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## ORIGINAL ARTICLE

# Cisplatin versus Cisplatin plus Doxorubicin for Standard-Risk Hepatoblastoma

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## ABSTRACT

**BACKGROUND**

Preoperative cisplatin alone may be as effective as cisplatin plus doxorubicin in standard-risk hepatoblastoma (a tumor involving three or fewer sectors of the liver that is associated with an alpha-fetoprotein level of >100 ng per milliliter).

**METHODS**

Children with standard-risk hepatoblastoma who were younger than 16 years of age were eligible for inclusion in the study. After they received one cycle of cisplatin (80 mg per square meter of body-surface area per 24 hours), we randomly assigned patients to receive cisplatin (every 14 days) or cisplatin plus doxorubicin administered in three preoperative cycles and two postoperative cycles. The primary outcome was the rate of complete resection, and the trial was powered to test the noninferiority of cisplatin alone (<10% difference in the rate of complete resection).

**RESULTS**

Between June 1998 and December 2006, 126 patients were randomly assigned to receive cisplatin and 129 were randomly assigned to receive cisplatin plus doxorubicin. The rate of complete resection was 95% in the cisplatin-alone group and 93% in the cisplatin–doxorubicin group in the intention-to-treat analysis (difference, 1.4%; 95% confidence interval [CI], –4.1 to 7.0); these rates were 99% and 95%, respectively, in the per-protocol analysis. Three-year event-free survival and overall survival were, respectively, 83% (95% CI, 77 to 90) and 95% (95% CI, 91 to 99) in the cisplatin group, and 85% (95% CI, 79 to 92) and 93% (95% CI, 88 to 98) in the cisplatin–doxorubicin group (median follow-up, 46 months). Acute grade 3 or 4 adverse events were more frequent with combination therapy (74.4% vs. 20.6%).

**CONCLUSIONS**

As compared with cisplatin plus doxorubicin, cisplatin monotherapy achieved similar rates of complete resection and survival among children with standard-risk hepatoblastoma. Doxorubicin can be safely omitted from the treatment of standard-risk hepatoblastoma. (ClinicalTrials.gov number, NCT00003912.)

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†The other members and institutions participating in the third study of the International Childhood Liver Tumour Strategy Group (SIOPEL 3) are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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**B**ETWEEN 1990 AND 1994, THE INTERNATIONAL Childhood Liver Tumour Strategy Group (SIOPEL) conducted its first cooperative trial (SIOPEL 1), which set the standard of care for hepatoblastoma in most European countries.<sup>1</sup> With a 5-year event-free survival of 66% and an overall survival of 75%, the trial duplicated the results obtained by other investigators, particularly in North America, during the same period.<sup>1-7</sup> SIOPEL 1 consisted of preoperative chemotherapy with a combination of cisplatin and doxorubicin followed by delayed surgery and further chemotherapy. Two pretreatment prognostic factors emerged from SIOPEL 1: intrahepatic tumor extension, as defined by a pretreatment tumor extension system (PRETEXT),<sup>8</sup> and lung metastases.<sup>9</sup> On the basis of these findings, two pretreatment risk groups of hepatoblastoma were identified. Standard-risk hepatoblastoma is a tumor confined to the liver and involving not more than three hepatic sectors. High-risk hepatoblastoma involves the entire liver; the portal vein, the right and left branches, or all three hepatic veins; or the inferior vena cava. High-risk hepatoblastoma may manifest with intraabdominal disease, metastases, or both.<sup>9,10</sup>

At the time SIOPEL 1 was closed, the data from a trial comparing an anthracycline-free regimen (cisplatin plus fluorouracil plus vincristine) with cisplatin-doxorubicin started to become available.<sup>6</sup> They showed that the anthracycline-free regimen resulted in a 3-year overall survival of 71% and a disease-free survival of 63%, with no statistical differences between the two groups and no cardiac toxicity in the anthracycline-free regimen. These findings prompted us to ask whether doxorubicin could be safely omitted, at least from the treatment of standard-risk hepatoblastoma, and whether cisplatin alone could be as effective as cisplatin plus doxorubicin. Consequently, we tested cisplatin alone in a pilot setting in 77 patients with standard-risk hepatoblastoma (SIOPEL 2) and found a response rate of 90% (95% confidence interval [CI], 80 to 96), a rate of complete resection of 97% (95% CI, 87 to 99), and a 3-year overall survival rate of 91% (95% CI, 84 to 98) and a progression-free survival rate of 89% (95% CI, 82 to 96).<sup>10</sup> On the basis of these encouraging results, we conducted the present prospective, randomized trial (SIOPEL 3) to compare the regimen of cisplatin plus doxorubicin with an experimental regimen of cisplatin alone in patients with standard-risk hepatoblastoma. The primary end point was the rate

of complete resection, and the secondary end points were 3-year overall survival and event-free survival and short-term toxicity.

## METHODS

### PATIENTS

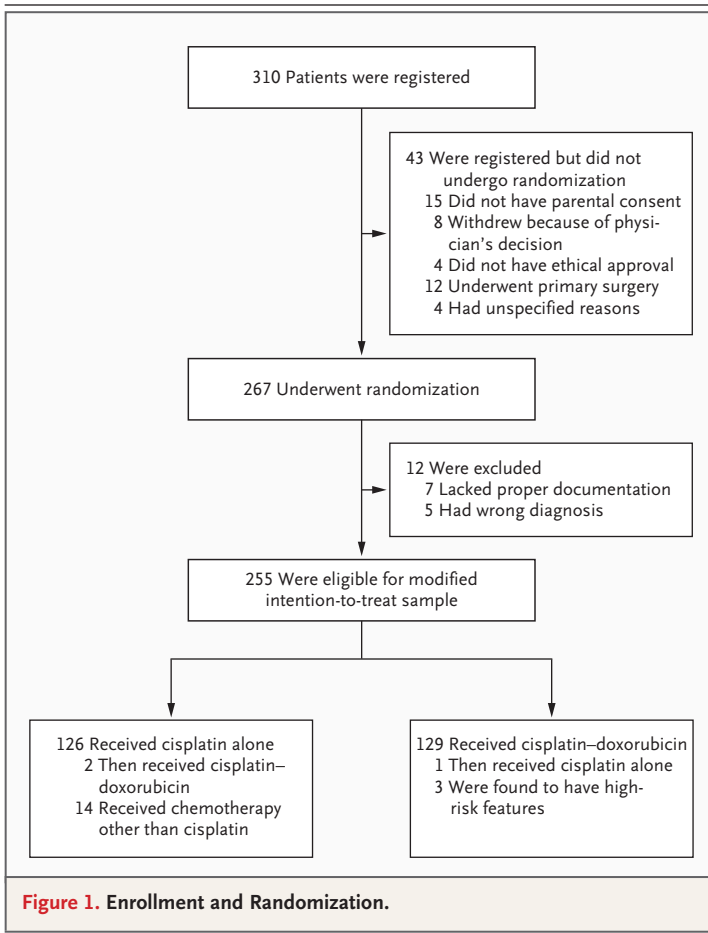
The SIOPEL 3 standard-risk hepatoblastoma trial was an international cooperative, prospective, randomized trial that was open for patient registration between June 1998 and December 2006. Children younger than 16 years of age who had a previously untreated hepatoblastoma with standard-risk features, defined as a tumor entirely confined to the liver and involving not more than three hepatic sectors,<sup>8-10</sup> were eligible for the trial. During the trial, the protocol was amended to exclude children presenting with hepatoblastoma and an alpha-fetoprotein level of less than 100 ng per milliliter, in view of mounting evidence of a poor outcome in these patients.<sup>11,12</sup> All participating centers were required to obtain written approval from their local research ethics committees and written informed consent from the parents or legal guardians of the patients.

### PRETREATMENT EVALUATION OF TUMOR EXTENSION

Tumor extension at diagnosis was assessed by abdominal ultrasonography and computed tomography (CT) with contrast medium, magnetic resonance imaging (MRI) with contrast enhancement, or both. Lung metastases were identified by chest CT. Tumor extension was graded with the use of the PRETEXT system (on a scale of I to IV, with higher grades indicating tumor involvement in more sectors of the liver)<sup>8</sup> (Fig. 1A in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients with a PRETEXT I, II, or III hepatoblastoma and no evidence of extrahepatic disease were eligible for the trial. In doubtful or borderline cases of risk assignment, participating centers could request a central review of radiologic images; replies were provided within 48 hours. Risk classification was confirmed in all 51 cases sent for central consultation. Central review of the histologic slides derived from tumor-biopsy specimens, resection, or both confirmed the histologic findings in all 175 cases submitted.

### DIAGNOSIS AND STUDY DESIGN

Diagnostic biopsy was mandatory in children younger than 6 months of age because of the wide



differential diagnosis of hepatic masses and the possible confounding effect of an “elevated” serum alpha-fetoprotein level at this age and in children older than 3 years because of the risk of misdiagnosing hepatocellular carcinoma. In the case of unequivocal clinical findings (e.g., a solid hepatic mass and an elevated alpha-fetoprotein level), the decision to perform a diagnostic biopsy in children between 6 months and 3 years of age was left to the individual center. If no biopsy was performed, hepatoblastoma-compatible images and an elevated alpha-fetoprotein level were mandatory for randomization.

Within 7 days after the diagnosis of hepatoblastoma, patients received a single cycle of cisplatin while awaiting risk assignment (standard risk or high risk). We adopted this strategy to avoid delaying therapy. Within 15 days after receiving a definitive diagnosis, patients were randomly assigned to the cisplatin or cisplatin–doxorubicin group (Fig. 1B in the Supplementary Appendix).

The initial cisplatin cycle (80 mg per square meter of body-surface area per 24 hours) was administered in a continuous intravenous 24-hour infusion. Subsequently, in the cisplatin group, cisplatin cycles (at the same dose) were administered at 14-day intervals. In the cisplatin–doxorubicin group, cisplatin–doxorubicin cycles were administered at 21-day intervals. Each cycle of cisplatin plus doxorubicin consisted of cisplatin on day 1, administered as described above, and doxorubicin at a dose of 30 mg per square meter of body-surface area per day, administered as a continuous intravenous 24-hour infusion on days 2 and 3. Four cycles of cisplatin (in the cisplatin group) or one cycle of cisplatin and three cycles of cisplatin plus doxorubicin (in the cisplatin–doxorubicin group) had to be administered before delayed surgery (preoperative chemotherapy).

The tumor response was assessed after four cycles of cisplatin (in the cisplatin group) or after one cycle of cisplatin and three cycles of cisplatin plus doxorubicin (in the cisplatin–doxorubicin group). If the tumor was considered to be resectable, radical surgery was attempted (delayed surgery). Patients with complete resection were scheduled to receive two more cycles of cisplatin or cisplatin plus doxorubicin. If, after the first four cycles of chemotherapy, the tumor had responded somewhat but was still considered to be unresectable, two more cycles were to be given before surgery, but none afterward. Thus, each patient was scheduled to receive a maximum of six cycles of cisplatin or one cycle of cisplatin and five cycles of cisplatin plus doxorubicin. The chemotherapy regimen was purposely designed to be flexible in order to take all possible clinical situations into account. We evaluated the tumor response on the basis of abdominal ultrasound, CT, or MRI findings using the same criteria we used in previous SIOPEL studies.<sup>1,10</sup> Detailed guidelines for adjustment of the drug dosage to the patient’s weight (if <10 kg) and in relationship to hematologic and organ toxicity were provided in the study protocol. The use of granulocyte colony-stimulating factor was not recommended. A system for monitoring serious adverse events was implemented.

#### Randomization Procedures

The United Kingdom Children’s Cancer Study Group Data Centre was the trial office. Participating institutions sent a prerandomization form

to the trial office to request randomization. Subsequently, eligible patients were randomly assigned to one of the two treatment groups by the minimization method, and the results were communicated to the participating center.

#### Outcome Definition

Complete resection was defined as resection of all tumor sites on the basis of surgical findings and on postsurgical images. Event-free survival was defined as the interval between diagnosis and disease progression, relapse, or death, whichever occurred first, and overall survival was defined as the interval between diagnosis and death from any cause or last contact. Patients who were alive at the last contact were excluded on that date. Severe acute toxicity was defined as the rate of grade 3 or 4 infection, stomatitis, febrile neutropenia, or all of these events, according to the National Cancer Institute Common Toxicity Criteria.

#### STATISTICAL ANALYSIS

The study design was based on a test of noninferiority of cisplatin as compared with cisplatin plus doxorubicin for the primary end point (the rate of complete resection after preoperative chemotherapy). The protocol stated that cisplatin would be considered to be noninferior to cisplatin plus doxorubicin if the rate of complete resection was not decreased by more than 10 percentage points from the 90 percentage points expected with cisplatin plus doxorubicin. This 10% margin was used for interim monitoring. Given the rarity of this tumor and the expected yearly recruitment of 30 to 35 patients, it was recognized that a tighter noninferiority margin could not be planned. A two-sided 95% confidence interval was chosen for the final evaluation of the primary end point. The sample size was estimated at 250 patients to test noninferiority with a one-sided, two-sample difference-in-proportions test for the comparison of the rates of complete resection, with an error rate fixed at 5% for incorrectly accepting noninferiority and a power of 80%. This sample size yields a two-sided 95% confidence interval with 60% power to exclude a 10% difference. To avoid a potential bias introduced by nonprotocol chemotherapy administered before surgery, a per-protocol analysis was performed in addition to the intention-to-treat analysis.<sup>13</sup> Toxicity rates were compared by means of odds ratios and 95% confidence intervals. Kaplan-Meier survival estimates were compared with the

**Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.**

Variable	Cisplatin (N=126)	Cisplatin plus Doxorubicin (N=129)	Total (N=255)
Sex (no.)			
Female	49	51	100
Male	77	78	155
Age (mo)			
Median	12	15	13.5
Range	0–134	0.2–133.0	0–134
PRETEXT stage (no.)			
I	9	9	18
II	64	69	133
III	53	51	104
Alpha-fetoprotein (no.)*			
<100 ng/ml	0	1	1
100–1,000,000 ng/ml	116	114	230
>1,000,000 ng/ml	9	13	22

\* Alpha-fetoprotein levels in two patients were not known.

use of the log-rank test.<sup>14</sup> SAS software, version 9.1, was used for all evaluations.

Interim results were evaluated yearly and were submitted in an unblinded fashion to an independent data and safety monitoring committee consisting of three pediatric oncologists and one statistician who were not involved in the trial. The independent data and safety monitoring committee endorsed continuation of the trial at all interim evaluations. A group-sequential approach involving a Lan-DeMets alpha-spending function with O'Brien-Fleming-type boundaries was used to calculate adjusted significance levels for five comparisons of the primary end point.

The SIOPEL 3 trial committee independently designed the study under the chairmanship of one of the authors. The United Kingdom Children's Cancer Study Group Data Centre collected the data. The study biostatistician performed the analyses. Finally, the trial committee, led by one of the authors, wrote the first and the final drafts of the manuscript.

## RESULTS

#### PATIENTS

Between June 1998 and December 2006, a total of 92 institutions from 24 countries randomly as-

**Table 2. Efficacy Measures, According to Treatment Group.**

Outcome	Cisplatin (N=126)	Cisplatin plus Doxorubicin (N=129)	Hazard Ratio (95% CI)	P Value
Partial response — no. (% [95% CI])	114 (90.5 [84 to 95])	122 (94.6 [89 to 98])		
Stable disease — no. (%)	5 (4.0)	3 (2.3)		
Progressive disease — no. (%)	6 (4.8)	1 (0.8)		
Not documented — no. (%)	1 (0.8)	3 (2.3)		
Complete resection — no. (% [95% CI])*	120 (95.2 [90 to 98])	121 (93.8 [88 to 97])		
Relapse or disease progression — no. (%)	19 (15.1)	15 (11.6)	0.81 (0.42 to 1.54)	0.52
Death — no. (%)	7 (5.6)	8 (6.2)	1.14 (0.42 to 3.2)	0.79
Overall survival at 3 yr — % (95% CI)	95 (91 to 99)	93 (88 to 89)		
Event-free survival at 3 yr — % (95% CI)	83 (77 to 90)	85 (79 to 92)		

\* The difference in the complete resection rate between the cisplatin group and the cisplatin–doxorubicin group was 1.4 (95% CI, –4.1 to 7.0).

signed 267 patients (Fig. 1). Of these patients, five patients were excluded because the diagnosis was revised locally soon after the initial diagnosis (nodular hyperplasia in one patient, hamartoma in one patient, and a benign lesion not otherwise specified in three patients). Seven patients were excluded because they lacked proper documentation. The modified intention-to-treat sample consisted of the 255 patients considered to be eligible and evaluable (126 patients in the cisplatin group and 129 in the cisplatin–doxorubicin group). The database was locked on August 20, 2008. The characteristics of the study population are summarized in Table 1. The diagnosis was based on biopsy findings in 172 patients and on unequivocal clinical findings, as per-protocol guidelines, in the remaining 83. The diagnosis was confirmed at surgery in all patients who received a diagnosis based on unequivocal clinical findings.

#### TREATMENT OUTCOMES

The response rate was 90% in the cisplatin group and 95% in the cisplatin–doxorubicin group (Table 2), and the rate of complete resection was 95% and 93%, respectively. The intention-to-treat analysis showed the noninferiority of cisplatin by a margin of 10%: the rate of complete resection in the cisplatin group minus the rate of complete resection in the cisplatin–doxorubicin group was 1.4% (95% CI, –4.1 to 7.0). We also carried out a per-protocol analysis after the exclusion of 20 patients (16 randomly assigned to cisplatin and 4 randomly assigned to cisplatin plus doxorubicin) be-

cause of presurgical therapy that was not in the protocol or categorization as high risk (Fig. 1). The rates of complete resection were 99% with cisplatin and 95% with cisplatin plus doxorubicin, with a difference of 3.9% (95% CI, –0.3 to 8.1). The 3-year overall survival rates were 95% with cisplatin versus 93% with cisplatin plus doxorubicin, and the event-free survival rates were 83% with cisplatin versus 85% with cisplatin plus doxorubicin (median follow-up time, 46 months) (Table 2 and Fig. 2).

#### DISEASE PROGRESSION, RELAPSE, AND DEATH

A total of 34 randomly assigned patients had a documented relapse or disease progression: 19 in the cisplatin group (15%) and 15 in the cisplatin–doxorubicin group (12%) (Table 2). Seven patients in the cisplatin group and eight in the cisplatin–doxorubicin group died. One death in the cisplatin group and two deaths in the cisplatin–doxorubicin group were due to surgical complications. Neither the risk of relapse nor the risk of death differed between the two groups. Of the 19 patients with relapse or disease progression in the cisplatin group, 13 had local progression and 6 had metastases. Of the latter six patients, five were alive with no evidence of disease (duration of follow-up, 18 months to 7.5 years; median, 5.5 years). Of the 15 patients treated with cisplatin plus doxorubicin who had a relapse, 9 had local progression and 6 had metastases. At the last observation, four of these six patients were alive without evidence of disease (duration of follow-up, 4 months to 6 years; median, 16 months).

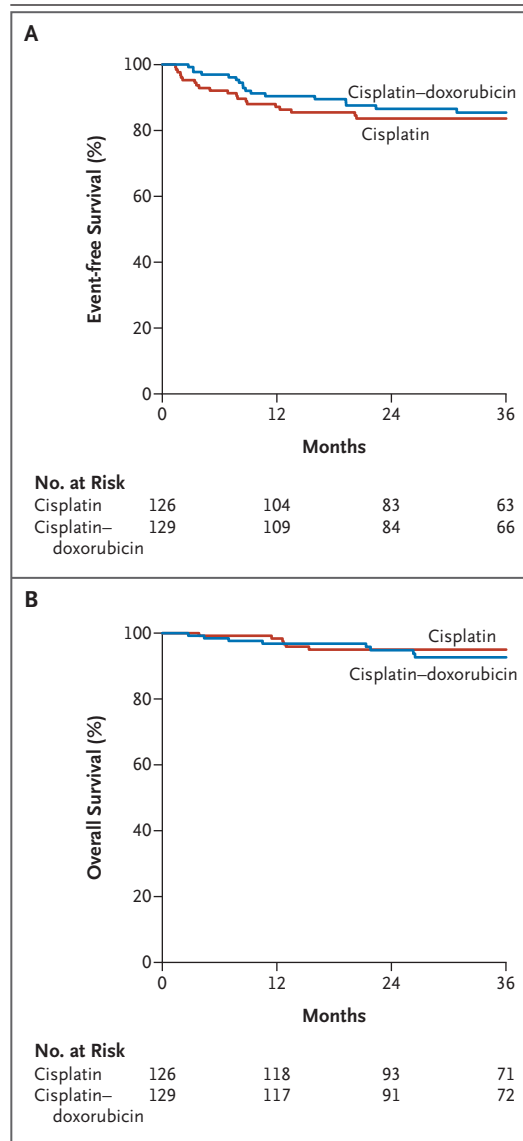
## ADVERSE EVENTS

The median number of cycles of preoperative chemotherapy in both groups was four as per protocol (three to six cycles in the cisplatin group and one to six cycles in the cisplatin-doxorubicin group), and the median number of postoperative cycles was two in both groups, as planned (zero to three cycles in the cisplatin group and zero to four cycles in the cisplatin-doxorubicin group). Four patients received seven cycles, and one patient received eight cycles. Table 3 summarizes the toxic events in each treatment group. Hearing loss was evaluated according to the criteria of Brock et al.<sup>15</sup> (on the basis of institutional reporting). Acute grade 3 or 4 adverse events were more frequent in the cisplatin-doxorubicin group than in the cisplatin-only group (74.4% vs. 20.6%). At least one hearing test was obtained during follow-up in 168 patients. Some hearing loss was documented in 32% of the patients tested (53 of 168). No differences in ototoxicity or nephrotoxicity were detected between the two groups.

Among the 80 patients in the cisplatin-doxorubicin group with at least one evaluation during follow-up, 1 had a left ventricular shortening fraction of less than 28% and 4 others had values between 29% and 30%. Of the 44 patients in the cisplatin group for whom a shortening fraction value was available during follow-up, 1 had a shortening fraction of less than 28% (at diagnosis it was 35%), but he received two cycles of doxorubicin postoperatively; 4 patients had shortening fraction values between 29% and 30%. Given these small numbers, a longer follow-up is needed to assess impairment of cardiac function accurately.

## DISCUSSION

The SIOPEL 3 trial demonstrates the noninferiority of the rate of complete resection observed in a cohort of patients with standard-risk hepatoblastoma treated with cisplatin alone as compared with cisplatin-doxorubicin. The rate of complete resection was chosen as the primary study end point, first because it allowed us to obtain meaningful data regarding the treatment of a very rare tumor in a reasonable time frame and second, and more importantly, because complete resection is the universally accepted, single most important prognostic factor for long-term overall survival and event-free survival in childhood hepatoblastoma.<sup>1-7,9-11</sup> Strict noninferiority in the sense of a



**Figure 2. Outcomes in Patients with Standard-Risk Hepatoblastoma Who Received Cisplatin Alone versus Cisplatin plus Doxorubicin.**

Panel A shows Kaplan-Meier curves for event-free survival, and Panel B shows Kaplan-Meier curves for overall survival.

clinically acceptable marginal difference could not be statistically proved because of the limited number of patients. Nevertheless, we were able to rule out, with 97.5% probability, a reduction of more than 4.1% in the rate of complete resection in the cisplatin group in the intention-to-treat analysis. In addition, the similar rates of 3-year overall survival (95% and 93%) and event-free survival (83% and 85%) in the cisplatin and cisplatin-doxorubi-

**Table 3. Adverse Events, According to Treatment Group.**

Variable	Cycles		Patients		Odds Ratio (95% CI)
	Cisplatin (N=727)	Cisplatin plus Doxorubicin (N=746)	Cisplatin (N=126)	Cisplatin plus Doxorubicin (N=129)	
	<i>number (%)</i>				
<b>Acute toxic effects</b>					
Grade 3 or 4 febrile neutropenia	12 (1.7)	158 (21.2)	7 (5.6)	82 (63.6)	9.1 (4.4–18.7)
Grade 3 or 4 infection	32 (4.4)	92 (12.3)	24 (19.0)	58 (45.0)	2.0 (1.4–2.9)
Grade 3 or 4 mucositis	2 (0.3)	31 (4.2)	2 (1.6)	20 (15.5)	5.9 (1.6–22.1)
Severe toxic effects (any of above)	40 (5.5)	204 (27.3)	26 (20.6)	96 (74.4)	3.5 (2.5–5.0)
<b>Cycles administered at reduced dose</b>					
Cisplatin	24 (3.3)	34 (4.6)			
Doxorubicin		44 (5.9)			
Cycle delays	54 (7.4)*	145 (19.4)†	38 (30.2)	79 (61.2)	
<b>Toxic effects during follow-up</b>					
Ototoxicity according to Brock et al. <sup>15</sup> — no./total no. (%)					
Grade 0			62/89 (69.6)	53/79 (67.1)	
Grade 1			9/89 (10.1)	11/79 (13.9)	
Grade 2			13/89 (14.6)	8/79 (10.1)	
Grade 3			2/89 (2.2)	5/79 (6.3)	
Grade 4			3/89 (3.4)	2/79 (2.5)	
Glomerular filtration rate — no./total no. (%)					
<60 ml/min/1.73 m <sup>2</sup>			3/80 (3.7)	3/71 (4.2)	
60–79 ml/min/1.73 m <sup>2</sup>			19/80 (23.7)	5/71 (7.0)	
≥80 ml/min/1.73 m <sup>2</sup>			58/80 (72.5)	63/71 (88.7)	
Subnormal magnesium level — no./total no. (%)					
			22/99 (22.2)	18/96 (18.7)	
Left ventricular shortening fraction — no./total no. (%)					
≤28%			1/44 (2.3)‡	1/80 (1.2)	
29 to <30%			4/44 (9.1)	4/80 (5.0)	
30%			39/44 (88.6)	75/80 (93.7)	

\* The median number of days in the cycle was 6 (range, 2 to 29).

† The median number of days in the cycle was 7 (range, 1 to 39).

‡ This patient received doxorubicin on an off-protocol basis.

cin groups, respectively, provide support for the noninferiority of cisplatin as compared with cisplatin–doxorubicin and bode well for the definitive cure of children with standard-risk hepatoblastoma.

We cannot compare our rate of complete resection and data on overall survival and event-free survival with those of other trials because of differences in risk stratification among studies.

The results of SIOPEL 3 are very encouraging. It has long been known that surgery has an excellent success rate in children with hepatoblastoma and that hepatoblastomas are very sensitive to cisplatin. However, the SIOPEL 3 trial shows that a selected group of patients with hepatoblastoma can be cured with a strategy consisting of cisplatin monotherapy administered preoperatively and postoperatively.



As predicted, cisplatin alone had significantly less hematologic toxicity than cisplatin plus doxorubicin and was equally as ototoxic and nephrotoxic. The every-14-day schedule of cisplatin administration in the cisplatin-alone group was feasible and accompanied by minimal hematologic toxicity and acceptable ototoxicity and nephrotoxicity. Four patients in the cisplatin group had a moderate reduction of the shortening fraction. A longer follow-up is needed to understand the real significance of this finding.

Therapeutic strategies consisting of primary surgery and three to four cycles of adjuvant multiagent, cisplatin-based chemotherapy have also resulted in excellent outcomes in patients with limited-extension hepatoblastoma.<sup>3,6</sup> In Intergroup Trial 0098, patients with hepatoblastoma who underwent a complete microscopic and macroscopic surgical excision (both stage I unfavorable histologic features and stage II) had a 5-year event-free survival of 91% and 100%, respectively, with four cycles of either cisplatin-doxorubicin or cisplatin plus fluorouracil plus vincristine.<sup>6</sup> Even more striking, the few hepatoblastomas with pure fetal histologic features and low mitotic rate seem to be curable with surgery alone.<sup>16</sup> However, emerging evidence indicates that small-cell undifferentiated

histologic features may have a negative impact on survival, regardless of tumor extension.<sup>16,17</sup> Therefore, the conceptualization of future clinical trials should take into account the data from all available trials to refine the appropriate therapy for subgroups of patients with limited-extension hepatoblastoma and to properly balance efficacy and long-term toxicity.

In summary, the SIOPEL 3 standard-risk hepatoblastoma trial demonstrates that a simple, moderately toxic, easy-to-administer monotherapy regimen with cisplatin is not inferior to the combination of cisplatin and doxorubicin in patients with accurately staged standard-risk hepatoblastoma in terms of the rate of complete resection, but it is, as predicted, less toxic.

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No potential conflict of interest relevant to this article was reported.

This article is dedicated to Dr. Jon Pritchard, who died on January 20, 2007. He was one of the founders of the SIOPEL group and a key figure in its leadership, and he inspired the fundamental concepts of this trial.

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