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Liver Transplantation Outcomes in Patients With Cirrhosis and Hepatocellular Carcinoma: Experience of a Single Center in a Viral Hepatitis Endemic Area

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ABSTRACT

Our center has performed 205 orthotopic liver transplantations (OLT) in 201 patients. Hepatocellular carcinoma (HCC) was discovered in 32 (15%) patients, 5 of whom were diagnosed incidentally in recipient explants. The main underlying diagnosis was viral hepatitis (n = 28; 87.5%). Most patients (17; 53.1%) were diagnosed as having Child class B cirrhosis. Single tumors measuring <3 cm were diagnosed in 29 (90.6%) patients. Downstaging chemoembolization was performed in 7 (21.8%) patients. Preoperative *aFP* levels were normal in 20 (62.5%) patients. In the rest (n = 12; 37.5%), *aFP* levels normalized immediately after the OLT. In the latter group, 2 patients had a delayed (2 years) postoperative increase in *aFP* levels; both patients had tumor recurrence in the graft. All patients with hepatitis B received antiviral treatment with HBIG and lamivudine. There were 9 deaths (28.1%) in the immediate postoperative period (<30 days). One-year survival rate was 62.5% (n = 20). Actuarial 5-year survival rate was 55%, and actuarial 10-year survival rate was 40%. In conclusion, OLT has become the standard treatment for patients diagnosed with HCC in a population that shows cirrhosis most of the time to be secondary to viral hepatitis, provided that recipients are selected according to the size of the neoplasm and that they receive adequate antiviral prophylaxis.

THE PREVALENCE of hepatitis B in Greece is approximately 10%. The observed range of the chronic state of this disease varies from 1% to 10%, depending on patient age and physical status.¹ Furthermore, approximately 10% of patients with chronic hepatitis B and up to 80% of those with hepatitis C develop some degree of cirrhosis. Cirrhotics develop hepatocellular carcinoma (HCC) at a rate of 5.8% per year.² Alcoholic cirrhosis is rare in Greece.

The current treatment of the cirrhotic patient who has developed a small-sized HCC (<3cm) is orthotopic liver transplantation (OLT).³ However, both hepatitis B and hepatitis C tend to recur in the graft with subsequent significant decrease in patient survival.⁴ Fortunately, the use of antiretrovirals successfully prevents the recurrence of viral hepatitis (especially hepatitis B) in the transplanted liver.⁵ This study was a single-center experience regarding the outcomes of OLT for HCC that developed because of cirrhosis from viral hepatitis in the majority of the cases.

PATIENTS AND METHODS

A retrospective study was conducted using our database. A total of 205 OLT were performed in 201 patients. HCC was discovered in 32 patients (15%). Mean age was 44 (±6) years. Women comprised 4 subjects (12.5%). The underlying diagnosis was hepatitis B in 17 patients (53.1%), hepatitis C in 4 patients (12.5%), hepatitis B and D in 4 patients (12.5%), cryptogenic hepatitis in 3 patients (9.38%), hepatitis B and C in 1 patient (3.13%), primary sclerosing cholangitis in 1 patient (3.13%), Budd-Chiari in 1 patient (3.13%), and fibrolamellar HCC in 1 patient (3.13%). Patients were selected for OLT according to the currently accepted criteria³ 29 patients had a single tumor measuring <3 cm, 2 patients had 3 tumors with each 1 measuring <3 cm. The only exception was the patient with the

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fibrolamellar HCC, whose tumor measured 7 cm. Cirrhosis was determined as Child class A in 7 patients (21.88%), class B in 17 patients (53.1%), and class C in 8 patients (25%). Downstaging chemoembolization was performed in 7 (21.8%) patients. Alcohol ablation was performed in 1 patient. All patients underwent OLT using either a standard⁶ approach (n = 7; 21.88%) or the piggy-back⁷ technique (n = 25; 88.12%). All patients received cyclosporine, mycophenolate mofetil, and methylprednisolone as the immunosuppressive regimen. All patients with hepatitis B received antiviral treatment with HBIG (Ab titer goal >500 U/mL) and lamivudine (100 mg/d). The follow-up period was up to 10 years with survivals calculated using Kaplan-Meier analysis.

RESULTS

Recurrence

HCC was discovered in 32 patients (15%). In 27 of those (84.4%), the tumor was diagnosed preoperatively (computed tomography [CT] scan), whereas in the other 5 (15.6%), it was an incidental finding (explant pathology). Preoperative aFP levels were normal in 20 (62.5%) patients. In the other 12 (37.5%), aFP levels normalized immediately after the OLT. From the latter group, 2 patients, 1 with hepatitis B cirrhosis and the 1 with the fibrolamellar HCC, showed a postoperative increase in aFP levels at 2 years, both of those patients displayed tumor recurrence in the graft. Hepatitis B recurred in 4 patients (12.5%). HBsAg seronegativity was achieved in all 4 patients within 19 to 28 months; none of these patients showed tumor recurrence.

Survival

There were 9 deaths (28.1%) in the immediate postoperative period (<30 days). Three patients died because of an acute coronary episode, 3 because of primary graft nonfunction, and 3 for other reasons: pseudoaneurysm rupture and technical complications. Three more patients died of uncontrollable sepsis during the first posttransplantation year, thus bringing survival to 62.5% (n = 20). Actuarial 5-year survival rate was 55% and 10-year survival rate was 40% (Fig 1). Causes of death after the first posttransplantation year were cardiovascular disease (n = 5) and tumor recurrence (n = 2).

DISCUSSION

Because of the high prevalence (10%) of hepatitis B in Greece, even with most modest calculations, the incidence of HCC reaches 50 cases per year per million population. Cirrhosis of various etiologies are not so common. Given the fact that only half of the Child A cirrhotics can withstand a curative resection and that the current standard of treatment in selected groups of cirrhotics with HCC is OLT,³ we allocated most of our grafts to patients with cirrhosis secondary to viral hepatitis. In the present study, 26 of the 32 patients who were diagnosed with HCC (87.5%) showed history of cirrhosis due to hepatitis B, C, D, or their combinations. Although both hepatitis B and hepatitis C tend to reinfect the graft with subsequent significantly decreased patient survival,⁴ modern antiretro-

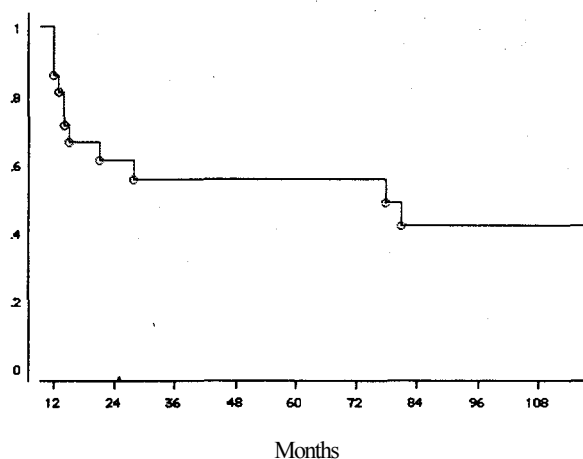


Fig 1. This survival curve incorporates the data of 32 patients who underwent OLT for HCC with underlying cirrhosis, mainly of viral etiology. Actuarial 5-year survival rate was 55% and 10-year survival rate was 40%.

viral therapies successfully prevent the recurrence of viral hepatitis (especially hepatitis B) in the transplanted liver.⁵ This conclusion is consistent with our observation that hepatitis recurred in 4 patients with a B infection (12.5%) and, remarkably, no patient with a C infection. Moreover, all 4 patients finally achieved HBsAg seronegativity with no subsequent sequelae. To maximize our therapeutic interventions, we used chemoembolization in 7 (21.8%) patients⁸ and EtOH ablation in 1 patient.⁹ None of these 8 patients had HCC recurrence in the graft. In the present study, the 1-year survival rate was 62.5%, which was significantly less than that documented in the literature. However, actuarial 5-year and 10-year survival rate appear to be similar to those reports.⁸ The low 1-year survival rate could be explained by the fact that until recently there was limited selection of patients based on the severity of the underlying cirrhosis. Thus very ill patients were receiving grafts. More reasonable selection criteria have been applied during the last 2 years, where the 1-year survival rate was 85%. Finally, a new increase in the posttransplantation normalized aFP showed 100% accuracy to diagnose HCC recurrence in the graft. In conclusion, OLT has become the standard treatment for patients diagnosed with HCC was a population in which cirrhosis is mostly secondary to viral hepatitis, provided that recipients are selected according to the size of the neoplasm and that they receive adequate antiviral prophylaxis.

REFERENCES

- Gogos CA, Fouka KP, Nikiforidis G, et al: Prevalence of hepatitis B and C virus infection in the general population and selected groups in South-Western Greece. *Eur J Epidemiol* 18:551, 2003
- Raptis I, Koskinas J, Emmanouil T, et al: Changing relative roles of hepatitis B and C viruses in the aetiology of hepatocellular carcinoma in Greece. Epidemiological and clinical observations. *J Viral Hepat* 10:450, 2003

3. 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
4. Dodson SF, Issa S, Bonham A: Liver transplantation for chronic viral hepatitis. *Surg Clin North Am* 79:131, 1999
5. Dodson SF, de Vera ME, Bonham CA, et al: Lamivudine after hepatitis B immune globulin is effective in preventing hepatitis B recurrence after liver transplantation. *Liver Transpl* 6:434, 2000
6. Knechtle SJ, Rikkers LF: Portal hypertension. Role of liver transplantation. In Cameron JL (ed): *Current Surgical Therapy*. Philadelphia: Mosby; 2004, p 366
7. Llovet JM, Bruix J, Gores GJ: Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. *Hepatology* 31:1019, 2000
8. Klintmalm GB: Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. *Ann Surg* 228:479, 1998
9. Shiina S, Teratani T, Obi S, et al: Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology* 62(suppl 1):S64, 2002