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Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial

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Summary

Background Sodium thiosulfate is an antioxidant shown in preclinical studies in animals to prevent cisplatin-induced hearing loss with timed administration after cisplatin without compromising the antitumour efficacy of cisplatin. The primary aim of this study was to assess sodium thiosulfate for prevention of cisplatin-induced hearing loss in children and adolescents.

Methods ACCL0431 was a multicentre, randomised, open-label, phase 3 trial that enrolled participants at 38 participating Children's Oncology Group hospitals in the USA and Canada. Eligible participants aged 1–18 years with newly diagnosed cancer and normal audiometry were randomly assigned (1:1) to receive sodium thiosulfate or observation (control group) in addition to their planned cisplatin-containing chemotherapy regimen, using permuted blocks of four. Randomisation was initially stratified by age and duration of cisplatin infusion. Stratification by previous cranial irradiation was added later as a protocol amendment. The allocation sequence was computer-generated centrally and concealed to all personnel. Participants received sodium thiosulfate 16 g/m² intravenously 6 h after each cisplatin dose or observation. The primary endpoint was incidence of hearing loss 4 weeks after final cisplatin dose. Hearing was measured using standard audiometry and reviewed centrally by audiologists masked to allocation using American Speech-Language-Hearing Association criteria but treatment was not masked for participants or clinicians. Analysis of the primary endpoint was by modified intention to treat, which included all randomly assigned patients irrespective of treatment received but restricted to those assessable for hearing loss. Enrolment is complete and this report represents the final analysis. This trial is registered with ClinicalTrials.gov, number NCT00716976.

Findings Between June 23, 2008, and Sept 28, 2012, 125 eligible participants were randomly assigned to either sodium thiosulfate (n=61) or observation (n=64). Of these, 104 participants were assessable for the primary endpoint (sodium thiosulfate, n=49; control, n=55). Hearing loss was identified in 14 (28·6%; 95% CI 16·6–43·3) participants in the sodium thiosulfate group compared with 31 (56·4%; 42·3–69·7) in the control group (p=0·00022). Adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the sodium thiosulfate group compared with the control group (odds ratio 0·31, 95% CI 0·13–0·73; p=0·0036). The most common grade 3–4 haematological adverse events reported, irrespective of attribution, were neutropenia (117 [66%] of 177 participant cycles in the sodium thiosulfate group vs 145 [65%] of 223 in the control group), whereas the most common non-haematological adverse event was hypokalaemia (25 [17%] of 147 vs 22 [12%] of 187). Of 194 serious adverse events reported in 26 participants who had received sodium thiosulfate, none were deemed probably or definitely related to sodium thiosulfate; the most common serious adverse event was decreased neutrophil count: 26 episodes in 14 participants.

Interpretation Sodium thiosulfate protects against cisplatin-induced hearing loss in children and is not associated with serious adverse events attributed to its use. Further research is needed to define the appropriate role for sodium thiosulfate among emerging otoprotection strategies.

Funding US National Cancer Institute.

Introduction

Cisplatin is an effective chemotherapeutic drug for treatment of many human cancers.[1] In paediatric oncology, cisplatin is a standard component of chemotherapy regimens for neuroblastoma, hepatoblastoma, medulloblastoma, osteosarcoma, malignant germ cell tumour, and nasopharyngeal carcinoma. More than 2000 children aged 1–15 years receive cisplatin annually in the USA alone.[2]

Unfortunately, cisplatin causes clinically significant cisplatin-induced hearing loss, which is characterised as progressive, irreversible, bilateral, and often accompanied by tinnitus.[3] Cisplatin-induced hearing loss affects all hearing frequencies through the progressive death of

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Research in context

Evidence before this study

Cisplatin is widely used for treatment of paediatric malignancies but often causes permanent sensorineural hearing loss and tinnitus resulting in functional disability and poor quality of life in survivors of childhood and adolescent cancer. Historically, cisplatin dose reduction, deletion, and delay have been the only options for ameliorating cisplatin-induced hearing loss. We searched the MEDLINE database for peer-reviewed reports of clinical trials published in any language between Jan 1, 2005, and Dec 31, 2015, using the search terms "ototoxicity", "hearing loss", "cisplatin", "carboplatin", "otoprotection", "amifostine", and "sodium thiosulfate". When the ACCL0431 trial was conceived, two randomised studies of amifostine found no evidence of protection against cisplatin-induced hearing loss. Sodium thiosulfate had been shown in preclinical studies to prevent cisplatin-induced hearing loss and in adults to prevent hearing loss caused by high-dose intra-arterial carboplatin given for brain tumours. Among children, sodium thiosulfate was found to be well tolerated when given for the same purpose. These findings formed the basis for developing ACCL0431, a randomised clinical trial done by the Children's Oncology Group, with the primary aim of determining whether sodium thiosulfate, compared with observation, prevented cisplatin-induced hearing loss in children receiving cisplatin for treatment of newly-diagnosed cancer. While ACCL0431 was in progress, the Childhood Liver Tumours Strategy Group launched SIOPEL-6, a randomised controlled trial to study sodium thiosulfate for preventing cisplatin-induced hearing loss in children with standard-risk hepatoblastoma; additionally, one comparative cohort study of double-dose amifostine was published that showed evidence of protection against cisplatin-induced hearing loss in children treated for medulloblastoma.

Added value of this study

To our knowledge, ACCL0431 is the first cooperative oncology group-sponsored, multicentre randomised controlled trial focused solely on prevention of cisplatin-induced hearing loss in children and adolescents treated for cancer with various disease-specific chemotherapy regimens. Our findings establish that sodium thiosulfate significantly reduces the incidence of cisplatin-induced hearing loss in children and adolescents. This benefit seems to be greatest in children younger than 5 years, who are most susceptible to cisplatin-induced hearing loss. We found no apparent effect on event-free survival or overall survival related to sodium thiosulfate in participants with localised disease, but in participants with disseminated disease overall survival was significantly lower.

Implications of all the available evidence

To our knowledge, sodium thiosulfate is the first proven drug tested under the conditions of this trial to reduce risk for cisplatin-induced hearing loss, thus representing an important development in translational otoprotection research. At the same time, the significantly lower overall survival seen in participants with disseminated disease who received sodium thiosulfate compared with those patients who did not necessitates caution when considering a future role for sodium thiosulfate. Recommendations for clinical practice and research will be further informed by the results of the ongoing SIOPEL-6 study involving only participants with standard-risk hepatoblastoma given a protocol-specified regimen of single-drug cisplatin. Additional research and thoughtful consideration is needed to understand what role sodium thiosulfate and other potential drugs should have in preventing cisplatin-induced hearing loss in specific subsets of at-risk patients.

cochlear outer hair cells mediated by cisplatin-induced cytosolic reactive oxygen species in the mitochondria.[4] About 40% of children receiving cisplatin develop cisplatin-induced hearing loss, but the incidence approaches 100% in specific subsets.[5–7] Risk factors for developing cisplatin-induced hearing loss include younger age (<5 years), higher cumulative cisplatin dose (>200–400 mg/m²), and cranial irradiation involving the cochlea.[3,8] The functional effect of even mild cisplatin-induced hearing loss for children and adolescents is substantial with many long-term implications, including impaired language acquisition, learning, academic performance, social–emotional development, and quality of life.[7,9] For young adults, tinnitus with or without cisplatin-induced hearing loss is a common, continuous, and annoying form of long-term cisplatin ototoxicity.[10]

Consequently, researchers, clinicians, parents, and cancer survivors are interested in the identification of otoprotectants that prevent cisplatin-induced hearing loss while preserving chemotherapeutic efficacy. One potential otoprotectant is sodium thiosulfate. Sodium thiosulfate is a thiol-containing antioxidant that is rapidly excreted by the kidneys after intravenous administration.[11] Sodium thiosulfate is approved by the US Food and Drug Administration for treatment of cyanide poisoning.[11] Biochemical effects of sodium thiosulfate relevant to its otoprotective potential include inactivation of oxygen free-radicals and electrophilic platinum species.[12–14] Animal studies[14,15] have shown that sodium thiosulfate prevents cisplatin-induced ototoxicity. In both animal model and cell culture systems, concurrent administration of sodium thiosulfate abrogates cisplatin cytotoxicity, which raises potential concern for tumour protection. However, preclinical testing[15,16] showed that when sodium thiosulfate administration is delayed until 4–8 h after cisplatin treatment, otoprotection can be retained without compromising cytotoxicity. Building on initial observations, clinical studies[17,18] in adults with brain tumours receiving an ototoxic regimen of high-dose intra-arterial carboplatin with blood–brain barrier disruption reported that similarly

delayed administration of sodium thiosulfate protected hearing. This combined regimen was well tolerated when given to 12 children aged between 17 months and 12 years.[19]

On the basis of this collective experience and studies suggesting sodium thiosulfate might prevent cisplatin-induced renal and haematological toxicity,[20] we developed ACCL0431, a multicentre, phase 3, randomised clinical trial sponsored by the Children's Oncology Group (COG) for children and adolescents with newly diagnosed cancer. The primary aim was to compare the proportional incidence of post-treatment cisplatin-induced hearing loss between participants randomly assigned to receive or not receive sodium thiosulfate.

Methods

Study design and participants

ACCL0431 was a multicentre, randomised, open-label, phase 3 trial. We enrolled participants at 38 participating COG hospitals in the USA and Canada (appendix p 3). We obtained written informed consent or assent from participants or their legal guardians before registration. The study was approved by the US National Cancer Institute (NCI) Central Institutional Review Board and site institutional review boards. The protocol is available in the appendix. Co-enrolment onto a companion observational cohort study of ototoxicity grading scales was mandatory (ACCL05C1; NCT00458887).

Participants were aged 1–18 years at study entry and were newly diagnosed with hepatoblastoma, germ cell tumour, medulloblastoma or CNS primitive neuro-ectodermal tumour, neuroblastoma, osteosarcoma, or other cancer types treated with cisplatin. Key eligibility criteria included planned cumulative cisplatin dose of 200 mg/m² or more and infusion duration of 6 h or less; performance score of 50 or more by the Karnofsky (>16 years) or Lansky (≤16 years) scales; no previous cisplatin or carboplatin treatment; no known thiol hypersensitivity; and normal institutional laboratory values reflecting haematological, renal, and hepatic function. Normal hearing was required before enrolment as defined by hearing thresholds of 20 dB hearing level (HL) or less at 500–8000 Hz when measured with earphones or 25 dB HL or less when measured in the sound field, or as defined by brainstem auditory evoked response thresholds equivalent to behavioural thresholds of 20 dB HL or less. Previous cranial irradiation was initially not allowed but later permitted, provided hearing was normal, by a protocol amendment (March 31, 2010) to augment trial recruitment. Patients were not eligible if they were registered on a cancer-directed COG therapeutic study to avoid potential confounding of the primary aims by the ACCL0431 randomisation.

Randomisation and masking

We enrolled and randomly assigned participants to either sodium thiosulfate or observation (control group) up to 5 days before they received any cisplatin. We generated the allocation sequence for each stratum according to a permuted block algorithm, where each block of four contained two sodium thiosulfate and two control randomisations. The randomisation was centrally computer-generated by the COG trial management system. Allocation was electronically concealed to all investigators, clinicians, and participants. Site research staff did the enrolment, entering eligibility confirmation and specification of stratification factors into the COG trial management system, and receiving the electronically generated allocation for the site. Randomisation was 1:1 and was initially stratified into four groups defined by age (<5 years or ≥5 years) and duration of cisplatin infusion (<2 h or ≥2 h). Later, we added one separate stratum for eligible participants who had previously received cranial irradiation, irrespective of age or duration of cisplatin infusion. Randomisation was masked for central reviewers of audiometry data, but was not placebo-controlled for participants or treating clinicians to minimise complexity and cost for participating sites.

Procedures

Cisplatin was to be administered as specified by each participant's cancer treatment plan. For participants randomly assigned to the control group, the cisplatin-containing treatment regimen alone was to be administered. Participants in the sodium thiosulfate group received sodium thiosulfate daily over 15 min beginning 6 h after the completion of each cisplatin dose. This sodium thiosulfate schedule was selected on the basis of preclinical studies that showed combined otoprotection and non-interference with cisplatin chemotherapeutic effect when sodium thiosulfate was delayed until 4–8 h post-cisplatin.[15,16] The protocol-specified sodium thiosulfate dose was 16 g/m² (533 mg/kg where the cisplatin dose was calculated by bodyweight) administered as a 12·5% solution. This sodium thiosulfate dose was selected because it was within the published effective dose range and was well tolerated by children.[14–19] For participants receiving multiday cisplatin regimens, a documented serum sodium concentration of less than 145 mEq/L was required before each sodium thiosulfate dose, and a minimum of 10 h was to have elapsed between sodium thiosulfate and the next cisplatin dose. Otherwise, no modifications of dose or administration of sodium thiosulfate or other chemotherapy drugs were to be made. Protocol guidelines for supportive care during the sodium thiosulfate infusion included routine administration of antiemetics, limited blood pressure monitoring, and, if applicable, administration of low-dose meperidine to manage infusion-related rigors. Concurrent use of other ototoxic drugs (eg, amino-glycosides and loop diuretics) was discouraged by protocol for all participants but captured in data reporting. Cisplatin dose modifications were not

See **Online** for appendix

captured as participants did not receive cancer treatment according to specified protocols.

Hearing assessments were to be done at baseline, up to 8 days before each cisplatin course, 4 weeks after completion of the final cisplatin course, and 1 year later. Audiometry was to include measurement of bilateral pure tone air conduction thresholds at 500–8000 Hz with earphones or in the sound field using paediatric hearing assessment methods; otoscopy; immittance evaluation of middle ear function; and evoked otoacoustic emissions, if available. For participants unable to cooperate due to very young age, developmental disability, or medical status, brainstem auditory evoked response thresholds were to be measured instead. Audiometry conformed to detailed testing procedures described in the protocol of the companion observational cohort study (ACCL05C1). In addition to institutional electronic entry of all required audiometry data, a copy of each audiogram was faxed to the COG Operations Center for independent review by two expert paediatric audiologists for whom randomisation was masked (KK, BB); differences in interpretation were resolved by consensus. Hearing loss was determined according to American Speech-Language-Hearing Association (ASHA) criteria.[21] In brief, ASHA is a binary criterion (yes or no) designed for early detection of ototoxicity. Ototoxicity is defined as a 20 dB or more worsening in pure tone threshold at one test frequency or a 10 dB or more worsening at two adjacent test frequencies by comparison with a normal baseline. ASHA criteria exceed test–retest variability, indicate hearing loss due to ototoxicity, and at the time ACCL0431 was designed, were regarded as the most sensitive criteria.

We assessed each participant-cycle for the presence of haematological and renal toxicity; haematological (complete blood count) and renal (serum creatinine, blood urea nitrogen, electrolytes, magnesium, and phosphorous concentrations) function were to be assessed 7–10 days after each cisplatin course for all participants. Using the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0), we defined haematological toxicity as the occurrence of grade 3 or higher anaemia, neutropenia, or thrombocytopenia. We defined nephrotoxicity as the occurrence of grade 3 or higher hypokalaemia, hypomagnesaemia, hypophosphataemia, acidosis, increased serum creatinine, or decreased glomerular filtration rate.

At a minimum, all participants were required to undergo disease assessments at baseline, after completion of the cancer treatment regimen, and then every 6 months for 3 years, as well as in the case of clinical suspicion for disease progression or recurrence. We assigned disease status on the basis of institutional report. Because of the heterogeneity of cancers, we did not accession disease-specific tumour stage and risk category at study entry. Later, to supplement the initial survival analysis, each participant's extent-of-disease at study entry was recorded

post hoc with a protocol-specific binary classification of localised versus disseminated.

We obtained a saliva or blood specimen from each participant who chose to take part in an exploratory optional aspect of the trial after a protocol amendment (March 31, 2010; samples taken retrospectively for those enrolled before the amendment) to assess mutations in the *TPMT* and *COMT* genes. Because of an insufficient number of samples, analysis and publication are not currently planned.

Criteria for ending protocol treatment included completion of the cancer treatment regimen, premature discontinuation of cisplatin, administration of cranial irradiation after enrolment but before measurement of the primary endpoint, and inability to continue sodium thiosulfate. Participants off protocol treatment were followed up for all endpoints. Criteria for removal from the study included death, loss to follow-up, or entry onto another COG therapeutic study for the underlying cancer (in which case we obtained survival data from that therapeutic study).

Outcomes

The primary endpoint was hearing loss at 4 weeks after final cisplatin treatment, but before any haemopoietic cell transplantation, according to the validated ototoxicity criteria. Participants were deemed not assessable for this outcome if we found during central review that audiometry data derived from headphone, sound field, or brainstem auditory evoked response testing at baseline or post-treatment were missing, incomplete, or technically unsatisfactory.

Secondary endpoints were frequency-specific hearing loss at 4 weeks (for 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz), haematological and renal toxicity, event-free survival (defined as the time from study enrolment until disease relapse or progression, diagnosis of a second malignant neoplasm, or death, whichever came first), and overall survival (defined as the time from enrolment to death or last date confirmed alive).

By protocol amendment on March 31, 2010, we added an exploratory secondary aim to assess the association of mutations in the *TPMT* and *COMT* genes with cisplatin-induced hearing loss and sodium thiosulfate effect.

Statistical analysis

The primary endpoint of hearing loss according to ASHA criteria compared the audiometric evaluation at enrolment (ie, baseline) with the first assessment done at least 4 weeks after the final dose of cisplatin (ie, post-treatment). Using a modified intention-to-treat approach, we analysed patients on the basis of their randomisation assignment, irrespective of treatment received, but included only eligible participants who completed both baseline and post-treatment hearing assessments.

The accrual goal was 108 participants with complete hearing evaluation allocated equally to the two study

groups. We compared the proportion that developed hearing loss by treatment group using a one-sided χ^2 test.[22] We deemed a p value of 0·05 or less to be significant. Assuming a 4-week cumulative hearing loss incidence of 45% in the control group and an incidence of 22·5% in the sodium thiosulfate group, the study as designed would provide 80% power. The probability of hearing loss among patients in the control group was based on a contemporary paediatric report involving multiple tumour types.[7] Reduction of this probability by half was deemed clinically relevant. Because participants who had received previous cranial irradiation were added through an amendment, we did a post-hoc sensitivity analysis that included only participants who were not enrolled in the new stratum. We also did a post-hoc analysis of hearing loss at the 1-year timepoint for participants who had interpretable audiometry data and had not had a survival event or haemopoietic cell transplantation; these participants were excluded due to the inability to control for additional ototoxic exposures.

We estimated the magnitude of the association between sodium thiosulfate assignment and hearing loss using the odds ratio (OR); p values for the test of OR=1 and corresponding 95% CI were derived using the Wald test for the parameter associated with the randomised treatment assignment from a logistic model.[22] The logistic model was stratified according to the strata used for randomisation. We estimated stratum-specific probabilities of hearing loss using the observed proportion of assessable participants in the particular stratum with hearing loss; we also calculated exact 95% CIs.[23]

We planned interim monitoring for futility of an otoprotective effect of sodium thiosulfate. After we ascertained the primary outcome measure in the first 60 patients, we calculated the probability of rejecting the null hypothesis at the end of planned enrolment on the basis of observed hearing loss to that point and the assumption that development of hearing loss for future participants would follow the alternative hypothesis. If this conditional probability was 0·10 or less, the study was to be identified to the COG Data and Safety Monitoring Committee for closure due to lack of efficacy.

The change in hearing threshold between baseline and post-treatment timepoint at different frequencies (500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz) was determined by the mean change, and assessed the hypothesis of no difference between groups using the Wilcoxon two-sample test for non-parametric data. Testing of the normality assumption is shown in the appendix (p 2). We deemed a one-sided p value 0·05 or less to be significant; we made no adjustment for multiple comparisons for this assessment.

For haematological and renal toxicity, denominators represent the number of participants who completed the required toxicity assessment during each cycle. For both types of toxicity, we assessed the hypothesis of no difference in incidence using a χ^2 test of proportions.

For event-free survival and overall survival, patients who did not have an event were censored at time of last contact. We estimated the probability of remaining event free as a function of time post-enrolment using the method of Kaplan and Meier.[24] We compared risk of event across groups defined by randomised regimen using the log-rank statistic. We generated relative hazard ratios (RHR) and 95% CIs by fitting a relative-risk regression model, using partial likelihood where the model contained the characteristic of interest as the only variable. We computed survival estimates as 3-year event-free survival and 3-year overall survival. We did a post-hoc analysis of event-free survival and overall survival by extent of disease using the same methods. We considered all eligible participants in the survival analyses by intention to treat. We did all statistical calculations using SAS (version 9.4) or Stata (version 14).

This trial is registered with ClinicalTrials.gov, number NCT00716976.

Role of the funding source
The NCI Cancer Evaluation Treatment Program and Division of Cancer Prevention had a role in study design through the required review process and approved the final protocol, but had no role in the data collection, data analysis, data interpretation, or writing of the report. Fennec Pharmaceuticals, which provided sodium thiosulfate at no cost, was permitted to review the final manuscript only for errors of fact or proprietary information. All authors had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between June 23, 2008, and Sept 28, 2012, we enrolled 131 participants from 38 institutions, reaching the planned accrual goal (figure 1). Six participants were deemed ineligible; four because they were co-enrolled on a disease-directed COG therapeutic study (with three participants randomly assigned to sodium thiosulfate and one to control), one because cranial irradiation was administered before reaching the primary endpoint (randomly assigned to control), and one because there was no source documentation of normal baseline serum electrolyte values (randomly assigned to sodium thiosulfate). Of the 125 eligible participants, 38 were enrolled before and 87 after the protocol amendment that allowed participants who had previously received cranial irradiation to enrol (n=9). 64 participants were randomly assigned to the control group and 61 to the sodium thiosulfate group. Interim monitoring resulted in recommendations to continue the trial as planned. Data current to March 31, 2015, were used in this analysis.

Baseline characteristics were similar between groups (table 1). The overall proportions of eligible participants with disseminated disease at study entry were similar;

four eligible participants in each group had previously received cranial irradiation. The disease-specific characteristics of participants by randomisation group with respect to age and extent of disease were balanced between groups (appendix p 1). The median cumulative cisplatin dose for the control group was 387 mg/m² (IQR 305–466) and for the sodium thiosulfate group was 393 mg/m² (290–420). The median cumulative sodium thiosulfate dose was 95·8 g/m² (60·1–127·6). The proportions of participants who had received loop diuretics or aminoglycoside antibiotics were similar in

the control (17 [27%] of 64 participants) and sodium thiosulfate (17 [28%] of 61 participants) groups. No participants underwent haemopoietic cell transplantation before assessment for the primary endpoint. Because of an insufficient number of samples (n=50), analysis of mutations in the *TPMT* and *COMT* genes are not currently planned.

104 participants were assessable for post-treatment hearing loss at 4 weeks (55 of 64 participants in the control group and 49 of 61 in the sodium thiosulfate group). Of these assessable participants, 14 (29%) in the sodium thiosulfate group and 15 (27%) in the control group were younger than 5 years. Hearing loss was identified in 14 (28·6%; 95% CI 16·6–43·3) participants in the sodium thiosulfate group compared with 31 (56·4%; 42·3–69·7) in the control group (p=0·00022). For participants younger than 5 years, the incidence of hearing loss was substantially lower in the sodium thiosulfate group than in the
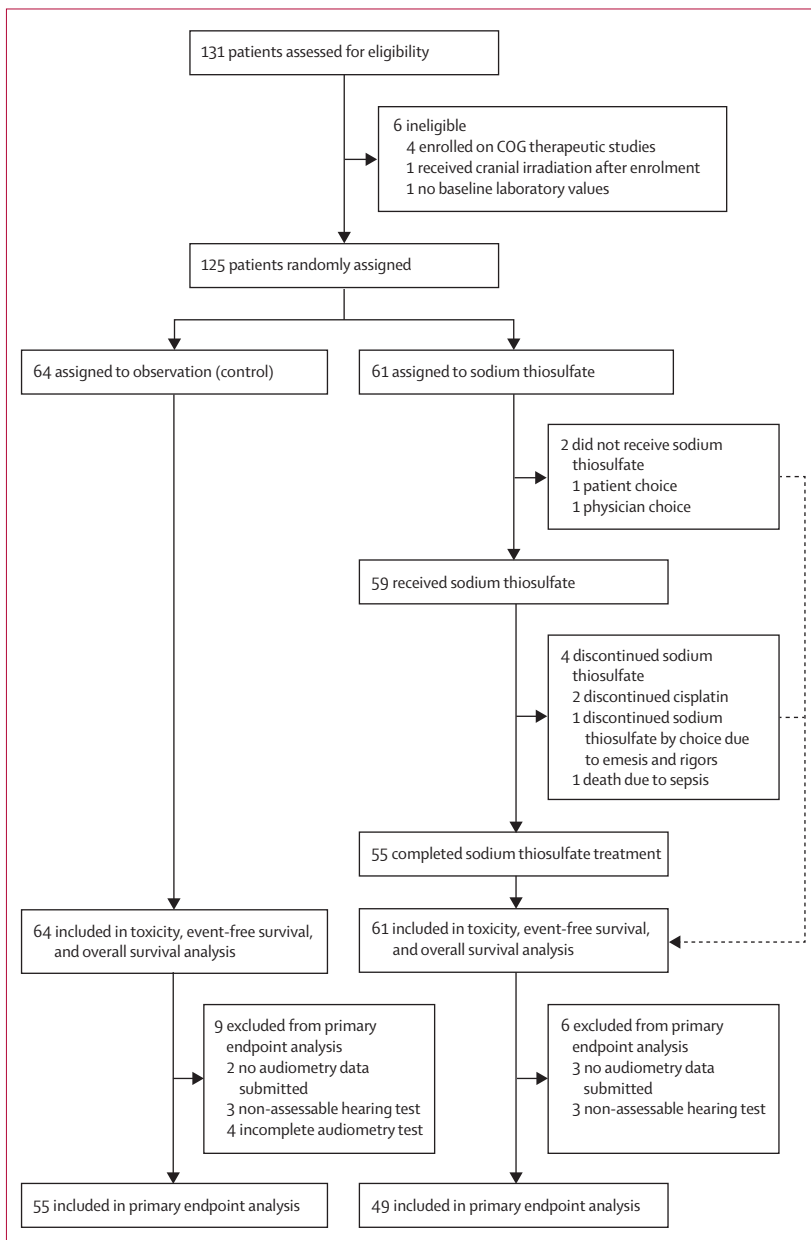

Figure 1: Trial profile
COG=Children's Oncology Group.

	Control (n=64)	Sodium thiosulfate (n=61)
Age (years)		
<5	22 (34%)	22 (36%)
5–9	13 (20%)	7 (11%)
10–14	14 (22%)	16 (26%)
15–18	15 (23%)	16 (26%)
Sex		
Male	41 (64%)	35 (57%)
Female	23 (36%)	26 (43%)
Race		
White	39 (61%)	42 (69%)
Black	10 (16%)	5 (8%)
Asian	2 (3%)	1 (2%)
Hawaiian/Pacific Islander	1 (2%)	1 (2%)
American Indian/Aleutian/Eskimo	0	1 (2%)
Other	8 (13%)	11 (18%)
Unknown	4 (6%)	0
Ethnicity		
Non-Hispanic	46 (72%)	41 (67%)
Hispanic	15 (23%)	18 (30%)
Unknown	3 (5%)	2 (3%)
Diagnosis		
Germ cell tumour	16 (25%)	16 (26%)
Hepatoblastoma	5 (8%)	2 (3%)
Medulloblastoma or CNS PNET	14 (22%)	12 (20%)
Neuroblastoma	12 (19%)	14 (23%)
Osteosarcoma	15 (23%)	14 (23%)
Other	2 (3%)	3 (5%)
Extent of disease*		
Localised	38 (59%)	39 (64%)
Disseminated	26 (41%)	21 (34%)
Unknown	0	1 (2%)

Data are n (%). PNET=primitive neuroectodermal tumour. *Determined post hoc (ie, retrospectively during the preliminary data analysis after completion of accrual).

Table 1: Baseline characteristics

control group (three [21·4%] of 14 participants [95% CI 4·7–50·8] vs 11 [73·3%] of 15 [44·9–92·2]); whereas the difference in incidence between groups was not as large for older patients (11 [31·4%; 16·9–49·3] of 35 vs 20 [50·0%; 33·8–66·2] of 40). The incidence of hearing loss was lower for participants in the sodium thiosulfate group than in the control group after cisplatin infusion of 2–6 h (ten [41·7%; 95% CI 22·1–63·4] of 24 vs 21 [70·0%; 50·6–85·2] of 30) and after cisplatin infusion of less than 2 h (four [16·0%; 4·5–36·1] of 25 vs ten [40·0%; 21·1–61·3] of 25). The stratum of previous cranial irradiation contained only eight assessable participants; hearing loss occurred in two (50%) of four sodium thiosulfate-treated participants versus four (100%) of four patients in the control group. When these eight irradiated participants were excluded in a post-hoc analysis, hearing loss was noted in 12 (26·7%; 95% CI 14·6–41·9) of 45 participants in the sodium thiosulfate group compared with 27 (52·9%; 38·5–67·1) of 51 in the control group (p=0·0045). By the logistic test adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the sodium thiosulfate group compared with the control group (OR 0·31, 95% CI 0·13–0·73; p=0·0036). When the eight irradiated participants were removed from the analysis, the unadjusted OR was 0·32 (95% CI 0·13–0·76; p=0·010). Of the 104 participants assessable for hearing loss at the primary endpoint, 67 were also assessable at 1 year in a post-hoc analysis; of these, nine (28%) of 32 participants who received sodium thiosulfate had ASHA-defined hearing loss compared with 19 (54%) of 35 controls (p=0·0015). For the eight assessable participants who had previously received cranial irradiation, none of their hearing outcomes at 1 year were changed from the 4-week timepoint.

The mean change in hearing threshold within key frequencies is shown in table 2. For the sodium thiosulfate group, the change in hearing threshold from baseline to 4 weeks after cisplatin treatment was smaller than in the control group, although there was no significant difference between the groups (table 2).

Haematological toxicity was not significantly different between the treatment groups, occurring in 137 (77%) of 177 participant cycles in the sodium thiosulfate group and 172 (77%) of 223 participant cycles in the control group (p=0·95; table 3). Aggregate nephrotoxicity was more common in the sodium thiosulfate group, in which 37 (25%) of 147 participant cycles were affected versus 25 (13%) of 187 controls (p=0·0059; table 4). Hypophosphataemia and hypokalaemia were more common in the sodium thiosulfate group than in the control group (table 4). Notably, no cases of either increased creatinine or reduced glomerular filtration rate met the CTCAE grade 3 threshold in either group (table 4).

The most common grade 3–4 haematological adverse events, irrespective of attribution, were neutropenia (117 [66%] of 177 participant cycles in the sodium thiosulfate group vs 145 [65%] of 223 in the control group),

whereas the most common non-haematological adverse event was hypokalaemia (25 [17%] of 147 vs 22 [12%] of 187). As part of the NCI Adverse Event Reporting System, this study included expedited reporting of serious adverse events. Reporting was required only for participants randomly assigned to the sodium thiosulfate group. 194 serious adverse events were reported in 26 patients; of these, 112 were deemed unrelated, 62 unlikely, 20 possibly, and none probably or definitely related to sodium thiosulfate. 85 were non-haematological adverse events, of which 49 were deemed unrelated, 25 unlikely, 11 possibly, and none probably or definitely related to sodium thiosulfate; 70 were haematological adverse events, of which 53 were deemed unrelated, 13 were deemed unlikely, four possibly, and none probably or definitely related to sodium thiosulfate. Of the 194 serious adverse events, the three most common were decreased neutrophil count (26 [13%] in 14 participants), decreased platelet count (23 [12%] in 12 participants), and anaemia (21 [11%] in ten participants). See appendix (p 4) for a summary of serious adverse events.

All 125 eligible patients were included in the analysis of event-free survival and overall survival. Median follow-up was 3·5 years (IQR 1·4–4·5) for event-free survival (median follow-up 3·4 years [IQR 2·9–4·3] for the sodium thiosulfate group, and 3·8 years [3·1–4·5] for the control group) and 3·5 years (1·5–4·5) for overall survival (median follow-up 3·4 years [2·9–4·3] for the sodium thiosulfate group, and 3·8 years [3·1–4·7] for the control group). Among the 61 participants assigned to sodium thiosulfate, 26 events and 17 deaths occurred; among the 64 participants in the control group, 24 events and ten deaths occurred. All events were relapse except for one participant in the sodium thiosulfate group who developed a second malignant neoplasm. As classified by site investigators, all deaths were deemed to be due to disease, except for one death in the sodium thiosulfate group that was attributed to cancer treatment-related sepsis but was not related to sodium thiosulfate. Considering the entire sample, no significant difference was noted between the sodium thiosulfate and control

	Control		Sodium thiosulfate		p value	Difference in mean change between groups (dB)
	Mean* (SD)	n	Mean* (SD)	n		
500 Hz	–1·1 (8·6)	45	–1·5 (5·8)	38	0·34	0·4
1000 Hz	–0·3 (9)	47	–0·7 (4·6)	37	0·36	0·4
2000 Hz	0·6 (12·7)	47	–1·2 (4·9)	38	0·42	1·8
4000 Hz	9·6 (20·5)	47	1·1 (7·1)	38	0·11	8·5
8000 Hz	17·0 (24·7)	42	9·7 (17·3)	37	0·18	7·3

*A negative value indicates a better mean hearing threshold compared with the baseline evaluation and a positive value indicates a poorer mean hearing threshold.

Table 2: Mean change in frequency-specific hearing thresholds

	Cisplatin cycle 1		Cisplatin cycle 2		Cisplatin cycle 3		Cisplatin cycle 4		Cisplatin cycle 5		Cisplatin cycle 6	
	Control (n=61)	Sodium thiosulfate (n=55)	Control (n=57)	Sodium thiosulfate (n=51)	Control (n=46)	Sodium thiosulfate (n=34)	Control (n=33)	Sodium thiosulfate (n=27)	Control (n=16)	Sodium thiosulfate (n=8)	Control (n=10)	Sodium thiosulfate (n=2)
Neutrophil count decreased	41 (67%)	36 (65%)	37 (65%)	34 (67%)	32 (70%)	22 (65%)	18 (55%)	18 (67%)	11 (69%)	6 (75%)	6 (60%)	1 (50%)
Platelet count decreased	27 (44%)	23 (42%)	24 (42%)	28 (55%)	22 (48%)	20 (59%)	19 (58%)	16 (59%)	8 (50%)	6 (75%)	6 (60%)	1 (50%)
Anaemia	21 (34%)	14 (25%)	23 (40%)	20 (39%)	17 (37%)	15 (44%)	17 (52%)	12 (44%)	10 (63%)	7 (88%)	7 (70%)	1 (50%)

Data are n (%). Denominators used for calculating the percentages were the number of patients assessed for the specified toxicity during the cisplatin cycle indicated. *Grade 3 or higher according to Common Terminology Criteria for Adverse Events (version 4.0).

Table 3: Components of reported haematological toxicity*

	Cisplatin cycle 1		Cisplatin cycle 2		Cisplatin cycle 3		Cisplatin cycle 4		Cisplatin cycle 5		Cisplatin cycle 6	
	Control (n=55)	Sodium thiosulfate (n=47)	Control (n=51)	Sodium thiosulfate (n=44)	Control (n=39)	Sodium thiosulfate (n=27)	Control (n=27)	Sodium thiosulfate (n=23)	Control (n=9)	Sodium thiosulfate (n=6)	Control (n=6)	Sodium thiosulfate (n=0)
Acidosis	1 (2%)	0	0	0	0	1 (4%)	0	1 (4%)	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0	0	0	0
Glomerular filtration rate	0	0	0	0	0	0	0	0	0	0	0	0
Hypokalaemia	7 (13%)	6 (13%)	8 (16%)	9 (20%)	5 (13%)	7 (26%)	1 (4%)	2 (9%)	0	1 (17%)	1 (17%)	0
Hypomagnesaemia	0	0	2 (4%)	1 (2%)	0	1 (4%)	0	0	0	1 (17%)	0	0
Hypophosphataemia	2 (4%)	3 (6%)	3 (6%)	2 (5%)	1 (3%)	5 (19%)	1 (4%)	4 (17%)	0	1 (17%)	0	0

Data are n (%). Denominators used for calculating the percentages were the number of patients assessed for the specified toxicity during the cisplatin cycle indicated. *Grade 3 or higher according to Common Terminology Criteria for Adverse Events (version 4.0).

Table 4: Components of reported nephrotoxicity*
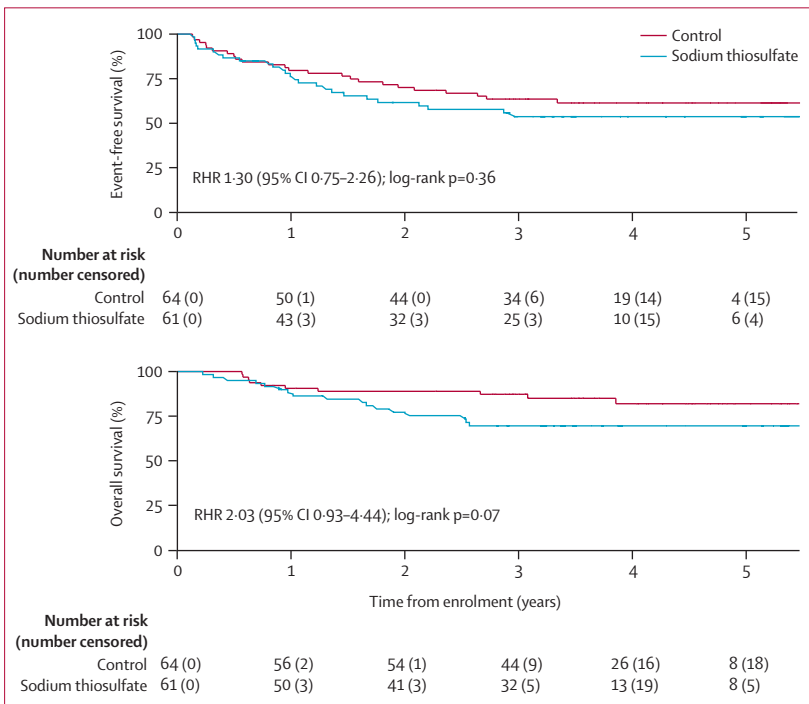

Figure 2: Event-free and overall survival for all participants
n=125. RHR=relative hazard ratio.

groups for event-free survival or overall survival (figure 2). 3-year event-free survival was 54% (95% CI 40–66) in the sodium thiosulfate group versus 64% (50–74) in the control group; 3-year overall survival was 70% (56–80) versus 87% (76–93).

Because of the possibility of an effect of sodium thiosulfate on survival that emerged for the sample as a whole, we did a post-hoc stratification of the sample by extent of disease at enrolment. Within the group deemed to have localised disease (n=77), we found no significant difference between treatment groups in event-free survival (median follow-up 3·4 years [IQR 3·2–4·3] for the sodium thiosulfate group, and 3·7 years [3·1–4·5] for the control group) or overall survival (median follow-up 3·5 years [3·2–4·3] for the sodium thiosulfate group, and 3·8 years [3·0–4·8] for the control group; figure 3). The 3-year event-free survival was 60% (95% CI 42–74) for the sodium thiosulfate group versus 66% (48–78) for the control group; 3-year overall survival was 83% (66–92) versus 89% (74–96). Among participants with localised disease, 14 events and six deaths in both the control and sodium thiosulfate groups occurred. Among participants deemed to have disseminated disease (n=47), we found no difference between treatment groups in event-free survival (median follow-up 3·2 years [IQR 3·0–4·3] for the sodium thiosulfate group, and 4·1 years [3·1–4·5] for
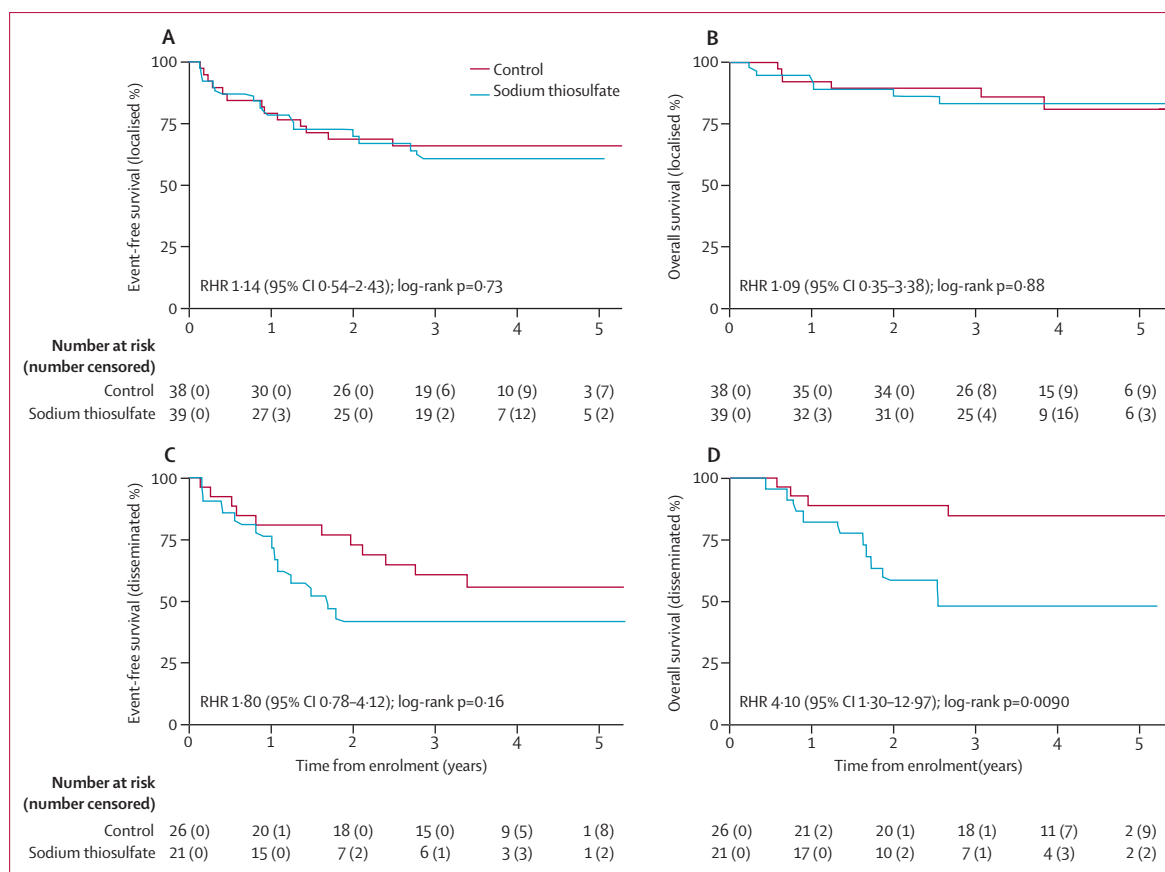
Figure 3: Event-free and overall survival by extent of disease*
(A, B) Participants with localised disease (n=77). (C, D) Participants with disseminated disease (n=47). RHR=relative hazard ratio. *Extent of disease unknown for one participant.

the control group), but overall survival was significantly lower in the sodium thiosulfate group compared with the control group (median follow-up 3·2 years [3·0–4·5] for the sodium thiosulfate group, and 3·8 years [3·1–4·5] for the control group; figure 3). 3-year event-free survival was 42% (95% CI 21–61) in the sodium thiosulfate group versus 61% (39–77) in the control group; 3-year overall survival was 45% (23–65) versus 84% (62–94). In participants with disseminated disease, 12 events and 11 deaths occurred in the sodium thiosulfate group and ten events and four deaths occurred in the control group.

Discussion
We report the results of a multicentre randomised controlled trial showing that sodium thiosulfate significantly reduces risk for developing cisplatin-induced hearing loss in children and adolescents treated for cancer. Consistent with our hypothesis, delayed post-cisplatin administration of sodium thiosulfate in a study population comprising a mixture of ages, diagnoses, and chemotherapy regimens reduced the cumulative incidence of ASHA-defined cisplatin-induced hearing loss by about 50%. To the best of our knowledge, with these results, sodium thiosulfate becomes the first

proven drug tested under these conditions and thus represents an important development in translational otoprotection research. Notably, to our knowledge, ACCL0431 is the first NCI-funded cooperative group clinical trial focused solely on prevention of cisplatin-induced hearing loss in either children or adults. As such, the ACCL0431 experience shows both the feasibility and scientific value of doing otoprotection studies in the cooperative group setting. This study addresses a clinically important goal because of the profound, negative effect of ototoxicity on quality of life for survivors of cancer treated during young childhood and adolescence. It is reasonable to assume the benefits of preventing cisplatin-induced hearing loss and chronic tinnitus include reduction of their many downstream effects on language acquisition, learning, psychosocial development, and social functioning.[9,10]

The absence of effective otoprotectants in human beings limits comparison of our results with the results of other drugs.[25] So far, amifostine has been studied more than any other medication for this purpose but showed no evidence of otoprotection against cisplatin-induced hearing loss in two embedded COG randomised controlled trials for hepatoblastoma and germ cell tumours.[26,27] In a more

recent non-randomised, comparative prospective cohort study[28] of children and adolescents treated with cisplatin for medullobastoma, Fouladi and colleagues reported otoprotection with a more dose-intensive amifostine regimen. Compared with amifostine, for which hypocalcaemia and hypotension are common adverse events that require monitoring and management protocols, sodium thiosulfate was substantially simpler to administer.[29] We were unable to detect any protective effect of sodium thiosulfate on renal or haemopoietic function. Nephrotoxicity, as defined in our study, was more common in the sodium thiosulfate group but, importantly, not because of an abnormal serum creatinine or glomerular filtration rate but rather because of hypophosphataemia and hypokalaemia—explanations for which are unknown. We did not collect data regarding clinical consequences and treatment of haematological or renal toxicity. We were unable to assess whether sodium thiosulfate could have helped preserve cisplatin dose intensity through avoidance of dose modifications because cancer treatment was not protocol specified.

Survival was a secondary endpoint of this study. We detected no significant difference in event-free survival or overall survival by treatment group among our participants as a whole. In the stratified post-hoc analysis by extent of disease at presentation, we saw no difference between treatment groups in event-free survival or overall survival for participants with localised disease. However, for participants with disseminated disease, we noted lower event-free survival and overall survival for patients treated with sodium thiosulfate than for patients in the control group. There are two broad potential explanations for this finding. First, sodium thiosulfate might be tumour protective in addition to being otoprotective, and this effect might be most pronounced in individuals with poorer prognosis, in whom the incremental effect of cisplatin is important for disease control. Additionally, we cannot exclude a tumour protective effect against other drugs used in combination with cisplatin. The second potential explanation could relate to disease characteristics that might affect outcome but that we were unable to measure directly because of the design of our study. For example, a wide range of tumours and tumour stages with varying prognoses were included in our trial. Although the diagnosis-specific distribution of participants by age and extent of disease seems well balanced between the randomisation groups, we did not capture disease biology, an important outcome determinant routinely incorporated in the risk classification of some paediatric cancers. This aspect of the trial design, combined with minor imbalances of uncommon poor-prognosis malignancies, could be relevant (appendix p 1). Among participants with disseminated disease, the magnitude of difference between treatment groups was greater for overall survival than for event-free survival, a finding also not readily accounted for. Perhaps relapsed patients

previously exposed to sodium thiosulfate responded less well to retrieval treatment than patients in the control group, but this possibility cannot be assessed because data collection regarding relapse treatment and responses were beyond the scope of this trial. Although relapses accounted for all but one event, our data did not suggest relapses occurred disproportionately in any particular diagnostic subset.

ACCL0431 was designed as a proof-of-concept study focused on the otoprotective effects of sodium thiosulfate. Participants ranged in age from infancy through adolescence and were diagnosed with one of several cancers treated with cisplatin. This design afforded several strengths for our study but introduced some potential weaknesses. The fact that ACCL0431 was a randomised, multicentre trial done in a cooperative group setting comprising both academic and community-based institutions of various sizes are notable strengths. The inclusion of diverse cancer diagnoses and risk groups offered an efficient accrual strategy and allowed sodium thiosulfate to be tested across a range of ages and treatment regimens. Another strength was the use of masked audiometry data by central reviewers who adjudicated the primary ototoxicity endpoint, thus reducing bias. However, the heterogeneity in participant and disease characteristics might have complicated our ability to understand potential differential effects of sodium thiosulfate on survival in view of other determinants such as stage and tumour biology. With hearing being the primary outcome, this study enrolled a diversity of cisplatin-treated cancers, with reliance on randomisation to balance such unmeasured factors. We calculated sample size for the primary outcome and monitored survival to detect large differences between groups. In our effort to elucidate an apparent survival difference that emerged in the sample as a whole, retrospective application of a simple binary classification for extent of disease to our diverse sample might have helped isolate an anatomic subset in which sodium thiosulfate might affect outcome, but this approach is unlikely to take account of all the factors that inform disease-specific risk classification. Although 21 (17%) of the 125 randomly assigned participants were not assessable for the hearing outcome, they were distributed fairly equally by randomisation and were similar to other participants except for predominantly being younger than 5 years. This high proportion of unassessable patients represents the unique challenges inherent to otoprotection studies involving young children, in whom developmental stage and medical disability can limit cooperation for audiometry. Despite these challenges, participants younger than 5 years constituted the largest age group on this trial, accounting for a third of all participants (44 of 125 participants). We recorded administration of potentially ototoxic loop diuretics and aminoglycoside antibiotics for all participants in this trial. Although we did not capture quantitative pharmacological data for loop

diuretics and aminoglycosides, or whether carboplatin was given, it is reasonable to assume these factors were similarly balanced through randomisation. Furthermore, all patients completed post-treatment audiometry before any haemopoietic cell transplantation, for which myeloablative carboplatin is typically used. In ACCL0431, hearing loss was graded according to the ASHA scale, which was selected because it was regarded as the most sensitive scale available at the time. Since then, the International Society of Paediatric Oncology (SIOP)-Boston scale has been developed and is thought to offer some advantages, including no requirement for a pretreatment baseline measurement.[4] Retrospective conversion of our results to the SIOP-Boston scale presented substantial methodological challenges and was not feasible for this report.

Despite these issues, the challenges associated with ACCL0431 have yielded valuable lessons for the design of future otoprotection trials involving systemic drugs. For example, we believe otoprotection studies should be linked, whenever possible, to disease-focused trials or protocol-specified regimens to ensure consistent diagnoses, staging and risk classification, treatment, data capture for cisplatin dose modifications, and collection of survival data. At the same time, it must be acknowledged that the design of ACCL0431, in the context of a large paediatric clinical trials group, needed to be responsive to understandable concerns about unforeseen interactions between sodium thiosulfate and chemotherapy that could obfuscate or change survival outcomes on key front-line trials. Since some ACCL0431 participants might have been included because they were not eligible for a therapeutic trial, the overall prognosis of the ACCL0431 cohort might have been different from that of all cisplatin-treated paediatric patients with cancer. However, this possibility does not detract from the internal validity of our study or our conclusions related to sodium thiosulfate-related otoprotection and potential survival effect. Additionally, the study of drugs requiring time-modulated administration post-cisplatin to avoid tumour protection presents challenges because interference might be a continuous rather than a dichotomous effect. Finally, otoprotectants that are mechanistically distinct from the cytotoxic effects of chemotherapy or that are administered by non-systemic routes (eg, intratympanic injection) might offer advantages.

In the interim, with this present report identifying sodium thiosulfate as a commercially available drug that reduces cisplatin-induced hearing loss, at least one immediate question is raised. About two-thirds of children enrolled on ACCL0431 were classified as having localised disease; no difference between treatment groups in either event-free survival or overall survival were noted in this patient group. Can sodium thiosulfate be used safely in this subset of children? In this regard, encouraging preliminary results have been reported from SIOPEL-6 (NCT00652132), an international randomised clinical trial for children with standard-risk hepatoblastoma treated with single-drug cisplatin with or without sodium thiosulfate 20 g/m² administered on the same schedule as ACCL0431. This important trial uses an alternative design involving only one cancer diagnosis treated with a protocol-specified regimen of single-drug cisplatin. Although hearing outcomes on that study are not expected until late 2017, a 2016 survival analysis[30] involving 109 patients revealed no difference between sodium thiosulfate and observation in 2-year event-free survival (89·0% vs 86·3%) and 2-year overall survival (97·7% vs 91·4%).

Only after final results are available from SIOPEL-6 to inform the interpretation of ACCL0431 will it become possible to develop firm recommendations concerning a potential future role for sodium thiosulfate in clinical practice or future randomised trials. The two trials seem likely to prove complementary and provide a more complete understanding of the effects of sodium thiosulfate than either study alone. Thoughtful discussion within the community of stakeholders involving paediatric oncologists, otolaryngologists, audiologists, parents, and survivors living with cisplatin-induced hearing loss will be needed. Whether consensus can soon be reached on the question of using sodium thiosulfate for carefully defined patient subsets, it seems clear that the completion of ACCL0431 signals a new era in which the historical acceptance of cisplatin-induced hearing loss as an inevitable consequence of curative cancer treatment has given way to more encouraging possibilities.

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