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Treatment of Hepatocellular Carcinoma With Liver Transplantation: A Single-Center Experience From Brazil

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ABSTRACT

Introduction. Orthotopic liver transplantation (OLT) is the treatment of choice of hepatocellular carcinoma (HCC) for patients with cirrhosis, mainly those with early HCC. Herein we have present the clinical characteristics and outcomes of cirrhotic patients with HCC who underwent OLT from cadaveric donors in our institution.

Methods. From May 2001 to May 2009, we performed 121 OLT including 24 patients (19.8%) with cirrhosis and HCC within the Milan criteria. In 4 cases, HCC was an incidental finding in the explants.

Results. The patients' average age was 55 ± 10 years, including 82% men. Fifty percent of patients were Child class B or C. The average Model for End Stage Liver Disease for Child A, B, and C categories were 11, 15, and 18, respectively. The HCC diagnosis was made by 2 dynamic images in 16 cases; 1 dynamic image plus alphafetoprotein >400 ng/mL in 4; and 4 by histologic confirmation. Twenty patients received a locoregional treatment before OLT: 6 percutaneous ethanol injection, 9 transarterial chemoembolization, 1 transarterial embolization, and 4 a combination of these modalities. The median follow-up after OLT was 19.7 months (range, 1–51). A vascular invasion was observed in the explant of 1 patient, who developed an HCC recurrence and succumbed at 8 months after OLT. Two further patients, without vascular invasion or satellite tumor displayed tumor recurrences at 7 and 3 months after OLT, and death at 2 and 1 month after the diagnosis. The remaining 25 patients have not shown a tumor recurrence.

Conclusion. In the present evaluation, OLT patients with early HCC and no vascular invasion showed satisfactory results and good disease-free survival. Strictly following the Milan criteria for liver transplantation in patients with HCC greatly reduces but does not completely avoid, the chances of tumor recurrence.

ORTHOTOPIC liver transplantation (OLT) is the best available treatment for hepatocellular carcinoma (HCC) in end-stage patients, mainly those with small cancers.[1] Considerable progress has been made in the diagnosis and treatment of HCC in the past years; results with liver transplantation have improved because of careful patient selection.[2] In 1996, Mazzafero et al[2] proposed the so-called Milan eligibility criteria for liver transplantation in cirrhotic patients with HCC: a single tumor ≤5 cm or no more than 3 tumor nodules, each ≤3 cm. Patients fulfilling these criteria achieved 5-year recurrence-free survival rates of 83%[2]. This system was adopted by the United Network for Organ Sharing (UNOS) in the United States. In Brazil, according to Ministry of Health, OLT is performed from deceased donors only for HCC patients who meet the Milan criteria. Other transplant groups have proposed expanded

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criteria to include larger tumors, for example the group from the University of California, San Francisco (UCSF). However, the results in the latter setting are unpredictable.[3] The aim of this study was to present the clinical characteristics and follow-up of our cirrhotic patients with HCC who underwent OLT from cadaveric donors.

MATERIALS AND METHODS

Among 121 patients who underwent OLT from cadaveric donors from May 2001 to May 2009, 24 (19.8%) exhibited cirrhosis and HCC, all of them meeting the Milan criteria. In 4 cases, the HCC was an incidental finding in the explant.

RESULTS

The average age of the patients was 55 ± 10 years, and 82% were men. The etiology of cirrhosis was hepatitis C (n = 11; 40%), alcohol plus hepatitis C (n = 5; 18%), alcohol (n = 8; 29%), hepatitis B (n = 2; 7%), autoimmune hepatitis (n = 1; 3%), or cryptogenic cirrhosis (n = 1; 3%) (Table 1). Fifty percent of the patients were Child class B or C. The average Model for End Stage Liver Disease (MELD) scores for the Child A, B, and C subjects were 11, 15, and 18, respectively. Nineteen patients (68%) underwent OLT under the MELD system which was implemented in Brazil since May 2006.

HCC diagnosis was established by two dynamic images, triphasic computed tomography scan, and magnetic resonance imaging with contrast or hepatic arteriography (n = 16), and one dynamic image plus an alphafetoprotein (AFP) >400 ng/mL (n = 4), or histologic confirmation (n = 4). Twenty patients underwent locoregional treatment before OLT: percutaneous ethanol injection (PEI; n = 6), transarterial chemoembolization (TACE; n = 9), transarterial embolization (TAE; n = 1), or a combination of modalities (TAE + PEI, n = 1; TACE + PEI, n = 1, or radiofrequency ablation + PEI, n = 2) (Table 2).

The median follow-up after OLT was 19.7 months (range, 1–51). Two patients died due to hemodynamic complications: 1 during surgery and another in the immediate postoperative period. One patient died due to primary graft nonfunction, and 3 from sepsis. Vascular invasion was observed in the explant of one patient, who developed recurrence of HCC and succumbed at 8 months after OLT. Another 2 patients, without vascular invasion or satellite tumor, developed recurrences at 7 and 3 months after OLT, succumbing at 2 and 1 months after the diagnosis. HCC recurrence involved the liver graft, the lungs, and the brain in 2 patients, while in the other case, the liver and the lung. Treatment of recurrence involved just supportive care in 2 cases and radiotherapy in 1 case. The remaining 25 patients have not displayed a tumor recurrence.

Table 1. Etiology of Cirrhosis in 28 Patients With HCC Submitted to Liver Transplantation

Etiology	n (%)
Hepatitis C	11 (40)
Alcohol plus hepatitis C	5 (18)
Alcohol	8 (29)
Hepatitis B	2 (7)
Autoimmune hepatitis	1 (3)
Cryptogenic	1 (3)

Table 2. Locoregional Treatment Before Liver Transplantation in 20 Patients With HCC

Locoregional Treatment	n (%)
PEI	6 (30)
TACE	9 (45)
TAE	1 (5)
TAE+PEI	1 (5)
TACE+PEI	1 (5)
RFA+PEI	2 (10)

PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; TAE, transarterial embolization; RFA, radiofrequency ablation.

DISCUSSION

HCC accounts for 85%–90% of primary liver cancers.[4] According to the GLOBOCAN 2000 database, South America is a low-rate area for liver cancer.[5] In Brazil, a national survey on HCC is being prepared. HCC usually develops in patients with chronic liver disease and cirrhosis, except in areas with endemic hepatitis B (HBV); where the increased risk is mainly due to chronic infection.[1,6,7] In other areas, chronic hepatitis C (HCV) infection is the major risk factor for the development of HCC in cirrhotic patients. A meta-analysis of 21 case-controlled studies documented to be anti-HCV positive, using a second generation immunoassay showed a 17-fold greater risk for the development of HCC compared with anti-HCV negative patients.[8] In the present study, chronic HCV infections and alcohol addiction were the main causes of cirrhosis among patients with HCC. This observation was expected since our region does not showed endemic HBV; whereas, alcohol is an important problem. In most of our patients the diagnosis of HCC was established by dynamic imaging studies and AFP levels. Biopsy was necessary for only a minority of patients (n = 4). According to the present guidelines of the American Association for the Study of Liver Diseases, the diagnosis of HCC can be established with a single dynamic imaging technique which detects a hypervascular lesion >2 cm in a cirrhotic patients in the arterial phase with subsequent washout in the venous phase.[4]

Eighty-three percent of our patients underwent locoregional therapy awaiting OLT. Despite the additional points offered to patients with HCC, according to the MELD system for allocation of organs in Brazil, the insufficient number of donors still results in waiting times frequently >6 months. According to the international literature, the risk of drop-out is primarily related to the numbers and sizes of the tumors, as well as to the waiting time; therefore therapeutic procedures such as radiofrequency ablation, PEI, and TACE have been used to reduce tumor progression while on the wait list.[9]

Despite strictly following the Milan criteria, HCC recurred in 11% (3/28) of our patients; in 1 case, microvascular invasion has been detected in the explant, which has been reported to be a predictive factor for posttransplant recurrence.[10,11] In contrast, the other 2 patients, did not display microvascular invasion or satellite lesions. We did not evaluate the degree of tumor differentiation in the present study.

In conclusion, HCV and alcohol were the most frequent causes of cirrhosis in patients with HCC in our region. In this experience, liver transplantation showed good results and tumor-free survivals among patients with early HCC without vascular invasion. Strictly following the Milan criteria for liver transplantation in patients with HCC greatly reduces but does not completely avoid the chance of tumor recurrence.

REFERENCES

1. Rampone B, Schiavone B, Martino A, et al: Current management strategy of hepatocellular carcinoma. World J Gastroenterol 15:3210, 2009

2. Mazzaferro V, Regalia E, Doci R, et al: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693, 1996

3. Yao FY: Liver transplantation for hepatocellular carcinoma: beyound Milan Criteria. Am J Transpl 8:1982, 2008

4. Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 42:1201, 2005

5. Ferlay J: GLOBOCAN 2000 cancer incidence, mortality and prevalence worldwidw, version 1.0. IARC Cancer Base No. 5. Lyon, IARCPress. Avaible: http://www-dep iarc fr/globocan/globocan htm 2001.

6. Mazzaferro V, Shin Chun Y, Poon RTP, et al: Liver transplantation for hepatocellular carcinoma. Ann Surg Oncol 15:1001, 2008

7. El-Serag HB: Epidemiollogy of hepatocellular carcinoma. In: Arroyo V, Sanchez-Fueyo A, Fernadéz-Gomez J, et al. Advances in the therapy of liver diseases. Barcelona: Ars Medica; 2007, p 159

8. Donato F, Tagger A, Gellati U, et al: Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in man and woman. Am J Epidemiol 155:323, 2002

9. Schwartz M, Roayaie S, Uva P: Treatment of HCC in patients awating liver transplantation. Am J Transpl 7:1875, 2007

10. Dedek K, Kornasiewicz O, Remiszewski K, et al: Impact of tumor characteristic on the outcome of liver transplantation in patients with hepatocellular carcinoma. Transplant Proc 41:3135, 2009

11. Vauthey JN, Ajani A: Liver transplantation and hepatocellular carcinoma biology: beginig of the end of the era of educated guesses. J Clin Oncol 21:4265, 2003