Clinical Features and Outcomes of Hepatoblastoma in Children

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Abstract: Background/Purpose: Hepatoblastoma (HB) is generally considered curable by complete surgical resection only. Preoperative chemotherapy, based on cisplatin (CDDP), and tetrahydropyranyl-adriamycin (THP-ADR), has improved the rate of resectability for HB in Japan. Since 1988, we have routinely performed preoperative chemotherapy after surgical biopsy and delayed surgery according to the protocol. The present study investigated clinical features and outcomes of HB in children with emphasis on the surgical contribution following preoperative chemotherapy.

Patients/Methods: Between 1988 and 2007, 13 children (6 males and 7 females) with HB were treated in our Department. We reviewed the clinical data and outcomes of the patients retrospectively.

Results: The median age at diagnosis was 1 year 2 months (range; 3 months to 11 years). The first symptoms included abdominal mass in 7, febrile episode in 2, hepatomegaly in 2, and abdominal pain, and incidental detection in one each. Final histological diagnoses of these 13 patients were well differentiated in 9, poorly differentiated in 3, and 1 case unknown. Pretreatment serum alpha-fetoprotein (AFP) ranged from 4,515 to 920,000 ng/ml (averaged 396,666 ng/ml). According to the PRETEXT grouping system, these patients were classified as PRETEXT group Ⅰ in one patient, group Ⅱ in 4, group Ⅲ in 7, and group Ⅳ in 1. All patients with HB showed a marked decrease in serum AFP after preoperative chemotherapy. Of 13 patients, 11 received delayed surgery after preoperative chemotherapy. All 11 patients showed down sizing of the tumor and 4 (36.4%) of the 11 could be down-staged in PRETEXT after preoperative chemotherapy. Postoperative complications included biliary fistula that needed surgical intervention in 1 patient. The overall survival rate was 76.9% (10/13). There was no local recurrence in children who received complete resection of tumor.

Conclusion: Preoperative chemotherapy facilitated easier and safer complete resection of HB in children. However, the overall survival rate remained unsatisfactory. Therefore, further advances in therapeutic strategy for PRETEXT Ⅳ tumor or unresectable tumor, including new chemotherapy regimens or liver transplantation, should be expected.

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Introduction

Malignant liver tumor of children, mainly hepatoblastoma (HB), is rare with an incidence of 0.7 to 1 per 1 million children under 15 years of age[1]. A good combination of preoperative chemotherapy and complete surgical resection may facilitate a cure in children with HB.

Preoperative chemotherapy, based on CDDP and THR-ADR, has improved the rate of resectability and the survival rate for HB in Japan[2]. However, the outcome of unresectable HB is still unsatisfactory. Since 1988 we have routinely performed preoperative chemotherapy after surgical biopsy and delayed surgery according to the JPLT protocol[2]. The current study investigated the surgical contribution with preoperative chemotherapy to children with HB, especially from the point of serial AFP levels.

Patients and Methods

Between 1988 and 2007, 13 patients with HB were treated in our Department. They included 6 males and 7 females. The clinical data, serial AFP levels, surgical procedures, and outcome were analyzed retrospectively.

We classified the stages according to the PRETEXT grouping system[3]. PRETEXT assesses the pretreatment risk factors of liver tumor based on radiological findings using the Pre Treatment Extent of Disease grouping system. It was adopted for use in studies that attempted to determine tumor extension at diagnosis and during therapy. This system assesses: (a) the amount and anatomic location of normal liver tissue present, which would indicate whether the tumor could be resected completely and if so which type of resection could be applied; and (b) whether the tumor extended beyond the liver into the veins, extrahepatic tissue or if metastasis were present. In the PRETEXT system, based on tumor extension within the liver, four groups were identified as follows: PRETEXT Ⅰ, three adjoining sectors free; PRETEXT Ⅱ, two adjoining sectors free; PRETEXT Ⅲ, one sector or two non-adjoining sectors free; and PRETEXT Ⅳ, no free sectors.

Results

Patients

The characteristics of patients at diagnosis are summarized in Table 1. The average age at diagnosis was 2.4 years and ranged from 3 months to 11 years. First symptoms included abdominal mass in 7, febrile episode in 2, hepatomegaly in 2, abdominal pain and incidental detection in one. According to the PRETEXT grouping system, these patients were classified into PRETEXT group Ⅰ in one patient, group Ⅱ in 4, group Ⅲ in 7, and group Ⅳ in 1. Pretreatment serum alpha-fetoprotein (AFP) was increased in all patients, ranging from 4,516 to 920,000 ng/ml (averaged 373,706 ng/ml).

In the final histological diagnosis of the 13 patients, 9 were classified as well differentiated, 3 as poorly differentiated, and the remaining 1 case had an unknown histology because the general condition of this patient was too poor to perform initial biopsy (Table 2).

Table 1. Patients and tumor characteristics at diagnosis

Characteristics	No. of patients
Gender	
Male	6
Female	7
Age (Year)	
Median	1.2
Range	0-11
PRETEXT group	
I	1
II	4
III	7
IV	1

Table 2. Histological diagnosis of 13 children with hepatoblastoma

Final histological diagnosis	No. of patients
hepatoblastoma	12
well differentiated	9
poorly differentiated	3
not available	1

Clinical course and outcomes

Therapeutic strategy was based on the JPLT protocol[2]. Delayed surgery with initial surgical biopsy after chemotherapy (mainly using CDDP and THP-ADR) was performed in 11 of the 13 (84.6%). Needle biopsy only was performed in one patient, and the remaining one patient with PRETEXT Ⅳ underwent only chemotherapy because of poor general condition (Table 3).

All 13 patients with HB showed a marked decrease in serum AFP levels after chemotherapy (Table 4). All 13 patients showed a decline of >1 log in serum AFP level after chemotherapy compared with the level before chemotherapy. Six of the 13 had a decline of >2 logs in the preoperative serum AFP level during chemotherapy. However, there was no significant difference in the decline in AFP level between patients with and without resectability of the tumor. All 11 patients who underwent delayed

Table 3. Therapeutic strategies for 13 children with hepatoblastoma

	No. of patients (%)
Delayed operation	11 (84.6%)
Chemotherapy only	2 (15.4%)

Table 4. Serial AFP levels, PRETEXT and outcomes in 13 patients with hepatoblastoma

Pt. No	Sex	Age at Diag.	Surgical procedures	AFP levels (ng/ml)		PRETEXT		Resectability	Postoperative complication	Outcome	Survival Priod
				Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy				
1	F	1Yr2Mo	DO	53,100	3,170	Ⅲ	Ⅲ	resectable	none	Dead *	-
2	F	7Yr	DO	440,000	53,100	Ⅲ	Ⅲ	resectable	biliary fistula	Alive	21Yr
3	F	1Yr6Mo	DO	18,360	1,200	Ⅲ	Ⅱ	resectable	none	Alive	21Yr
4	F	3Mo	DO	920,000	930	Ⅲ	Ⅱ	resectable	none	Alive	18Yr
5	M	3Yr5Mo	DO	514,000	3,160	Ⅲ	Ⅱ	resectable	none	Alive	17Yr
6	M	1Yr1Mo	DO	220,000	6,000	Ⅱ	Ⅱ	resectable	none	Alive	17Yr
7	M	7Mo	DO	200,000	670	Ⅲ	Ⅱ	resectable	none	Alive	17Yr
8	M	5Mo	DO	349,000	15,100	Ⅱ	Ⅱ	resectable	none	Alive	15Yr
9	F	1Yr3Mo	DO	520,000	1,200	Ⅰ	Ⅰ	resectable	none	Alive	14Yr
10	M	3Mo	DO	639,000	436	Ⅱ	Ⅱ	resectable	none	Alive	9Yr
11	F	8Mo	NO	870,255	107,340	Ⅱ	Ⅱ	unresectable	none	Dead	-
12	F	1Yr10Mo	DO	4,515	8	Ⅲ	Ⅲ	resectable	none	Alive	3Yr
13	M	11Yr	NO	408,425	17,168	Ⅳ	Ⅳ	unresectable	none	Dead	-
Ave.				396,666±299,302	16,114±31,023						

Abbreviation; AFP, alpha feto-protein; DO, delayed operation; NO, no operation (including biopsy)

*, non-tumor associated death

surgery showed down sizing of the tumor after preoperative chemotherapy. Moreover, 4 of the 13 patients (30.8%) were also down-staged in the PRETEXT system after preoperative chemotherapy. All four patients were classified from the PRETEXT Ⅲ to the PRETEXT Ⅱ after preoperative chemotherapy.

Surgical complications were encountered in 2 patients; Massive bleeding of 700 ml at open biopsy was observed in one patient. The other one patient had a postoperative biliary fistula, in which case percutaneous transhepatic biliary drainage and biliary fistulojejunostomy were done later.

The overall survival rate was 76.9% (10/13) and 3 patients died. One patient died from aspiration and asphyxiation, which was a non-tumor associated death after treatment. The remaining two patients died of disease-related causes. Neither of these two patients became resectable after chemotherapy due to tumor size and/or location. None of the patients had surgery-related death. There was no local recurrence found in 11 patients with complete resection of the tumor.

Discussion

Malignant liver tumor in children, including HB, hepatocellular carcinoma, and other non-epithelial sarcoma, is comparatively rare accounting for not more than 1% of all pediatric malignancies. Surgical complete resection obviously plays an important role in the treatment strategy of these tumors. Recently chemotherapy, based on CDDP, THP-ADR or doxorubicin has improved the survival rate of malignant liver tumor[2)4-7)].

We had used cyclophosphamide and/or vincristine in addition to cisplatin and THP-adriamycin until 1994 for chemotherapy. After 1995, however, we began to apply the JPLT protocol.

Open biopsy might be performed safely with minimal complication and contribute to an effective outcome in the treatment of malignant liver tumor[8)]. Therefore, we recommend pretreatment tumor

biopsy to obtain a precise histological diagnosis; however, for patients in poor general condition with bleeding and so on, it may be accepted that high dose chemotherapy should be started as soon as possible without biopsy.

In the majority of HB patients receiving preoperative chemotherapy, there is a marked decrease in the serum AFP level and down-sizing of chemosensitive tumors, which may lead to down-staging in the PRETEXT grouping system. The level of serum AFP at complete resection of the tumor should decrease one or more log against pretreatment level. It may be one of the helpful markers for the decisions regarding the timing of complete resection along with findings on various imaging studies. Von Tornout et al. has emphasized that the timing and magnitude of the decline of AFP were associated the outcomes of children with hepatoblastoma[9]. On the contrary, preoperative chemotherapy should not bring any relevant drawback for the patients, such as enlargement of tumor or up-staging.

Complete surgical resection with preoperative chemotherapy is crucial to cure malignant liver tumor in children. Therefore, it is important for surgical resectability to be increased by down-sizing and/or down-staging in the PRETEXT owing to new chemotherapeutic agents or more effective regimen.

It is important to improve the overall survival of malignant liver tumor in children that treatment strategy, including liver transplantation, and a new regimen for PRETEXT Ⅳ tumors or so-called unresectable tumors should be developed.

Conclusion

A complete surgical resection with preoperative chemotherapy is crucial for curing hepatoblastoma in children. Preoperative chemotherapy facilitated easier and safer resection of HB. The PRETEXT grouping system and decline by more than 2 logs in serum AFP may be a good marker indicating the possibility of complete resection of HB. However, the overall survival rate of malignant liver tumor remains unsatisfactory. In order to improve the overall survival rate further therapeutic strategy for the PRETEXT Ⅳ tumor or unresectable tumor, including new anti-cancer agents and/or more effective chemotherapeutic regimens should be designed.

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〈和文抄録〉

小児肝芽腫の臨床的特徴と治療成績

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小児肝芽腫（以下 HB）の根治のためには外科的完全切除が必須である．日本においてはシスプラチン（CDDP），アドリアマイシン（THP-ADR）を中心とした術前の化学療法が HB の切除率を向上させ，予後を改善してきた．1988 年以降我々の施設においても生検の後，術前化学療法を伴った待機的手術を施行してきた．本研究では小児 HB 症例における術前化学療法と外科手術の役割を中心に，その臨床的特徴および予後について検討した．対象症例は 1988 年から 2007 年まで 13 人で，年令中央値は 1.2 歳，男児 6 例，女児 7 例であった．初発症状は腹部腫瘤 7 例，発熱 2 例，肝腫大 2 例，そして腹痛と偶然発見された症例が 1 例であった．最終組織診断は高分化型 9 例，低分化型 3 例，不明 1 例であった．治療前の血清 AFP は平均 396,666 ng/ml であった．PRETEXT 分類では group Ⅰが 1 例，Ⅱが 4 例，Ⅲが 7 例，そしてⅣが 1 例であった．すべての患児は術前化学療法にて著名な AFP の低下を認めた．13 例中 11 例に術前化学療法後に待機的手術を施行した．11 例全例に腫瘍の縮小を認め，内 4 例（36.4％）は PRETEXT 分類において stage の改善が得られた．術後合併症は胆汁瘻を 1 例に認めた．全生存率は 76.9％で，腫瘍の完全切除術を行った症例では局所再発は認められなかった．小児肝芽腫における術前化学療法は腫瘍切除術をより簡易に，そしてより安全に施行することができる．しかし全生存率は満足できるものではなく，PRETEXT Ⅳ や切除不可能な腫瘍に対する新たな治療戦略の進歩が期待される．

キーワード：肝芽腫，AFP（α フェトプロテイン），術前化学療法，待機的手術．