a diagnosis of HCC in the explant.

Results. Among 29 patients, including 12 who were diagnosed by the explant and 17 prior to transplantation, 88% underwent bridge therapy during a mean waiting time to OLT of 12 months. Among the 23 procedures, namely 1.5 procedures per patient, included most frequently chemoembolization (48%), alcohol ablation (30%), radiofrequency ablation (13%), and surgery (9%). Thirty-three percent of the explants contained lesions within the Milan criteria. In our series the 5-year survival rate for patients transplanted for HCC was 86%; in the bridge therapy group, it was 73%.

Conclusions. The incidence of patients who underwent bridge therapy (52%) was similar to other reported experiences, but the fulfillment of Milan criteria in the explants was lower. Among the bridge therapy group, the survival was slightly lower, probably because this group displayed more advanced disease.

HEPATOCELLULAR carcinoma (HCC) is the most common malignant tumor of the liver. It is the fifth most common malignancy in men and the eighth in women.[1] Although palliative treatment algorithms vary among centers, transplantation, resection, or both offers the only chance for a cure.[2] Most HCC develop in the setting of cirrhosis; therefore, many patients with HCC are not candidates for hepatic resection due to inadequate functional hepatic reserve. In this scenario orthotopic liver transplantation (OLT) offers the best results in terms of overall and disease-free survival among selected patients.[3] These patients must have a single tumor measuring ≤5 cm in diameter or no more than 3 tumors each not exceeding 3 cm plus no proven vascular invasion. In this setting the 4-year survival rate is 85% and the recurrence-free survival rate is 92%.[4] To maintain patients within these criteria until OLT, liver-directed therapies are necessary. They encompass a broad range of modalities including transarterial chemotherapy (TACE), alcohol ablation (AA), radiofrequency thermal ablation (RFA), and surgery (SU).[5] Our aim was to

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assess the outcomes of patients with HCC treated with OLT who were previously treated with liver-directed therapies.

METHODS

This study was a nonconcurrent, cohort design based on databases received between 1993 and 2009. We obtained the characteristics of every as well as selected patients with an HCC diagnosis prior to transplantation and in the explant. We analyzed demographics, liver-directed therapies, and survival. The mean follow-up was 4 years. Survival plots were estimated using the Kaplan-Meier method with survival differences analyzed with the log-rank test. The closing date for the survival analysis was August 31, 2009. The SPSS program 15.0 for Windows was used for statistical analyses with a significance level defined as $<.05$.

RESULTS

During the study period 250 OLTs were performed in adults, including 29 subjects with HCC; this diagnosis was confirmed preoperatively in 17 patients and upon histological examination of the explanted liver in 12.

OLT for HCC represented 11.6% of all transplanted cases. The patients were predominantly men, ranging in age from 15–71 years. The mean waiting time was 12 months until the liver transplantation. Table 1 shows the demographic characteristics of all patients.

Among the patients in whom the diagnosis was made before transplantation, 88%(15) had received 23 prior liver-target therapies: TACE (48%), RFA (30%), AA (13%), and SU (9%).

At the end of the study 11 patients from the liver-targeted therapies group were alive. The 5-year overall survival rate of patients who had therapies before transplantation was 73%. If we divided this group based upon whether they met Milan criteria in the explant, the 5-year survival rate for those who did was 91% versus 66%. Figure 1 shows the overall survivals for transplant recipients with versus without liver-targeted therapies; Figure 2 shows the overall survival for transplant recipients with liver-targeted therapies according to fulfillment of the Milan criteria.

Table 1. Demographic Characteristics

	HCC	Other Diagnoses
Transplants (n)	29	221
Age (y)	56*	48
Male (%)	77.8*	44.7
Female (%)	22.2	55.3*
Cause of liver disease		
Hepatitis C virus (%)	44*	15.7*
Hepatitis B virus (%)	0	1.3†
Alcohol (%)	31*	10.7
Child-Pugh class n (%)		
A	8	—
B	17	—
C	4	—

*$P < .05$.
†Not significant.

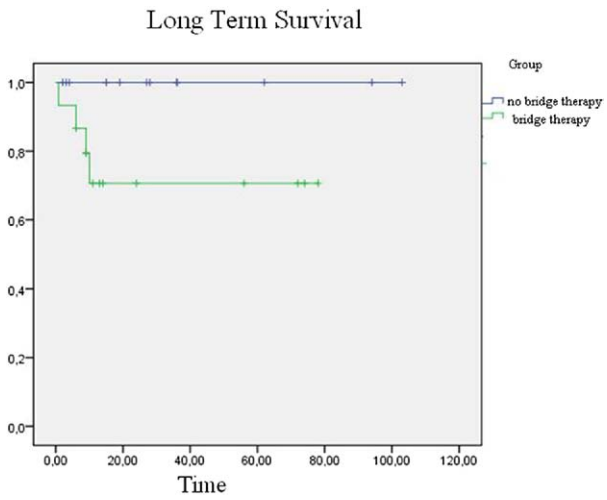

Fig 1. Overall survival of bridge therapy group vs no bridge therapy.

DISCUSSION

In our study there was a significant difference in survival between transplant recipients with versus without liver-targeted therapies. Patients undergoing these therapies displayed more advanced disease. In the majority of patients who did not receive therapies before transplantation, the HCC was an incidental finding in the explants. In 2008 Freeman et al[6] reported a significant survival difference between patients with or without bridge therapy among recipients of liver and intestinal transplantations in the United States. But the report included a limited number of patients with an obvious selection bias. The bridge therapies group showed low rates of fulfillment of the Milan criteria (33%), although the survival rate in this group was unexpectedly high (70%), which may be explained by tumor size not only being the single prognostic

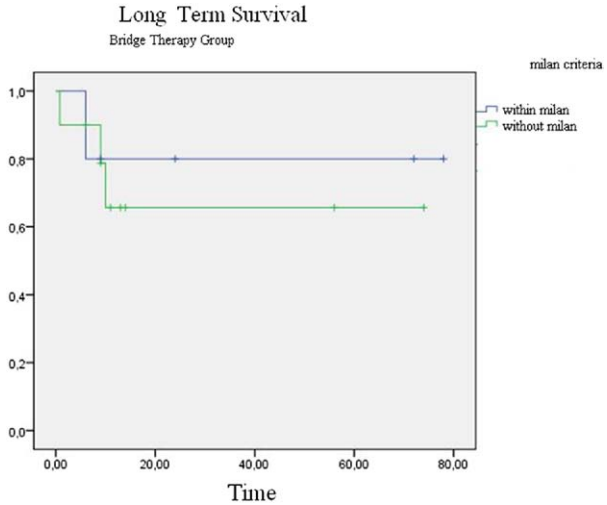

Fig 2. Overall survival of bridge therapy group and Milan criteria fulfillment.

factor. As suggested by Del Gaudio et al,[7] vascular invasion and alfa fetoprotein >300 mg/dL prior to transplantation are negative prognostic factors, affecting the long-term survival and disease-free survival.

An important issue in OLT for HCC is the length of waiting time for a suitable graft. Some studies have reported that waiting time is an important prognostic factor for survival.[8,9] In our cohort the mean waiting time was 12 months. Llovet et al[10] reported that 23% of patients dropped out during the first 6 months while waiting due to tumor progression.

Bridge therapy was a valid option for patients awaiting transplantation in our experience due to the scare organ donations. Although survival was not markedly enhanced by any type of therapy, randomized controlled trials are required to determine the role and application of bridge therapy.

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