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Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

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Abstract

BACKGROUND—Cisplatin chemotherapy and surgery are effective treatments for children with standardrisk hepatoblastoma but may cause considerable and irreversible hearing loss. This trial compared cisplatin with cisplatin plus delayed administration of sodium thiosulfate, aiming to reduce the incidence and severity of cisplatin-related ototoxic effects without jeopardizing overall and event-free survival.

METHODS—We randomly assigned children older than 1 month and younger than 18 years of age who had standard-risk hepatoblastoma (≥3 involved liver sectors, no metastatic disease, and an alpha-fetoprotein level of >100 ng per milliliter) to receive cisplatin alone (at a dose of 80 mg per square meter of body-surface area, administered over a period of 6 hours) or cisplatin plus

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sodium thiosulfate (at a dose of 20 g per square meter, administered intravenously over a 15-minute period, 6 hours after the discontinuation of cisplatin) for four preoperative and two postoperative courses. The primary end point was the absolute hearing threshold, as measured by pure-tone audiometry, at a minimum age of 3.5 years. Hearing loss was assessed according to the Brock grade (on a scale from 0 to 4, with higher grades indicating greater hearing loss). The main secondary end points were overall survival and event-free survival at 3 years.

RESULTS—A total of 109 children were randomly assigned to receive cisplatin plus sodium thiosulfate (57 children) or cisplatin alone (52) and could be evaluated. Sodium thiosulfate was associated with few high-grade toxic effects. The absolute hearing threshold was assessed in 101 children. Hearing loss of grade 1 or higher occurred in 18 of 55 children (33%) in the cisplatin-sodium thiosulfate group, as compared with 29 of 46 (63%) in the cisplatin-alone group, indicating a 48% lower incidence of hearing loss in the cisplatin-sodium thiosulfate group (relative risk, 0.52; 95% confidence interval [CI], 0.33 to 0.81; P=0.002). At a median of 52 months of follow-up, the 3-year rates of event-free survival were 82% (95% CI, 69 to 90) in the cisplatin-sodium thiosulfate group and 79% (95% CI, 65 to 88) in the cisplatin-alone group, and the 3-year rates of overall survival were 98% (95% CI, 88 to 100) and 92% (95% CI, 81 to 97), respectively.

CONCLUSIONS—The addition of sodium thiosulfate, administered 6 hours after cisplatin chemotherapy, resulted in a lower incidence of cisplatin-induced hearing loss among children with standard-risk hepatoblastoma, without jeopardizing overall or event-free survival. (Funded by Cancer Research UK and others; SIOPEL 6 ClinicalTrials.gov number, NCT00652132; EudraCT number, 2007–002402-21.)

Hepatoblastoma is a rare primary liver cancer with an age-adjusted incidence of 0.13 patients per 100,000 population.[1] Hepatoblastoma can be categorized as standard-risk or high-risk disease according to the serum alpha-fetoprotein level in addition to the results of the revised Pretreatment Extent of Disease (PRETEXT) assessment, which includes metastatic disease.[2–4] The combination of cisplatin monotherapy and surgery is the standard of care for children with standard-risk disease and results in good long-term survival.[5] However, hearing loss constitutes a serious and permanent side effect of cisplatin chemotherapy; even mild hearing loss may severely affect learning, development, and quality of life in young children.[6–8] Key consonants are heard at high frequencies (4 kHz through 8 kHz), and so their loss is debilitating, particularly in young children in whom speech has not yet developed (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[9] Brock grading is used to distinguish among hearing-loss levels defined as minimal, mild, moderate, marked, or severe (grades 0 to 4, respectively) and has a low false positive rate as compared with other ototoxicity grading systems.[10,11] In previous studies conducted by the International Liver Tumor Strategy Group (SIOPEL), more than 60% of the children in whom hearing levels were assessed by pure-tone audiometry had permanent high-frequency hearing loss of Brock grade 1 or higher, affecting the frequencies of 8 kHz and below.[12] The question was whether the risk of hearing loss could be reduced by the introduction of an otoprotectant.

Nonclinical studies and initial phase 1–2 trials indicated that sodium thiosulfate has a potential otoprotective effect, with maximum efficacy occurring when sodium thiosulfate is administered 4 to 8 hours after cisplatin,[13–20] and that the potential tumor-protective effect

could be managed.[21,22] Pharmacokinetic data and further analysis showed that 6 hours was a safe timing for the delayed administration of sodium thiosulfate in order to avoid tumor protection.[23,24] Since children with standard-risk hepatoblastoma can be treated with cisplatin alone, they represent an appropriate group in which to explore otoprotection with the delayed administration of sodium thiosulfate. Hence, this randomized, phase 3 trial, SIOPEL 6, was designed to investigate the question of whether delayed administration of sodium thiosulfate would reduce the incidence and severity of hearing loss caused by cisplatin.

METHODS

PATIENTS

We conducted this international, cooperative, prospective, randomized trial over a period of 7 years. The trial data were blinded for the audiology central reviewer. Children younger than 18 years of age who had standard-risk hepatoblastoma that had not been treated previously were eligible. Written approval from local research ethics committees was obtained, and written informed consent was provided by all the parents or legal guardians.

PRETREATMENT EVALUATION OF TUMOR EXTENT

The intrahepatic extent of tumor at diagnosis was assessed by means of ultrasonography of the abdomen as well as by computed tomography (CT) or magnetic resonance imaging with the use of contrast material. Lung metastases were identified on CT of the chest. Tumor extent was graded according to the PRETEXT system (on a scale of I to IV, with higher scores indicating increased extent of the disease in the liver) (see the Supplementary Appendix). Children with PRETEXT I, II, or III hepatoblastoma and with no evidence of extrahepatic disease were eligible.[2,5]

TRIAL DESIGN, DATA COLLECTION, AND ANALYSIS

The main trial was designed in line with previous SIOPEL trials by the first two authors and the last author. Platinum-DNA adduct studies were designed and carried out by one of the authors at the Northern Institute for Cancer Research, Newcastle University.

A diagnosis of hepatoblastoma on the basis of histologic testing, imaging, and an elevated serum alpha-fetoprotein level confirming standard-risk hepatoblastoma were required before randomization to the cisplatin group or the cisplatin-sodium thiosulfate group. Cisplatin was administered at a dose of 80 mg per square meter of body-surface area in a continuous intravenous 6-hour infusion for four preoperative and two postoperative courses at 14-day intervals, with or without the administration of sodium thiosulfate. Tumor response was assessed after two and four courses of therapy. Sodium thio-sulfate at a dose of 20 g per square meter was administered intravenously, over a period of 15 minutes, 6 hours after the end of the cisplatin infusion. This dose was chosen to achieve maximum peak serum levels and effective otoprotection on the basis of studies involving children with central nervous system tumors.[16]

Radical surgery was attempted after four courses or, if the tumor was considered to be unresectable, postponed until the end of treatment. The trial design is shown in Figure S1 in the Supplementary Appendix. Detailed guidelines regarding the adjustment of the cisplatin and sodium thiosulfate doses in children weighing less than 10 kg and regarding hematologic and organ toxic effects were provided in the protocol (available at NEJM.org), as were guidelines for stopping sodium thiosulfate and introducing doxorubicin in the case of progressive disease. Sodium thiosulfate was supplied free of charge by Fennec Pharmaceuticals, which had no role in the design of the trial, the collection or analysis of the data, or the writing of the manuscript.

Data were collected by means of a Web-based electronic clinical research form that was designed and monitored by the authors in collaboration with Consorzio Interuniversitario (CINECA) under the responsibility of the national principal investigators. The authors vouch for the accuracy and completeness of the data and analyses and affirm that the trial was conducted with adherence to the protocol. The first draft of the manuscript was written by the first author, and the SIOPEL 6 trial committee made the decision to submit the manuscript for publication. No commercial support for the trial was obtained, and no one who is not an author contributed to the manuscript. This academic trial was conducted and charity-funded in each country under the responsibility of the national principal investigator.

Adverse events were documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Serious adverse events were defined in accordance with the harmonized tripartite guidelines for Good Clinical Practice.

ASSESSMENTS

Audiologic assessments by means of pure-tone audiometry were performed before and throughout treatment when possible and were performed in all the children who were alive at 3.5 years of age or older. Audiograms were uploaded, centrally reviewed by one of the authors, and graded on the Brock scale (grades 0 to 4) because the trial was developed before the 2010 International Society of Pediatric Oncology Boston consensus ototoxicity grading scale was designed.[25] A Brock grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades of 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively.[10] The grade was determined according to the hearing level in the child's better ear.

The primary end point in this trial was the absolute hearing threshold, as measured by pure-tone audiometry, at a minimum age of 3.5 years. Secondary end points were the response to preoperative chemotherapy, complete resection, complete remission, event-free survival, overall survival, toxic effects, long-term renal clearance or glomerular filtration rate, and the feasibility of central audiologic review.

Renal function was monitored at baseline, throughout treatment, and at follow-up by measurement of the glomerular filtration rate. When possible, this was done by radioisotope (^{51}Cr-EDTA) or iohexol methods[26,27] or, alternatively, was estimated from the serum creatinine level. At diagnosis, a glomerular filtration rate of less than 75% of the lower limit

of the normal range for age (<60 ml per minute per 1.73 m^2 in children >2 years of age) was an exclusion criterion. The serum sodium level and blood pressure were monitored before, during, and after the administration of sodium thiosulfate.

The response criteria for the trial were the following: complete response (no evidence of disease and a normal serum alpha-fetoprotein value for age); partial response (any tumor-volume shrinkage and a decreased serum alpha-fetoprotein level of >1 log below the original measurement); stable disease (no tumor-volume change and a decrease of <1 log in the serum alpha-fetoprotein level); and progressive disease (unequivocal increase in the tumor in ⩾1 dimensions or any unequivocal increase in the serum alpha-fetoprotein level [three successive determinations at intervals of 1 to 2 weeks], even without clinical [physical or radiologic] evidence of tumor regrowth). Complete resection was the total macroscopic removal of tumor. Total hepatectomy followed by liver transplantation was considered as complete resection and not treatment failure.[28] Tumor removal with microscopic residual disease, confirmed on histopathological testing but not on imaging, was considered as complete resection.[29] Disease status was determined at the end-of-treatment visit after the postsurgery chemotherapy and was defined as complete remission (no evidence of tumor on imaging), partial remission (residual tumor or an alpha-fetoprotein level above the age-standardized upper limit of the normal range), progressive disease (as defined above), or death. Relapse was defined as recurrent tumor detected on imaging and a serial elevation in the serum alpha-fetoprotein level (⩾3 consecutive rising values at a minimum of weekly intervals) or as recurrent tumor detected on imaging, with a normal serum alpha-fetoprotein level, and histologically confirmed on biopsy.

Platinum-DNA adduct levels were measured in whole-blood samples (5 to 10 ml) that were obtained before cisplatin treatment and 24 hours after the start of a 6-hour cisplatin infusion. Adduct levels were assessed by inductively coupled plasma mass-spectrometry analysis in peripheral-blood lymphocytes, as described previously.[30,31]

STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a difference of 25 percentage points in the rate of the primary end point of hearing loss of grade 1 or higher (a 60% rate of hearing loss in the cisplatin-alone group vs. a 35% rate of hearing loss in the cisplatin-sodium thiosulfate group) with the use of a chi-square test at a significance level of 5%. We used an early-stopping rule for efficacy with O'Brien-Fleming boundaries[32] and interim analyses involving 34 children and 68 children who could be evaluated. The test statistic for the final analysis was adjusted for interim looks and conducted at an alpha level of 0.045, with an estimated sample of 102 children who could be evaluated. A stratified Cochran-Mantel-Haenszel test was also performed with adjustment for the stratification factors of age at randomization (⩾15 months vs. >15 months), tumor extent (PRETEXT score of I or II vs. III),[4] and country.

Overall survival was calculated from the time of randomization to death or last follow-up. Event-free survival was calculated from the time of randomization until disease progression, disease relapse, second primary cancer, death, or last follow-up, whichever came first. The final evaluation was conducted once all surviving children had reached the age of 3.5 years.

RESULTS

PATIENTS

From 2007 through 2014, a total of 116 children were enrolled at 52 centers in 12 countries. A total of 113 children underwent randomization; 4 children were found to be ineligible, so the intention-to-treat population included 109 children. A total of 101 children could be evaluated for the primary end point (Fig. S2 in the Supplementary Appendix). The characteristics of the patients were well balanced in the two groups (Table 1).

PRIMARY END POINT AND SECONDARY END POINT OF FEASIBILITY

Figure 1 shows the centrally reviewed Brock grading with pure-tone audiometry that was performed in children at a minimum age of 3.5 years. Final audiometry was performed at a median of 3 years (range, 3 months to 6.9 years) after randomization. The primary end point of any hearing loss (defined as grade 1, 2, 3, or 4) could be assessed in 101 children. A total of 5 children died before the definitive hearing assessment, definitive audiometry was not feasible for health reasons in 2 children, and the parents of 1 child declined further follow-up.

Hearing loss occurred in 18 of 55 children (33%; 95% confidence interval [CI], 21 to 47) who could be evaluated in the cisplatin-sodium thiosulfate group, as compared with 29 of 46 (63%; 95% CI, 48 to 77) in the cisplatin-alone group (P=0.002 by the chi-square test). The relative risk of any hearing loss with cisplatin-sodium thiosulfate treatment was 0.52 (95% CI, 0.33 to 0.81), which translates to a 48% lower risk with cisplatin-sodium thiosulfate than with cisplatin alone. A stratified Cochran-Mantel-Haenszel test that was adjusted for the stratification factors of age at randomization (⩾15 months vs. >15 months), tumor extent (PRETEXT score of I or II vs. III),[4] and country resulted in a P value of 0.002 (which was lower than the protocol-specified significance level of 0.045).

Central review of the results of pure-tone audiometry was feasible as long as the high frequencies up to 8 kHz had been measured. In several cases, repeat audiograms measuring the high-frequency range had to be requested.

EFFICACY

Results regarding the centrally reviewed response to chemotherapy at two and four cycles, surgeries performed, and status at the end-of-treatment visit and at last follow-up are presented in Table 2. A total of 6 children died: 2 children in the cisplatin-sodium thiosulfate group and 4 in the cisplatin-alone group (1 child in the cisplatin-alone group had PRETEXT III disease and the other 5 children had PRETEXT I or II disease) (see the Supplementary Appendix). During or after treatment, 11 of 57 children in the cisplatin-sodium thiosulfate group and 10 of 52 in the cisplatin-alone group had progressive disease (6 and 8 children, respectively), relapse (3 and 0), or both (2 and 2).

The median follow-up of the patients was 52 months. The 3-year data regarding overall survival and event-free survival were similar to those previously reported[5] and are shown in Figure 2. The 3-year rate of overall survival was 98% (95% CI, 88 to 100) among children in

the cisplatin-sodium thiosulfate group and 92% (95% CI, 81 to 97) among those in the cisplatin-alone group. The corresponding 3-year rates of event-free survival were 82% (95% CI, 69 to 90) and 79% (95% CI, 65 to 88).

TREATMENT-RELATED ADVERSE EVENTS

Adverse-event data for all 109 children who could be evaluated and the numbers of children with adverse events of grade 3 or 4 are presented in Table 3. The maximum grade of targeted events over all cycles is reported according to treatment group.

A total of 68 serious adverse events were reported (including 16 serious adverse reactions). One unexpected serious adverse reaction was reported in a child in whom metabolic acidosis developed during the third infusion of sodium thiosulfate. The sodium thiosulfate infusion was stopped, the child recovered rapidly with fluid resuscitation, and no further sodium thiosulfate was administered in subsequent cycles. The child was alive and free from disease 52 months after randomization, but grade 4 hearing loss has developed. No reason could be found for the sudden deterioration in the child's general condition, so the event was considered by the investigators to be related to sodium thiosulfate. Of the 16 serious adverse reactions, 8 were coded by the investigator as being possibly, probably, or definitely related to sodium thiosulfate, including grade 3 infections in two children, grade 3 neutropenia in two children, grade 3 anemia leading to transfusion in one child, and tumor progression in two children. In one child, grade 2 nausea and vomiting were reported, and the parents declined further sodium thiosulfate after cycle 2.

RENAL FUNCTION

Four children (two in each group) had an end-of-treatment or follow-up assessment in which the glomerular filtration rate was less than 60 ml per minute per 1.73 m^2. The glomerular filtration rate decreased similarly from baseline to follow-up in the two groups, by a median of 12 ml per minute per 1.73 m^2 in the cisplatin-sodium thiosulfate group and 6 ml per minute per 1.73 m^2 in the cisplatin-alone group.

ADDITIONAL TREATMENT

A total of 21 children (12 children in the cisplatin-sodium thiosulfate group and 9 in the cisplatin-alone group) received additional doxorubicin. Doxorubicin was administered in 9 children for progressive disease (4 children in the cisplatin-sodium thiosulfate group and 5 in the cisplatin-alone group) and in 12 for other reasons, mainly at the request of the surgeon. In no patient did the addition of doxorubicin reduce the size of the tumor further.

PLATINUM-DNA ADDUCTS

Blood samples were obtained from 36 children, including 24 children (67%) in the cisplatin-sodium thiosulfate group and 12 (33%) in the cisplatin-alone group. Platinum-DNA adduct levels ranged from 4.3 to 166 nmol per gram of DNA. No correlations were observed between platinum-DNA adduct levels and outcome in terms of hearing loss, response, or event-free or overall survival. Figure S3 in the Supplementary Appendix shows the relationship between plati-num-DNA adduct level and hearing loss.

DISCUSSION

In this trial, the addition of delayed sodium thiosulfate to cisplatin led to a 48% lower risk of hearing loss. Hearing loss of grade 1 or higher occurred in 63% of the children who did not receive otoprotection, as compared with 33% of those who did. The administration of sodium thiosulfate was associated with a trend toward reduced ototoxicity in all the Brock grades. Children with hearing of grade 0 may not have completely normal hearing but can manage life with little or no additional help. Children with hearing loss of grade 1 or higher typically receive further intervention with each increasing grade of hearing loss, with children with any grade of hearing loss receiving educational support. In the United Kingdom, young children with hearing loss of grade 1 and all children with hearing loss of grade 2 or 3 are offered hearing aids. Children with hearing loss of grade 4 are offered cochlear implants. Similar reductions in the incidence and severity of cisplatin-induced ototoxic effects were reported with the delayed administration of sodium thiosulfate in the ACCL0431 trial.[34,35] The effect of high-frequency hearing loss and hearing support varies across the world, the reasons for which are multifactorial but include the variation in sound frequencies that are used in different languages. The analysis of these variables was beyond the scope of this trial.

In this trial, progressive tumor developed in the same number of children in each group. There was no significant difference in the rates of event-free survival or overall survival between the two groups.

The incidence of acute adverse events was as expected,[5,36] and an unexpected reaction developed in one child. Neither hypertension nor a high serum sodium level resulted in the discontinuation of sodium thiosulfate treatment in any of the children. The otoprotective dose of sodium thiosulfate was associated with a high sodium load, which is a factor to consider in planning treatment. Sodium thiosulfate was emetogenic despite the use of prophylactic antiemetic agents, with nausea and vomiting being common adverse events. Sodium thiosulfate did not alter the use of 24-hour hydration after the administration of cisplatin. Renal function was acceptable in these young children, with four children having a glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 at the end of treatment or follow-up.[26,37] The initiation of sodium thiosulfate after a 6-hour delay from the completion of cisplatin administration caused no tumor protection and did not adversely affect disease outcome.

Platinum-DNA adduct formation as measured in peripheral-blood lymphocytes showed no correlation between adduct levels and outcome in terms of hearing loss or clinical response. This finding confirms results from previous studies suggesting that the quantification of platinum-DNA adduct levels in peripheral-blood lymphocytes does not provide a useful biomarker of patients' response or platinum-induced toxic effects because of a lack of correlation between adduct levels in lymphocytes and those in tumor and other host tissues.[30,38,39] Recent evidence suggests that cisplatin-induced ototoxic effects are associated with long-term retention of cisplatin, specific to the cochlea.[40]

In conclusion, in this randomized, phase 3 trial involving children with localized hepatoblastoma who were undergoing chemotherapy with cisplatin alone or cisplatin plus sodium thiosulfate, we found that the delayed administration of sodium thiosulfate resulted in a significantly lower incidence of cisplatin-induced hearing loss, with no evidence of tumor protection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Hiyama reports receiving drugs provided by Fennec Pharma. Dr. Neuwelt reports receiving grant support from Fennec, holding pending patents (U.S. patent numbers, 11/273,723 and 15/284,950), licensed to Fennec Pharmaceuticals, on the administration of a thiol-based chemoprotectant compound, and holding patents (U.S. patent numbers, 7,022,315; 1328253; 60118172; and 2001253919), licensed to Fennec Pharmaceuticals, on the administration of a thiol-based chemoprotectant compound; he has divested himself of all financial interest regarding these patents. No other potential conflict of interest relevant to this article was reported.

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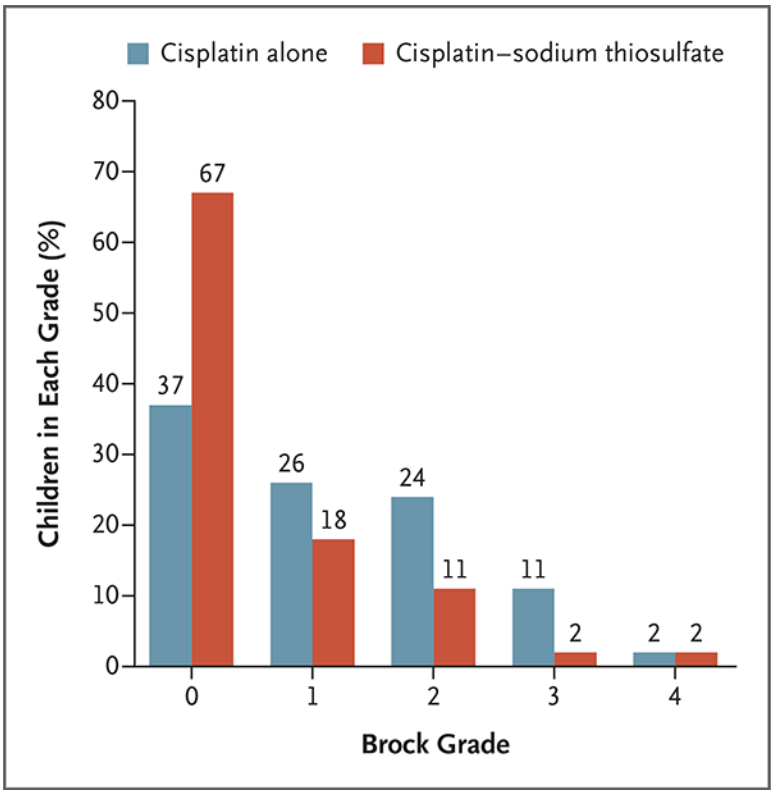

Figure 1. Hearing Level among 101 Children Who Could Be Evaluated.

A Brock grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively.[10] The grade was determined according to the hearing level in the child's better ear. The numbers of children with each Brock grade are provided in Table S2 in the Supplementary Appendix.

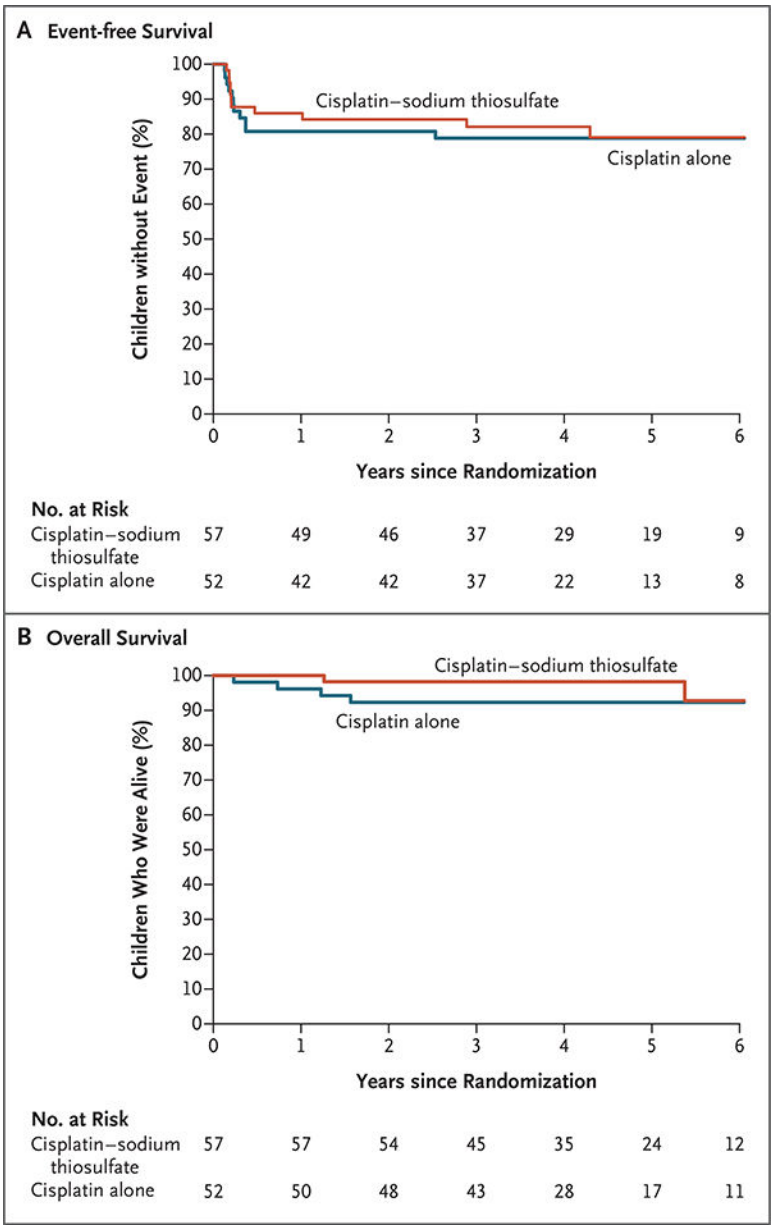

Figure 2.
Event-free Survival and Overall Survival.

Table 1.

Demographic and Clinical Characteristics of the Children at Baseline.*

Characteristic	Cisplatin Alone (N = 52)	Cisplatin-Sodium Thiosulfate (N = 57)
Age — mo		
Median	13.4	12.8
Range	3.0–70.2	1.2–98.6
Male sex — no. (%)	29 (56)	30 (53)
Alpha-fetoprotein level — ng/ml		
Median	73,760	154,638
Range	187–2,175,690	273–4,536,500
PRETEXT score — no. (%)†		
I or II	31 (60)	41 (72)
III	21 (40)	16 (28)

*Cisplatin was administered at a dose of 80 mg per square meter of body-surface area in a 6-hour intravenous infusion. Sodium thiosulfate was administered at a dose of 20 g per square meter in a 15-minute intravenous infusion 6 hours after cisplatin was stopped. There were no significant differences between the groups in any of the above characteristics.

†Tumor extent was assessed with the use of the Pretreatment Extent of Disease (PRETEXT) system. Scores range from I to IV, with higher scores indicating increased extent of the disease in the liver. Children with a score of IV were not included in this trial.

Table 2.

Status after Preoperative Chemotherapy.*

Response	Cisplatin Alone (N = 52)	Cisplatin-Sodium Thiosulfate (N = 57)
	no. of patients (%)	
Response after two cycles		
Partial response	28 (54)	23 (40)
Stable disease	24 (46)	34 (60)
Response after four cycles		
Partial response	39 (75)	38 (67)
Stable disease	5 (10)	11 (19)
Progressive disease	5 (10)	5 (9)
Not evaluated†	3 (6)	3 (5)
Resection after preoperative chemotherapy		
Partial hepatectomy	48 (92)	53 (93)
Liver transplantation	4 (8)	4 (7)
Status at end of treatment		
Complete remission	44 (85)	52 (91)
Partial remission	4 (8)	5 (9)
Progressive disease	2 (4)	0
Died	1 (2)	0
Not evaluated	1 (2)	0
Status at last follow-up		
Complete remission	48 (92)	55 (96)
Partial remission	0	0
Recurrent disease	0	0
Died‡	4 (8)	2 (4)

*The response criteria are explained in the Methods section. Doxorubicin may have been administered in cases of progressive disease (or for other reasons, such as a surgeon's request). A total of 21 children received 1 to 6 courses of doxorubicin during initial therapy, including 9 children in the cisplatin-alone group (who received a total of 30 courses) and 12 in the cisplatin-sodium thiosulfate group (who received a total of 28 courses).

†In the cisplatin-alone group, response in two children was not evaluated after four cycles, and treatment in one child was switched to a dose-dense regimen, on the basis of the International Liver Tumor Strategy Group (SIOPEL) 4 study,[33] at the request of the surgeon. In the cisplatin-sodium thiosulfate group, two children had a response that had been sufficiently good for them to undergo surgery after three cycles, which made them unable to be evaluated for chemotherapy response after four cycles, and response was not evaluated in one child after four cycles.

‡The deaths in the cisplatin-alone group were due to surgical complications (in one child), due to cardiac arrest after treatment with paclitaxel after progression (in one), and due to disease (in two). The two deaths in the cisplatin-sodium thiosulfate group were due to disease.

Table 3.

Children with Grade 3 or 4 Adverse Events.*

Adverse Event and Grade	Cisplatin Alone (N = 52)	Cisplatin-Sodium Thiosulfate (N = 57)
	no. of patients (%)	
Allergy, grade 3	1 (2)	0
Febrile neutropenia, grade 3	10 (19)	8 (14)
Infection, grade 3	16 (31)	13 (23)
Hypomagnesemia, grade 3	1 (2)	1 (2)
Hypernatremia, grade 3	0	1 (2)
Vomiting, grade 3	2 (4)	4 (7)
Nausea, grade 3	3 (6)	2 (4)
Left ventricular systolic dysfunction, grade 3 or 4	0	0
Renal event, grade 3 or 4	0	0
Anemia		
Grade 3	8 (15)	10 (18)
Grade 4	0	1 (2)
Leukopenia, grade 3	2 (4)	2 (4)
Neutropenia		
Grade 3	3 (6)	7 (12)
Grade 4	3 (6)	3 (5)
Thrombocytopenia		
Grade 3	1 (2)	1 (2)
Grade 4	1 (2	1 (2)
Gastrointestinal event	2 (4)	3 (5)
Elevated liver-enzyme level		
Grade 3	6 (12)	3 (5)
Grade 4	0	1 (2)
Elevated serum glucose level, grade 3	2 (4)	1 (2)
Hypermagnesemia, grade 3†	2 (4)	5 (9)
Hypophosphatemia, grade 3	0	5 (9)
Hyperkalemia, grade 3	2 (4)	0
Hypokalemia		
Grade 3	0	4 (7)
Grade 4	0	1 (2)
Dyspnea, grade 3	1 (2)	0

*If grade 4 is not shown, there was no grade 4 adverse event. This table includes adverse events that were associated with additional treatment (mostly doxorubicin) given to children in each group.

†The protocol specified the addition of magnesium to the hydration fluid administered with cisplatin therapy.