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Liver transplantation for primary liver tumors in pediatrics. A case series

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ABSTRACT

Primary liver tumors are an increasing indication for pediatric liver transplantation. Here we report the cases of 10 patients who underwent liver transplantation for primary liver tumors in our hospital, from 2001 to date. Up to 2011, 1 transplant due to hepatoblastoma was done out of 117 liver transplants (0.8%). Since 2012, there were 9 patients out of 141 (6.4%) (5 due to hepatoblastoma, 2 due to hepatocellular carcinoma, 1 due to hepatic epithelioid hemangioendothelioma, and 1 due to hepatic mesenchymal hamartoma). Follow-up: 13.2 months (median); age at transplantation: living 4.7 years (median); weight: 17.6 kg (median). Eighty percent of patients received grafts from living donors. No tumor recurrence was observed. Survival was 100% in the follow-up period. In our series, patients with primary liver tumors requiring transplantation showed an adequate course, even in the case of hepatocellular carcinoma, Related living donors liver transplantation shortened the time between the indication and the surgery.

Keywords: *liver transplantation; hepatoblastoma; liver neoplasms.*

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INTRODUCTION

The frequency of primary liver tumors in children has grown in recent years due to an increase in the number of cases and an improvement in diagnostic tools. The indication for liver transplantation (LT) in cases of unresectable tumors, no response to treatment, or recurrence has increased from 2% of the total number of transplants to 10% at present, as per the different series.[1,2] Hepatoblastoma (HB) is the most frequent primary malignant liver tumor in pediatrics and the one for which there is the greatest experience in transplantation; 20% requires LV.[3,4] Advances in treatment have increased the survival rate from 35% in the 1970s to 90% in standard-risk tumors today.[5] Hepatocellular carcinoma (HCC) —which is much less frequent (0.4% of HCC cases occur in the pediatric age)— is seen in older children, most commonly in patients with chronic liver disease, although this is more marked in adults. Unlike HB, HCC is typically chemoresistant, so its treatment and course depend on an early diagnosis and complete resection.[6] Patients with benign liver tumors (hepatic mesenchymal hamartoma, adenomas, focal nodular hyperplasia, among others) or with tumors of intermediate behavior (hepatic epithelioid hemangioendothelioma) may require liver transplantation due to obstructive complications, extrahepatic dissemination, or other indications.[7–9]

It is important to report cases of transplant indication with increasing frequency and difficulties in decision-making, such as primary liver tumors in pediatrics.

OBJECTIVE

To report a series of patients who required liver transplantation due to primary liver tumors in our hospital, their characteristics, and outcomes.

POPULATION AND METHODS

Patients younger than 17 years who underwent liver transplantation in our hospital due to a primary liver tumor or with a finding of a primary liver tumor in the explant between January 2001 and February 2023 were included. Data were obtained from the analysis of electronical medical records. The SPSS software was used for the statistical analysis. The cases in our series were separated by type of neoplasm (HB and other tumors) for analysis and 2 periods were described (from January 2001 to December 2011 and from January 2012 to February 2023). We analyzed the outcomes and characteristics of transplantation, complications, mortality, and tumor recurrence.

RESULTS

General characteristics

Since 2001, 258 pediatric liver transplants were performed in our hospital in 237 patients; 65% were from living donors (LD) at the beginning of the program, increasing to 83% in the last 12 years. Patients' median age at transplantation was 15 months (r: 28 days–17 years) and their median weight was 9 kg (r: 2–66 kg). The main indication for transplant was biliary atresia (56.7%). Their overall survival is 83.2%, with a 94% survival at 1 year after the transplant. Until December 2011, only 1 patient received a transplant due to HB out of 117 transplants performed (0.8%). From January 2012 to February 2023, 9 patients underwent a liver transplantation due to primary liver tumors (5 girls) out of 141 transplants performed in the same period (6.4%); 5 were due to HB (3.5% of all transplant indications), 2 due to HCC (1.4%), 1 due to hepatic epithelioid hemangioendothelioma (HEHE), and 1 due to hepatic mesenchymal hamartoma (HMH). Characteristics, stage, treatment, and course are described in *Tables 1 and 2*. The mean follow-up duration for the entire series was 13.2 months (r: 1–36 months). The mean age at diagnosis was 2.04 years, while the mean age at transplantation was 4.7 years. Diagnosis (mean age: 1.08 years) and transplantation (mean age: 2.29 years) occurred at an earlier age in patients in the HB group. Patients' median weight at transplantation was 17.6 kg (r: 7.6–48 kg).

Treatments prior to transplantation

In our series, only the patient with HMH was treated with an attempted resection, and the rapid growth of the lesion resulted in the indication for liver transplantation. In the remaining 8/9 patients, the indication for liver transplantation was due to unresectable lesions; in 1 of the patients with HCC, the tumor was observed in liver explant (transplant due to decompensated biliary cirrhosis). In patients with HB, liver transplantation accounted for the first surgical approach; our series did not include rescue transplants. Four patients were staged as PRETEXT IV and 2, as PRETEXT III with vascular involvement. The 6 patients received pre-transplant chemotherapy and only 2 received post-transplant chemotherapy without complications or modifications in their immunosuppressive regimen during that

Table 1. Characteristics of patients, tumor diagnosis, and treatments

Patient	Tumor	Dx (m)	Tx (m)	Stage	Place of origin	Pre-transplant CT	AFP (Dx) (ng/mL)	AFP (LT) (ng/mL)	Post-transplant CT	Last AFP measured during follow-up
1	Mixed epithelial and mesenchymal HB	22	31	PRETEXT IV - P	Argentina	SIOPEL protocol. Size reduction and AFP.	500 000	58	Not administered	0.6
2	Epithelial HB (embryonal-fetal)	99	108	PRETEXT IV	Peru	SIOPEL protocol. Size reduction and AFP.	7357	3.3	Not administered	1.5
3	Multifocal HEHE	189	195	Multifocal HEHE, lung metastases	Argentina	No -	Normal	-	-	
4	Multifocal, moderately differentiated HCC	38	44	Multifocal HCC (5 lesions measuring 6, 4.5, 0.7, 0.9, 0.7 cm), thrombosis of segmental branch of portal vein, no metastases	Peru	No	57 000	166 262	Not administered	5.6
5	Embryonal epithelial HB	5.	10	PRETEXT IV - M (lung metastases)	Peru	SIOPEL protocol Size reduction and AFP, metastases resolution.	711	25.6	Not administered	11.2
6	Mesenchymal hamartoma	1	14	Resection of intracardiac tumor	Argentina	No	Normal	-	-	-
7	Epithelial HB (embryonal-fetal)	6	11	PRETEXT III - P and C	Argentina	SIOPEL protocol. Size reduction, increased AFP in last pre-transplant block.	205 000	50 000	SIOPEL block	2
8	Fetal epithelial HB	20	24	PRETEXT III - C	Argentina	SIOPEL protocol. Size reduction and AFP reduction.	17 016	26	17 016	3.9
9	Multifocal HCC	93	92	Multifocal HCC (3 lesions measuring < 1 cm), early, no vascular dissemination, negative lymph nodes	Ecuador	No	Normal	1.8	Not administered	1.2
10	Mixed epithelial and mesenchymal HB	27	40	PRETEXT IV - M (lung metastases)	Ecuador.	SIOPEL protocol Size reduction and AFP reduction, metastases resolution.	60 500	215	Not administered	3.5

AFP: alpha fetoprotein. Dx: diagnosis. HB: hepatoblastoma. HCC: hepatocellular carcinoma. HEHE: hepatic epithelioid hemangioendothelioma. HMH: hepatic mesenchymal hamartoma. MTP: methylprednisolone. PRETEXT: pre–treatment tumour extension staging system. CT: chemotherapy. SIOPEL: International Childhood Liver Tumors Strategy Group. LT: liver transplantation.

period. The patients with HCC did not receive chemotherapy; 1 had tumor thrombosis in the segmental branch arising from the portal vein and cirrhosis due to progressive familial intrahepatic cholestasis, so, although the Milan Criteria were exceeded, liver transplantation was decided.

Transplantation characteristics, complications, and length of stay

Eight patients received grafts from living donors; 1 of them, who underwent transplantation due to HMH, required retransplantation from a deceased donor due to hepatic artery thrombosis 4 days after the transplantation. One patient developed bile duct stenosis, which was managed with an interventional treatment. No tumor recurrence was observed in our series during the follow-up period; the survival rate was 100%. The initial immunosuppression indicated to all patients was methylprednisolone/tacrolimus; it was changed to mTOR inhibitors (sirolimus/everolimus) 2 months after transplantation in 4 patients due to their cancer history. The median length of stay in the pediatric intensive care unit was 5 days (r: 2–36 days). The median length of stay in the hospital was 16 days (r: 5–55 days), which was consistent with the length of stay in our unit due to other indications (data not published).

Table 2. Characteristics of liver transplantation and complications

Patient	Weight at LT (kg)	Donor type	Baseline IS	Follow-up IS	Post-transplant complications	Complication management	Tumor recurrence	Death
1	12.5	DD	MTP/tacrolimus	Sirolimus	No	-	No	No
2	25.5	RLD	MTP/tacrolimus	Tacrolimus	No	-	No	No
3	48	DD	MTP/tacrolimus	Tacrolimus	No	-	No	No
4	15	RLD	MTP/tacrolimus	Everolimus	Bile duct stenosis	Interventional dilatation	No	No
5	9	RLD	MTP/tacrolimus	Tacrolimus	No	-	No	No
6	8	RLD	MTP/tacrolimus	Sirolimus	Hepatic artery thrombosis	Liver retransplantation with DD	No	No
7	7.6	RLD	MTP/tacrolimus	Tacrolimus	No	-	No	No
8	13	RLD	MTP/tacrolimus	Sirolimus	No	-	No	No
9	22	RLD	MTP/tacrolimus	Tacrolimus	No	-	No	No
10	15	RLD	MTP/tacrolimus	Tacrolimus	No	-	No	No

AFP: alpha fetoprotein. DD: deceased donor. RLD: related living donor. Dx: diagnosis. IS: immunosuppression. MTP: methylprednisolone. PRETEXT: pre–treatment tumour extension staging system. SIOPEL: International Childhood Liver Tumors Strategy Group. LT: liver transplantation.

DISCUSSION

We analyzed the patients who underwent liver transplantation due to primary liver tumors in our hospital between January 2001 and February 2023. We observed an increase in the number of transplant patients diagnosed with primary liver tumors since 2012; the most frequent diagnosis was HB, which is consistent with other case series. This is due to an increased incidence, a better response to neoadjuvant therapy, and an earlier consultation in transplant centers.[10] This group was diagnosed at a younger age, and the time between diagnosis and transplantation was shorter than in patients whose tumors had a different etiology.

Most of our patients received a liver transplantation from a living donor; this is because of a strategy implemented in our hospital and due to the fact that an important group of patients (5/10) were in the programs of international patients who cannot have access to deceased donors as per the Argentine law. This made it possible to shorten the time between diagnosis and transplantation, mainly in the HB group. In Argentina, between 2000 and 2015, 19 patients received a liver transplantation due to HB out of 207 cases (9.1%), while 11 patients did so due to HCC out of 73 diagnosed in that period (15%).[11]

The initial immunosuppression included methylprednisolone at 5–10 mg/kg in the anhepatic phase, with subsequent tapering for 7 days (continuing with meprednisone at 0.3 mg/kg/day with progressive tapering until 6 months post-transplant), and tacrolimus from 24 hours post-transplant in all cases (trough levels of 7–10 ng/mL) as in patients transplanted for other etiologies. The most common maintenance immunosuppression included tacrolimus, which was changed to mTor inhibitors in 4 patients (4/10), unlike other series. This was partly due to the unavailability of these immunosuppressants in the country of origin of the patients from abroad. In those cases, lower serum tacrolimus levels were maintained like in patients transplanted for other etiologies.

Although the follow-up period was short (mean: 13.2 months) and varied greatly, we did not observe post-transplant recurrence; and the survival rate was 100%.

Another series published in our country by Lauferman et al. analyzed prognostic factors for event-free survival in 21 patients with liver transplantation due to unresectable hepatoblastoma, describing AFP levels > 16 000 ng/dL at the time of liver transplantation as a predictor of tumor recurrence.[12]

Our study had several limitations; its retrospective nature and the fact that the study period was long enough for changes to emerge in surgical techniques, cancer diagnostic and treatment criteria, immunosuppression strategies, and indications for transplantation in a group of patients with rare heterogeneous diagnoses. To our knowledge, this is the first report of a series of patients with primary liver tumors who underwent transplantation in our country that

included etiologies other than hepatoblastoma, which account for a growing problem in pediatric hepatology.

CONCLUSIONS

Liver transplantation due to primary liver tumors has increased in recent years in all published series. In our series, although our population was heterogeneous, the patients had a good outcome, even those with HCC. Living donor liver transplantation shortened the time between the indication and the surgery, mainly in HB. ■

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