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ORIGINAL REPORT

Intensified Platinum Therapy Is an Ineffective Strategy for Improving Outcome in Pediatric Patients With Advanced Hepatoblastoma

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ABSTRACT

Purpose
The INT-0098 Intergroup Liver Tumor Study demonstrated no statistically significant differences in event-free and overall survival between patients randomized to treatment with either cisplatin + fluorouracil + vincristine (C5V) or cisplatin + doxorubicin. Results from this and other therapeutic trials suggested that cisplatin was the most active agent against hepatoblastoma. To increase the platinum dose-intensity, a novel regimen was developed alternating carboplatin and cisplatin (CC) every 2 weeks. The P9645 study was designed to compare the risk of treatment failure for patients with stage III/IV hepatoblastoma randomized to either C5V or CC.

Methods
C5V was given according to INT-0098 and CC consisted of carboplatin at 700 mg/m^2 on day 0 (560 mg/m^2 after two cycles) followed by cisplatin 100 mg/m^2 on day 14. Granulocyte colony-stimulating factor was used after each CC cycle. All patients received four to six cycles of chemotherapy.

Results
From the time the study was opened until the time that random assignment was halted, 56 patients received CC and 53 patients received C5V. The 1-year event-free survival was 37% for patients receiving CC and 57% for those receiving C5V ($P = .017$). Patients randomly assigned to CC required more blood product support. As a result of a semiannual review by the Children's Oncology Group Data and Safety Monitoring Committee, random assignment 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.

Conclusion
Intensification of therapy by alternating platinum analogs increased the risk of adverse outcome in children with unresectable or metastatic hepatoblastoma.

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INTRODUCTION

The addition of cisplatin in the mid-1980s by both the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) in treatment protocols has drastically improved the survival of children with hepatoblastoma.[1,2] The recently completed Intergroup Liver Tumor Study (INT-0098) demonstrated no differences in event-free (EFS) or overall survival between the two treatment regimens used (regimen A [C5V]: cisplatin + fluorouracil [FU] + vincristine; 5-year EFS, 57%; standard deviation [SD], 5%; regimen B [: cisplatin + doxorubicin; 5-year EFS, 69%; SD, 5%).[3] The doxorubicin-containing regimen proved more toxic; therefore,

regimen A was recommended for treatment. Although EFS of patients with unresectable disease showed a definite increase over previous studies, it remains unsatisfactory at approximately 50%. The survival of patients with metastatic disease remained poor (37%).[3] Ortega et al indicated that C5V should be considered the standard therapeutic approach for these patients.[3]

In neuroblastoma, the dose-intensity of agents has been shown to affect outcome.[4] Dose intensification of cisplatin in pediatric germ cell tumors significantly improved outcome, but toxicity was also dramatically increased.[5] POG 9345, a phase II study for advanced-stage hepatoblastoma demonstrated the efficacy of carboplatin for this disease.

Approximately 60% of patients had a tumor response to carboplatin as a single agent, and 82% demonstrated a response to carboplatin in combination with FU and vincristine.[6] Cisplatin is a highly active agent for the treatment of hepatoblastoma.

In a pilot study for CCG, Malogolowkin et al used carboplatin alternating with cisplatin every 2 weeks for the treatment of 13 patients with hepatoblastoma.[7] Ten patients were assessable for response after four courses of chemotherapy, two achieved a complete response (CR), and eight, a partial response (PR). Complete resection was achieved in four patients, and resection with microscopic residual disease was achieved in four patients. To date, nine patients are alive with no evidence of disease at follow-up of more than 60 months.[7] Therefore, we hypothesized that dose-intensification of therapy could be accomplished without unacceptable toxicity by alternating carboplatin and cisplatin.

To test this hypothesis, the POG and Children's Oncology Group (COG) undertook an intergroup study of all patients with newly diagnosed hepatoblastoma. Patients with stage III and IV disease who had demonstrated 3-year progression-free survival of approximately 50% when randomly assigned to C5V on INT-0098, were to be randomly assigned between the standard therapy (C5V) and a regimen consisting of alternating administration of carboplatin and cisplatin (CC).[3]

At the time the study was designed, there was evidence that amifostine, a cytoprotective agent, could ameliorate toxicities associated with cisplatin administration. These early observations were later verified with respect to hematologic toxicity in adults[8] and children.[9] We hypothesized that amifostine could provide protection against both hematologic and audiologic toxicities leaving unaffected the antitumor effect of the chemotherapy regimens employed. To test this hypothesis, we employed a second random assignment to receive or to not receive amifostine concomitant with each patient's randomly assigned chemotherapy regimen.

METHODS

Patients

The Pediatric Intergroup Hepatoblastoma Study P9645 was opened in March 1999. The study was designed as a factorial random assignment for patients with stage III or IV disease. The details of the study are described in Figure 1. Patients were eligible for study entry if they were younger than 21 years at diagnosis and had biopsy-proven previously untreated heptoblastoma. The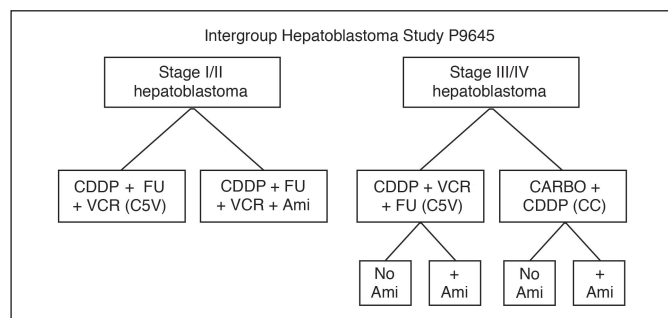 protocol required normal renal function as defined by serum creatinine within normal limits for age or glomerular filtration rate within normal limits for age if creatinine was not within normal limits. Random assignment to CC was suspended in January 2002. Subsequently all patients were assigned to received C5V. Patients enrolled up to December 2003 were considered in the preparation of this report. The protocol was approved by the National Cancer Institute, and prior to study entry, we obtained informed consent according to individual institutional review board requirements for participating POG- or CCG-affiliated institutions for all patients.

Stage of disease was determined by surgical criteria following the assessment of initial resectability as determined by the institutional surgeon in consultation with the treating oncologist, and after either a surgical resection or biopsy was performed before the initiation of chemotherapy: stage I, complete gross resection with clear margins; stage II, gross total resection with microscopic residual disease at the margins of resection; stage III, gross total resection with nodal involvement or tumor spill, or incomplete resection with gross residual intrahepatic disease; stage IV, metastatic disease with either complete or incomplete resection or biopsy. Central pathologic review of representative tissue slides was required for all patients enrolled onto the study with pure fetal tumors that were completely resected before the administration of chemotherapy. Staging was also confirmed by review of institutional pathology and surgical reports.

Treatment

Patients with stage I or II disease were assigned therapy and were not considered for the chemotherapy randomization. We report subsequently on patients with stage III or IV disease.

Patients were randomly assigned to receive C5V or CC with or without amifostine, as shown in Figure 1. Each course C5V consisted of intravenous (IV) CDDP (100 mg/m^2 or 3 mg/kg for patients < 1 year of age) administered over 4 hours followed by IV hydration on day 1 and vincristine (VCR; 1.5 mg/m^2, IV push) and FU (600 mg/m^2 IV push) on day 2. Each course of CC consisted of carboplatin at 700 mg/m^2 given IV over 1 hour (23 mg/kg for patients < 10 kg) on day 0 (560 mg/m^2 or 18.5 mg/kg for patients < 10 kg after two cycles) followed by cisplatin 100 mg/m^2 on day 14 administered as described above. Granulocyte colony-stimulating factor was used after each CC cycle. No modification of VCR or FU dosing was made on the basis of age or weight. Patients with a GFR less than 100 mL/min/1.73 m^2 were to have carboplatin dose calculated on the Calvert's formula to achieve an area under the curve of 6. Patients were re-evaluated at the end of the initial chemotherapy phase of four cycles. Patients with unresectable disease at that time were considered as treatment failures. If the patient had tumor resection at that time and residual disease was detected, the patient received two more cycles of the therapy to which she or he had been randomized. Each cycle of C5V was given at least 3 weeks apart, depending on recovery of peripheral neutrophil and platelet counts to $\geq$ 500 cells/μL and $\geq$ 75,000 cells/μL, respectively. Initial chemotherapy was delayed for at least 2 weeks for any patient in whom $\geq$ 50% of the liver was resected. Audiometry was to be performed before the initiation of therapy, after the fourth cycle and at completion of therapy.

Evaluation of Response

Physical examination, CBCs, serum alpha-fetoprotein (AFP) levels, and appropriate imaging studies, including computed tomography of the chest and abdomen, were performed before therapy. Subsequent examinations and AFP assays were done before every additional cycle of chemotherapy. AFP was to be monitored monthly for 6 months, then every 2 months until 2 years off therapy, then every 3 months until 4 years off therapy, then yearly subsequently. Imaging studies were repeated after cycles 2, 4, and 6, and then at 2, 4, 6, 12, 18, and 24 months off therapy. CR (no evidence of disease) was defined as no evidence of tumor by physical examination and computed tomography scans or magnetic resonance imaging of the liver, and a normal AFP level for at least 4 weeks. PR was defined as a decrease of $\geq$ 50% in the sum of the products of the maximum perpendicular diameters of all measurable lesions, with no evidence of new lesions or progression in any lesion. Stable disease was defined as any response less than a partial response, without an increase in tumor size and without appearance of new lesions. For purposes of this manuscript, residual disease was defined as either a partial response or stable disease. Progressive disease (PD) was defined as the unequivocal increase of at least

Fig 1. Intergroup Hepatoblastoma Study P9645. CDDP, cisplatin; FU, fluorouracil; VCR, vincristine; Ami, amifostine; C5V, CDDP + FU + VCR; CARBO, carboplatin; CC, CDDP + CARBO.

25% in the size of any lesion, the appearance of new lesions, or a 20% increase of AFP on two consecutive weekly measurements.

Toxicity of Treatment

The individual incidents of various toxicities were graded on a scale of 1 to 4, according to National Cancer Institute guidelines. Limits for toxicity grades were dependent on both patient age and the particular organ system involved; the specific toxicity scales employed in this study are available at the Web site http://ctep.cancer.gov/reporting/ctc.html.

Statistical Design and Analysis

Study design. Patients were randomized after initial surgical procedure, and randomization was stratified according to stage of disease. The study was planned to enroll patients for 5.5 years and follow the last patient for 3 years after enrollment. The projected patient enrollment rate, based on the previous COG study of newly diagnosed hepatoblastoma, was 65 patients per year. The primary outcome comparison between the two treatment regimens was risk for an adverse event. The equality of risk was to be assessed with a log-rank statistic stratified by stage of disease. We projected this design would have 80% power to detect a 1.7-fold decrease in risk for adverse events for stage III or IV when using a two-sided test of size .05. Interim monitoring was performed every six months after the 30th event was observed. The method of O'Brien and Fleming,[10] with a P value of .005 for the stratified log-rank test, was required to identify the study for possible termination of accrual.

Outcome definitions. EFS was defined as the period from the date chemotherapy was started until evidence of an event (progressive disease, death, diagnosis of a second malignant neoplasm) or last contact, whichever occurred first. Survival time was defined as the period from the date chemotherapy was started until death or last contact, whichever occurred first. A patient who died was considered to have experienced an event, regardless of the cause of death. Patients who did not experience an event were censored on the date of last contact.

Analytic methods. Statistical analysis was conducted with data current to December 2003. Life-table estimates were calculated by the method of Kaplan and Meier,[11] and the SD of the Kaplan-Meier estimate of the survivor function at selected points was calculated using Greenwood's formula.[12] Risk for adverse event and death was compared across therapies and groups of patients using the log-rank statistic. Estimates for relative risks and 95% CIs were calculated using a proportional hazards regression model with the relevant characteristic as the only variable and stratified as indicated.[12] Outcome analysis was based on the assigned randomized treatment (ie, even if the patient was treated with the other regimen, the patient's outcome was assigned to his or her original random assignment.)

RESULTS

One hundred ninety-two eligible patients with stage III or IV disease were enrolled onto this study as of December 2003. Seventy-six patients had experienced an adverse event at the time of the analysis. Seventy-two patients had disease progression as the first analytic event. Four patients died while on protocol therapy, without evidence of disease progression. One patient died of unexplained cardiopulmonary arrest, one patient died of postoperative complications, and two died of multiorgan failure; one of these was attributed to complications from infection.

A total of 56 eligible patients were randomly assigned to receive CC, and 53 were randomly assigned to receive C5V at the time the random assignment was halted. As a result of a semi-annual review by the COG Data and Safety Monitoring Committee, random assignment 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. The study was continued, with patients assigned to receive C5V and randomly as-

signed to receive amifostine according to Figure 1. We have included stage III or IV patients who were assigned to receive C5V up to the time of this analysis. As a result, the cohort of patients includes 136 patients assigned to receive C5V. The risk of an adverse event was not significantly different when patients randomly assigned to C5V before random assignment was stopped were compared with patients assigned to C5V after randomization was stopped (P = .78). Table 1 describes selected patient characteristics according to their randomized treatment assignment. Seventy-three percent of patients assigned to receive C5V had stage III disease, whereas 63% of patients assigned to receive CC had stage III disease (P = .21).

The 3-year EFS was 38% (90% CI, 27% to 49%) for CC patients and 60% (90% CI, 51% to 68%) for C5V (P = .025; Fig 2). The increased risk for adverse event was evident after accounting for amifostine randomization and stage of disease (Table 2). The 3-year survival was 56% (90% CI, 44% to 68%) for CC patients and 74% (90% CI, 64% to 84%) for C5V (P = .035).

Table 3 describes the most common toxicities associated with these regimens. The toxicity profiles for the two chemotherapy regimens were similar except patients randomized to CC experience higher rates of thrombocytopenia and requirements for transfusion of blood products. Ototoxicity, as described by the National Cancer Institute Common Toxicity Criteria (version 2), was similar when the two chemotherapy regimens were compared. For both regimens, the cumulative incidence of grade 3 or 4 ototoxicity was less than 8%.

DISCUSSION

The recently completed INT-0098 demonstrated no differences in EFS or overall survival between the two treatment regimens used (regimen A: cisplatin + FU + vincristine, and regimen B: cisplatin + doxorubicin).[3] Based on the results of this study, as well as other international studies,[13-15] which used cisplatin-based therapies, we concluded that cisplatin was a very active agent in therapies for hepatoblastoma. In other embryonal tumors such as neuroblastoma, the dose-intensity of agents has been shown to affect outcome.[4] Dose intensification of cisplatin in pediatric germ cell tumors significantly improved outcome, but toxicity was also dramatically increased.[5]

Carboplatin, an analog to cisplatin, is associated with less renal and ototoxicity and showed to be an efficacious agent when used as a

Table 1. Selected Patient Characteristics by Random Treatment Assignment

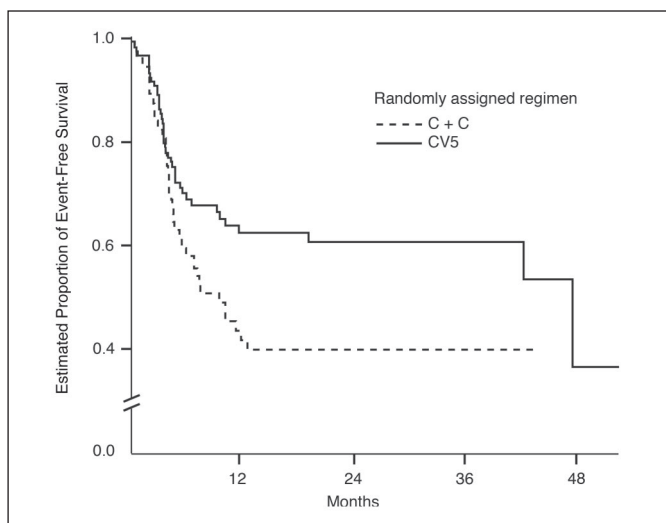| Characteristic	Carboplatin + Cisplatin		Cisplatin + Fluorouracil + Vincristine	
	No. of Patients	%	No. of Patients	%
Age at enrollment, years				
Median	1		1	
Range	0-12		0-14	
Sex				
Male	26	46.3	80	58.8
Female	30	53.6	56	41.2
Randomly assigned to amifostine				
Yes	28	50.0	67	49.3
No	28	50.0	69	50.7

Fig 2. Estimated proportion of patients surviving event-free according to randomized chemotherapy regimen (*P* = .025). C + C, cisplatin + carboplatin; C5V, cisplatin + fluorouracil + vincristine.

single agent in a phase II study for the treatment of advanced stage hepatoblastoma.[6] A pilot study of intensification of the platinum agent, by alternating carboplatin and cisplatin, in an attempt to maintain the intensity of therapy without the increased toxicity was conducted in patients with hepatoblastoma. This approach was efficacious and was associated with acceptable toxicity.[7] We therefore implemented the CC regimen from the pilot without modifying the guidelines for treatment modification and supportive care.

To prospectively test this platinum intensification approach, the COG conducted the P9645 study. In this study patients with advanced hepatoblastoma (stage III or IV) were randomly assigned between standard therapy (C5V) and a regimen consisting of CC. Patients were also randomized to receive or not to receive amifostine. There was no evidence of interaction between the use of amifostine and the randomized chemotherapy regimen on outcome as assessed by proportional hazards regression (Table 2).

The experimental arm with carboplatin alternating with cisplatin was associated with an increased risk for adverse events when compared with the C5V arm. The results of the C5V arm on P9645, however, were comparable with those of both regimens of INT-0098.[3]

A recent follow-up of the outcome of INT-0098[23] demonstrated that patients with disease progression after initial treatment with C5V can be successfully rescued with cisplatin, doxorubicin, and surgery. This strategy spares a significant number of very young patients exposure to the cardiotoxicity of anthracyclines. Other investigators used anthracycline-based chemotherapeutic regimens and obtained similar results. The German cooperative study HB94[16] utilized a three-drug combination of ifosfamide, cisplatin, and doxorubicin. Three-year EFS was 76% for patients with stage III disease and 21% for patients with stage IV disease. In the Japanese study for pediatric liver tumors, JPLT-1, conducted between 1991 and 1999, stage I and II patients received chemotherapy courses of cisplatin (40 mg/m^2) and tetrahydropyranyl-adriamycin (30 mg/m^2). For stage IIIA, IIIB, and IV patients, the doses of cisplatin and adriamycin were increased to 80 mg/m^2 and 30 mg/m^2, respectively, for 2 days. Overall survival and EFS for the entire cohort of 134 hepatoblastoma patients was 73% and 66%, respectively.[14] In the second study of the International Society of Pediatric Oncology (SIOPEL) the investigators used a risk-adapted treatment strategy that segregated patients according to the Pretreatment Extent of Disease (PRETEXT) staging system. Patients with high-risk disease received a chemotherapy regimen consisting of cisplatin alternating with carboplatin and doxorubicin. These patients are comparable with stage III and IV patients presented in this manuscript. The 3-year survival and progression-free survival for these patients were 53% and 48%, respectively.[17] Based on these results, we cannot identify the best cisplatin-containing regimen for initial therapy for advanced-stage hepatoblastoma.

This study illustrates the strength of randomized trials as a means to definitively evaluate evidence provided by pilot investigations. Randomized studies provide the most sound evidence for clinical decision making.[18,19] There are many examples in which the outcome of pilot studies were not replicated in subsequent randomized studies.[20] We developed the CC regimen based on inferences from our previous Intergroup study, INT-0098. We piloted this regimen to confirm that it could be delivered feasibly and the outcome was within acceptable limits before proceeding with a definitive randomized trial.

The use of carboplatin in the dose and schedule employed here, was inferior to the addition of vincristine and FU to cisplatin-based therapy. Our results, coupled with other recent observations[22] regarding carboplatin used in other combinations suggest that carboplatin is an inferior agent when compared with cisplatin for the treatment of

	Randomized Amifostine Assignment			Stage		
Randomized Chemotherapy Regimen	Yes	No	Stratified Relative Risk for Adverse Event	III	IV	Stratified Relative Risk for Adverse Event
C5V	1.0	1.0	1.0	1.0	1.0	1.0
CC	1.6	1.7	1.7*	1.8	1.2	1.8†
95% CI			1.1 to 2.6‡			1.1 to 3.0‡

Table 2. Risk for Adverse Event According to Randomized Chemotherapy Assignment Stratified by Random Amifostine Assignment

Abbreviations: C5V, cisplatin + fluorouracil + vincristine; CC, cisplatin + carboplatin.
*There is no evidence of interaction between randomized chemotherapy regimen and randomized amifostine assignment as assessed using proportional hazards regression (*P* = .96).
†There is no evidence of interaction between randomized chemotherapy regimen and randomized amifostine assignment as assessed using proportional hazards regression (*P* = .19).
‡From the stratified proportional hazards regression model.

Toxicity	Courses With Toxicity Present (CC)		Courses With Toxicity Present (C5V)		
	No.	%	No.	%	P
Grade 3 or 4					
Hemoglobin*	69	29	175	24	.15
Neutropenia*	104	44	314	48	.30
Grade 4 neutropenia†	55	23	214	32	< .01
Grade 3 or 4 thrombocytopenia*	68	29	31	4	< .01
Platelet transfusions required	36	15	25	3	< .01
Packed RBC transfusions required	78	33	146	20	< .01
Grade 3 or 4 proteinuria	0	0	0	0	.99
Grade 3 or 4 renal failure	0	0	0	0	.99

Table 3. Toxicity According to Treatment Regimen

Abbreviations: C5V, cisplatin + fluorouracil + vincristine; CC, cisplatin + carboplatin.
*Grade 3 or 4 toxicity: hemoglobin, less than 8 g/dL; neutropenia, less than $1,000/mm^3$; thrombocytopenia, less than $50,000/mm^3$.
†Grade 4 toxicity only: neutropenia-less than $500/mm^3$.

advanced-stage hepatoblastoma. Thus, attempts to intensify exposure to platinum by adding carboplatin to cisplatin is not a strategy that can be recommended.

Although patients randomized to the carboplatin alternating with cisplatin arm were at increased risk for adverse outcome, we cannot infer that intensification of therapy is an invalid approach for the treatment of advance stage hepatoblastoma. But it does raise the issue of how one should intensify therapy. With this study we chose to use a substitution to approach this problem by replacing FU and vincristine with carboplatin. Intensification of therapy by augmenting the dose of existing agents[4,5] or by interval compression[21] have demonstrated to be efficacious for the treatment other tumors. We therefore believe that exploration of intensification of therapy for advanced hepatoblastoma is still warranted, but that it should be done by the addition of effective agents, like doxorubicin to the standard regimen of cisplatin, FU, and vincristine.

REFERENCES

1. Ortega JA, Krailo MD, Haas JE, et al: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: A report from the Children's Cancer Study Group. J Clin Oncol 9:2167-2176, 1991

2. Douglass EC, Reynolds M, Finegold M, et al: Cisplatin, vincristine, and flourouracil therapy for hepatoblastoma: A Pediatric Oncology Group Study. J Clin Oncol 11:96-99, 1993

3. Ortega JA, Douglass EC, Feusner JH, et al: Randomized comparison of cisplatin/vincristine/flurorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 18:2665-2675, 2000

4. Cheung NV, Heller G: Chemotherapy dose intensity correlates strongly with response, median survival, and median progression-free survival in metastatic neuroblastoma. J Clin Oncol 9:1050-1058, 1991

5. Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: A pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691-2700, 2004

6. Katzenstein HM, London WB, Douglass EC, et al: Treatment of unresectable and metastatic hepatoblastoma: A Pediatric Oncology Group phase II study. J Clin Oncol 20:3438-3444, 2002

7. Ortega JA, Rios P, Malogolowkin, MH: Successful treatment of hepatoblastoma (HB) with an intensified platinum regimen. Proc Am Soc Clin Oncol 17:545a, 1998 (abstr 2091)

8. Kemp G, Rose P, Lurain J, et al: Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: Results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol 14:2101-2112, 1996

9. Borsi JD, Csaki C, Ferencz T, et al: Administration of ethyolyl (amifostine) to a child with medulloblastoma to ameliorate hematological toxicity of high dose carboplatin. Anticancer Drugs 7:121-126, 1996

10. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trial. Biometrics 35:549-556, 1979

11. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

12. Kalbfleisch JD, Prentice RL: The statistical analysis of failure time data. New York, NY, John Wiley and Sons, 1980

13. von Schweinitz D, Byrd DJ, Hecker H, et al: Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma: Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology. European J Can 33:1243-1249, 1997

14. Sasaki F, Matsunaga T, Iwafuchi M, et al: 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 Ped Surg 37:851-856, 2002

15. Ninane J, Perilongo G, Stalen JP: Effectiveness and toxicity of cisplatin and doxorubicin (PLADO) in childhood hepatoblastoma and hepatocellular carcinoma: A SIOP pilot study. Med Ped Oncol 19:199-203, 1991

16. Fuchs J, Rydzynski J, Von Schweinitz D, et al: Pretreatment prognostic factors and treatment results in children with hepatoblastoma: A report from the German Cooperative Pediatric Liver Tumor Study HB 94. Cancer 95:172-182, 2002

17. Perilongo G, Shafford E, Maibach R, et al: Risk-adapted treatment for childhood hepatoblastoma: Final report of the second study of the International Society of Paediatric Oncology—SIOPEL 2. Eur J Cancer 40:411-421, 2004

18. Brown B: The randomized clinical trial. Stat Med 3:307-311, 1984

19. Chalmers CT: The randomized clinical trial as a basis for therapeutic decisions in, The Randomized Clinical Trial as a Basis for Therapeutic Decisions. New York, NY, Marcel Dekker, 1982

20. Pinsky CM: Experience with historical control studies in cancer immunotherapy. Stat Med 3:325-329, 1984

21. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-1439, 2003

22. Dall'Igna P, Cecchetto G, Dominici C, et al: Carboplatin and doxorubicin (CARDOX) for nonmetastatic hepatoblastoma: A discouraging pilot study. Med Ped Oncol 36:332-334, 2001

23. Malogolowkin M, Katzenstein HM, Krailo M, et al: Outcome of patients with recurrent or progressive hepatoblastoma: A report of the intergroup liver tumor study INT-0098. Pediatr Blood Cancer 45:404, 2005 (abstr 083)

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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