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ORIGINAL ARTICLE

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Midterm results with hepatectomy after preoperative chemotherapy in hepatoblastoma

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Abstract We evaluated the results of surgical treatment for hepatoblastoma in infants and children after intensive preoperative chemotherapy, with special reference to histology and extent of liver involvement. The clinical features of 10 children with hepatoblastoma were reviewed regarding response to neoadjuvant chemotherapy, histological subtypes, extent of hepatectomy, operative complications, and prognosis. Response to chemotherapy was measured by volumetric assessment of tumour size by computed tomography scan. Cisplatin and Adriamycin (PLADO regime) up to three cycles markedly reduced the tumour volume on computed tomography (mean regression rate 65.9%); alpha-foetoprotein (AFP) levels also decreased from an initial mean of 16,116.4 ng/ml to 2,050.9 ng/ml. Five patients underwent right hepatectomy, two had right trisegmentectomy, two had left hepatectomy, and one had left trisegmentectomy. Histopathology of resected specimens revealed foetal histology in four patients, poorly differentiated (anaplastic) subtype in three, and mixed histology with mesenchymal components and osteoid formation in three. There was 100% resectability including six unresectable tumours (prechemotherapy). Moreover, hepatic resection tended to be less invasive in patients whose tumours had been much reduced after preoperative chemotherapy. Preoperative administration of cisplatin and Adriamycin reduces the tumour size significantly so that a safe radical hepatectomy can be performed. It also allows early administration of postoperative chemotherapy. Although overall good results were obtained with the current protocol, we also document our experience of unfavourable outcomes in patients with bilobar tumours (despite trisegmentectomy), patients with tumours showing poor response to neoadjuvant chemotherapy, and patients with anaplastic histology. Overall, at a 60-month follow-up we report an 80% survival rate by a combined approach.

Keywords Hepatoblastoma · Trisegmentectomy · Hepatic resection · Cisplatin · Adriamycin

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Introduction

Hepatoblastoma, the most common primary malignant liver tumour in infants and children, has been traditionally associated with poor prognosis [1]. Unresectability is largely due to the size of the tumour with attendant invasion of hepatic vessels and the inferior vena cava [2, 3]. Although there are rare reports of long-term survivors treated with chemotherapy alone, complete surgical resection is essential for cure in most cases [4–7]. Reports relating histological features of hepatoblastoma to survival indicate improved prognosis with foetal histology compared with anaplastic and other histological subtypes [8, 9]. Although the usefulness and relative safety of extended hepatic resections is well documented in the adult population, trisegmentectomy is rarely done in childhood [10, 11]. Moreover, it is increasingly being realised that in bilobar tumours, even extensive hepatic resections, such as trisegmentectomies, are inadequate to ensure cure. Poorly responding tumours with a large size and those in proximity to a major vascular axis also pose a challenge for adequate surgical resection.

In this study we report our results with preoperative chemotherapy in effectively reducing tumour size. The

pretreatment extent of disease (PRETEXT) was used for the clinical groupings of hepatoblastoma. This approach enabled us to perform radical liver resections in all, including 50% of our patients who had bilobar involvement. This series includes two right trisegmentectomies and one left trisegmentectomy and histological subtypes ranging from poorly differentiated (anaplastic) subtype to foetal histology and mixed histology with mesenchymal components and osteoid formation. All hepatic resections were performed by one surgeon (M.B.). Although overall good results were obtained with the current protocol, we also document our experience of unfavourable outcomes in patients with bilobar tumours (despite trisegmentectomy), patients with tumours showing poor response to neoadjuvant chemotherapy, and patients with anaplastic histology.

Materials and methods

Ten patients with hepatoblastoma underwent liver resections after a predetermined protocol. The age range varied from 16 months to 38 months with a mean of 27.2 months, and the male-to-female ratio was 1.5:1. The drugs used were cisplatinum and Adriamycin (PLADO regime). When necessary we used an alternative regimen, namely vincristine, 5-fluorouracil (5-FU), and cisplatin. Initial and last alpha-foetoprotein (AFP) levels were 16,116.4 and 2,050.9 ng/ml. Follow-up ranged from 11 to 60 months with a mean of 36.1 months. Mean operating time was 125 ± 15 min, and mean blood loss was 80 ± 30 ml. All children had scanning with spiral volumetric acquisition computerized tomography (three-dimensional CT), which obtained images during continuous rotation of the x-ray source while the patient moved at a constant velocity through the gantry. Tumour volume was assessed simply by calculating the product of maximal length, width, and depth as shown on CT scans. Based on the pretreatment extent of the disease (PRETEXT), four groups were identified as follows: PRETEXT I—three adjoining areas were free; PRETEXT II—two adjoining sectors were free; PRETEXT III—one sector or two adjoining sectors were free (the tumour involved two or three sectors); PRETEXT IV—no free sector was observed.

Our protocol for managing cases of hepatoblastoma is as follows: Diagnosis is made on the basis of CT findings and AFP levels, and metastatic disease is determined by chest x-rays and CT of the abdomen and chest. Preoperative PLADO chemotherapy is given when the tumour is bilobar or large enough to increase the risk of operative mortality. Hepatic resection is done after three cycles of preoperative chemotherapy (Table 1). In cases showing no response or poor response to PLADO even after two cycles as assessed by volumetric measurement by CT scan (Table 2), we changed the drugs to vincristine, 5-FU, and cisplatin. Postoperatively, continuation chemotherapy is started at postoperative days 7–10 and is continued for a total of six cycles. Monitoring of AFP is done 3-monthly; CT scanning is done within 1 month postoperatively, at 3 months, and then every 6 months for 2 years. After the 2nd year, ultrasound and CT scan are alternated on a 6-month basis. No life-threatening complications were noted with chemotherapy.

Results

The clinical characteristics and treatment of 10 hepatoblastoma patients are shown in Table 1. The PRETEXT I grouping was $n = 0$, PRETEXT II was $n = 3$, PRETEXT III was $n = 2$, and PRETEXT IV was $n = 5$. No patient had metastasis at the time of surgery, and lymph nodes at the porta were negative.

Volumetric assessment of tumour size by CT scan showed an average reduction in tumour size of 65.9% (Table 2) following three cycles of chemotherapy (PLADO), except in one patient who required alternate chemotherapy when two cycles of PLADO failed to produce any response. Five patients underwent right hepatectomy, two had right trisegmentectomy, two had left hepatectomy, and one had left trisegmentectomy (Table 1). Both the intraoperative and postoperative course were smooth with minimal blood loss, a short operating time, and an average hospital stay of 8 days. We had used the Cavitron ultrasonic aspirator in three cases but reverted to finger-fracture technique as we found it to be more comfortable. All resected specimens showed microscopically free margins. AFP levels returned to normal values within 30 days of surgery. Histopathological examination of resected specimens revealed foetal histology in four patients, poorly differentiated (anaplastic) subtype in three, and mixed histology with mesenchymal components and osteoid formation in three. There were three (P6, P9, P10) tumour recurrences, and two of those patients (P6, P9) died. P6 was the patient with bilobar tumour who had undergone right trisegmentectomy following good response to chemotherapy, but he had a tumour recurrence and died within 6 months of surgery. P9 was the patient with left lobar hepatoblastoma who had undergone left hepatectomy following moderate response to standard chemotherapy. He developed local recurrence at 3 months postsurgery, showed partial response to the alternate regime (vincristine, 5-FU, cisplatin), and died within 8 months of surgery with widespread metastases. The other patient (P10), also with bilobar tumour, had a poor response to standard chemotherapy but showed moderate response to the alternate regime. She underwent a left trisegmentectomy but developed recurrence 2 months postsurgery. However, presently she is showing response to continued chemotherapy with the same alternate regime.

Table 1 Results of reduced-size hepatic resection following preoperative chemotherapy (*Rt*. right, *Lt*. left, *Triseg* trisegmentectomy)

Patient no.	Age (months)/ gender	Liver segments involved prechemotherapy	PRETEXT staging	Liver segments involved postchemotherapy	Extent of hepatic resection	Histology	Follow-up (months)	Final status
1	18/F	Rt. lobe: segments 6, 7, 8	II	Rt. lobe: segments 7, 8	Rt. lobe	Foetal	60	No recurrence
2	24/M	Bilobar: segments 1, 4, 5, 6, 7, 8	IV	Bilobar: segments 4, 5, 6	Rt. triseg	Foetal with mesenchymal elements	58	No recurrence
3	30/F	Rt. lobe: segments 5, 6, 7	II	Rt. lobe: segments 5, 6	Rt. lobe	Foetal	56	No recurrence
4	36/M	Bilobar: segments 1, 2, 3, 4, 5	IV	Lt. lobe: segments 1, 2, 3, 4	Lt. lobe	Foetal mixed with mesenchymal elements	42	No recurrence
5	26/M	Rt. lobe: segments 5, 6, 7, 8	III	Rt. lobe: segments 6, 7, 8	Rt. lobe	Mixed with mesenchymal elements	40	No recurrence
6	38/M	Bilobar: segments 3, 4, 5, 6, 7, 8	IV	Bilobar: segments 4, 5, 6	Rt. triseg	Anaplastic	32	Recurrence 2 months postop; died 6 months postop
7	32/M	Bilobar: segments 1, 4, 5, 6, 7, 8	IV	Rt. lobe: segments 5, 6, 7	Rt. lobe	Foetal	24	No recurrence
8	28/M	Rt. lobe: segments 5, 6, 7	II	Rt. lobe: segments 5, 6, 7	Rt. lobe	Anaplastic	20	No recurrence
9	24/M	Lt. lobe: segments 1, 2, 3, 4	III	Lt. lobe: segments 1, 2, 3	Lt. lobe	Anaplastic	8	Recurrence 3 months postop; alternate regime (vincristine, 5-FU, cisplatin); died 8 months postop due to metastases plus chemotherapy complications
10	16/F	Bilobar: segments 1, 3, 4, 5, 6	IV	Bilobar: segments 1, 3, 4, 5	Lt. triseg	Mixed mesenchymal with osteoid	11	Recurrence 2 months postop

Discussion

Traditionally, hepatoblastomas were considered to be tumours of poor prognosis with a survival rate of only 25% until the late 1970s [1, 2]. With the introduction of multidisciplinary approaches and combination chemotherapy with cisplatin and doxorubicin as both pre- and postoperative therapy, outcomes have improved significantly [5, 6, 11–18]. Several series [5, 6, 11, 13–18] have

Table 2 Results of volumetric reduction in hepatoblastoma following chemotherapy, as assessed by computed tomography (product of maximal length, width, and depth)

Patient no.	Liver lobe involved prechemotherapy	CT parameters prechemotherapy (cc)	CT parameters after three cycles (cc)	Volumetric reduction (%)
1	Right	480	144	70
2	Bilobar	960	384	60.0
3	Right	770	210.2	72.7
4	Bilobar	440	139.92	68.2
5	Right	720	216	70.0
6	Bilobar	1,180	540	54.5
7	Bilobar	1,650	264	84
8	Right	1,200	300	75.0
9	Left	1,200	504	58
10	Left	720	144	46.6

shown cisplatin and Adriamycin combination therapy to be the most effective preoperative combination chemotherapy for reducing tumour size, allowing many initially unresectable or metastatic hepatoblastomas to be resected. In a recent series [17] of stage III hepatoblastomas, 71.9% survival was reported. These authors recommend reduced-size hepatectomy after not more than three cycles of preoperative chemotherapy because of the possibility of developing resistance to the drugs. Some surgeons still believe that initial complete resection is the primary goal even in the era of advanced chemotherapy [5–7]. They have reported higher operative morbidity after delayed hepatic resection in those who received preoperative chemotherapy. Takashiko et al. [19] reported that delayed primary resection without an initial open biopsy does not increase operative morbidity. Survival chiefly depends on complete surgical resection. There are some reports in the literature on reduced-size hepatectomy. Langevin et al. [15] and Filler et al. [16] mentioned that partial lobectomy was possible in four of 13 children after preoperative chemotherapy. Recent reports [1–5] depict a less favourable outcome, especially in bilobar hepatoblastomas and poorly responsive and anaplastic hepatoblastomas even following radical surgery, including trisegmentectomies. In our series we could perform radical hepatectomy in all of our patients (100%) after preoperative chemotherapy using cisplatin and Adriamycin (PLADO regime). Volumetric assessment of tumour size by CT scan showed an average reduction of 65.9% following three cycles of PLADO except in one patient who received alternate chemotherapy when two cycles of PLADO failed to show any response [19]. Three out of 10 patients required extended hepatic resections (two right trisegmentectomies and one left trisegmentectomy). The mean response to volumetric reduction was 53.7% in the three patients who required trisegmentectomies compared with 71.12% in the seven patients who underwent lobectomies (five right lobectomies and two left lobectomies). Two of these three patients with bilobar tumours who underwent trisegmentectomies had recurrences, and one patient died due to widespread metastasis and poor response to chemotherapy; his tumour showed anaplastic histology. Another patient showed poor response to standard chemotherapy (46.6%), had mixed histology with mesenchymal elements, osteoid formation, and calcification, and is presently showing moderate response to alternate chemotherapy. One out of the five patients with unilobar tumours showed moderate response to chemotherapy (58%); the tumour had anaplastic histology and was closely related to major vasculature, causing some difficulty in achieving adequate resection. Tumour recurred locally 3 months postsurgery and showed a partial response to an alternate regime. However, this patient died 8 months postoperatively due to widespread metastasis.

The location of the tumour is often a factor that limits the extent to which normal hepatic tissues can be preserved. The main hepatic and portal veins are sometimes involved, even after effective preoperative chemotherapy with marked shrinkage of the tumour. Moreover, aggressive procedures such as vascular occlusion, hypothermia, and liver transplantation may be necessary [6, 20]. Ito et al. [21] and Seo et al. [22] have advocated isolated hepatic perfusion with an extracorporeal blood circuit for patients with tumours too large to be resected by conventional hepatectomy or that invade the hepatic vessels or inferior vena cava. It is increasingly being realised that in bilobar tumours, even such extensive hepatic resections as trisegmentectomies are inadequate to ensure cure. Poorly responding tumours with large size and in proximity to a major vascular axis also pose a challenge for adequate surgical resection. Some authors [23–27] have recently published their experiences with such cases in which total hepatectomy and liver transplantations were successfully performed in patients with poor response to chemotherapy, patients with unresectable tumours, and patients having recurrence confined to liver after initial hepatectomies including trisegmentectomies. Some authors have gone a step further to advocate that primary liver transplantation should be offered to chemosensitive tumours that remain unresectable or carry a high risk of recurrence, i.e. resection line at tumour margin (PRETEXT III tumours with close relationship with the main vessels) [27]. They have reported disease-free survival of 100% when primary transplantation was performed in patients with good response to chemotherapy. In none of our patients did we encounter an actual involvement of major hepatic vasculature with the need for the above-mentioned procedures.

The survival rate (80%) in our series compares favourably with those of other reports [5, 6, 14, 15, 17–19]. The short operative time and reduced blood loss in our patients were important factors responsible for reducing intra- and postoperative morbidity as well as enabling us to start early postoperative chemotherapy. We attribute the reduced intraoperative blood loss to two factors: (1) marked reduction in tumour size as a result of chemotherapy and (2) prior isolation of vessels supplying the area to be removed (initial isolation of the vessels at the hilum and outside the liver substance, followed by ligation and division of these structures and subsequent parenchymal transection; hepatic veins were secured by retrohepatic dissection and control of the major veins outside the liver substance). Before the era of preoperative chemotherapy, perioperative mortality was 10%. Excessive blood loss was the most common complication and was often followed by cardiac arrest [12].

Histomorphology of the tumour also determines the response to treatment, thereby affecting the outcome. The foetal subtype of hepatoblastoma (well differentiated) is a favourable histologic pattern [28–30] and was seen in four of our patients. The anaplastic (poorly differentiated) subtype, seen in three of our patients, does not respond to treatment. Mixed histology with mesenchymal component behaves in between the two

and was found in three of our patients. All of these tumours showed focal osteoid formations and calcifications. One of the patients with anaplastic subtype and bilobar involvement who had undergone right extended hepatectomy died of recurrence 6 months after the operation. Another patient with unilobar hepatoblastoma had anaplasia and showed poor response to chemotherapy. He died within 8 months after surgery because of local recurrence and widespread metastasis. One patient with a poorly differentiated lesion and an extensive initial tumour showed poor response to the PLADO regimen but moderate response to the alternate regimen (vincristine, 5-FU, cisplatin). Although she had a tumour recurrence 2 months after surgery, she is showing good response to postoperative continuation of chemotherapy.

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