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Liver Transplantation for Hereditary Tyrosinemia in the Presence of Hepatocellular Carcinoma

Carlos O. Esquivel, Luis Mieles, Ignazio R. Marino, Satoru Todo, Leonard Makowka, Giovanni Ambrosino, Paul Nakazato, and Thomas E. Starzl

HEREDITARY TYROSINEMIA is a metabolic disorder characterized by deficiency of the enzyme fumarylacetoacetate, resulting in the accumulation of tyrosine metabolites, which are toxic to the liver. Hepatic dysfunction, associated with tyrosinemia, varies from an acute form of liver failure to a chronic, progressive form that leads to cirrhosis and hepatocellular carcinoma (HCC).[1,2]

Liver transplantation is the treatment of choice for end-stage hepatic disease brought about by several metabolic disorders, including tyrosinemia. Liver replacement has also been offered to patients with primary hepatic malignancies.[3] Despite the fact that liver transplantation cures the underlying metabolic defect in patients with tyrosinemia,[4] little is known about the proper timing for transplantation in such patients and the potential consequences of replacing the liver in the presence of HCC.

The purpose of this investigation is to report our experience with hepatic transplantation for tyrosinemia in the presence of HCC.

PATIENTS AND METHODS

Between March 1980 and December 1987, 1043 patients underwent liver transplantation at the University of Pittsburgh. Ten patients received 11 liver transplants for tyrosinemia. Nine were children (less than 18 years of age), and one was a 21-year-old adult. The records of these 10 patients were carefully reviewed, and the following information was obtained: demographic data, biochemical/histologic analysis for tyrosinemia, location of tumor, vascular invasion, recurrence, and survival in months. Liver function tests and the patient's quality of life at the time of last follow-up were also recorded. In each case, a diagnosis of tyrosinemia was made based on the clinical findings, the presence of elevated plasma and urine tyrosine, phenylalanine, and methionine, and the presence of succinylacetone in the urine.

RESULTS

Five of the 10 patients had HCC at the time of transplantation, with follow-up ranging from five months to 78 months (Table 1). One patient died of recurrence of malignant disease five months following transplantation, with widespread metastases involving the hepatic allograft, lungs, bones, and brain. This patient had HCC involving the right lobe, with invasion of the portal and hepatic veins. The other four patients are alive and free of recurrence (median 56, ranging from 42 to 78 months). At the time of the last follow-up, these four patients had normal liver function tests. Three are performing well at school, and one is working full time.

All five patients with HCC were older than two years of age. Three of the 10 patients were under two years of age, and although their excised livers showed severe dysplasia, none had HCC. Nine patients had markedly elevated alpha-fetoprotein. This information was not available in one patient.

Table 1. Clinical Features of Five Liver Transplant Recipients for Tyrosinemia and HCC

Case No.	Age at OLT (yr)	Indication for OLT	Location	Survival (mo)	Follow-up
1	2¾	Hepatoma	Both lobes	78	School, normal LFTs
2	21	Liver failure p resection for HCC	Right lobe	56	Working, normal LFTs
3	3½	Cirrhosis + suspected hepatoma	Both lobes	48	School, normal LFTs
4	3	Cirrhosis	Both lobes	42	School, normal LFTs
5	5¹¹/₁₂	Hepatoma	Right lobe	5	Recurrence

Note: HCC = Hepatocellular carcinoma; OLT = Orthotopic liver transplantation; LFTs = Liver function tests

DISCUSSION

Liver transplantation is an effective mode of therapy for patients with liver disease secondary to inborn errors of the metabolism, but the results have been disappointing when the indication for transplantation is HCC due to the high recurrence rate.[5,6] Most of the recurrences seem to occur within the first year following transplantation. On the other hand, the recurrence rate is almost nonexistent in patients

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania.

Address reprint requests to Carlos O. Esquivel, MD, PhD, Pacific Presbyterian Medical Center, PO Box 7999, San Francisco, CA 94120.

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with HCC in whom the main indication for transplantation is an underlying nonmalignant liver disease, such as cirrhosis.[6] This is probably the result of tumor involvement, since in the former group, the tumor is usually so extensive that a conventional subtotal hepatectomy is not possible, whereas in the latter group, resection of the tumor would be possible, if the underlying liver parenchyma was normal. However, in the present study, the extent of tumor involvement of the liver did not seem to have any prognostic significance, since four patients with bilateral involvement of the liver have had no evidence of recurrence thus far.

Interestingly, the patient with tumor confined to the right lobe of the liver died of recurrence shortly after transplantation. Unlike the other cases, this particular patient had extensive invasion of the portal and hepatic veins.

The proper timing for hepatic replacement in patients with tyrosinemia is a topic of confusion among pediatricians and surgeons. Careful consideration should be given to patients older than two years of age, since the incidence of HCC increases considerably beyond that age.[7] The follow-up on these patients is particularly difficult, since the alphafetoprotein is usually elevated and the presence of nodules makes it difficult for the radiologist to distinguish between a benign regenerative nodule and malignancy.

In conclusion, the presence of hepatocellular carcinoma and cirrhosis due to hereditary tyrosinemia is not a contraindication for liver transplantation.

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