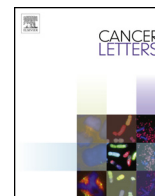




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## Original Articles

## Multidisciplinary effort in treating children with hepatoblastoma in China



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## ABSTRACT

The purpose of this study is to report the first nationwide protocol (*Wuhan Protocol*) developed by Chinese Children's Cancer Group and the results of multidisciplinary effort in treating hepatoblastoma. In this study, we reported the final analysis, which includes 153 hepatoblastoma patients in 13 hospitals from January 2006 to December 2013. The 6-year overall survival and event-free survival rates were  $83.3 \pm 3.1\%$  and  $71.0 \pm 3.7\%$ , respectively, in this cohort. The univariate analysis revealed that female ( $P = 0.027$ ), under 5 years of age ( $P = 0.039$ ), complete surgical resection ( $P = 0.000$ ), no metastases ( $P = 0.000$ ), and delayed surgery following neoadjuvant chemotherapy ( $P = 0.000$ ) had better prognosis. In multivariate analysis, male, 5 years of age or above, stage PRETEXT III or IV, and incomplete surgical resection were among the some adverse factors contributing to poor prognosis. The preliminary results from this study showed that patients who underwent treatment following *Wuhan Protocol* had similar OS and EFS rates compared to those in developed countries. However, the protocol remains to be further optimized in standardizing surgical resection (including liver transplantation), refining risk stratification and risk-based chemotherapy.

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## Introduction

Hepatoblastoma (HB) is one of the most common liver malignancies in children. Recent data showed that the incidence of HB

has increased by 2.18% annually in patients under 20 years of age. Ninety percent of patients with liver malignancies under 5 years of age were diagnosed with HB [1]. In the past, the main treatment for HB was surgical resection; however, complete tumor resection could be achieved only in a few patients [2]. The use of chemotherapy improved the survival rate dramatically since 1970s [3]. The multidisciplinary team (MDT), which included pediatric surgeons, oncologists, radiologists, and pathologists, played an essential role in HB treatment, with a survival rate of over 80% reported elsewhere in the world [4]. However, there was no report on overall survival (OS) and event-free survival (EFS) study in pediatric HB patients in China. In 2006, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine developed a protocol and the preliminary data showed a satisfactory survival rate in 12 HB patients [5]. In order to improve the outcome in HB patients and standardize the

*Abbreviations:* AFP,  $\alpha$ -fetoprotein; CCG, Chinese Children's Cancer Group; CHIC, Children's Hepatic tumor International Collaboration; CI, confidence interval; COG, Children's Oncology Group; CT, computed tomography; CR, complete remission; EFS, event-free survival; GPOH, German Liver Tumor Study; HB, hepatoblastoma; HR, hazard ratio; JPLT, Japanese Study Group for Pediatric Liver Tumor; LT, liver transplantation; MDT, multidisciplinary team; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; PR, partial remission; PRETEXT, pretreatment extent of disease; SD, stable disease; SIOPEL, Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group.

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treatment regimens in China, using protocols from Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group (SIOPEL) and Children's Oncology Group (COG) as references, Chinese Children's Cancer Group (CCCG) developed the *Multidisciplinary Treatment Guideline for Chinese Children with Hepatoblastoma* in the city of Wuhan, Hubei Province, in 2009, also referred to as *Wuhan Protocol*. This protocol focused on pre-operative chemotherapy and MDT effort in treating HB patients; thirteen CCCG member hospitals adopted this protocol. The purpose of this study is to assess the feasibility and effectiveness of the first nationwide protocol and the results of multidisciplinary effort in treating HB in China.

## Materials and methods

### Inclusion and exclusion criteria

From January 2006 to December 2013, there were 162 cases of pediatric HB treated in 13 CCCG member hospitals following *Wuhan Protocol* but 153 patients were enrolled in this study. The enrollment criteria for patients in this study were: (1) patients must be younger than 18 years of age; (2) patients had not had any chemotherapy before inclusion; and (3) pathological diagnosis confirmed by ultrasound-guided fine-needle biopsy or surgical resection. Patients with great risk for biopsy at the onset were temporarily diagnosed with clinical findings, including age, clinical history, physical examination, serum  $\alpha$ -fetoprotein (AFP) level, and computed tomography (CT) scan or magnetic resonance imaging (MRI). After two or more cycles of neoadjuvant chemotherapy, the diagnoses of all patients were pathologically confirmed after a subsequent surgical tumor resection. Patients who underwent treatment following *Wuhan Protocol* for less than one cycle of chemotherapy were excluded from this study. The medical records of all enrolled cases were retrospectively reviewed, and their information (including medical history, physical examination, CT/MRI images, serum AFP, chemotherapy regimens, surgery, and outcome) was collected and verified by CCCG senior pediatricians and radiologists (CT/MRI images were used to define the stage). The Ethics Committee of each individual hospital had reviewed and approved this study. The consent from each patient's parents or legal guardians was obtained before treatment.

### Stage, pathology, and risk stratification

Patients were classified using PRETEXT (pretreatment extent of disease) system [6] before treatment and COG staging [7] after surgery. The stage of each patient was verified by Dr. Yu-Hua Li, a CCCG senior pediatric radiologist from Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. Based on WHO pathological diagnostic criteria [8], patients were divided into the pure fetal pattern, the combined fetal and embryonal epithelial pattern, the mixed epithelial and mesenchymal pattern, and other patterns (including the macrotrabecular, the small cell undifferentiated and the mixed with teratoid feature patterns). The paraffin sections from the tumor specimens of all patients were reviewed by Dr. Min-Zhi Yin, a CCCG senior pathologist at Shanghai Children's Medical Center, Shanghai, China.

To compare the treatment outcome among different risk groups with *Wuhan Protocol* and provide the basis for risk-based chemotherapy in future revision of the protocol, we retrospectively classified the patients into two groups based on the criteria of SIOPEL risk stratification [9,10]: standard-risk group and high-risk group. Standard-risk is defined as PRETEXT I, II or III, without any manifestation listed in high risk group; high-risk is defined as PRETEXT IV, or any PRETEXT stage with tumor infiltration of the inferior vena cava (IVC)/hepatic veins (+V), portal vein (+P), extrahepatic abdominal (+E), distant metastases (+M), the small cell undifferentiated (SCU), AFP <100 ng/mL, or tumor rupture.

### Treatment procedure

Patients who were diagnosed with HB and met the enrollment criteria were treated following *Wuhan Protocol*. In this protocol (shown in Fig. 1), PRETEXT I patients were recommended to have surgical tumor resection followed by either two or four courses of post-operative chemotherapy. The preferred regimen was C5V, which consisted of cisplatin (90 mg/m<sup>2</sup>, >1 year old, or 3 mg/kg, <1 year old) on day 1, vincristine (1.5 mg/m<sup>2</sup> with a maximum dose of 2 mg) and 5-fluorouracil (600 mg/m<sup>2</sup>) on day 2.

All PRETEXT II, III, and IV patients usually received the same two courses of chemotherapy (C5V regimen) after diagnosis, with a 21-day interval between two courses. Patients' AFP level and CT scan were repeated after the second course of chemotherapy (defined as the first evaluation). Based on the first evaluation results, MDT members made a decision as when to have surgery. If the patients had complete surgical tumor resection, they were followed by either two or four courses of post-operative chemotherapy (C5V regimen). The total courses of chemotherapy for these cases were four to six.

Patients who could not undergo surgery after the first evaluation would receive two more courses of chemotherapy (C5V regimen). However, the patients whose

first evaluation showed no response to initial chemotherapy (without reduced serum AFP level or tumor size), or the tumor was progressing, were subsequently switched to PLADO regimen. As an alternative regimen, PLADO was consisted of cisplatin (80 mg/m<sup>2</sup>) on day 1, and doxorubicin (30 mg/m<sup>2</sup>/d) on day 2 and day 3. The results of second evaluation by MDT after four courses of chemotherapy were used to determine the proper time-point of surgery. Patients with complete surgical resection received two to four more courses of post-operative chemotherapy. There would be a total of six to eight courses of chemotherapy. Those patients whose tumors could not be resected completely continued to receive two more courses of PLADO regimen. After the third evaluation, some of the patients underwent surgery and then received two to four courses with C5V or PLADO regimen.

Those patients who had finished six courses of pre-operative chemotherapy, but not responding to the chemotherapy as determined during the evaluations at different intervals, were excluded from *Wuhan Protocol*. These patients would be adjusted with other regimens (e.g. C5VD, ICE, and cyclo/topo) based on drug sensitivity results; each patient received an individual treatment plan.

### Statistical analysis

Data statistics were performed using SPSS (Statistical Package for the Social Sciences), version 19.0 (SPSS Inc, Chicago, IL, USA). Survival curves were estimated by Kaplan–Meier method; the survival rates were reported as mean  $\pm$  standard error (SE). Log-rank test was used to analyze prognostic univariate. Variables with a P-value <0.05 in univariate analysis were entered into the multivariate Cox proportional-hazards regression model. A P-value <0.05 was considered to be of statistical significance.

### Follow-up

The last follow-up date for this study was May 31, 2015. Overall survival (OS) was calculated as time (in months) from diagnosis to death of any cause. Event-free survival (EFS) was calculated as time (in months) from definitive clinical diagnosis to event happening (including disease progression, recurrence, abandonment or death of any cause, whichever occurred first). Complete remission (CR) means that there is no evidence of tumor in CT or MRI, and normal serum AFP level for at least 4 weeks. Partial remission (PR) means a decrease of at least 50% in size of all measurable lesions, with no evidence of new lesions or progression in any lesion. Stable disease (SD) refers to any remission without an increase in tumor size and new lesions. Progressive disease (PD) refers to an increase of at least 25% in the size of any lesion, any new lesion, or a rising AFP level. Lost to follow-up is defined as that patient who failed to be followed up for at least 6 months.

Follow-ups were conducted in patients' primary hospital for at least 5 years from the date of treatment completion or the cut-off date for this report. The AFP level was checked monthly in the first year of follow-up, then every three months in the second year and third year, and every six months in the fourth and fifth years. MRI or CT scan was performed every two months in the first year, every three months in the second year, every six months in the third year, and annually during the last two years.

## Results

### Patients' characteristics

From January 2006 to December 2013, a total of 162 patients from 13 CCCG member medical centers were registered for this study. Nine cases were excluded from the cohort, of which 4 patients abandoned treatment (two of which abandoned treatment due to financial reasons and the other two suffered from heart failure), one patient was misdiagnosed with HB (the patient was clinically diagnosed with HB, but the pathological result after a subsequent surgery was confirmed as yolk sac tumor after 4 cycles of chemotherapy), and 4 cases lacked complete documentations. Therefore, 153 cases were included, analyzed and reported in this study. The group included 104 males and 49 females (the male to female ratio was 2.1:1); the median age at diagnosis was 16.0 (1.3–132.0) months, median follow-up time was 52.9 (1.0–116.6) months. The demographic and clinical characteristics of 153 HB patients were listed in Table 1. There were 6 (6/153, 3.9%) preterm patients and none was very low birth weight infant.

### Staging, metastases and risk stratification

Patients were staged according to PRETEXT system before treatment. The number of cases of PRETEXT I is 16 (10.4%), PRETEXT II

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