European Review for Medical and Pharmacological Sciences 2014; 18: 1018-1026

Clinical effectiveness of multimodality treatment on advanced pediatric hepatoblastoma

Y. ZHANG[1,2], W.-L. ZHANG[2], D.-S. HUANG[2], L. HONG[2], Y.-Z. WANG[2], X. ZHU, H.-M. HU[2], P.-W. ZHANG[2], Y. YI[2], T. HAN[2]

[1]Department of Pediatrics, Chinese PLA General Hospital, Beijing, P.R. China
[2]Department of Pediatrics, Beijing Tongren Hospital, Capital Medical University, Beijing, P.R. China

Abstract. – OBJECTIVES: To investigate the effect of multimodality treatment of advanced paediatric hepatoblastoma and the factors affecting the prognosis.

PATIENTS AND METHODS: 35 childhood patients were treated with multimodality treatments consisting of chemotherapy, surgery, interventional therapy, and autologous peripheral blood stem cell transplantation. Patients were followed up every month.

RESULTS: 33 patients completed the follow-up, of which 17 were in complete remission, 5 were in partial remission, 1 case got worse, and 10 died. The remission rate was 66.7% (22/33), and the overall survival rate was 69.7% (23/33). 1 patient with advanced hepatoblastoma got high-dose chemotherapy combined with autologous peripheral blood stem cell transplantation (APBSCT) treatment, and a primary lesion by 18 x 15 x 9 cm reduced to 10 x 8 x 4 cm. Remote metastases significantly alleviated, and partial remission reached six months. The overall survival was 9 months after transplantation. Patients with the mixed phenotype of hepatoblastoma had a worse prognosis than with the epithelial phenotype ($p < 0.001$), and patients in stage IV had a lower survival rate than in stage III ($p < 0.001$).

CONCLUSIONS: Multimodality treatment can effectively improve remission rate and prolong the survival of children with the advanced hepatoblastoma. In addition, alpha-fetoprotein (AFP), hepatoblastoma pathological classification and staging are of great use in prediction of prognosis.

Key Words:
Paediatric hepatoblastoma, Multimodality treatment, Prognosis.

Introduction

Hepatoblastoma is the most common malignant liver tumor in children, which accounts for 50% of the liver tumors and 1.3% of malignant tumors in children [1]. Hepatoblastoma is generally sensitive to chemotherapy. Recently, surgery therapy combined with chemotherapy can significantly improve the clinical remission rate which is up to 70%[2]. But patients with advanced hepatoblastoma have a poor prognosis, especially the patients with distant metastases (cancer spreads to other organs and tissues of the body)[3]. In this study we summarized the clinical data of 35 patients with advanced hepatoblastoma from April 2006 to January 2012 in our Hospital and analyzed the clinical therapeutic effects of chemotherapy, interventional therapy, surgery and autologous peripheral blood stem cell transplantation (Auto-PBSCT).

Patients and Methods

Patients

35 patients (25 males and 10 females) with hepatoblastoma were recruited in this study, which were pathologically confirmed and diagnosed by tumor markers and imaging from April 2006 to January 2012 (Figure 1). The median age was 3 years (5 months to 11.5 years). According to international staging system for hepatoblastoma of American Pediatric Oncology Group (POG/CCG), there were 14 cases in stage III and 21 cases in stage IV, and the other clinical data was shown in Table I.

Comprehensive Diagnosis and Treatment Programs

Histopathological diagnosis is the gold standard for the diagnosis of hepatoblastoma. For the huge tumor cases without surgical resection, it is feasible for fine-needle aspiration to diagnose. For the huge tumor cases with hemorrhagic tendency, imaging diagnosis, (alpha-fetoprotein) AFP, and whether there is distant metastasis would be used for clinical diagnosis.

According to international staging standard for hepatoblastoma of POG/CCG[4,5], hepatoblastoma

Corresponding Author: Dongsheng Huang, Ph.D; e-mail: dongshenghuang99@163.com

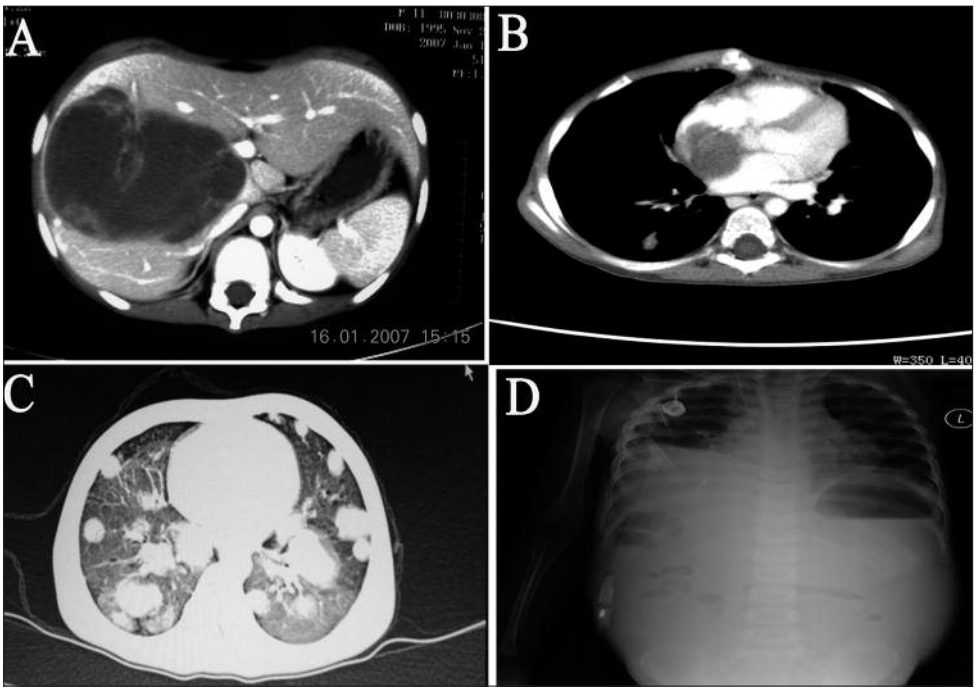

Figure 1. ***A,*** A large space-occupying lesion in the right lobe of the live. ***B,*** The advanced HP with right atrial metastasis. ***C,*** Hepatoblastoma with multiple lung metastases. ***D,*** HB with pleural effusion.

Table I. Clinical data of 35 cases of advanced HB.

Groups	Cases
Gender	
Male	25
Female	10
CCG/POG stages	
Stage III	14
Stage IV	16
Progression of stage IV	5
Metastatic sites of stage IV	
Lung metastasis	12
Bone metastasis	3
Bone marrow metastasis	4
Thoracic cavity or pleural metastasis	2
Mediastinum metastasis	4
Transverse colon metastasis	1
The right atrium metastasis*	1
The peritoneum or ascites metastasis	1
Primary sites	
Left hepatic space-occupying lesions	3
Right hepatic space-occupying lesions	22
Giant liver	10
Histological features and pathological classification*	
Epithelial type	17
Mesenchymal type	2
Fetal type	2
Mixed type	13
Mxed type	17
Epithelial and mesenchymal mixed type	16
Giant girder type	1

Note: After intervention twice, the right atrium metastases observed, then after surgery twice, 11 cycles of chemotherapy, progress of the disease got worse and the patient died.

is divided into stage I to stage IV. Stage III and stage IV are considered as advanced stage. In this work, 14 patients in stage III showed either incisal edge residue or tumor residue after surgery. Patients in stage IV showed intrahepatic metastasis and/or distant organs and tissues metastases.

Comprehensive diagnosis and treatment programs were shown in Figure 2. The commonly used chemotherapy regimens to advanced hepatoblastoma were AEP (asparagine endopeptidase), ACP (adriamycin, cyclophosphamide), ICE (Ifosfamide, Carboplatin, Etoposide) and refractory chemotherapy regimen was CTX + CBP + VP-16 + VCR (vincristine). According to clinical staging, pathological and histological classification and the progress of HB, chemotherapy regimens were chosen with chemotherapy or alternative chemotherapy treatment (Table II)[5].

For advanced HB children on stage IV or progression of stage IV, autologous peripheral blood stem cell transplantation (APBSCT) were carried on after surgery or chemotherapy achieving complete remission or partial remission. For HB children with distant metastasis of systemic tissues and organs or with bone marrow transplant, radiotherapy or bone marrow purging therapy would be used before APBSCT.

Pretreatment program of APBSCT: CEM method was taken as described[4]: carboplatin (CBP) 235 mg/m^2.d was injected before 8 to 5

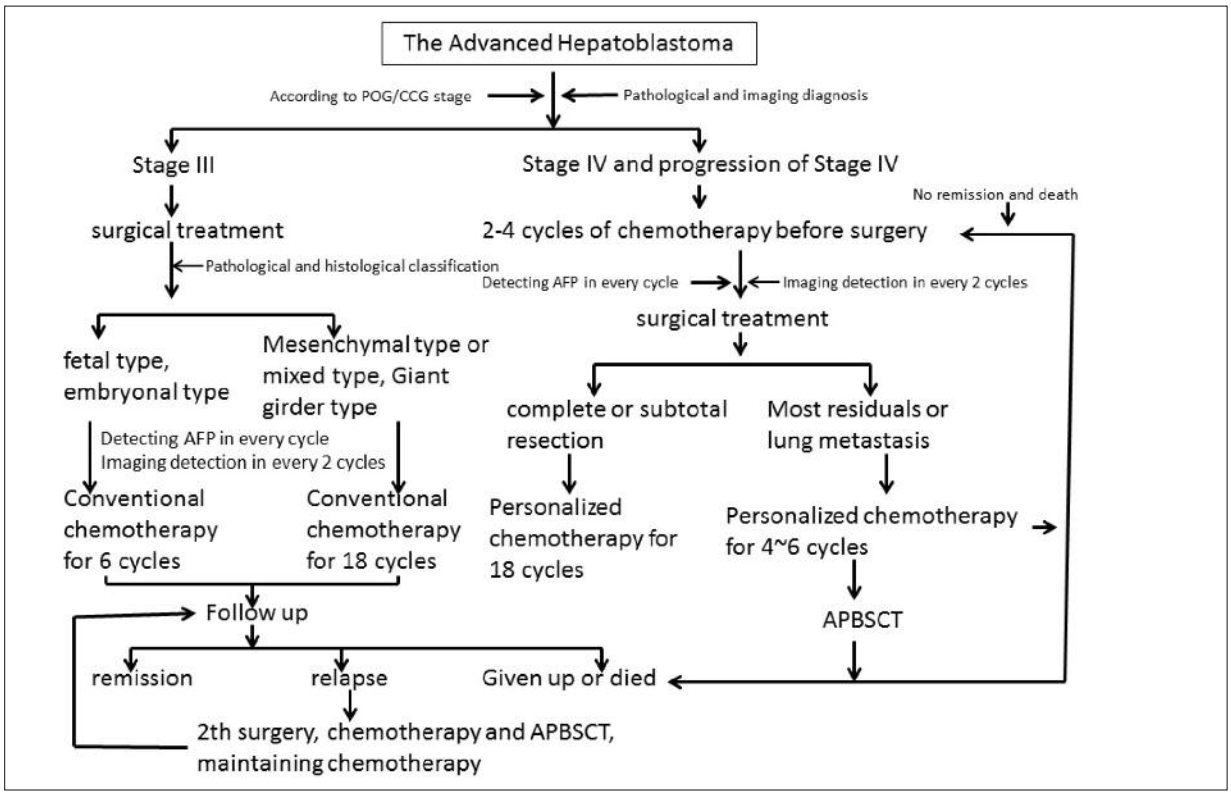

Figure 2. Comprehensive diagnosis and treatment programs.

days; etoposide (VP-16): 338 mg/m^2.d was injected before 8 to 5 days; melphalan 70 mg/m^2.d was injected before 8 to 6 days.

APBSCT: Chemotherapy combined with recombinant human granulocyte colony-stimulating factor (rhGGSF) was used as a mobilizing agent. When the concentration of peripheral leukocytes reduced to lower than 2×10^9/L, rhGGSF was injected subcutaneously every day until the last day before the end of autologous periph-

Table II. Chemotherapy regimens with advanced HB.

	Chemotherapy dose	Course of treatment and programs
Stage III		AEP/ACP alternatively used for chemotherapy; once/3weeks
AEP treatment:	Cisplatin (CDDP): 20 mg/m^2 /d,d1-5 Pirarubicin (ADM): 25 mg/m^2/d, d1-3 Etoposide (VP16): 100 mg/m^2/d, d1-4	
ACP treatment:	Cisplatin (CDDP): 20 mg/m^2/d, d1-5 Pirarubicin (ADM): 25 mg/m^2/d, d1-3 CTX: 800-1000 mg/m^2/d, d1	
Stage IV or progression of stage IV		According to the children's reaction to chemotherapy
ICE treatment:	Ifosfamide (Ifo): 1.5 g/m^2/d,d1-5 Mesna: 300 mg/m^2/times, Q3h*4 times Carboplatin (CBP): 450 mg/m^2/d,d1 Etoposide (VP16): 100 mg/m^2/d, d1-3	
Refractory treatment:	CTX: 250 mg/m^2/d, d1-3 CBP: 300 mg/m^2/d,d1-2 VP-16: 100 mg/m^2/d, d1-5 Vincristine (VCR): 2 mg/m^2/d, d1	

eral blood stem cells (APBSCT) acquisition. The daily dose of rhGGSF was 5 μg/kg. When leukocytes concentration recovered to more than 5×10^9/L, APBSCTs were collected by CS-3000-plus blood cell separator. The acquisition was doing in the every morning. When mononuclear cells (MNC) were collected totally up to 5×10^8/kg or/and CD34 $^+$ cells were more than 3×10^6/kg, APBSCT collection were stopped. The collected peripheral blood were frozen at –196°C, and immediately thawed in water of 39°C before intravenous reinfusion.

Locally interventional chemotherapy cannot be hospitalization. However, the children with advanced HB, especially those with portal vein tumor thrombus, interventional treatment easily led to intrahepatic metastasis and hematogenous spread. Thus, it is not the preferred choice of treatment for advanced HB children (Figure 2).

Of 35 cases, all were performed 1 to 6 cycles of chemotherapy before surgery except 1 was lost to follow-up, and the average cycles of chemotherapy was 5.8 (2-22 cycles). Preoperative embolization interventional therapy was performed in 3 cases in stage III, and Auto-PBSCT was carried out in 1 case in stage IV.

Methods

The hospitalization data and follow-up data of patients were collected to evaluate and compare primary sites and initial symptom of patients, clinical characteristics of pulmonary metastases, serum AFP, clinical therapeutic effect and prognosis. Primary end points were determined by recurrence, death and recurrence-free survival.

Therapeutic efficacy evaluation[6]: Complete remission (CR) means that there are no radiographic signs of tumor residue and the normal level of serum AFP lasts more than 4 weeks. Partial remission (PR) means that tumor shrinks by more than 50%, there are no new metastases proved, and the serum AFP level reduces significantly. Effectiveness (CR or PR) refers to the situation where tumor shrinks by less than 50% in stabilization of disease (SD) and there are no increase in primary tumor volumes and no new metastases. No remission (NR) means that primary tumor is less than 25% and there are no new metastases. Progressive disease (PD) means that tumor volume increases more than 25% during the treatment or there are new metastases, or serum AFP level is 20% higher than normal level for 2 weeks. The normal reference value of serum AFP at our Hospital was 0-20 μg/dL.

Statistical Analysis

Statistical analysis of clinical data of patients was performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). χ^2 test was adopted in measurement data. Enumeration data was expressed by percentage and rate, and *t*-test was adopted in comparison of rates. $p < 0.05$ was considered statistically significant.

Results

The Clinical Value of High-Dose Chemotherapy Combined with Autologous Peripheral Blood Stem Cell Transplantation

1 case of 10 year old male child with stage IV initially diagnosed as large space occupying lesion with intrahepatic metastasis, lung metastasis, extensive bone metastases and bone marrow metastasis. The pathological typing was epithelial type. The AFP value was initially diagnosed as more than 1210 ng/mL. Autologous peripheral blood stem cell mobilized program was the AFP treatment. The MNC was collected 6.396 × 10-8/kg, and CD34 positive cells were 2.18 × 10-6/kg. Hematopoietic stem cells were transfused at 0, +1 day, and hematopoietic reconstitution time were 26 days (peripheral blood nucleated cell count ≥ 0.5 10^9/L, PLT ≥ 20 10^9/L). 30 days after transplantation, the results of abdominal CT was showed that primary lesion was reduced to 10 × 8 × 4 cm from 18 × 15 × 9 cm. Bone marrow metastasis were relieved, and bone metastasis and lung metastasis were also reduced (Figure 3). Partial remission was up to six months, and the diagnosis and treatment process were seen as Figure 4.

Preferred Method of Treatment Significantly Affected Prognosis

In order to investigate the effects of locally interventional chemotherapy and APBSCT treatment, 18 cases of children with HB were treated by systemic chemotherapy before surgery, next surgery, and chemotherapy after surgery. In contrast, 3 cases of children with HB were treated by locally interventional chemotherapy before surgery, next surgery, and chemotherapy/APBSCT after surgery. The statistical analysis showed that the preferred interventional treatment affected prognosis, and there was a statistically significant difference ($p = 0.024$) (Table III), which suggested that the preferred interventional treatment would induce prognosis of the advanced HB patients in stage IV.

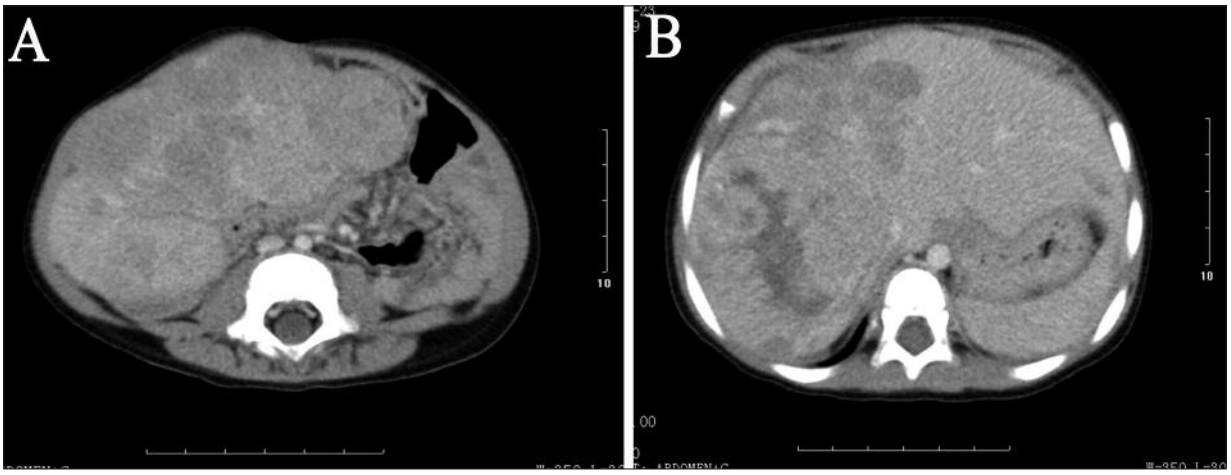

Figure 3. ***A,*** Multiple large lesions in liver were observed before APBSCT. ***B,*** Large lesions in liver alleviated after APBSCT.

Table III. The prognosis effect of stage IV patients with or without preferred interventional preoperative chemotherapy.

	Locally interventional chemotherapy treatment (LICT) in Stage IV patients			
	Reveiced LICT (N)	Didn't receive LICT (N)	χ^2	*p*
Survival	3	0	6.25	0.024
Death	5	13		

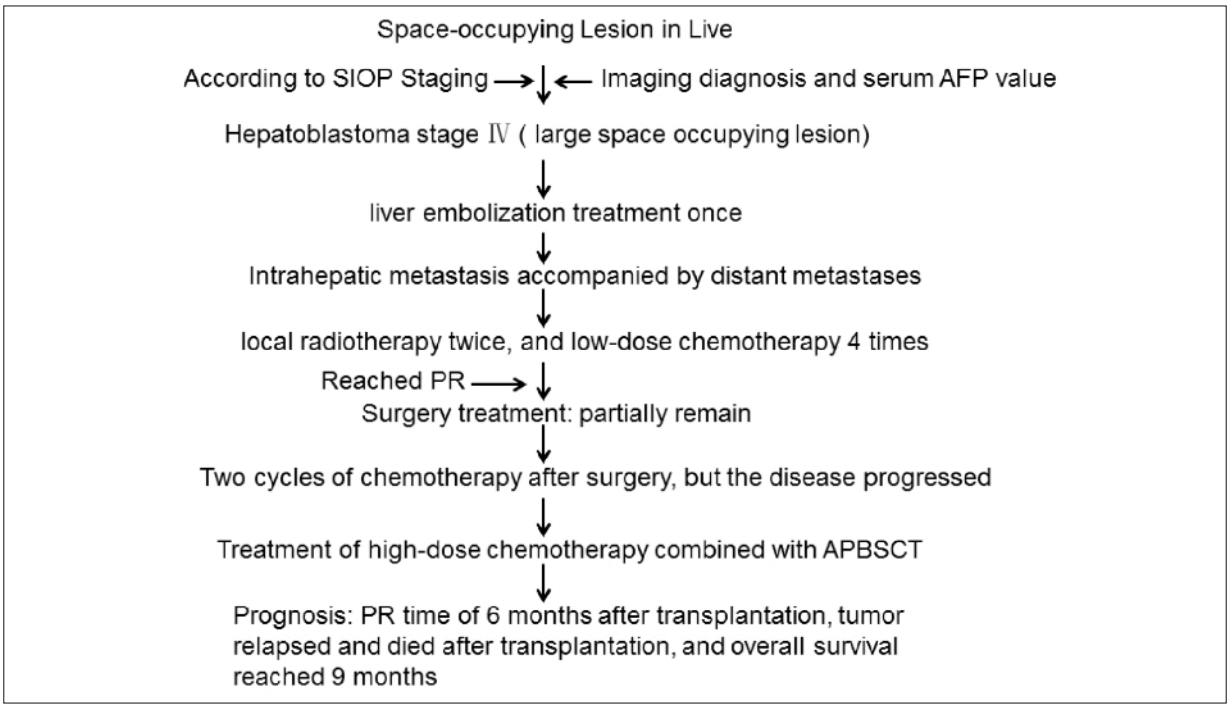

Figure 4. Diagnosis and treatment process of high-dose chemotherapy combined with autologous peripheral blood stem cell transplantation.

Serum AFP in Children with Hepatoblastoma is Closely Associated with Cancer Stages

In this study, of the 35 patients at admission, the serum AFP levels in 33 patients increased significantly ($p = 0.0002$). The data also demonstrated that 1 patient was slightly higher than normal level (25.08 ng/dl), and 1 patient was normal (1.2 ng/dl). Patients with increased serum AFP accounted for 97.1% (34/35). The highest value of serum AFP of patients in stage III was 36403 ng/dl, while the lowest value was 962.3 ng/dl. The highest value of serum AFP of patients in stage IV was 484 000 ng /dL, while the lowest value was 1.2 ng/dL. The value of serum AFP was correlated positively with clinical stages for patients, and there has statistically significant difference ($t = 2.333$, $p = 0.002$). In 35 cases, except 1 case was lost to follow-up, 1 case gave up the following treatment and the serum AFP level didn't significantly increase in 2 cases. Of the remaining 31 cases, 15 cases got complete remission and the serum AFP level returned to normal in 13 cases and decreased significantly in 2 cases, while the serum AFP level in 1 case with PD didn't reduce significantly. Of 5 cases who obtained partial remission, the serum AFP level of 3 cases returned to normal, 2 cases of which decreased significantly. Ten cases died of recurrence, whose serum AFP levels increased significantly. The changes of serum AFP level and prognosis had statistical significance by analysis ($t = 3.273$, $p = 0.001$) (Table IV), which showed that the increase of serum AFP level was correlated positively with prognosis.

Multimodality Treatment Effectively Improves Remission Rate and Prolongs the Survival of Children with the Advanced Hepatoblastoma

The follow-up was performed until March 2012. With median follow-up period of 25 (2-67) months, 1 case gave up treatment, 1 case was lost to follow-up, of the remaining 33 cases, 17 children patients acquired complete remission (CR), 5 cases obtained partial remission, 1 case was aggravated, 10 patients died. The remission rate was 66.7% (22/33), and overall survival rate was 69.7% (23/33). The total median survival time was 51 months, 95% confidence interval of average survival was 37.1 m-58.2 m and 5 year estimated survival rate was 40% by the analysis of advanced hepatoblastoma performed by Kaplan-Meier analysis (Figure 5A).

Hepatoblastoma Pathological Phenotypes and Stages are Closely Related to Prognosis of Childhood Patients with Hepatoblastoma

In this study, the histological types of 34 cases were clear, consisting of epithelial type and mixed type of 17 respectively. In 10 death cases, the histological types of 9 cases were clear, consisting of mixed type of 5 and epithelial type of 4. The follow-up was performed until March 2012, and the median time of follow up to patients with epithelial type and mixed type was 59 (8-86) and 21 (7-65) months, respectively. The prognosis of epithelial type was worse than that of the mixed type analyzed by Kaplan-Meier Survival Function ($t = 8.050$, $p < 0.001$) (Figure 5D). The long term survival rate in stage IV was lower than that in stage III, the difference had statistical significance ($\chi^2 = 9.0345$, $p < 0.001$) (Figure 5C). In advanced HB patients of stage III and IV, year survival rates were compared. There was no significant difference in 1 year, 2 year survival rates ($p = 0.75$). However, there was a significant difference on 4 year survival rates ($p = 0.012$).

The Prognosis Effectively Improved in Hepatoblastoma Children with Lung Metastasis

In these cases, 12 cases were hepatoblastoma associated with lung metastasis. Bilateral pulmonary metastases were prevalent which account-

Table IV. The correlation analysis between AFP concentration and clinical stages of initial diagnosis.

	The cases of stage III	The cases of stage IV	*p* value
AFP (No.)			0.0002
Higher or slightly higher	12	21	
Normal	2	0	
AFP concentration (ng/ml)			0.0001
The highest	36403	484000	
The lowest	1.2	962.3	

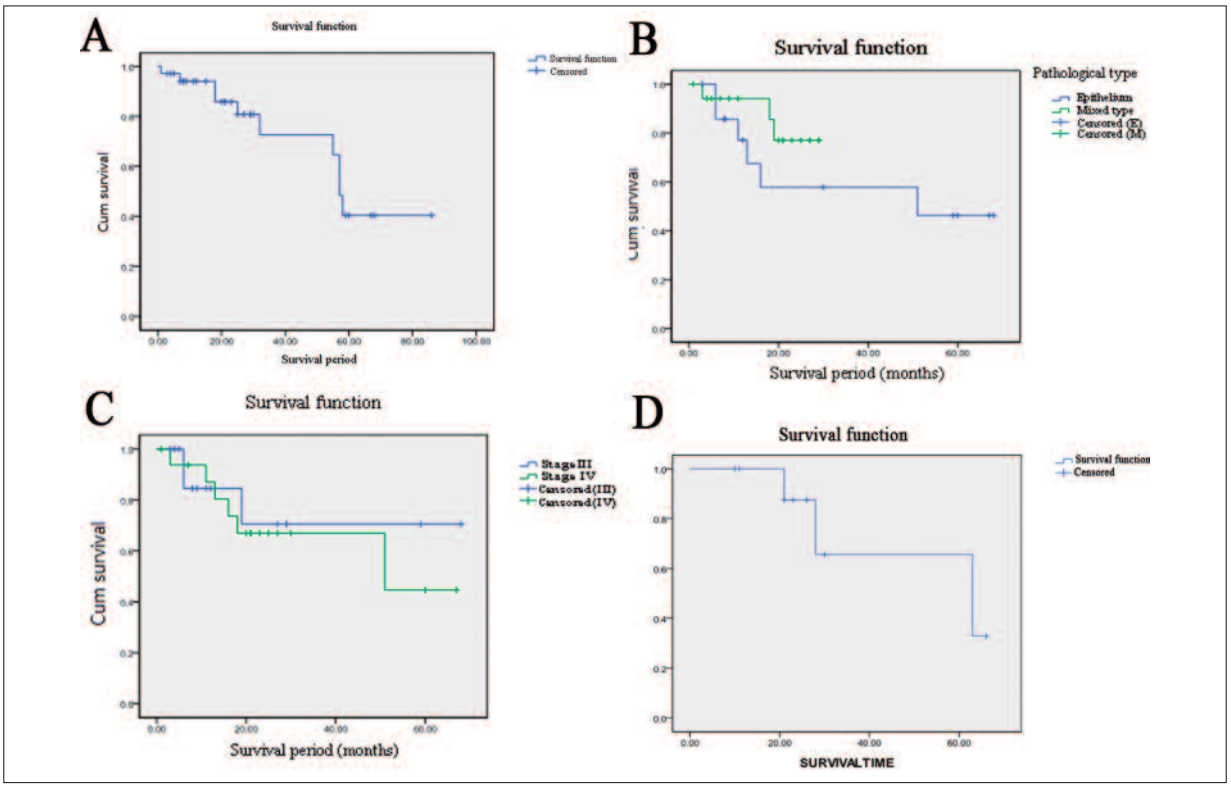

Figure 5. ***A,*** Survival curve of 35 hepatoblastoma children receiving multimodality treatment. ***B,*** Survival curve of different pathological types of 35 hepatoblastoma children. ***C,*** Survival curve of different stages of 35 hepatoblastoma children. ***D,*** Survival curve of 12 children of hepatoblastoma with pulmonary metastasis.

ed for 58.3% (7/12). The right lung metastases accounted for 41.7% (5/12), and the left lung metastases were not observed (0/12). 12 patients were all followed up until March 2012, with a median follow-up time of 23 months. After the comprehensive treatment, including chemotherapy, interventional and surgical treatment, etc., 3 cases got complete remission, 4 cases got partial remission, 4 cases died, and 1 case was progressed. The remission rate was 58.3% (7/12), and overall survival rate was 66.66% (8/12).

The survival rates of children of hepatoblastoma with pulmonary metastasis were analyzed by SPSS17.0 statistical software. The 95% confidence interval of average survival rates was 46.651 to 71.747 months, and 5 year survival rates were estimated to 30.41% (Figure 5 D).

Discussion

Hepatoblastoma is one of the most common malignant liver tumors in children, which accounts for 25%-45% of the liver tumors. Hepatoblastoma is commonly seen in infants and patients under age 3 accounts for 85%-90%[7]. In this study, the median age of disease onset was 3 years, which was in agreement with that reported in the literature. Generally, hepatoblastoma is commonly seen in boys, occurrence proportion of male and female is about 3: 2-2: 1. In this study, although all the cases were advanced ones, it was still commonly seen in boys (25/35).

Hepatoblastoma may involve the left lobe or the right lobe of liver, and it's commonly seen in the right lobe of liver. In this study, there were only 3 cases whose primary site located in the left lobe of liver. The right lobe of liver was common, which accounted for 62.8% (22/35) of primary sites. The giant tumor, which invaded the left and right lobes of liver at the same time, accounted for 28.5% (10/35). This result was in agreement with that reported in the literature [8]. Main clinical features of hepatoblastoma are intrahepatic solid nodules which appear to be single globular or lobular fusion and lead to deformity and displacement of the liver. Most of the masses have tumor capsules, a few masses are

diffuse lesions. In this study, there were only 2 cases with diffuse lesions of the right lobe. Generally, patients with hepatoblastoma don't have symptom in the initial stage, while patients who have symptom seem to be more serious. In this study, all the cases were the advanced ones, abdominal mass was the most common symptom of hepatoblastoma 68.6% (24/35), and then was atypical symptom including fever, abdominal pain and abdominal distension and gastrointestinal symptoms. Therefore, painless abdominal mass in patients with uncertain reasons should be suspected this disease highly.

Embolization is easy to locate in the portal vein in the advanced cases, because hepatoblastoma has abundant blood supply. Circulatory metastasis is the most common metastatic mode of hepatoblastoma. Previous study showed that lung was the most common metastatic site in patients with hepatoblastoma, and then were intrahepatic metastasis, bone, bone marrow, superior vena cava tumor thrombus and so on. In this study, in 21 cases, there were 12 patients with lung metastasis, 10 patients with intrahepatic metastasis. The remaining cases had bone, mediastinum, transverse colon, right atrium metastasis and so on. The result was in agreement with that reported in the literature[9]. Therefore, chest radiological examination, bone marrow examination, ultrasonic cardiography, bone scanning and so on should be performed on patients who are suspected this disease to understand the patient's condition and determine clinical stage.

Histological types of hepatoblastoma were classified as epithelial type and mixed type, while epithelial type can be further classified as mesenchymal type, fetal type and embryonic type. It has been reported that mesenchymal type and mixed type generally are undifferentiated tumor and/or poorly differentiated tumor, which have a poor prognosis. Among these types, the prognosis of fetal type is better than others, embryonic type is next[10]. However, in this study has been found that the prognosis of epithelial type was worse than that of mixed type, which wasn't in agreement with that reported in the literature. It was possible that the median follow-up time of epithelial type was longer than that of mixed type. Although it was reported that patients with epithelial type have a better prognosis, once patients accompanied with tumor residue or distant tissue and organ metastases, the prognosis would be worse.

According to international staging standard for hepatoblastoma of POG/CCG, both stage III and stage IV are in high risk groups, but this study showed that the prognosis of stage III was better than stage IV. Hence, early diagnosis has positive meaning to improve the prognosis of patients with advanced hepatoblastoma. In recent years, by the immunohistochemical study of hepatoblastoma, CK, AFP and CEA displayed different positive rates in hepatoblastoma. Serum AFP is an important tumor marker of hepatoblastoma and the AFP level of patients with fetal type was higher than that of other types[11]. In this work, the serum AFP level of 34 cases displayed different increases, the AFP level of patients with progressive disease, recurrence and death abnormally increased, and the highest value of serum AFP of patients was 484,000 ng/dl. The serum AFP level of patients who obtained complete remission and partial remission after treatment decreased significantly. Hence, serum AFP level had some clinical significance in the early diagnosis, follow-up and prognosis of hepatoblastoma.

At present, survival rate of patients with hepatoblastoma who were treated with chemotherapy, interventional therapy, surgery and Auto-PBSCT improves significantly, 5 year survival rate reaches 70%. However, the survival rate of patients who accompanied by distant organs and tissues metastases is still unsatisfactory; the lowest value of the survival rate is only 15%-20%. In this study, 5 year estimated survival rate was only 40%. Hence, hepatoblastoma accompanied by distant organs and tissues metastases suggests that patients have a worse prognosis, and patients should prolong chemotherapy period and accept Auto-PBSCT treatment.

Conclusions

Patients with advanced hepatoblastoma have a worse prognosis, especially for patients who accompanied by distant organs and tissues metastases. Because patients with hepatoblastoma don't have symptom in the initial stage, clinical manifestation is not evident and it's difficult for early diagnosis. The symptoms including abdominal distension, abdominal mass, fever, and abdominal pain in patients with uncertain reasons should be pay attention to. Although generally patients with advanced hepatoblastoma have a worse prognosis, in this study, it showed that 95% confidence interval of average survival was

37.1 m-58.2 m after comprehensive treatment, and 2 year survival rate reaches 66.7%. Therefore, even if patients have worse clinical conditions, there is still therapeutic value. Patients with advanced hepatoblastoma should receive multidisciplinary cooperation, long-term and regular treatment to improve clinical remission rate and prolong the survival time.

Acknowledgements

This work was supported by grants from clinical featured projects of Beijing Science Committee (Grant No. D101100050010052).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Schoofs G, Braeye L, Vanheste R, Verswijvel G, Debiec-Rychter M, Sciot R. Hepatic rhabdomyosarcoma in an adult: a rare primary malignant liver tumor. Case report and literature review. Acta Gastroenterol Belg 2011; 74: 576-581.
2) Goedeke J, Haeberle B, Schmid I, von Schweinitz D. AFP negative cystic liver lesion in a child should let one think of hepatoblastoma. J Pediatr Hematol Oncol 2011; 33: e245-247.
3) Iacob D, Serban A, Fufezan O, Badea R, Iancu C, Mitre C, Neamtu S. Mixed hepatoblastoma in child. Case report. Med Ultrason 2010; 12: 157-162.
4) Bensimhon P, Villablanca JG, Sender LS, Matthay KK, Park JR, Seeger R, London WB, Yap JS, Kreissman SG. Peripheral blood stem cell support for multiple cycles of dose intensive induction therapy is feasible with little risk of tumor contamination in advanced stage neuroblastoma: a report from the Childrens Oncology Group. Pediatr Blood Cancer 2010; 54: 596-602.
5) Corrias MV, Haupt R, Carlini B, Parodi S, Rivabella L, Garaventa A, Pistoia V, Dallorso S. Peripheral blood stem cell tumor cell contamination and survival of neuroblastoma patients. Clin Canc Res 2006; 12: 5680-5685.
6) 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 2003; 19: 142-146.
7) Courtier JL, Perito ER, Rhee S, Tsai P, Heyman MB, MacKenzie JD. Targeted MRI contrast agents for pediatric hepatobiliary disease. J Pediatr Gastroenterol Nutr 2012; 54: 454-462.
8) Malogolowkin MH, Katzenstein HM, Krailo M, Meyers RL. Treatment of hepatoblastoma: the North American cooperative group experience. Front Biosci 2012; 4: 1717-1723.
9) Shen WJ, Zhang P, Liu XL, Yu WN. [Pulmonary metastasis from the malignant neoplasms of major salivary gland: Clinical analysis of 22 patients]. Shanghai kou qiang yi xue = Shanghai J Stomatol 1996; 5: 179-180.
10) von Schweinitz D. Hepatoblastoma: recent developments in research and treatment. Semin Pediatr Surg 2012; 21: 21-30.
11) Shim YH, Park HJ, Choi MS, Kim JS, Kim H, Kim JJ, Jang JJ, Yu E. Hypermethylation of the p16 gene and lack of p16 expression in hepatoblastoma. Modern Pathology 2003; 16: 430-436.