Liver Transplant in Children with Hepatoblastoma

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Abstract

Objectives: In this paper, the results of liver transplant due to hepatoblastoma in 10 pediatric patients at Istanbul Şişli Memorial Hospital Transplantation Center are presented.

Materials and Methods: We retrospectively evaluated medical records of pediatric patients diagnosed with hepatoblastoma and who underwent liver transplant at our clinic between January 2009 and March 2014. We examined age, weight, chemotherapy regimen, graft type for liver transplant, duration of hospital stay, complications, follow-up duration, and survival information.

Results: The median age of the 10 patients included in our study was 13.5 months (range, 8-120 mo), and the median weight was 10 kg (range, 6.5-30 kg). Two of the patients were twins. Five patients had pretreatment extent of disease III (centrally placed cases), and five had pretreatment extent of disease IV hepatoblastoma. Preoperative chemotherapy was given to 7 patients as cisplatin plus doxorubicin and to 3 patients per the International Childhood Liver Tumors Strategy Group 3 High-Risk Protocol at external centers. These protocols were administered according to treatment center preference. Nine patients received transplants from living donors. Two grafts were right lobes, and 7 were left lateral segments. In the remaining patient, a whole liver was received from a deceased donor. The histopathologic subgroups were epithelial in 5 patients, with others being of mixed type. Postoperative complications occurred in 3 patients as infection, intra-abdominal fluid collection, and acute rejection. The median follow-up was 32 months. One patient died because of lung metastasis within 9 months after transplant.

Conclusions: Centers should offer liver transplant to patients with centrally located tumors. For centers that have an insufficient number of deceased donors, living-donor liver transplant with optimal planning and early treatment can be performed.

Key words: Cancer, Transplantation, Treatment

Introduction

Hepatoblastoma occurs in about 0.5 to 1.5 patients per 1 million population. It occurs more than 1.2 to 3.6 times in boys than in girls.1-3 Adrenocortical tumors have been accompanied by familial hepatoblastoma.4 Although resection may be the optimal first treatment, chemotherapy plays a critical role. After chemotherapy, 80% of the cases are resectable.5 In cases when surgery is not possible after chemotherapy, liver transplant is the only treatment option. Liver transplant can be done using a graft from a living or deceased donor.6 Use of livers from living donors has some advantages over the use of livers from deceased donors. The examination of survival rates and follow-up procedures after transplant because of hepatoblastoma remains an important area of study. In this study, we present the results of 10 pediatric patients at the Istanbul Şişli Memorial Hospital Transplantation Center who underwent liver transplant because of hepatoblastoma that could not be resected.

Materials and Methods

We retrospectively evaluated medical records of patients with the diagnosis of hepatoblastoma with unresectable tumors and who underwent liver transplant and were seen at our clinic between January 2009 and March 2014. We recorded patient age, weight, sex, and family history. Patients were classified according to liver placement of the hepatoblastoma according to the pretreatment extent of disease by using radiologic imaging methods.
(computed tomography or magnetic resonance imaging). Tumor extent was assessed by computed tomography or magnetic resonance imaging of the abdomen and intrathoracic lesions.

We recorded levels of alpha-fetoprotein (AFP) before transplant and chemotherapy regimens of the patients. Patients who had tumors that could not be resected (because of possible multicentric location or localization and vascular involvement) underwent liver transplant. We recorded the graft type used in transplant, any complications, duration of hospital stay, posttransplant AFP level, follow-up duration, and survival rate. All patients received chemotherapy regimens at external centers. We obtained written informed consent from parents of pediatric patients before study inclusion.

Results

Of the 186 pediatric patients who had a liver transplant in our clinic during the 6-year period, 10 patients were diagnosed with hepatoblastoma (7 girls and 3 boys). Median age was 13.5 months (range, 8-120 mo). Median weight was 10 kg (range, 6.5-30 kg). Pretransplant median AFP level of the 10 patients was 470 ng/mL (range, 20-484 000 ng/mL). Two of the patients were female twins. No additional anomalies were found in any of the patients.

The diagnoses of patients were confirmed through biopsies taken before chemotherapy administration. Five patients had pretreatment extent of disease level III (centrally placed cases), and 5 patients had pretreatment extent of disease level IV hepatoblastoma. Lung metastasis was not detected in any patient at the time of diagnosis. Preoperative chemotherapy was given to 7 patients as cisplatin plus doxorubicin and to 3 patients per the International Childhood Liver Tumors Strategy Group 3 High-Risk Protocol (all at external centers). Because of adverse effects of chemotherapy treatment, one patient required discontinuation after the second dose (hematologic effect of grade 3/4 neutropenia and renal complications in the form of acute renal failure). These protocols were administered to patients in accordance with the preference of the treatment centers.

In our patient group, 9 patients received grafts from living donors (2 were right lobes and 7 were left lateral segments); the other patient in our study group received a whole liver from a deceased donor. The histopathological subgroups were epithelial in 5 patients and mixed type in the remaining 5 patients (Table 1). Vascular dissemination was determined in 3 patients, and these patients were included in the epithelial subgroup.

Three patients had complications. One patient had acute rejection, diagnosed clinically and biochemically and confirmed histopathologically on day 7 posttransplant, with treatment received after diagnosis. The second complication was intra-abdominal fluid collection, which was drained with an ultrasonography-guided percutaneous method on day 9 posttransplant. The third patient experienced urinary tract infection, which was treated medically. The median AFP level of patients after transplant was 8 ng/mL at week 2 (range, 1-52 ng/mL). We recorded a median hospital stay of 13 days (range, 8-18 d). Patient follow-up ranged from 9 months to 69 months, with median follow-up of 32 months. During follow-up, lung metastasis was detected at posttransplant month 31 in 1 patient, who showed an AFP level of 994 ng/mL. During follow-up, 3 thoracotomies, a stereotactic radiotherapy, and 2 different relapse regimens were administered in this patient. At last follow-up, the patient was alive with disease and had been continuing treatment.

One patient died as a result of diffuse lung metastasis, which was determined at month 9 after

<p>| Table 1. Clinical Features of Patients |
|--------------------------|-------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>Age, mo/ Sex</th>
<th>AFP Pretransplant, ng/mL</th>
<th>PRETEXT</th>
<th>Histology Type/ Vascular Invasion</th>
<th>Donor (living/deceased)</th>
<th>Hospitalization Time, d</th>
<th>AFP Posttransplant, ng/mL</th>
<th>Follow-Up, mo</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/F</td>
<td>14.144</td>
<td>III</td>
<td>Epithelial/No</td>
<td>Living</td>
<td>16</td>
<td>10</td>
<td>69</td>
<td>Alive</td>
</tr>
<tr>
<td>106/M</td>
<td>490</td>
<td>III</td>
<td>Epithelial/No</td>
<td>Living</td>
<td>8</td>
<td>2</td>
<td>65</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>14/F</td>
<td>484.000</td>
<td>III</td>
<td>Epithelial/Yes</td>
<td>Deceased</td>
<td>12</td>
<td>1</td>
<td>62</td>
<td>Alive</td>
</tr>
<tr>
<td>8/F</td>
<td>86</td>
<td>III</td>
<td>Mixed type</td>
<td>Living</td>
<td>18</td>
<td>18</td>
<td>46</td>
<td>Alive</td>
</tr>
<tr>
<td>120/M</td>
<td>12.448</td>
<td>IV</td>
<td>Epithelial/Yes</td>
<td>Living</td>
<td>14</td>
<td>19</td>
<td>9</td>
<td>Died</td>
</tr>
<tr>
<td>11/F</td>
<td>20</td>
<td>IV</td>
<td>Mixed type</td>
<td>Living</td>
<td>11</td>
<td>1</td>
<td>32</td>
<td>Alive</td>
</tr>
<tr>
<td>11/F</td>
<td>112</td>
<td>IV</td>
<td>Mixed type</td>
<td>Living</td>
<td>11</td>
<td>5</td>
<td>32</td>
<td>Alive</td>
</tr>
<tr>
<td>13/F</td>
<td>450</td>
<td>III</td>
<td>Mixed type/ Epithelial/Yes</td>
<td>Living</td>
<td>17</td>
<td>6</td>
<td>23</td>
<td>Alive</td>
</tr>
<tr>
<td>18/F</td>
<td>12.100</td>
<td>IV</td>
<td>Epithelial</td>
<td>Living</td>
<td>15</td>
<td>52</td>
<td>21</td>
<td>Alive</td>
</tr>
<tr>
<td>8/M</td>
<td>78</td>
<td>IV</td>
<td>Mixed type</td>
<td>Living</td>
<td>8</td>
<td>13</td>
<td>15</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; F, female; M, male; PRETEXT, pretreatment extent of disease
transplant. This patient who died had pretreatment extent of disease level IV hepatoblastoma and was given the International Childhood Liver Tumors Strategy Group 3 High-Risk Protocol, but this regimen was discontinued after the second dose due to the adverse effects preoperatively; a postoperative chemotherapy regimen was later given to this patient.

Discussion

Hepatoblastomas constitute 79% of malignant liver tumors in pediatric patients. Previous research has found that it is 1.2 to 3.6 times more common in boys, but it was 2.3 times more common in girls in our patient group. Previous studies have reported sisters who shared a hepatoblastoma diagnosis, but only Riikonen and associates have previously reported hepatoblastoma in one case of twin male infants. In that previous study, Riikonen and associates treated one of the twins with chemotherapy and radiotherapy and the other twin underwent resection. Our twin case is important because they were girls who underwent simultaneous liver transplant procedures from living donors.

Survival of patients with hepatoblastoma has increased in recent years because of developments in immunosuppression agents, surgical techniques, and chemotherapy. Hepatoblastomas are chemoresponsive tumors, and multidisciplinary and multiinstitutional trials have been conducted and discussed. The International Childhood Liver Tumors Strategy Group proposed that pre- and postoperative chemotherapy regimens are necessary to improve patient outcomes. Srinivazan and associates and Otte and associates have stated that postoperative chemotherapy increases survival. Chemotherapy is used to reduce tumors that appear unresectable at diagnosis and to control residual microscopic disease after definitive resection. Many tumors can be shrunk to permit partial hepatectomy. Chemotherapy was given to our patients after the operation, with 1 patient developing lung metastases at month 9 posttransplant. We agree that postoperative chemotherapy should be given with careful consideration in terms of relapse.

Complete resection without transplant is possible in most children with hepatoblastomas, but liver transplant is a lifesaving option for those who have unresectable tumors. About 20% of cases are unresectable because of multicentric (pretreatment extent of disease grade IV tumors) localized and large-diameter tumors; tumors involving the portal and/or hepatic vein are invasive, and, because they are close to major vessels, curative resection is not possible. In 1968, Starzl and associates described the first liver transplant in a child who had a liver tumor that could not be resected. Cases of centrally located hepatoblastomas are controversial; these cases should be considered individually to determine whether liver transplant or tumor resection would be most beneficial. Although some authors claim that aggressive resection is possible, others do not recommend extensive liver resection. In our clinical approach, decisions are made after the administration of neoadjuvant chemotherapy and reassessment of the tumor extent. If there is no change in tumor size, we make the decision during surgery and simultaneously prepare the child for possible transplant. If the tumor mass cannot be removed during surgery, total hepatectomy and living-donor liver transplant are performed simultaneously.

We prepared for simultaneous transplant in 2 patients with centrally located hepatoblastomas, but the tumors were resected completely and transplant was thus canceled; these patients were excluded from this study. Centers should offer simultaneous liver transplant to patients with centrally located tumors. Liver transplant can be done using a living or a deceased donor. In our clinic, 9 patients received livers from living donors. For countries in which allografts from deceased donors are less available, transplant from a living donor seems more appropriate since the surgery timing can be better planned and arranged.

Some studies have stated that survival is 30% lower in patients who must undergo liver transplant after a relapse after a partial resection than in patients who have primary liver transplants without resection. Other studies have found that a transplant procedure is relatively contraindicated in patients who have relapses after a resection. In our study, all patients who could not have resection underwent liver transplant. Tiao and associates have stated that they see rejection primarily as a complication. Rejection was seen in one of our patients, and this patient was treated successfully. Patients who have rejection must be treated carefully because postoperative immunosuppression and steroid use can cause undesirable results (including death). With
primary liver transplant, mortality has been shown to be 20% to 25% within 2 years after transplant. In our patients with primary liver transplant, 1 patient (10%) died, and the survival rate after transplant was determined to be 90% at 21-month follow-up; a close cooperation between the surgeon, oncologist, and family is important for survival. The increase or decrease in the AFP level can affect the postoperative treatment, as has been stated in the literature. Also, some studies have stated that vascular invasion is important and should be monitored closely.

The high AFP levels of our patients decreased after transplant; therefore, an AFP measurement may be an easy and inexpensive parameter to use for follow-up. Previous research has stated that vascular invasion is related to high recurrence. In contrast, other groups have reported that vascular invasion is not important. In our study, 30% of our patients had vascular invasion, and 1 of the 2 patients who had vascular invasion died; thus, we believe that vascular invasion is important and should be monitored closely.

Conclusions

Centers should offer liver transplant to patients with centrally located tumors. For centers that have an insufficient number of donations from deceased donors, living-donor liver transplant with optimal planning and early treatment should be selected. The influence of genetic predisposition should not be ignored.

References