

Multidisciplinary Treatment in Children with Non-Metastatic Hepatoblastoma: Treatment Results at the National Cancer Institute, Cairo University

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ABSTRACT

Purpose: The aim of this study is to evaluate our experience at the NCI, Cairo University in the management of non-metastatic hepatoblastoma (HB). Also to improve survival of children with HB and reduce the operative morbidity and mortality by using preoperative chemotherapy.

Patients and Methods: After biopsy and assessment of the extent of disease, all patients were treated with a 6-hour continuous intravenous infusion of cisplatin (PLA) 90mg/m² on day one followed by doxorubicin (DO) 20mg/m² per day administered as 1-hour infusion on days 2,3 and 4. After four courses of preoperative chemotherapy, patients were reassessed. Whenever possible, the primary tumor was resected and the treatment was completed with two more courses of chemotherapy.

Results: Twenty children with HB were registered between January 1999 and December 2000, the median age at diagnosis was 12 months (range, 40 days to 11 years). All the 20 patients had received preoperative chemotherapy (PLADO). Fifteen patients (75%) showed partial response with tumor shrinkage and serial decrease of serum alpha-fetoprotein levels. Sixteen patients underwent surgery, fourteen of them had complete resection of the primary tumor (87.5%). The median duration of follow-up was 26 months (range 1-55 months). The three year disease-free survival was 68.4% and event-free survival was 65%.

Conclusion: We can advocate the use of PLADO chemotherapy and delayed surgery to be the standard treatment for children with HB. Other treatment programs should be measured against this standard.

Key Words: Hepatoblastoma - Preoperative chemotherapy - Hepatectomy.

INTRODUCTION

Hepatoblastoma (HB) is a rare malignant liver tumor which occurs almost exclusively in childhood. It accounts for approximately 1%

of all pediatric cancers [1]. There is general agreement that complete surgical resection is the cornerstone of treatment for children with HB and the only way for eventual cure [2]. At diagnosis about 50% of patients have unresectable disease, either because of extensive unifocal or multifocal primary tumor or because pulmonary metastases are present, or both [3]. Before the introduction of chemotherapy, the cure rate for HB was only 25% [1]. In the 1970s evidence began to emerge that HB is a chemoresponsive tumor [4,5] and during the 1980s cisplatin and doxorubicin were introduced [6,7]. In the 1990s most chemotherapy regimens for HB contained one or both of these two drugs [8-10].

The aim of this study was to evaluate our experience at the National Cancer Institute (NCI), Cairo University, in the management of non-metastatic HB. Also to improve survival of children with HB and reduce the operative morbidity and mortality by using preoperative chemotherapy.

Patients and Methods

This prospective study was open for patients entry between January 1999 and December 2000. Children less than 16 years of age at diagnosis with previously untreated non-metastatic HB presenting to the pediatric oncology and surgical oncology clinics of the NCI, Cairo University were eligible for entry.

Study Design:

The study is a prospective single arm study. Open or closed surgical biopsy was obtained

for accurate diagnosis. All materials obtained at diagnosis and resection were revised at the pathology department of the NCI. Initial treatment was with four courses of preoperative PLADO chemotherapy every 3 weeks. An attempt of resection of the primary tumor was recommended after the 4th or 6th PLADO courses.

Investigations at Diagnosis:

Demographic details and physical examination including nutritional status were documented. Peripheral blood was analyzed for full blood count, electrolyte levels, including magnesium and serum alpha feto-protein (AFP) concentrations. Hepatic, renal, auditory and cardiac functions were also measured.

Staging Procedures:

Pretreatment assessment of the primary tumor was by abdominal ultrasound, computed tomography (CT) scan, and/or magnetic resonance imaging (MRI). Metastatic spread was assessed by chest radiographs (postero-anterior and lateral) and lung CT scan. The children's Cancer Group/ Pediatric Oncology Group surgical pathologic staging system [11] was used in this study (Table 1).

Preoperative Chemotherapy:

Each course of PLADO chemotherapy consists of cisplatin (PLA) on day 1 at a dose of 90mg/m² in a 6 hours infusion and Doxorubicin (DO) at a dose of 20mg/m² per day administered as 1 hour infusion on days 2, 3 and 4 (total dose per course 60mg/m²). Doses recommended for children weighing less than 10 kg were calculated per kg on the basis that one m² of surface area corresponds to a body weight of approximately 30 kg. Courses of PLADO were repeated every 21 days if the absolute neutrophil count was more than 1.0X10⁹/L and the platelet count was more than 100X10⁹/L. If blood counts were below these levels, they were repeated every 2-3 days and the next PLADO course was given as soon as these values were achieved. Older children received pre-PLA hydration at a rate of 125 ml/m²/h for 12 hours and children weighing less than 10kg received it at a rate of 5ml/kg/h. The pre-PLA infusion contained 10mmol of potassium chloride, 2 mmol of magnesium sulphate and 1.5 mmol of calcium chloride per 500ml of glucose 5%, sodium chloride 0.45%.

During and after PLA administration, IV fluids were given at the same rate but with an additional 30ml of 20% mannitol solution every 500ml of the glucose-electrolyte solution. If the urine output fell below 400ml/m² in 6 hours, IV frusemide was recommended. The use of nephrotoxic antibiotics was discouraged during and immediately after PLA infusion. Electrolytes were monitored carefully throughout chemotherapy, particularly in infants.

Monitoring for Toxicity:

Before each course of chemotherapy, physical examination was performed and full blood count, urea, creatinine clearance, electrolytes, liver function tests and AFP. Cardiac and auditory functions were assessed after alternate courses of PLADO. Cardiac function was monitored by two-dimension derived mode echocardiography and ototoxicity was recorded according to the system developed by Brock et al. [12]. Other forms of toxicity were graded according to the World Health Organization criteria [13]. The following dose reductions were recommended in the event of toxicity: (1) if a low neutrophil count or platelet count had delayed the previous course of PLADO by more than one week, the dose of DO was reduced by 25%. (2) if hepatic dysfunction was detected (serum bilirubin concentration > 3mg/100ml and liver enzymes (AST & ALT) > 5 times the normal value) the DO dose was reduced by 50%. (3) if the left ventricular ejection fraction decreased below 50% DO was discontinued, (4) if creatinine clearance was > 60ml/min/1.73m², PLA was discontinued.

Tumor Response:

Abdominal ultrasound, CT and/or MRI were used to evaluate tumor response. Tumor was measured in each of three dimensions. Complete response was defined as the disappearance of all clinical and radiologic evidence of disease and a normal serum AFP concentration. Partial response was defined as any tumor shrinkage associated with a serial decrease in serum AFP concentration. Stable disease was defined as no evidence of tumor shrinkage and no serial decrease of serum AFP concentration. Progressive disease was defined as any unequivocal evidence of increase in tumor volume or the appearance of new lesions irrespective of serum AFP concentration.

Response to Chemotherapy and Timing of Surgery:

Tumor response was evaluated after the 2nd and 4th courses of PLADO. If there was clear-cut evidence of progressive disease at either point, PLADO was stopped and another treatment was given. After the fourth course of PLADO, tumor resectability was assessed. If feasible, partial hepatectomy was performed and then two final PLADO courses were given postoperatively. If the tumor was responding, but was still considered unresectable, a maximum of two more courses of PLADO were recommended before surgery. Therefore, the total planned doses of cisplatin and doxorubicin were 540mg/m² and 360mg/m², respectively. This was to reduce the incidence of renal damage and ototoxicity of cisplatin and cardiotoxicity of doxorubicin.

Surgical Procedure:

Surgery was performed 4 weeks after completion of the preoperative chemotherapy. The treatment protocol allowed atypical (synonymous wedge) resection and anatomic tumor resection.

Laparotomy is performed by a midline incision in cases of left lateral hepatectomy. This incision is extended into an inverted T shaped incision in cases of formal right or left hepatectomy. Mobilization of the liver is obtained by cutting the falciform ligament up to its division; exposing the suprahepatic portion of the vena cava and continuing the division of the right or left triangular and coronary ligaments according to which lobe is resected. The liver is then raised and dissected from the vena cava, dividing the short hepatic veins which are variable in number and size that drain the liver directly into the inferior vena cava. The hilum is then approached by identifying the left and right hepatic arteries, the portal vein and the bile ducts. Temporary clamping of the corresponding right or left artery and portal vein will clearly identify the resection plane which will be marked on the surface of the liver by cautery. We usually prefer to perform temporary clamping by vascular tapes to the whole of the portal elements for 20 minutes and release for 5 minutes during parenchymal transection. Hepatic transection is performed along the resection line by crushing hepatic parenchyma and ligation of vessels as they cross the interlobar tissue. Haemostasis

is secured after removal of vascular taps and the raw surface is usually not covered. Suction drains are fixed with mass closure of the wound.

Follow-Up Evaluation:

After completion of treatment, patients were followed with physical examination and measurements of AFP concentration monthly for the first year, every 2 months for the second year, every 3 months during the 3rd year and every 6 months for the 4th and 5th years. Chest radiograph and abdominal ultrasound were performed every 2 months during the first year, every 4 months during the 2nd and every 6 months during the third year of follow-up. Long-term toxicity was assessed by annual echocardiogram, creatinine clearance and audiometry.

Data Collection and Statistical Methods:

The results of this study are expressed in terms of (1) response to PLADO chemotherapy, (2) the surgical resection rate, (3) disease-free survival, (4) event-free survival and (5) toxicity. Event-free survival was defined as the time interval from date of diagnosis to (1) date of alternative treatment because of failure of PLADO regimen, (2) date of relapse, (3) date of death (from any cause), or (4) date of last follow-up, whichever occurred first. Disease-free survival was measured from the date of complete resection to the date of relapse or death or lost to follow-up were regarded as censored events. Tumor recurrence was identified from unequivocal imaging and increasing serum AFP levels or biopsy confirmation.

Last follow-up of these patients was July 2003. The cutoff date for analysis was August 2003. The Kaplan-Meier method was used to estimate survival curves [14]. Toxicity data was derived from results documented on chemotherapy data sheets.

RESULTS

Clinico epidemiologic Data:

Twenty children with hepatoblastoma were registered between January 1999 and December 2000. The median age at diagnosis was 12 months (range, 40 days to 11 years). Ten patients were males. The most frequent clinical presentation included hepatomegaly, abdominal enlargement, fever, anorexia, and weight loss. Alpha-fetoprotein was tested in all patients and was raised for age in 19/20 patients (95%)

(median 793 ng/ml; range, 85 to 755360 ng/ml). Fourteen patients (14/20, 70%) had thrombocytosis with a platelet count $> 500 \times 10^9/L$ at diagnosis. Histology of different types of HB were: mixed (n=8), embryonal (n=5), fetal (n=4) and undetermined (n=3). None of the studied children had associated congenital anomalies.

Therapy Results:

All the 20 patients had received preoperative chemotherapy. There was no complete radiological response to preoperative PLADO, but 15 (75%) children had partial response. Two patients were recorded as having stable disease (10%), two had progressive disease (10%) and one patient (5%) died within the first month of diagnosis before response could be assessed (chemotherapy toxicity).

Of the 20 patients who had received preoperative PLADO, only 16 patients underwent surgery, and 4 did not because of early death in one patient and because of unresectability after PLADO in 3 patients (2 PD & 1 SD).

The fifteen partial responders had partial hepatectomy after 4 courses of PLADO to resect the primary tumor. Rt. hepatectomy was performed in (4 patients), Lt. hepatectomy (in 5), central hepatectomy (in 2), extended Rt. hepatectomy (in 2) and segmental resection (in 2 patients). While 14 of these children (14/15) had pathologically documented complete resection, one patient had positive surgical margins. One of the two patients with stable disease underwent exploration and resection after 6 courses of PLADO, but surgical margins were positive by histopathology. The overall complete resection rate was 87.5% (14/16).

After resection, the 14 patients who underwent complete resection had received 2 further courses of PLADO. While the 2 patients who had positive resection margins (one was a partial responder and one had stable disease) the serum AFP concentration remained elevated and both died, one from progressive hepatic failure post-operatively and the other from increasing disease despite further treatment.

Out of the 14 patients who underwent complete surgical resection and normalization of serum AFP concentration, only one patient developed local recurrence after 10 months of follow-up. Relapse was preceded by elevation

of serum AFP concentration, and it was associated with pulmonary metastases. This patient died of progressive disease irrespective of salvage chemotherapy.

Chemotherapy Toxicity:

A total of 111 courses of PLADO were given in this study. There was one chemotherapy-related toxic death, but this child who died of septicemia after one course of PLADO was severely malnourished at diagnosis. Toxicities caused by doxorubicin and cisplatin are listed in tables (2-4).

Post-Operative Morbidity and Mortality:

Most of the patients (15/16) had an uneventful post-operative course. The surgical mortality rate was 6.25% (1/16); this patient died from progressive liver failure. He had partial response after 4 courses of chemotherapy and underwent Rt. trisegmentectomy, developed ascites, progressive liver failure and died in the immediate post-operative period.

Another case of extended Rt. hepatectomy developed ascites with elevated transaminase levels and improved by liver support.

Survival:

At the time of this analysis, for all patients, the median duration of follow-up was 26 months (range 1 to 55 months). As of August 2003, a total of 7 children had died. Five of these deaths (71%) were caused by tumor progression or recurrence, one death (14%) as a result of chemotherapy toxicity and one patient died due to postoperative progressive hepatic failure. For all the 20 patients, the 3-year disease-free survival was 68.4% and the event-free survival was 65%. For the 16 patients who had surgical resection, the 3-year disease-free survival and event-free survival were 81.25%. Figs. (1-4) show the Kaplan-Meier curves for DFS and EFS for all patients and for the 16 patients who underwent surgical resection.

Table (1): Tumor staging in patients with hepatoplastoma [11].

Stage I	Completely resected tumors
Stage II	Grossly resected tumors with evidence of microscopic residual
Stage III	Unresectable tumors Lymph node involvement is considered to constitute disease
Stage IV	Metastatic disease to lungs or other organs

Table (2): Toxicity of doxorubicin.

Toxicity	Patient with Toxicity (N=20)		Courses with Toxicity (N=115)	
	No.	%	No.	%
Febrile neutropenic	12	60	29	26
Septicemia	3	15	4	3.6
Grade 3 infection*	2	10	3	2.7
Grade 4 infection*	1	5	1	0.9
Mucositis	4	20	8	7.2

*According to World Health Organization criteria [13].

Table (3): Toxicity of platinol.

Toxicity	Patient with Toxicity n=20 (%)
Creatinine clearance < 60ml/min/1.73m ²	0 (0)
Hypomagnesemia	5/20 (25)
Hearing loss grade1/2	1/20 (5)

Table (4): Cardiotoxicity of doxorubicin.

Cardiotoxicity	No. of Patient with Toxicity
Ejection fraction < 50%	*1/20 (5%)
Ejection fraction < 28%	0 (0%)

* This patient with ejection fraction < 50% had normal cardiac function on follow-up.

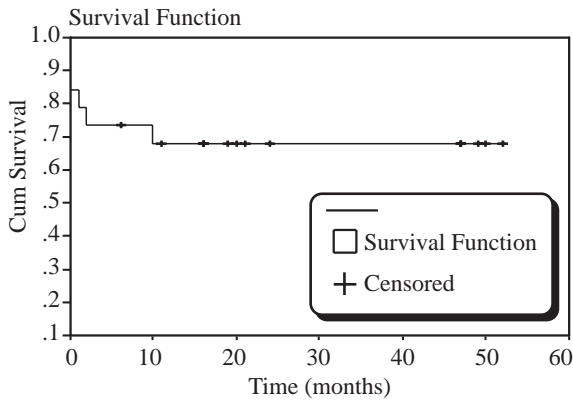


Fig. (1): Disease-free survival (all patients).

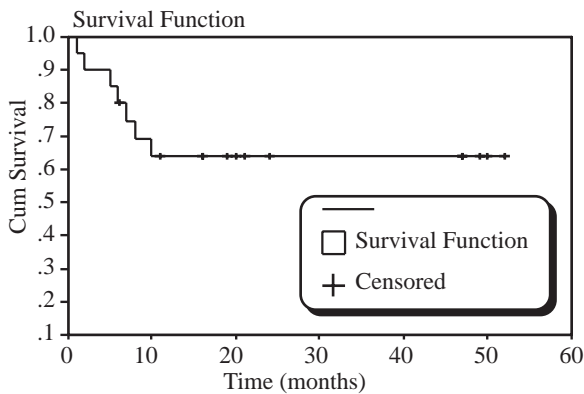


Fig. (2): Event-free survival (all patients).

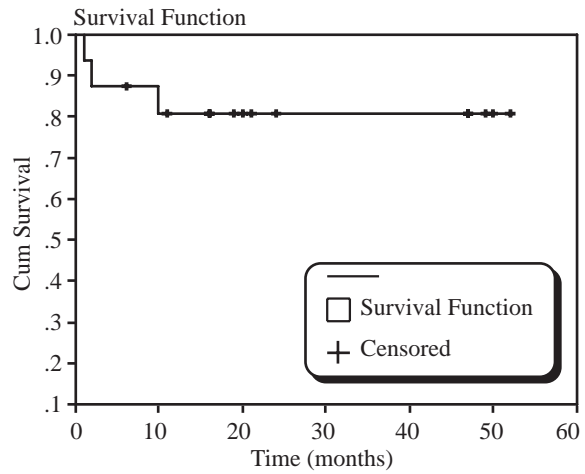


Fig. (3): Disease-free survival (surgical group).

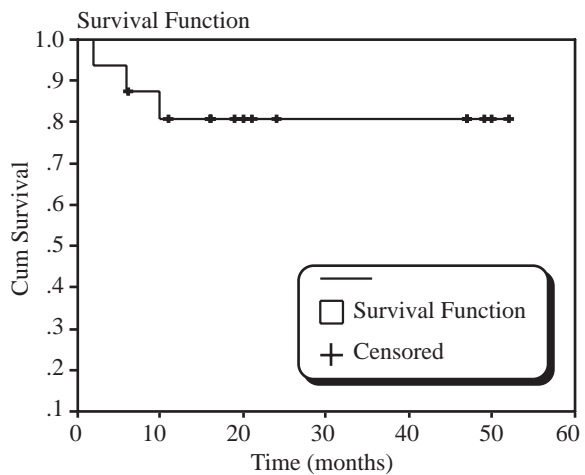


Fig. (4): Event-free survival (surgical group).

DISCUSSION

Hepatoblastoma is the most common primary malignant tumor of the liver in children [1]. The aim of this study was to improve the outcome for children with hepatoblastoma by applying pre-operative chemotherapy aiming to increase the resectability rate. Complete surgical resection is the mainstay of therapy for hepatoblastoma [11].

The two most striking laboratory parameters observed in our patients are elevated AFP and thrombocytosis; both testimony of the resumption of primitive liver function by the tumor. The serum level of AFP, a product of embryonal endoderm, was elevated in 95% of our patients, similar to 70-97% found in the literature [11,15]. Monitoring of serum AFP levels was a valuable marker for response to preoperative chemotherapy, to assess the results of postoperative resection, as well as to allow an early detection of

recurrence in almost all patients. There was an increase in the AFP level after the first course of PLADO in one responding patient. We attributed this finding to a tumor lysis syndrome with intracellular AFP released into the circulation from lysed tumor cells.

In this trial, we chose a relatively straightforward chemotherapy regimen with agents whose effects and side effects were easily monitored. We recommended delayed surgery to reduce morbidity and mortality of difficult surgical procedures. We introduced easily applied definitions of response/no response to therapy. The unconventional definition of partial response is due to the observation that some HBs could respond without shrinking as PLADO can induce maturation of tumor cells into differentiated mesenchymal tissue especially cartilage and osteoid tissue [16].

The toxicity of the PLADO regimen was acceptable & manageable. There was low incidence of febrile neutropenia and sepsis with only one death in a malnourished child with advanced disease. Specific toxicity from either drugs was also uncommon and not life-threatening. Nephrotoxicity as well as ototoxicity were uniformly mild and not of clinical significance with none of our children requiring hearing aids. The reasons for the relatively low overall toxicity of PLADO were possibly the limitation of cumulative doses of platinum and doxorubicin to 540mg/m² and 360mg/m², respectively.

Technically, successful hepatic resections require a thorough knowledge of liver and porta hepatic anatomy. The technical details of various forms of hepatic resection in children are similar to those described in adults. The standard approach in this study has been to attempt initial complete excision. The low incidence of surgical complications were (one surgical death) because (1) preoperative chemotherapy caused a reduction in tumor size and vascularity, (2) surgery was performed by surgeons well trained in liver surgery, (3) all patients were admitted to pediatric ICU post-operatively.

The event-free survival and disease-free survival in this study exceeded expectation. Most tumors responded to PLADO and most primary tumors were completely excised. In 4/16 cases who underwent surgery there was

complete necrosis with no evidence of viable HB cells (25%). After complete surgical resection, tumor recurrence occurred in 1 case who showed partial response with viable HB cells in more than 50% of the excised tumor.

At the time of this report, the median follow-up period of our patients is more than 2 years (26 months) & as all recurrences occurred during the first year of follow-up and because almost all relapses from HB occur within 2 years from the end of treatment [3,8], we believe that most of our survivors are completely cured of their disease.

Direct comparisons between our results and the results of other studies are difficult because of the difference in staging systems and surgical procedures after preoperative chemotherapy. Liver transplant was added to partial hepatectomy in most of the multicenter trials [17,18]. Three multicenter studies have studied PLADO or modifications of PLADO regimen. In Europe, the International Society of Pediatric Oncology (SIOP) used PLADO regimen with a 5-year EFS of 66% and OS of 75% [3]. Their results are almost comparable to ours. The United States of America Intergroup randomized patients to receive either PLADO or PLA/Fluorouracil/Vincristine [19]. Survival in the two arms were identical. The German Cooperative Group added ifosfamide to the cisplatin/doxorubicin regimen (9.20) but their results were no better than our study and toxicity was potentially greater. The Japanese Study Group for Pediatric Liver Tumor (JPLT-1) Studied 145 patients with hepatoblastoma between 1991 and 1999. JPLT-1 protocols 91A and 91B consisted of cisplatin/doxorubicin/Tetrahydropyranyl. The overall survival rate at 3-year, 6-year was 77.8% and 73.4%, respectively [21]. Their results were slightly better than ours and comparable with the results of other multi-center studies in Europe and the United States.

An important outcome of this study is the demonstration that pediatric oncologists, radiologists, pathologists and surgeons can work together to improve the outcome of children with HB. The improved survival rate of HB in childhood is dependent on both complete resection and appropriate combination chemotherapy. Therefore, we can advocate the use of preoperative chemotherapy as standard practice in the management of HB.

The excellent results achieved in our study and other multi-institutional studies concluded that HB is regarded as one of the curable solid tumors of childhood, a remarkable change from only 15 years ago, when it was regarded as one of the most dangerous solid tumors [22]. The rarity of this tumor (only 0.5 to 1.5 cases per million total population per annum) [23,24] means that national and international collaboration are essential.

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