

UNRESECTABLE HEPATOBLASTOMA: THE ROLE OF PREOPERATIVE CHEMOTHERAPY

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Although rare, hepatoblastoma is the most common primary malignant tumor of the liver in infancy and childhood.^{1,2} In the past, the prognosis of hepatoblastoma was generally poor, and very few who did not have their tumor removed survived, as complete surgical resection is the only treatment that can offer a cure for these children.³ Unfortunately, more than 50% of children with hepatoblastoma have extensive disease by the time of diagnosis, which makes the tumor unresectable.³ For these patients, the administration of preoperative chemotherapy becomes an effective method of rendering these tumors resectable.⁴⁻⁸ This report outlines our experience with 11 children with unresectable hepatoblastoma, with emphasis on the value of preoperative chemotherapy.

Patients and Methods

Between June 1983 and October 1997, 11 children with unresectable hepatoblastoma were treated at Tawam Hospital, United Arab Emirates. The charts of these patients were reviewed for age at presentation, sex, clinical features, associated anomalies, investigations, site of tumor, preoperative treatment, the type of surgery, histology, postoperative treatment and outcome. The resectability of these tumors was judged either preoperatively by radiological investigations (one patient), or more commonly during open biopsy.

Results

The 11 children with unresectable hepatoblastoma comprised seven females and four males, a F:M ratio of 1.75:1. At presentation, their ages ranged from 1 month to 3 years (mean 9.9 months). Their clinical features and investigations are shown in Table 1. In four of the children, the tumor involved mainly the right lobe of the

liver and in three, the tumor involved mainly the left lobe. Four patients had diffuse hepatoblastoma involving both lobes of the liver. Alpha-fetoprotein was elevated in all patients except one, and eight had thrombocytosis. Three patients had associated anomalies: one had left-sided extralobar pulmonary sequestration, another had Beckwith-Wiedemann syndrome and hemihypertrophy, while the third had Beckwith-Wiedemann syndrome and bilateral undescended testes.

There were tumor calcifications in four patients. Two of the patients treated in 1983 and 1984, respectively, did not receive preoperative chemotherapy. One of them had diffuse hepatoblastoma involving both lobes of the liver. This patient had a preoperative biopsy which confirmed hepatoblastoma, followed by radiotherapy. Radiotherapy decreased the tumor only slightly, but the patient died one year later because of diffuse advanced hepatoblastoma. The second patient was treated in 1983, had only right hepatectomy and did well for almost two years, but then had a relapse in the chest and spine with paraplegia. She was treated with chemotherapy and radiotherapy, but died five months after the relapse. The nine remaining patients were treated with preoperative chemotherapy. One patient with diffuse hepatoblastoma (Figure 1), who had preoperative biopsy which confirmed hepatoblastoma, was

TABLE 1. Clinical features and investigations of patients with unresectable hepatoblastoma.

Age/sex	Site of tumor	Platelets	Alpha-fetoprotein
6 mon/F	Right lobe	351x10 ³	575,000 µg/L
2 mon/F	Diffuse	199x10 ³	226 ng/mL
9 mon/F	Left lobe	587x10 ³	5 IU/mL
10 mon/F	Diffuse	1364x10 ³	196,000 ng/L
3 mon/M	Left lobe	690x10 ³	70,000 µg/L
1 mon/M	Diffuse	62x10 ³	271 µg/L
12 mon/F	Right lobe	716x10 ³	>500,000 µg/L
10 mon/F	Diffuse	798x10 ³	1600 µg/mL
8 mon/F	Right lobe	1340x10 ³	3470 µg/mL
3 yrs/M	Right lobe	540x10 ³	179,000 µg/L
12 mon/M	Left lobe	912x10 ³	675,750 IU/mL

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FIGURE 1. CT scan showing diffuse hepatoblastoma.



FIGURE 2. CT scan of the liver showing a large extensive hepatoblastoma.

treated with chemotherapy. This patient responded well to chemotherapy only, with total disappearance of the hepatoblastoma. She was followed up for 10 years with no evidence of recurrence.

The two remaining patients with diffuse hepatoblastoma were treated with preoperative chemotherapy, with no significant change in tumor size. Both patients died, one four months after diagnosis because of *Klebsiella* septicemia and multiple organ failure, and the other two weeks after diagnosis, because of disseminated hepatoblastoma involving the liver, lungs, kidneys and brain. Of the other six patients, one died about three weeks after initiation of chemotherapy due to brain and pulmonary

edema, while the other five showed significant reduction in the size of the tumor (Figures 2 and 3). All five patients who had preoperative chemotherapy followed by surgery are alive and well (Table 2). Thus, 6 of our 11 patients with unresectable hepatoblastoma are alive and well (Table 2).

Discussion

Although malignant tumors of the liver are rare in infancy and childhood, hepatoblastoma is the most common of these. An estimated incidence of 1.33 cases of malignant liver tumors per million children per year was reported from Victoria, Australia,⁹ and 1.9 cases per million children per year from the U.S.¹⁰ Because of this low incidence, single institution experience with hepatoblastoma is usually small. Davidson et al. saw only 25 cases of hepatoblastoma over a period of 33 years.¹¹ The exact incidence of hepatoblastoma in the United Arab Emirates is not known.

Associated anomalies are not uncommon with hepatoblastoma. Three of our patients had associated anomalies. Two of them had Beckwith-Wiedemann syndrome, which in one patient was also associated with hemihypertrophy. The presence of associated extralobar sequestration in one of our patients was unique, as such an association had not been reported before. Children with Beckwith-Wiedemann syndrome are known to have an increased risk of developing a variety of tumors, including Wilms' tumor, adrenal tumor and hepatoblastoma. An estimated tumor risk of 7.5% has been reported among children with Beckwith-Wiedemann syndrome,¹² but fortunately, these children have an improved survival rate.¹³ Also of interest was the finding of thrombocytosis in eight of our patients.

During the past two decades, there has been a marked improvement in the outcome of children with hepatoblastoma, a tumor known in the past to have a poor prognosis. This is attributed to advancement in chemotherapeutic agents, as well as improved surgical techniques, including hepatic transplantation. Complete surgical resection of hepatoblastoma is the treatment of choice that can offer long-term survival for these children. Unfortunately, this is sometimes not feasible, as more than 50% of children with hepatoblastoma present late, with a large size tumor that is unresectable.³ Such cases judged intraoperatively or by preoperative radiological investigations should be treated with preoperative chemotherapy in an attempt to shrink the tumor and to make it resectable.⁴⁻⁸ A survey of the Surgical Section of the American Academy of Pediatrics in 1974 has shown that none of 51 children with unresectable hepatoblastoma was cured.³ Subsequently, preoperative chemotherapy for unresectable hepatoblastoma became the only effective method in rendering these tumors resectable.⁴⁻⁸ Five of our patients with unresectable hepatoblastoma who had



FIGURE 3. CT scan of the liver showing marked reduction in tumor size following chemotherapy.

TABLE 2. Treatment and outcome in patients with unresectable hepatoblastoma.

Preoperative treatment	Type of surgery	Outcome
CDPP, ADR	Right hepatectomy	20 months postoperative now
VCR, ADR	No surgery	10 years post-chemotherapy now
CDPP, ADR	Left lobectomy	7 years postoperative now
CDPP, ADR	No surgery	4 months post-chemotherapy*
CDPP, ADR	Left lobectomy	2 years postoperative now
VCR,CTX,ADR	No surgery	2 weeks post-chemotherapy*
VCR, ADR	No surgery	4 weeks post-chemotherapy*
Preoperative radiotherapy	No surgery	1 year post-radiotherapy*
None	Right hepatectomy	2 years and 4 months postoperative*
CDPP, ADR	Extended right hepatectomy	2.5 years postoperative now
CDPP, DOXO, CARBO	Left lobectomy	6 months postoperative now

*These patients died; CDPP=cisplatin 80 mg/m² 24 hours continuous infusion; DOXO=doxorubicin, 60 mg/m² 48 hours continuous infusion; CARBO=carboplatin, 500 mg/m² 1 hour infusion; ADR=adriamycin, 30 mg/m² 48 hours continuous infusion; VCR=vincristine 1.5 mg/m²; CTX=cyclophosphamide 1 g/m².

preoperative chemotherapy followed by surgical resection are alive and well, and in one, there was total tumor disappearance with chemotherapy only. In all of the patients, there was a significant shrinkage of the tumor which made it easier to resect.

There is now a consensus on the role of preoperative chemotherapy in the management of hepatoblastoma that are extensive and not amenable to surgical resection, but complete resection remains necessary for cure.^{3,5} Of five patients who did not have surgery, only one survived. This patient had diffuse multifocal hepatoblastoma involving both liver lobes, but with chemotherapy only there was total disappearance of the tumor. Sporadic cases similar to

ours with long-term survival have been reported.^{8,14,15} To achieve tumor reduction, a variety of chemotherapeutic agents have been used. In 1975, Tan¹⁶ reported the efficacy of adriamycin as a single agent to treat hepatoblastoma, and in 1985, Quinn et al.⁸ reported the efficacy of the combination of doxorubicin and cisplatin in children with unresectable hepatoblastoma. In the Children's Cancer Study Group, 20 of 34 patients (59%) whose tumors were considered to be unresectable received continuous infusion of doxorubicin and cisplatin, following which there was a significant decrease in tumor size.⁵ Subsequently, other combinations of chemotherapeutic agents have been used to treat children with unresectable hepatoblastoma with good results. Adriamycin alone,^{16,17} or more commonly in combination with cisplatin,⁸ was shown to be particularly effective in reducing the size of unresectable hepatoblastoma. Over the years, we have used different combinations of chemotherapeutic agents (Table 2), but in all except one case, adriamycin was used, and in six patients it was used in combination with cisplatin. This proved to be effective. Of the nine patients who received chemotherapy, there was a marked response in six (66.7%), with total disappearance of the tumor in one. Only one of our patients received postoperative chemotherapy. This patient had an extended right hepatectomy, and there was fear of the presence of residual microscopic tumor. Despite recent advances in chemotherapeutic agents against hepatoblastoma, some of these tumors will remain unresectable, irrespective of how aggressive the chemotherapy. Such patients are to be considered candidates for hepatic transplantation.¹⁸

Our series was relatively small, although it clearly shows the beneficial effect of preoperative chemotherapy in the management of children with unresectable hepatoblastoma. Such an approach is to be recommended. The value of preoperative chemotherapy for all children with resectable hepatoblastoma should also be considered. Knowing that there are regional variations in the incidence as well as behaviors of tumors around the world points out the need for the establishment of a National Tumor Registry and local/regional study group in this part of the world. We think this will have a positive impact on the future evaluation, management and outcome of such patients.

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