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Treatment of hepatoblastoma: the North American cooperative group experience

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1. ABSTRACT

In North America, children with malignant liver tumors have been treated in a cooperative group study since early 1970s. This manuscript describes the results of these studies.

2. INTRODUCTION

Complete tumor resection is the cornerstone of therapy for liver tumors and offers the only realistic chance of long term disease free survival (1-4). The introduction of effective chemotherapeutic regimens for the treatment of hepatoblastoma has significantly improved the survival of children with this tumor by increasing the number of patients who can ultimately undergo tumor resection. Chemotherapy has been used as adjuvant therapy for patients who undergo complete tumor resection at the time of diagnosis, to preoperatively induce tumor shrinkage in initially unresectable tumors and to control metastatic disease.

The investigators from the International Liver Tumors Strategy Group of the International Society of Pediatric Oncology (SIOPEL) have used the strategy of delayed surgery following initial chemotherapy. In contrast, the Children's Oncology Group (COG) investigators have favored the use of initial surgical resection whenever this is feasible followed by adjuvant chemotherapy as a strategy to minimize overall chemotherapy exposure and toxicity. In contrast

3. COOPERATIVE GROUP STUDIES RESULTS

The first North American cooperative group study for the treatment of children with malignant liver tumors was started in 1972 by members of the Childrens Cancer Study group (CCSG) and of the Pediatric Division of the Southwest Oncology Group (SWOG) (5). In this study, patients were grouped according to the extent of the tumor and the surgical resection. Patients with disease limited to one lobe and completely resected tumors (Group I) received no further chemotherapy, while those with residual disease received sequential chemotherapy with actinomycin D, vincristine, and cyclophosphamide for 18 months with or without radiation therapy. Seven of the 11 patients (64%) with Group I developed metastatic disease, and only 7of the 40 patients entered onto this study survived. All survivors had either complete surgical resection of the tumor or minor residual disease that received concomitant radiation. No tumor response was seen with chemotherapy alone. This important early study suggests that while surgery is important in achieving a cure, some chemotherapy appears to be necessary as well. The caveat to this is that this is from an era with less sophisticated imaging techniques to accurately detect and assess disease.

Due to the lack of chemotherapy response with this regimen, in 1976 the two cooperative groups elected to study a new more aggressive regimen consisting of vincristine, cyclophosphamide, doxorubicin and 5-fluorouracil in 6 weekly cycles given for one year (5). All patients received chemotherapy including those with

Table 1. INT-0098 Outcomes according to stage and histology

	# Patients	5-year EFS	5-year OS
Stage I-FH	9	100%	100%
Stage I-UH	43	91% (SD=4%)	98% (SD=2%)
Stage II	7	100%	100%
Stage III	83	64% (SD=5%)	69% (SD=5%)
Stage IV	40	25% (SD=7%)	37% (SD=8%)

(FH = favorable histology; UH = unfavorable histology; EFS = event-free survival; OS = overall survival; SD = standard deviation)

completely resected tumors. A total of 62 patients were entered onto study. One child with recurrent disease initially entered on the previous study and 10 patients, who died within one month of study entry, were considered to have had inadequate trials of chemotherapy and were not included in the outcomes analysis. Twenty-four (24) patients following initial surgical treatment had no measurable disease and 27 patients had measurable disease at the time of study entry. The response rate to chemotherapy was 44% (12/27 patients), and 20 of the 24 with no measurable disease following initial surgical resection continued relapse-free for > 20 months. In this study, only 1 of 16 patients (6%) in Group I developed metastatic disease. This was significantly lower than the 64% metastatic rate observed for similar patients on the first study who did not receive adjuvant chemotherapy, demonstrating the benefit of adjuvant therapy for these patients.

The introduction of cisplatin in combination with other chemotherapeutic agents resulted in a significant improvement in the outcome of patients with unresectable tumors at diagnosis. In 1991, CCSG reported that the use of chemotherapy with cisplatin (90 mg/m^2 infusion over six hours) followed by doxorubicin (80mg/m^2 continuous infusion over 96 hours) for patients with stage III and IV tumors improved their three year disease-free survival to 55% and 30%, respectively (6). Douglass *et al*, reported for the Pediatric Oncology Group (POG), event-free survivals of 67% and 12.5% for patients with stage III and IV tumors, respectively, when treated with a combination of cisplatin (90mg/m^2 infusion over six hours on day 1), vincristine (1.5mg/m^2 on day 2) and 5-fluorouracil (600mg/m^2 on day 2) (7). In both studies staging was based on the extent of surgical resection and histology as determined prior to initiation of chemotherapy.

The subsequent North American Intergroup study (INT-0098) was designed with the main objective of determining in a randomized fashion, which of the above regimens was superior (8). In this study, patients with stage I were further classified as having favorable histology (FH) meaning pure fetal histology with minimal mitotic activity (< 2 mitoses/10 high power microscopic fields) or unfavorable histology (UH), which included all other histologic forms (9). Patients with stage I-UH, stage II, stage III, and stage IV were randomized to receive chemotherapy with cisplatin, vincristine, and 5-fluorouracil (C5V) or with cisplatin and doxorubicin (CD). Patients with stage I-FH were treated with 4 cycles of doxorubicin alone and all were alive and free of disease at time of last contact. The five year event-free survival for all patients (except Stage I with pure fetal histology) was 57% for patients treated with C5V and 69% for those treated with CD. Outcomes according to stage are shown on Table 1. Although the difference in outcome between the two regimens was not statistically significant, the types of events associated with each regimen were notably different. While tumor progression accounted for 86% of all reported events for patients treated with C5V, it represented only 56% of all events observed in those patients treated with CD. However, CD was associated with an increased number of treatment complications and toxic deaths. Based on these results, the COG investigators adopted the C5V regimen as the standard for the treatment of children with hepatoblastoma. These results also suggested that cisplatin was the most effective chemotherapeutic agent for the treatment of hepatoblastoma.

Katzenstein *et al*, reported the results of POG 9345, a study designed to increase therapeutic efficacy and diminish toxicity in children with unresectable and metastatic hepatoblastoma by incorporating carboplatin in lieu of cisplatin, eliminating doxorubicin, and adding weekly vincristine and continuous infusion of fluorouracil (10). Patients received one course of carboplatin and were assessed for response. Patients then received 3 courses carboplatin, vincristine, and fluorouracil followed by tumor resection if feasible. Patients whose tumors were completely resected received 2 more courses of the same chemotherapy. Those patients whose tumors remained unresectable or showed no response to chemotherapy were switched to therapy with high-dose cisplatin and etoposide. Twenty-two patients with stage III and eleven with stage IV hepatoblastoma were treated sequentially with one course of carboplatin followed by three courses of carboplatin, vincristine, and fluorouracil. The five-year event-free survival estimates were 59% for stage III disease and 27% for stage IV disease, respectively (P = .037). Twenty –seven (82%) of 33 patients had at least a partial response to chemotherapy; 18 (55%) of 33 responded to carboplatin alone; 24 (80%) of 30 responded to carboplatin, vincristine, and fluorouracil; and nine (75%) of 12 responded to high-dose cisplatin and etoposide. Surgical resection was achieved in 19 (58%) of 33 patients, including 15 (68%) of 22 stage III patients and four (36%) of 11 stage IV patients. Overall this regimen had results that were comparable to other therapeutic regimens, and demonstrated the efficacy of carboplatin in the treatment of hepatoblastoma.

There was important experience gained from the intensification of cisplatin in pediatric germ cell tumors (11), together with the results of POG9345, and preliminary data from Malogolowkin et al., using a regimen of carboplatin alternating with cisplatin every two weeks for hepatoblastoma (12). Subsequently, COG investigators developed a study to determine if the intensification of platinum agents would improve the outcome for patients with advanced stage hepatoblastoma.

The next COG study, P9645, a Phase III Protocol for the Treatment of Children with Hepatoblastoma, opened in March 1999 and had as its main objectives: 1) to compare "standard" C5V therapy to a regimen of alternating cisplatin and carboplatin; 2) to determine whether amifostine is effective in reducing the toxicities

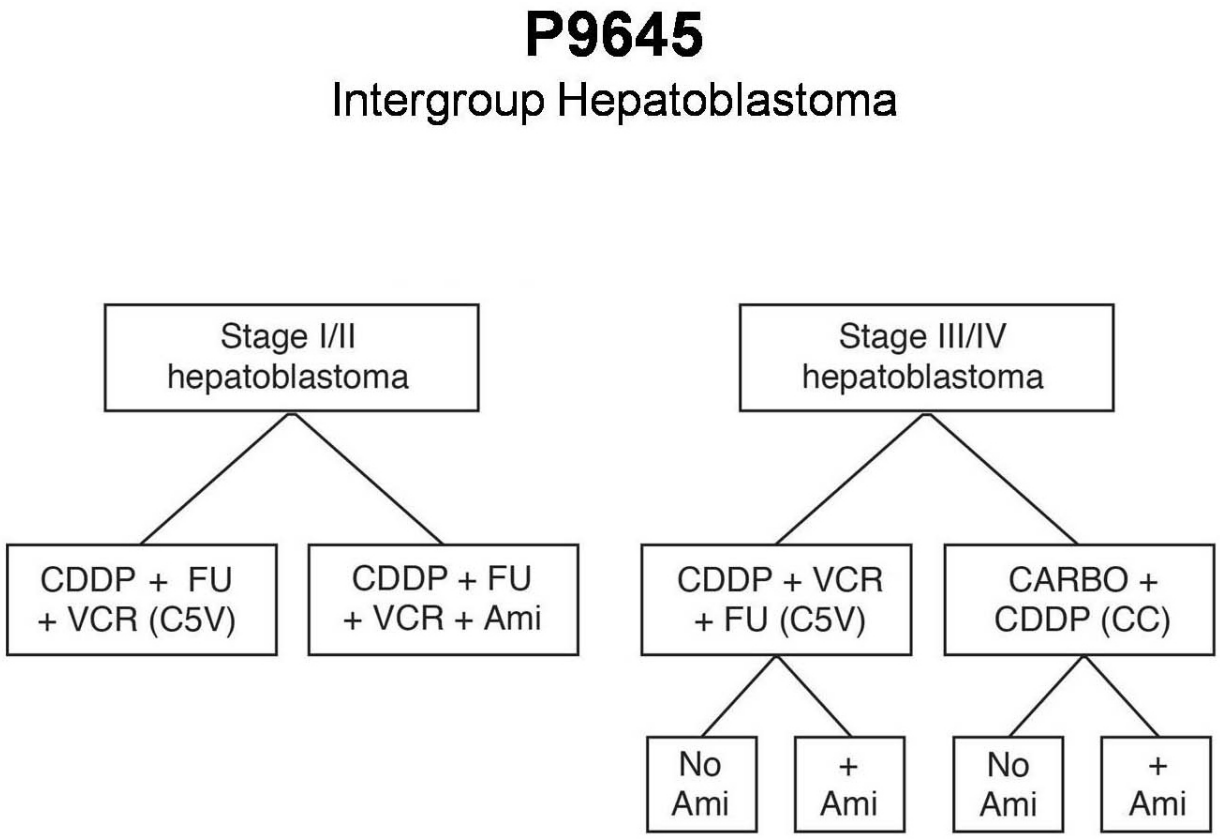

Figure 1. Intergroup P9645 study design.

associated with the administration of platinum-containing regimens; and 3) to estimate the event-free survival of patients with stage I pure fetal histology treated with surgery alone (Figure 1).

In this study, patients with stage III/IV hepatoblastoma were randomized to receive either an intensified platinum regimen with carboplatin alternating with cisplatin (CC) with or without amifostine or the standard C5V regimen with or without amifostine (13). Patients were re-evaluated at the end of 4 cycles of the assigned chemotherapy. Patients with unresectable disease at that time were considered treatment failures. If the patient had tumor resection at that time, the patient received 2 more cycles of the therapy to which she or he had been randomized. From the time the study was opened until the time that random assignment was halted, 56 eligible patients received CC and 53 received C5V. The 1-year event-free survival was 37% for patients receiving CC and 57% for those receiving C5V (p=0.017). Patients randomized to CC required more blood product support. There were no differences between the regimens when the other toxicities were compared. The randomization was discontinued after 3 years of enrollment because the projected improvement in long-term outcome associated with CC was statistically excluded as a possible outcome of this trial. Subsequently all patients were assigned to receive C5V with or without amifostine.

Patients with stage I/II hepatoblastoma received treatment with 4 cycles of the standard C5V regimen with or without amifostine (14). All patients randomized to receive amifostine were given a dose of 740 mg/m^2 intravenously over 15 minutes before each administration of a platinum agent. In October 2003, the randomization to receive amifostine was terminated as a result of an interim toxicity analysis that determined that amifostine in the dose and schedule used did not provide significant benefit with respect to the amelioration of hematological toxicity or ototoxicity associated with platinum agents. This analysis included 82 patients randomized to receive platinum-containing therapy with or without amifostine. The disease outcome for patients who received amifostine was similar to the outcome for patients who did not receive amifostine (p=0.22). The incidence of significant hearing loss (>40dB) according to the modified Brock criteria (15) was similar for patients who received (38% -14/37 patients) or did not receive amifostine (38% - 17/45 patients; p=0.68). There were no differences in the incidence of renal or bone marrow toxicities evaluated, however patients who received amifostine had a higher incidence of hypocalcemia (5% vs. 0.5%; p=0.00006).

Preliminary analysis of this study has demonstrated that all 9 patients with stage I pure fetal histology hepatoblastoma were alive and free of disease at the time of last contact (16). This experience suggests that children with completely resected (stage I) pure fetal histology hepatoblastoma can achieve long term survival without further chemotherapy, and that upfront surgical resection of hepatoblastomas when feasible, may identify children for whom no further therapy is necessary. Final outcome analysis of patients entered onto this study has not been completed as of the time of submission of this manuscript.

Although in North America the C5V regimen continued to be the standard treatment of children with hepatoblastoma, other international cooperative groups have continued to favor the use of cisplatin and doxorubicin (17-20). Because of these divergent treatment strategies, COG investigators decided to revisit the role of doxorubicin for the treatment of children with hepatoblastoma by reanalyzing the data from the INT-0098 study (21). The outcomes of the patients with hepatoblastoma entered on this study were reviewed with emphasis on the post-event survival time for both regimens (C5V and CD) to elucidate the role of doxorubicin in their retrieval. Fifty-five of the 173 randomized patients experienced tumor progression or recurrence after initial treatment. Eleven (31%) of the 36 patients treated with C5V were successfully retrieved with a doxorubicin-containing regimen and surgery and remain alive at last contact, whereas only one (6%) of the 18 patients treated with CD was alive after retrieval therapy. The COG investigators concluded that: 1) C5V is an effective therapy for stage I or II hepatoblastoma, and that doxorubicin can be omitted as part of the initial therapy in the majority of these patients, potentially limiting the long-term cardiac toxicities without compromising outcomes; 2) doxorubicin is effective in rescuing patients with recurrent disease after C5V treatment and should be incorporated as a means of intensifying therapy for advanced-stage, non-metastatic hepatoblastoma; 3) outcomes for patients with metastatic hepatoblastoma at diagnosis are poor, and improving their survival will require new therapeutic approaches.

The identification of new, effective chemotherapeutic agents for the treatment of hepatoblastoma is a challenge, since phase I and II studies include very few patients with this type of tumor. A recent COG phase II study of single agent oxaliplatin in children with recurrent solid tumors showed no response in ten children with recurrent hepatoblastoma previously treated with cisplatin (22). Anecdotal data from members of the COG Liver Tumor committee exist for a total of approximately 10 patients with recurrent or progressive hepatoblastoma who have been treated with irinotecan (Beaty O: Personal Communication). Of the 10 patients, 6 achieved a PR lasting 3 to 12 months. Two patients with lung metastases had complete disappearance of lung nodules and normalization of AFP levels (6 and 11 months). The remaining 2 patients showed no response to therapy. Overall therapy was well tolerated with myelosuppression and diarrhea as the most common side effects. PRs in 6 of these very heavily pretreated patients suggest that irinotecan may be an active drug in this disease and justifies its evaluation in a group of patients who have a 70% chance of eventually succumbing to their disease with “standard therapy”.

The review of the North American results as well as of the SIOPEL (International Society of Pediatric Oncology Liver Tumor Study Group) and the GPOH (German Study Group) indicates that: 1) upfront surgery may identify a group of children for whom no further therapy or minimal therapy is necessary, therefore reducing acute and long term toxicities; 2) patients with unresectable tumors at diagnosis may benefit from intensification of therapy which may lead to increased numbers of resectable tumors and improved survival; 3) new agents need to be identified for the treatment of patients with hepatoblastoma.

The current COG phase study for children with newly diagnosed hepatoblastoma (AHEP0731) builds on the results of the last 35 years of hepatoblastoma clinical trials (Figure 2). The main hypothesis of this study is that a risk-based treatment approach will maintain or improve event-free survival (EFS), decrease acute and long-term chemotherapy toxicity, and identify new agents in the treatment of children with hepatoblastoma. All patients with Stage I pure fetal histology (PFH) hepatoblastoma will be classified as very low-risk and will be treated with surgery only. Patients with Stage I non-PFH, non-small cell undifferentiated (SCU) hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk and will be treated with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk. In an attempt to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the standard C5V regimen (C5VD). However due to the toxicities experienced with the CD regimen on the INT-0098 study, the doxorubicin will not be given as a continuous infusion over 96 hours and the dose doxorubicin will be decreased by 25%. All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP < 100 ng/mL will be classified as high-risk and will be treated with a novel agent (irinotecan) in order to improve survival. This regimen includes 2 cycles of “up-front” vincristine and irinotecan window therapy. Patients who respond to vincristine/irinotecan (VI) will continue to receive these agents, and will receive a total of 6 cycles of C5VD therapy with 2 more cycles of VI (total of 4). Non-responder patients will only receive the 6 cycles of C5VD following the “up-front” window therapy. This study will also investigate the role of liver transplantation for patients whose tumors remain unresectable after 4 cycles of chemotherapy, the value of the PRETEXT (*pret*reatment *ext*ent of disease) staging system in predicting tumor respectability (23,24), and will continue to collect tumors samples to support further studies on the biology of these rare tumors.

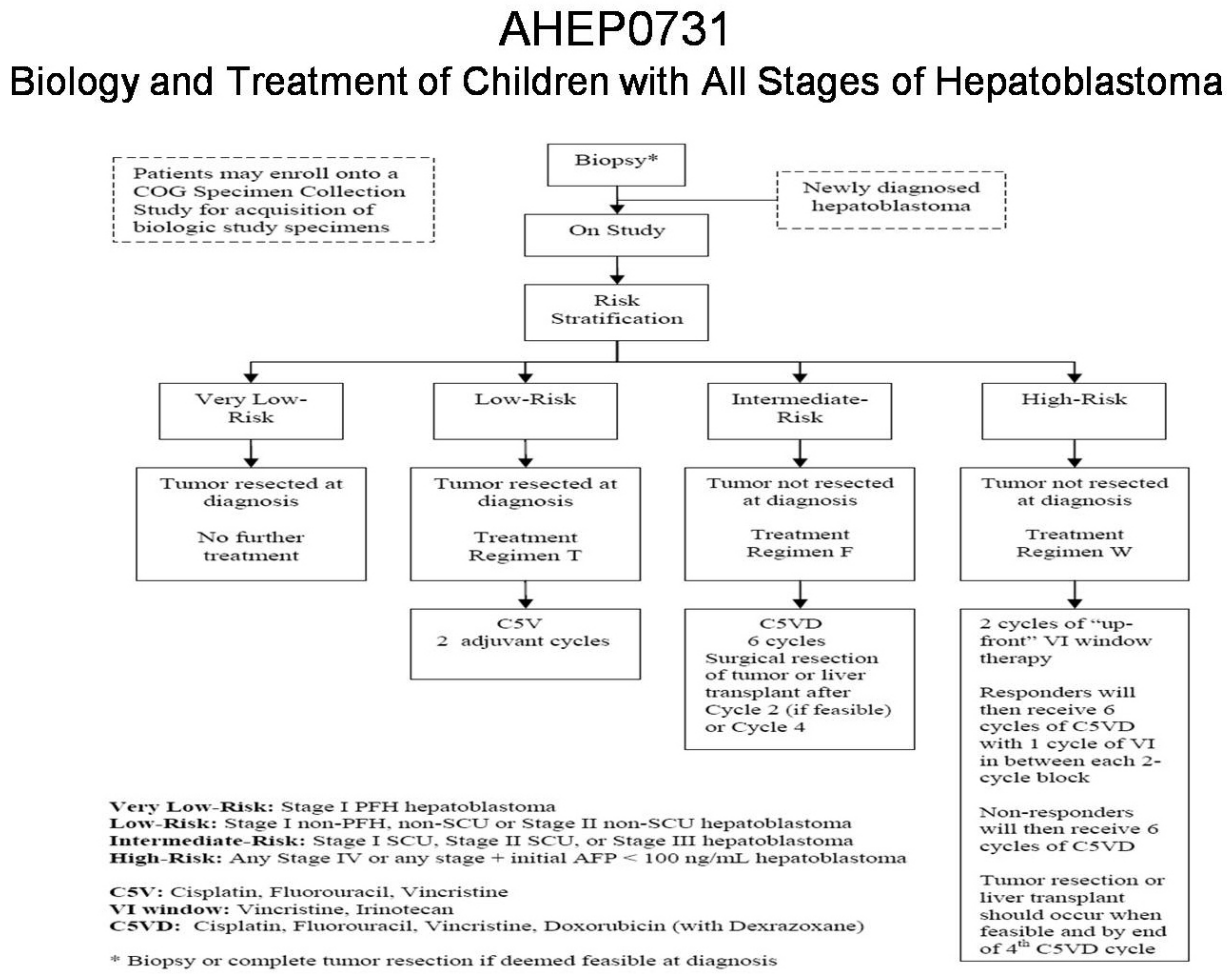

Figure 2. AHEP0731 study design.

4. CONCLUSIONS

Efforts directed towards the early detection of hepatoblastoma in high-risk populations would increase the possibility of complete tumor resection at diagnosis. Patients with predisposing conditions such as the Beckwith-Wiedemann syndrome, hemihypertrophy, familial adenomatous polyposis and possibly premature babies, should be closely monitored during the first four years of life. Epidemiological studies may reveal important factors related to the cause of hepatic tumors in children, and eventually allow for the eradication of these tumors. The role of liver transplantation and the use of living related donors require further evaluation. International cooperative groups should carry out the development of a universal staging system that will allow the comparison between different therapeutic approaches. Finally, due to the small number of children diagnosed with hepatoblastoma, international cooperation will also be essential in the future design and implementation of biologic and therapeutic studies.

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