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Treatment of infantile hepatoblastoma and related complications

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Hepatorblastoma is an uncommon childhood malignant tumor of hepatic origin and recent progress of treatment strategy resulted in improved prognosis of patients with hepatoblastoma. Although patients within one year of age were considered to have better prognosis than those over that age, the treatment related deaths have been reported to be the only cause of the treatment failure of the infantile hepatoblastoma. We have successfully treated 4 infants including one with spontaneous rupture and the other with recurrence. Treatment protocol was preoperative chemotherapy using cisplatin and THP-ADR, doses of which were modified according to the age, with optional radiological interventions followed by resection of the primary tumor. This report would describe their clinical courses and experienced side effects of the treatment in order to demonstrate its risk. Trans-arterial embolizations were beneficial to stop bleeding due to rupture and to reduce intraoperative blood loss. In spite of dose modifications high hematological side effects were inevitable and cisplatn-induced hearing loss persisted in one case. In coclusion, for small infants with hepatoblastoma, controlling the inevitable side effects and active but strategic surgical and radiological interventions are essential for successful treatment.

Key words: hepatoblastoma, infant, cisplatin, complication

INTRODUCTION

Hepatoblastoma is an uncommon childhood malignant tumor of hepatic origin. Recent progress of treatment strategy resulted in improved prognosis of patients with hepatoblastoma [12-14]. The first outcome results of the Japanese Pediatric Liver Tumor Study Group (JPLT)(n = 134) have reported 3-year event free survival rate as 66% and overall 6- year survival rate as 73% [14]. They reported that prognosis of the patients less than one year of age has been better than those over one year of age (3-year EFS 86.3% vs. 57.8%) and it was speculated that the younger a patient less advanced of the tumor would be. However, treatment related deaths have been reported to be the sole cause of treatment failure of the infantile hepatoblastoma and accounted for no less than 11% [9] although treatment side effect of the JPLT protocol has not been elucidated. This report would describe clinical courses of four infants successfully treated with JPLT-based protocol and side effects encountered in order to demonstrate the risk of the protocol and to minimize treatment failure.

CASE REPORTS

Since 1992 we have treated 10 patients with hepatoblastoma by the JPLT-based protocol including 4 infants with the disease. The overall result of our experience is summarized in Table 1. One patient (Case 7) died of the extensive disease in spite of vigorous treatment and the other (Case 9) is under treatment because of the local and lung recurrence long after remission. Eight patients including all infants presented here are alive without any evidence of disease.

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Table 1 Hepatoblastoma cases treated in 1992-2004. Case 1-4 are presented cases.

Case	Age	Gender	PRETEXT[1] (Stage[2])	Pathology[3]	Recurrence	Outcome[5]
1	8 m	M	3 (ⅢA)	Poorly	+	8 y. NED
2	2 m	F	2-R[4] (Ⅱ)	Well		4 y. NED
3	3 m	F	2 (Ⅱ)	Well		1 y. NED
4	10 m	M	2 (Ⅱ)	Poorly		1 y. NED
5	3 y	M	3 (ⅢA)	Well		12 y. NED
6	1 y	M	2 (Ⅱ)	Well		8 y. NED
7	3 y	M	4 (ⅢB)	Poorly	+	Dead
8	2 y	M	Ⅰ (Ⅰ)	Well + Poorly		4 y. NED
9	2 y	F	3 (ⅢA)	Well + Poorly	+	4 y. AWD
10	3 y	F	2 (Ⅱ)	Well		2 y. NED

1: Pretreatment extension of disease (PRETEXT). Number indicates how many sectors are occupied by the tumor.
2: Stage indicates the extent of the tumor and ⅢA occupies 3 segments and ⅢB occupies all 4 segments.
3: R means rupture.
4: Pathological classification is according to the system recommended by The Japanese Society of Pathology
5: NED: no evidence of disease. AWD: alive with disease

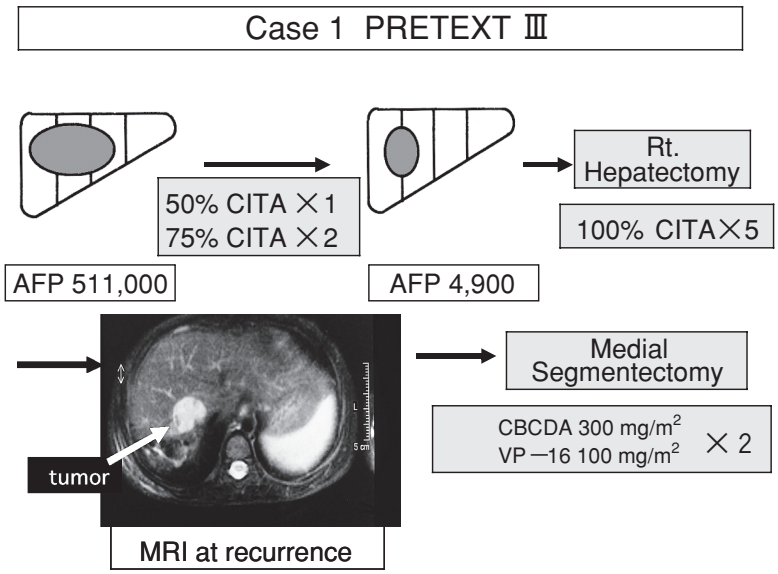

Fig. 1 Treatment summary of Case 1.

Treatment protocol recommended by JPLT is designated as CITA, which consists of 80 mg/m^2 of cisplatin for one day followed by 30 mg/m^2 of tetrahydropyranyladriamycin (THP-ADR) for two days. Several courses of CITA are given preoperatively where their doses are modified according to the patient age followed by tumor resection. In JPLT protocols, the dose is recommended to be reduced in infants: The first JPLT (JPLT-1) recommends to use half dose at the initial course and 75% thereafter and the next JPLT-2 protocol recommends to reduce dosage of each agent to 30% in infants less

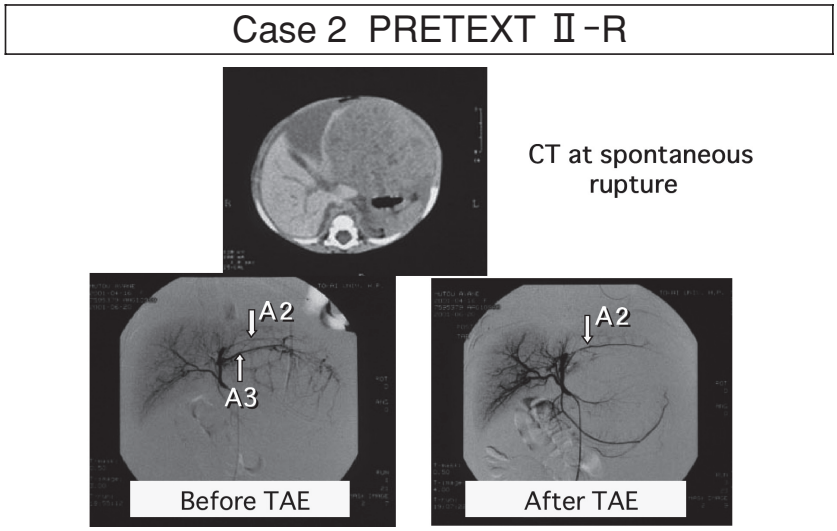

Fig. 2 Trans-arterial embolization in Case 2. A tumor vessel (A3) was embolized at the time of spontaneous rupture.

than 5 months of age and 50% in 6-month-olds and then to increase dosage gradually to full at 12-months. Several courses of less intensive "Low-CITA" (cisplatin 40 mg/m^2 ×1 day + THP-ADR 30 mg/m^2 ×1 day) are mostly used after tumor resection for consolidation in JPLT-2 protocol.

Case 1

Eight-month-old boy, who had been pointed out to have abdominal mass when he had visited a clinic with a symptom of upper respiratory tract infection before he was referred to our hospital. He was with markedly elevated serum alpha-fetoprotein (AFP)(511,000 ng/ml) and confirmed to have PRETEXT 3 (stage IIIA) hepatoblastoma, which occupied the three segments of the liver. He was treated with one course of 50% and two courses of 75% dose of CITA preoperatively according to the JPLT-1 dose modification protocol. And then he underwent right hepatectomy followed by 5 cycles of CITA without dose modification. Resected specimen contained poorly differentiated hepatoblastoma but its surgical margin was positive for the tumor. Although his serum AFP level decreased under the cut-off point it re-elevated 6 months later and was found to have local recurrent tumor. Additional segmental resection successfully removed the tumor and AFP returned to normal. After 2 courses of chemotherapy with carboplatin (300 mg/m^2) and etoposide (100 mg/m^2) he has been well for 9 years without any sign of recurrence. Figure 1 summarizes the treatment course. However, he has a significant hearing loss at the 3000 Hz level, which requires special teaching program.

Case 2

A two-month-old girl, who was referred to our hospital after visiting to a local hospital with an episode of seizure and cyanosis. She was noticed to have abdominal distension with marked anemia (Hb 4.7 g/dl) and fluid collection in the abdominal cavity. Rupture of the hepatic tumor was suspected and a emergent transarterial embolization (TAE) by gelfoam succeeded in stopping bleeding (Fig. 2). Transient pulmonary edema nessecitated ventilatory support for several days after TAE and she was diagnosed to have PRETXT 2 (stage II) hepatoblastoma as she had serum AFP highly elevated (852,331 ng/ml After recovered from the complication, she was treated with 2 courses of 30 and 40% dose of CITA preoperatively based on the JPLT-2 protocol, which resulted in marked decrease of the tumor size as well as serum AFP level (675 ng/ml). She underwent lateral segmentectomy followed by 2 courses of 50 and 60% dose of CITA because of her age. Low-CITA was not used considering the previous rupture might have spread tumor cells. The resected tumor was pathologically diagnosed as well

Table 2 Bone marrow suppression due to CITA (cisplatin and THP-ADR).

	WBC (/mcl) (gr)	Neutrophil (/mcl) (gr)	Hb (g/dl) (gr)	Platelet (10^4/mcl) (gr)
low-CITA (n = 6)	2100 (2)	395 (4)	8.9 (2)	11.8 (0)
30% CITA (n = 2)	3300 (1)	132 (4)	9.4 (1)	26.2 (0)
40% CITA (n = 3)	2900 (2)	522 (3)	8.3 (2)	21.8 (0)
50% CITA (n = 3)	2000 (2)	280 (4)	7.8 (3)	18.6 (0)
60% CITA (n = 1)	2100 (2)	273 (4)	7.3 (3)	13 (0)
75% CITA (n = 2)	2200 (2)	49 (4)	7.7 (3)	6.1 (2)
90% CITA (n = 2)	1600 (3)	36 (4)	6.6 (3)	3.3 (3)
100% CITA (n = 5)	1200 (3)	0 (4)	7.3 (3)	1.5 (4)

Bottom line and the side effect grade according to WHO criteria are indicated in ( ).

Table 3 Interventional radiology: Transarterial embolizations (TAE) and intraoperative blood loss

TAE cases					
Case	Age	Purpose	Complications	Operation	Estimated Blood Loss
2	2 m	Rupture	Lung edema	Lateral segmentectomy	16.9 ml/kg
3	6 m	Preope	None	Lt. Lobectomy (atypical)	12.0 ml/kg
4	12 m	Preope	None	Tumor resection	18.3 ml/kg
Non TAE cases					
Case	Age	Purpose	Complications	Operation	Estimated Blood Loss
1	11 m	Angiography	None	Rt. Lobectomy	47.8 ml/kg
1	32 m	Angiography	None	Medial segmentectomy	36.7 ml/kg

differentiated hepatoblastoma. She has been well without any sign of recurrence 4 years after treatment.

Case 3

A three-month-old girl, who was pointed out to have abdominal mass incidentally as she was referred to our hospital for abdominal distension suspected of Hirschsprung disease. Ultrasonography revealed a hepatic tumor in the left lobe and her serum AFP was 96,747 ng/ml, which implied the tumor as hepatoblastoma. She was treated with 2 courses of 30 and 40% dose of CITA protocol preoperatively according to the JPLT-2 dose recommendation, which achieved 50% decrease of AFP and underwent TAE followed by left lobectomy. The resected specimen contained well differentiated hepatoblastoma. Postoperatively, treatment with 4 courses of chemotherapy containing CITA were added and she has been well after 1 year follow up.

Case 4

A ten-month-old boy, who was pointed out to have abdominal mass when visiting a clinic due to URT infection. He was referred to our hospital suspected to have hepatoblastoma after detecting a hepatic tumor in the right lobe and elevated serum AFP (476,156 ng/ml). He was treated with 2 courses of 90% dose of CITA preoperatively according to the JPLT-2 dose recommendation, which achieved 72% decrease of AFP and underwent TAE followed by tumor resection in the right lobe. The resected specimen contained poorly differentiated hepatoblastoma. Postoperatively, treatment with 4 courses of CITA regimen was added and she has been well after 7

months follow up.

Side effects of the chemotherapeutic agents

Most regimen used consisted with cisplatin and THP-ADR. Bone marrow suppression observed after chemotherapy was graded according to WHO standard system and summarized in Table 3. It was demonstrated that the neutropenia with a number of neutrophil less than 500/mcl was observed even in the lowest dose of CITA regimen. Grade 3 thromocytopenia was observed by more than 75% CITA and the moderate grade anemia has developed in every protocol used. They were treated with occasional administrations of granulocyte colony stimulating factors (G-CSFs), platelet and red blood cell transfusions for preventing untoward incidents. There were no toxicity related mortality or serious complications even in full dose CITA treatment.

In case 1, however, who had the local tumor recurred after initial remission and the long term treatment was necessary, impaired hearing loss was detected as a result of treatment using total dose of 560 mg/m^2 of cisplatin followed by 600 mg/m^2 of carboplatin.

Interventional radiology

In three cases, transarterial embolizations (TAE) were incorporated into their therapy. Case 2 had a ruptured hepatoblastoma and the emergent TAE controlled the bleeding successfully. In other two cases, TAEs were used preoperatively on purpose of reducing the blood loss during hepatic resection. Compared to the case 1, who had preoperative angiography but without TAE, TAE apparently reduced intraoperative blood loss (Table 3).

DISCUSSION

Progress of hepatoblastoma treatment and prognosis

Recent progress of treatment strategy resulted in improved prognosis of patients with hepatoblastoma [12-14]. Major change of the treatment strategy of the disease was the shift from surgical resection of the tumor alone to the combination of the preoperative chemotherapy including most effective cisplatin and delayed resection of the primary tumor. Serial Childhood Liver Tumor Strategy Group of the International Society of Pediatric Oncology (SIOPEL) studies demonstrated the outcome improvement in Europe. The most recent SIOPEL-2 reported the 89% (±7%) 3-year progression free survival in patients with hepatoblastoma confined within the liver and 48% (±13%) in those with a tumour involving all four hepatic sectors or with extrahepatic disease [13]. In Japan, the first outcome results of the Japanese Pediatric Liver Tumor Study Group (JPLT-1) have reported 6-year overall survival (OS) rate as 73% [14].

Prognosis of patients within one year of age had better prognosis than those over that age (6-year OS rate 89% vs 68%) in JPLT-1 report. The extent of the tumor, as defined by the pretreatment extension of disease (PRETEXT) system, was considered as the only statistically significant prognostic factor for survival in SIOPEL [2]. Therefore, the apparently better prognosis in infants is because the younger a patient is the less advanced the tumor would be.

Complete resection of the tumor has been considered as the most important factor for long-term survival and the presence of residual or metastatic tumor is the risk factor for the successful treatment [4]. In our 4 infant cases, complete resection of the tumor was achieved and no metastatic lesion was found throughout the treatment course in spite of recurrence and spontaneous rupture. Good prognosis is expected as is reported cases within one year of age.

Treatment toxicity

Pre- and postoperative chemotherapy can cause hematological and other drug-induced toxicity, which is considered a major setback of the treatment. The treatment related deaths have been reported to be the only cause of the treatment failure of the infantile hepatoblastoma and accounted for no less than 11% as reported in the JPLT-1 [9] and the dose of CITA is to be reduced for infants with the disease in JPLT-2 protocol [9]. In our series, however, high grade neutropenia was encountered even as low as 30% CITA even if the dose was modified because of the patient age. In SIOPEL-2 when a treatment strategy based on surgery and cisplatin alone (CDDP 'monotherapy') was tried for patients with hepatoblastoma completely confined to the liver and involved, at most, three hepatic sectors the haematological toxicity of CDDP

monotherapy was reported to be moderate [13].

Bone marrow suppression observed in our series where CITA protocol was maily used is supposed to be due to THP-ADR administration. If the most effective drug against hepatoblastoma is considered to be cisplatin, THP-ADR and other agent can be eliminated in PRETEXT 1, 2 and 3, as SIOPEL protocol. In treating infants with hepatoblastoma with more advanced tumor, the hematologic side effects can be a major threat for successful outcome when other agents and modalities have to be used.

High-frequency hearing loss persisted after treatment in case 1 and it is considered to be cisplatin ototoxicity. Ototoxicity as well as renal impairment was most often observed after cisplatin treatment. It has been reported that age at treatment and the cumulative dose of cisplatin were the two most important risk factors of hearing loss in children and the totoxicity was most often observed after a total cisplatin dose of at least 400 mg/m^2 and no improvement was expected with time [1, 7]. In case 1 suspected microscopic residual tumor after hepatic resection constrained dose modification of CITA postoperatively and the total dose of cisplatin exceeded that amount. The cumulative dose of cisplatin should have been limited below this amount or the agent should have been changed to the alternative.

Interventional radiology (IVR) for hepatoblastoma

Interventional radiological procedures have been demonstrated to be effective in treating patients with hepatoblastoma as in our series. Several cases of successful emergent TAE for attempting to control intraperitoneal bleeding due to spontaneous rupture have been reported in small infants [5, 3] even in a neonate [6]. In case 2, emergent TAE stopped bleeding due to spontaneous rupture of the tumor, which lead to regression of the tumor and successful resection. In other two cases, preoperative TAE apparently reduced intraoperative blood loss.

Another IVR technique, trans-arterial chemoembolization (TACE), also have been reported to be an effective modality to convert an unresectable hepatoblastoma into a resectable one and even cure without tumor resection [11, 15], and it is incorporated into the JPLT-2 protocol [9] where the TACE can be chosen as a preoperative treatment for PRETEXT 3 or 4 hepatoblastoma.

However, procedures need special technique and might cause unexpected complications in children especially in infants, which would hinder us to apply them to all cases. The TAE is most indicated at spontaneous rupture of the tumor considering the risk of emergent resection of the large hepatoblastoma. On the other hand, TACE and TAE prior to surgery can be optional for reducing the tumor size and/or minimizing blood loss during hepatic resection. Therefore, TACE should be considered only when the tumor size is large and its resection is expected to have a considerable risk. The TAE prior to surgery may not be considered as necessity especially in cases with tumor occupied less than two segments but when the IVR procedures are technically feasible resection after TAE is warranted for the easiest and least complicated hepatoblastoma surgery.

Treatment of recurrent hepatoblastoma

It was speculated that the younger a patient the less advanced the tumor be likely to be. However, the recurrent tumor necessitated additional segmental resection in case 1. Matsunaga et al. reported that the recurrent local or lung lesions of the hepatoblastoma can be treated successfully by surgical resection [8]. For hepatoblastoma that remains unresectable by partial hepatectomy after chemotherapy, total hepatectomy with orthotopic liver transplantation (LTX) has been advocated as the best treatment option [10] but the role of LTX in the overall management of hepatoblastoma is still unclear. Active surgical intervention and a more intensive chemotherapy to facilitate complete resection of primary hepatic tumor is the most appropriate approach for children with refractory hepatoblastoma.

CONCLUSION

Reported four infant cases with hepatoblastoma were treated successfully by the JPLT-based protocol, which consists of preoperative chemotherapy followed by resection of the primary tumor. Recurrence of the tumor was encountered but treated by additional resection and a spontaneous rupture was controlled by the trans-arterial embolization. However, side effects were encountered including hematologic short-term

ones and long-term cisplatin ototoxicity.

Interventional radiological techniques could be a very effective treatment option for infants with hepatoblastoma although procedural difficulty might hinder its application. Although active surgical intervention and more intensive chemotherapy is necessary for children with refractory hepatoblastoma, good prognosis is expected since it is speculated that the younger the patient the less advanced the tumor likely to be. Hepatoblastoma can be treated successfully even in small children with care of the protocol risk to minimize treatment failure.

REFERENCES

1) Bertolini P., Lassalle M., Mercier G., Raquin M.A., Izzi G., Corradini N. and Hartmann O. Platinum compound-related ototoxicity in children: Long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hemato/Oncol 26: 649-655, 2004.
2) Brown J., Perilongo G., Shafford E., Keeling J., Pritchard J., Brock P., Dicks-Mireaux C., Phillips A., Vos A., Plaschkes J. Prognostic factors in childhood hepatoblastoma—results of the first prospective clinical trials of the International Society of Pediatric Oncology SIOPEL 1. Eur. J. Cancer 36: 1418-1425, 2000.
3) Chan K.L., Fan S.T., Tam P.K.H., Chiang A.K.S., Chan G.C.F., Ha S.Y. Management of spontaneously ruptured hepatoblastoma in infancy. Med Pediatr Oncol 38: 137-138, 2002.
4) Exelby P.R., Filler R.M. and Grosfeld Y.L., Liver tumors in children in particular reference to hepatoblastoma and hepatocellular carcinoma. American Academy of Paediatrics Surgical Section Survey—1974. J Pediatr Surg 10: 329-337, 1975.
5) Kitahara S., Makuuchi M., Ishizone S., Terada M., Kawasaki S., Nakahata T., Komiyama A. Successful left trisegmentectomy for ruptured hepatoblastoma using intraoperative transarterial embolization. J Pediatr Surg 30: 1709-1712, 1995.
6) Lee S.-C., Chung J.-W., Kim K.-H., Kim W.-K. Successful transumbilical embolization of congenitally ruptured hepatoblastoma. J Pediatr Surg 34: 1851-1852, 1999.
7) Li Y., Womer R.B. and Silber J.H. Predicting cisplatin ototoxicity in children: The influence of age and the cumulative dose. Eur J of Cancer 40: 2445-2451, 2004.
8) Matsunaga T., Sasaki F., Ohira M., Hashizume K., Hayashi A., Hayashi Y., Mugishima H., Ohnuma N. Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma. Pediatr Surg Int 19: 142-146, 2003.
9) Ohnuma N., Matsunaga T., Sasaki F., Ohira M., Hashizume K., Hayashi A., Hayashi Y., Matsuyama K., Mugishima H. New therapeutic approach for hepatoblastoma in children. Jpn J Pediatr Surg 33: 1247-1251, 2001. (Japanese with English abstract)
10) Otte J.B., Pritchard J., Aronson D.C., Brown J., Czauderna P., Maibach R., Perilongo G., Shafford E. and Plaschkes J. Liver Transplantation for Hepatoblastoma: Results from the International Society of Pe+diatric Oncology (SIOP) Study SIOPEL-1 and Review of the World Experience Pediat Blood and Cancer 42: 74-83, 2004.
11) Oue T., Fukuzawa M., Kusafuka T., Kohmoto Y., Okada A., Imura K. Transcatheter arterial chemoembolization in the treatment of hepatoblastoma. J Pediatr Surg 33: 1771-1775, 1998.
12) Perilongo G., Shafford E., Maibach R., Aronson D., Brugières L., Brock P., Childs M., Czauderna P., MacKinlay G., Ottej J. B., Pritchardk J., Rondellil 1, R., Scopinarom M., Staalmann C. and Plaschkeso J. Risk-adapted treatment for childhood hepatoblastoma final report of the second study of the International Society of Paediatric Oncology—SIOPEL 2 Eur J of Cancer 40: 411-421, 2004,
13) Pritchard J., Brown J., Shafford E., Perilongo G., Brock P., Dicks-Mireaux C., Keeling J., Phillips A., Vos A., Plaschkes J. Cisplatin, doxorubicin and delayed surgery for childhood hepatoblastoma: a successful approach—results of the first prospective study of the International Society of Paediatric Oncology. J Clin Oncol 18: 3819-3828, 2000.
14) Sasaki F., Matsunaga T., Iwafuchi M., Hayashi Y., Ohkawa H., Ohira M., Okamatsu T., Sugito T., Tsuchida Y., Toyosaka A., Nagahara N., Nishihira H., Hata Y., Uchino J., Misugi K., Ohnuma N. Outcome of hepatoblastoma treated with the JPLT-1 (Japanese Study Group for Pediatric Liver Tumor) Protocol-1: A report from the Japanese Study Group for Pediatric Liver Tumor. J Pediatr Surg 37: 851-856, 2002.
15) Xianliang H., Jianhong L., Xuewu J. and Zhongxian C. Cure of Hepatoblastoma with Transcatheter Arterial Chemoembolization. J Pediatr Hemato/Oncol 26: 60-63, 2004.