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EFFECTS OF SODIUM THIOSULFATE VERSUS OBSERVATION ON DEVELOPMENT OF CISPLATIN-INDUCED HEARING LOSS IN CHILDREN WITH CANCER: RESULTS FROM THE CHILDREN'S ONCOLOGY GROUP ACCL0431 RANDOMISED CLINICAL TRIAL

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Study conception and design (DRF, LC, MDK, KK, BHP, BL, EAN, LS). Study conduct (all authors). Central audiometry review (KK, BB). Statistical analyses (LC, MDK, BHP, DV). Data interpretation (all authors). First draft of manuscript (DRF with input from LS, BHP, MDK). Review of manuscript drafts and approval of final manuscript (all authors).

DECLARATION OF INTERESTS

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SUMMARY

Background—Sodium thiosulfate (STS) is an antioxidant shown in preclinical studies to prevent cisplatin-induced hearing loss (CIHL) but not compromise anti-tumour efficacy with timed administration post-cisplatin. The primary study aim was to evaluate STS for prevention of CIHL.

Methods—ACCL0431 was an open-label, phase 3 randomised cooperative group trial. Eligible participants 1–18 years old with newly diagnosed cancer and normal audiometry were randomly allocated (1:1) to receive STS or not in addition to their planned cisplatin-containing chemotherapy regimen using permuted blocks of 4. Randomisation was initially stratified by age (< or ≥ 5 years) and duration of cisplatin infusion (< or ≥ 2 hours). Stratification by prior cranial irradiation was added later. Sequence was computer-generated centrally and concealed to all personnel. If allocated to STS, participants received STS 16 grams/m^2 intravenously 6 hours after each cisplatin dose. Hearing was measured using standard audiometry and reviewed centrally by audiologists masked to allocation using American Speech-Language-Hearing Association criteria. The primary endpoint was incidence of hearing loss 4 weeks post final cisplatin dose. Analysis was by intention to treat and restricted to evaluable participants. Enrollment is complete and this report represents the final analysis. This trial is registered with ClinicalTrials.gov, number NCT00716976.

Findings—Between June 23, 2008 and September 28, 2012, 125 eligible participants were enrolled from 38 sites in the United States (US) and Canada. Of these, 104 were evaluable for the primary aim. The proportion with hearing loss for STS versus control (%, 95% confidence interval) was 14/49 (28.6%, 16.6, 43.3) and 31/55 (56.4%, 42.3, 69.7), respectively (p=0.00022). Adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the STS group compared with control group (odds ratio 0.31, 95% confidence interval 0.13, 0.73; p=0.0036). The most common grade 3–4 haematological adverse events (AE) reported in STS and control participants, irrespective of attribution, were neutropaenia in 117/177 (66.1%) and 145/223 (65.0%) participant-cycles, while the most common non-haematological AE was hypokalaemia in 25/147 (17.0%) and 22/187 (11.8%) participant-cycles, respectively. Of 194 serious AEs reported in STS recipients, none were considered probably or definitely related to STS; the most common was neutrophil count decreased in 26/194 (13.4%).

Interpretation—STS protects against CIHL in children and is not associated with serious adverse events attributed to its use. Further research is needed to define the appropriate role for STS among emerging otoprotection strategies.

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INTRODUCTION

Cisplatin is an effective chemotherapeutic agent 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. Over 2,000 children 1–15 years of age receive cisplatin annually in the United States alone.[2]

Unfortunately, cisplatin causes clinically significant cisplatin-induced hearing loss (CIHL), which is characterized as progressive, irreversible, bilateral, and often accompanied by tinnitus.[3] CIHL affects all hearing frequencies through the progressive death of cochlear outer hair cells mediated by cisplatin-induced cytosolic reactive oxygen species in the mitochondria.[4] Approximately 40% of children receiving cisplatin develop CIHL, but the incidence approaches 100% in certain subsets.[5–7] Risk factors for developing CIHL include younger age (< 5 years) and higher cumulative cisplatin dose (> 200–400 mg/m^2), as well as cranial irradiation involving the cochlea.[3,8] The functional impact of even mild CIHL 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 CIHL is a common, continuous and annoying form of long-term cisplatin ototoxicity.[10]

Consequently, there is interest in identifying otoprotectants that prevent CIHL while preserving chemotherapeutic efficacy. One potential otoprotectant is sodium thiosulfate (STS). STS is a thiol-containing antioxidant that is rapidly excreted by the kidneys following intravenous (IV) administration.[11] STS is approved by the United States (US) Food and Drug Administration (FDA) for treatment of cyanide poisoning.[11] Biochemical effects of STS relevant to its otoprotective potential include inactivation of oxygen-free radicals and electrophilic platinum species.[12–14] Animal studies have demonstrated that STS prevents cisplatin-induced ototoxicity.[14,15] In both animal model and cell culture systems, concurrent administration of STS abrogates cisplatin cytotoxicity, which raises potential concern for tumour protection. However, preclinical testing by Neuwelt and others showed that when STS administration is delayed until 4–8 hours after cisplatin, otoprotection can be retained without compromising cytotoxicity.[15,16] Building on initial observations, Neuwelt conducted clinical studies in adults with brain tumours receiving an ototoxic regimen of high-dose intra-arterial carboplatin with blood-brain barrier disruption, and reported that similarly delayed administration of STS protected hearing.[17,18] This combined regimen was tolerated well when administered to twelve children 17 months to 12 years of age.[19]

Based on this collective experience and studies suggesting STS may prevent cisplatin-induced renal and haematological toxicity,[20] we developed ACCL0431, a multicentre, phase III, randomised clinical trial (RCT) 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 CIHL between those randomised to receive or not receive STS. We hypothesized that use of STS would result in a 50% reduction in CIHL compared with the control group. Secondary study aims were to compare the mean change in hearing thresholds and incidence of cisplatin-induced renal and haematological toxicity; and to monitor event-free survival (EFS) and overall survival (OS).

METHODS

Study Design and Participants

Participants were enrolled onto ACCL0431 at participating COG sites and randomised either to receive or not receive STS in the context of their planned cancer-specific treatment regimen. Written informed consent/assent of participants or their legal guardians was

obtained prior to registration. The study was approved by the US National Cancer Institute (NCI) Central Institutional Review Board (IRB) and site IRBs. This trial is registered with ClinicalTrials.gov, number NCT00716976. The protocol is available beginning on page 4 of the Appendix.

Participants were 1–18 years old at study entry and newly-diagnosed with hepatoblastoma, germ cell tumour, medulloblastoma/central nervous system primitive neuroectodermal tumour (CNS PNET), neuroblastoma, osteosarcoma or other cancer treated with cisplatin. Key eligibility criteria included the following: planned cumulative cisplatin dose of ≥ 200 mg/m^2 and infusion duration ≤ 6 hours; performance score ≥ 50 by the Karnofsky (> 16 years) or Lansky (≤ 16 years) scales; no prior cisplatin or carboplatin; no known thiol hypersensitivity; and normal institutional laboratory values reflecting haematological, renal and hepatic function. Normal hearing was required prior to enrollment as defined by hearing thresholds ≤20 dB HL at 500–8000 Hertz (Hz) when measured with earphones or ≤25 dB HL when measured in the sound field; or brainstem auditory evoked response (BAER) thresholds equivalent to behavioural thresholds of ≤ 20 dB HL. Prior cranial irradiation was initially not allowed but later permitted by study amendment dated March 31, 2010, provided hearing was normal, to augment trial recruitment. Patients were not eligible if registered on a cancer-directed COG therapeutic study to ensure there would be no confounding of primary aims by the ACCL0431 randomization.

Randomisation and Masking

Participants were enrolled and randomised within 5 days prior to receiving any cisplatin. The allocation sequence was generated for each stratum described below, according to a permuted block algorithm where each block of 4 contained 2 STS and 2 control randomisations. The randomisation was centrally computer-generated by the COG trial management system. Allocation was concealed to all investigators, clinicians and participants. Enrollment was performed by site research staff; eligibility confirmation and specification of stratification factors were entered into the COG trial management system and allocation was electronically generated for the site. Initially, randomisation was 1:1 and stratified into four groups defined by age (< or ≥ 5 years) and duration of cisplatin infusion (< or ≥ 2 hours). Later, one separate stratum was added for eligible participants who had received prior 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 in order 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 randomised to the control group, the cisplatin-containing treatment regimen alone was to be administered. For participants randomised to receive STS, STS was to be administered intravenously over 15 minutes beginning 6 hours following the completion of each cisplatin dose daily. This STS schedule was selected based on preclinical studies that showed combined otoprotection and non-interference with cisplatin chemotherapeutic effect when STS was delayed until 4–8 hours post-cisplatin.[15,16] The protocol-specified STS dose

was 16 gm/m^2 (533 mg/kg where the cisplatin dose was calculated by body weight) administered as a 12.5% solution. This STS dose was selected because it was within the published effective dose range and was well tolerated by children.[14–19] For participants receiving multi-day cisplatin regimens, a documented serum sodium level of < 145 mEq per liter was required prior to each STS dose, and a minimum of 10 hours was to have elapsed between STS and the next cisplatin dose. Otherwise, there were to be no modifications of dose or administration for STS or other chemotherapy drugs. Protocol guidelines for supportive care during the STS 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 medications, e.g., aminoglycosides and loop diuretics, was discouraged by protocol for all participants but captured in data reporting. Cisplatin dose modifications were not captured as participants did not receive cancer therapy according to specified protocols.

Outcomes

Hearing assessments were to be performed at baseline, within 8 days prior to each cisplatin course, 4 weeks following completion of the final cisplatin course, and 1 year later. The definition of the primary endpoint was hearing loss at 4 weeks post-final cisplatin, but prior to any haematopoietic cell transplant (HCT), according to the validated ototoxicity criteria described below. 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 (OAE), if available. For participants unable to cooperate, BAER thresholds were to be measured instead. Audiometry conformed to detailed testing procedures described in the protocol of a companion observational cohort study of ototoxicity grading scales on which co-enrollment was mandatory (ACCL05C1; NCT00458887). 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/no) designed for early detection of ototoxicity. Ototoxicity is defined as ≥ 20 dB decrease in pure tone threshold at one test frequency or ≥ 10 dB decrease at two adjacent test frequencies in comparison to a normal baseline. ASHA criteria exceed test-retest variability, indicate hearing loss due to ototoxicity, and at the time ACCL0431 was designed were considered to be the most sensitive criteria. Participants were considered not evaluable for this outcome if during central review it was discovered that audiometry data derived from headphone, sound field, or BAER testing at baseline or post-treatment were missing, incomplete, or technically unsatisfactory. Hearing outcomes were analysed *post hoc* at the 1-year time point for participants who had interpretable audiometry data and had not experienced an event or undergone HCT, due to inability to control for additional ototoxic exposures.

For secondary endpoints related to potential prevention of cisplatin toxic effects on the bone marrow and kidneys by STS, haematological (complete blood count, CBC) and renal (serum

creatinine, BUN, electrolytes, magnesium and phosphorous levels) 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), haematological toxicity was defined as the occurrence of ≥ grade 3 anaemia, neutropaenia or thrombocytopaenia. Nephrotoxicity was defined as the occurrence of ≥ grade 3 hypokalaemia, hypomagnaesemia, hypophosphataemia, acidosis, serum creatinine elevation or glomerular filtration rate (GFR) reduction. For secondary endpoints related to survival, at a minimum, all participants were required to undergo disease assessments at baseline, following completion of the cancer treatment regimen, then every 6 months for 3 years and for clinical concern for disease progression or recurrence. Disease status was assigned on the basis of institutional report. Due to the heterogeneity of cancers, disease-specific tumour stage and/or risk category were not accessioned at study entry. Later, in order to supplement the initial survival analysis, each participant's extent-of-disease at study entry was required *post hoc* using a protocol-specific binary classification of "localised" versus "disseminated." By amendment on March 31, 2010, an exploratory secondary aim was added to evaluate the association of mutations in the thiopurine S-methyltransferase (*TPMT*) and catechol-O-methyltransferase (*COMT*) genes with CIHL and STS effect. A saliva or blood specimen was to be obtained from each participant who elected to take part of this optional aspect of the trial (retrospectively for those enrolled prior to the amendment). Due to an insufficient number of samples (n=50), analysis and publication are not currently planned but may be conducted if a feasible mechanism for obtaining additional samples is identified.

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

Statistical Analysis

Primary Endpoint—The primary endpoint was development of hearing loss according to ASHA criteria when the audiometric evaluation at enrollment ("baseline") was compared to the first evaluation conducted at least 4 weeks following the final dose of cisplatin ("post-treatment"). Using an intent-to-treat approach, the outcome was assigned to the participants as randomised regardless of treatment received. Only eligible participants who completed both baseline and post-treatment evaluations were considered in this analysis.

The accrual goal was 108 participants with complete hearing evaluation allocated equally to the two study arms. We compared the proportion that developed hearing loss by treatment group using a one-sided χ^2 test.[22] A p-value ≤ 0.05 was considered statistically significant. A 4-week cumulative hearing loss incidence of 45% in the control arm and an incidence of 22.5% in the STS arm were presumed for the study design. With these assumptions, the testing procedure described above would provide 80% power. The probability of hearing loss among controls was based upon a contemporary paediatric report involving multiple tumour types.[7] Reduction of this probability by half was considered clinically relevant.

Because participants who had received prior cranial irradiation were added through an amendment, we conducted a *post hoc* sensitivity analysis that included only those who were not enrolled in the new stratum.

We estimated the magnitude of the association between STS assignment and hearing loss using the odds ratio (OR), p-values for the test of OR=1, and corresponding 95% confidence interval (95%CI) 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 described above. Stratum-specific probabilities of hearing loss were estimated by the observed proportion of evaluable participants in the particular stratum with hearing loss; exact 95%CI were also calculated.[23]

Interim monitoring was planned for futility of an otoprotective effect of STS. After the primary outcome measure was ascertained on the first 60 patients, the probability of rejecting the null hypothesis at the end of planned enrollment was calculated 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, the study was to be identified to the COG Data and Safety Monitoring Committee for closure due to lack of efficacy.

Secondary Endpoints

Frequency-specific Hearing Loss: For each participant, the change in hearing threshold between baseline and the post-treatment time point was computed for 500, 1000, 2000, 4000 and 8000 Hz. For each frequency, the mean change for the randomisation group was determined and the hypothesis of no difference between groups was assessed using the Wilcoxon two sample test for non-parametric data (see Appendix, page 2). A one-sided p-value ≤ 0.05 was considered significant; no adjustment for multiple comparisons was made for this exploratory assessment.

Haematological and Renal Toxicity: Each participant-cycle was evaluated for the presence of haematological and/or renal toxicity as previously defined. Denominators represent the number of participants who completed the required toxicity assessment during each cycle. For both, the hypothesis of no difference in incidence was assessed using a χ^2 test of proportions.

Event-free and Overall Survival: EFS was defined as the time from study enrollment until disease relapse or progression, diagnosis of a second malignant neoplasm (SMN), or death, whichever came first. Participants who experienced any of these were considered to have had an EFS-event, or otherwise were considered censored. For each participant, OS was defined as the time from enrollment to death or last date confirmed alive. Participants who died were considered to have experienced an OS-event, or otherwise were considered censored at time of last contact.

The probability of remaining event-free as a function of time post-enrollment was estimated by the method of Kaplan and Meier.[24] Risk of event was compared across groups defined by randomised regimen using the log-rank statistic. Relative hazard ratios (RHR) and 95%CI

were generated by fitting a relative risk regression model using partial likelihood where the model contained the characteristic of interest as the only variable. Survival estimates were computed as 3-year EFS and OS (denoted as EFS_3 and OS_3, respectively). All eligible participants were considered in the survival analyses. The outcome of each participant was associated with that participant's randomised treatment assignment (intent-to-treat). All statistical calculations were performed using SAS version 9.4 or STATA version 14.

Role of the Funding Source

There was no external sponsor for this study. 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 collection, analysis or interpretation of the data, or in the writing of this report. Fennec Pharmaceuticals, which provided STS 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 of the data and the final responsibility to submit for publication.

RESULTS

ACCL0431 was activated on June 23, 2008 and closed on September 28, 2012 for having reached its planned accrual goal. Interim monitoring was performed as specified and resulted in recommendations to continue the trial as planned. Data current to March 31, 2015 were used in this analysis.

Participants

The flow of participant enrollment and analysis is shown in the Trial Profile (Figure 1). A total of 131 participants were enrolled from 38 institutions. Six were deemed ineligible because of being co-enrolled on a disease-directed COG therapeutic study (n=5, with 3 randomised to STS and 2 to control) or not having documentation of normal baseline serum electrolyte values (n=1, randomised to STS). Of the 125 eligible participants, 38 were enrolled before and 87 following the amendment allowing participants who had received prior cranial irradiation (n=9). As shown in Table 1, there were no significant differences in baseline characteristics by randomisation group. In both groups, germ cell tumour was the most common diagnosis followed by approximately equal numbers of medulloblastoma/CNS PNET, neuroblastoma and osteosarcoma. The overall proportions with disseminated disease at study entry were similar. The proportions who had received prior cranial irradiation were similar. The diagnosis-specific distribution of participants by randomisation group with respect to age and extent of disease is summarised on page 1 of the Appendix; characteristics were relatively well-balanced between groups. The median cumulative cisplatin dose (range) for the control and STS groups was 387 mg/m^2 (198–625) and 393 mg/m^2 (91–605), respectively. The median cumulative STS dose (range) was 95.8 gm/m^2 (12.9–383.5). The proportion of participants who had received loop diuretics or aminoglycoside antibiotics was similar in the control (17/64, 26.6%) and STS (17/61, 27.9%) groups. No participants underwent HCT prior to evaluation for the primary endpoint.

Hearing Loss

The primary study aim was to compare the proportional incidence of post-treatment hearing loss in the two randomised groups at 4 weeks post-completion of all cisplatin. As shown in Figure 1, there were 104 participants evaluable for this outcome, 55/64 in the control group and 49/61 in the STS group. Of these, participants < 5 years old accounted for 15/55 (27.2%) in the control group and 14/49 (28.6%) in the STS group. Hearing loss was identified in 14/49 (28.6%, 95%CI 16.6, 43.3) of the STS group compared with 31/55 (56.4%, 95%CI 42.3, 69.7) of the control group (p=0.00022). Hearing loss was compared within the three pre-randomization strata of age, duration of cisplatin infusion, and prior cranial irradiation. For age < 5 years, the incidence of hearing loss was strikingly lower with STS than control (3/14 [21.4%, 95%CI 4.7, 50.8] versus 11/15 [73.3%, 95%CI 44.9, 92.2], respectively) and somewhat less so for older patients (11/35 [31.4% 95%CI 16.9, 49.3] versus 20/40 [50.0%, 95%CI 33.8, 66.2], respectively). The incidence of hearing loss was lower for STS than control after cisplatin infusion of 2–6 hours (10/24 [41.7%, 95%CI 22.1, 63.4] versus 21/30 [70.0%, 95%CI 50.6, 85.2], respectively) and after cisplatin infusion of < 2 hours (4/25 [16.0%, 95%CI 4.5, 36.1] versus 10/25 [40.0%, 95%CI 21.1, 61.3], respectively). The stratum of prior cranial irradiation contained only 8 evaluable participants, where hearing loss occurred in 2/4 (50.0%) STS-treated participants versus 4/4 (100.0%) controls. When these 8 irradiated participants were excluded from the analysis, hearing loss was noted in 12/45 (26.7%, 95%CI 14.6, 41.9) of the STS group compared with 27/51 (52.9%, 95%CI 38.5, 67.1) of controls (p=0.0045). By the logistic test adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the STS group compared with control group (OR 0.31, 95%CI 0.13, 0.73; p=0.00036). When the 8 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 evaluable for hearing loss at the primary endpoint, 67 were also evaluable at 1 year; of these, 9/32 (28.1%) who received STS exhibited ASHA-defined hearing loss compared with 19/35 (54.3%) of controls (p=0.0015). For the 8 evaluable participants who had received prior cranial irradiation, none of their hearing outcomes changed at 1 year.

A secondary study aim was to compare mean frequency-specific hearing thresholds measured at baseline and post-treatment. For each randomised group, the mean change in hearing threshold was computed within key frequencies and compared. As shown in Table 2, for the STS group the change in hearing threshold following cisplatin treatment was smaller, indicating more normal hearing, at every frequency above 1000 Hz, most notably at 4000 Hz and above.

Toxicity

Another secondary aim was to compare the incidences of Grade 3–4 haematological and renal toxicity by STS assignment. Haematological toxicity was not significantly different between the groups, occurring in 172/223 (77.1%) and 137/177 (77.4%) of participant-cycles in the control and STS groups, respectively (p=0.95); details regarding the individual haematological toxicity components are shown in Table 3. Aggregate nephrotoxicity was more common in the STS group, where 37/147 (25.2%) of participant cycles were affected versus 25/187 (13.4%) among controls (p=0.0059). Details regarding the individual

nephrotoxicity components are displayed in Table 4, where hypophosphataemia and hypokaalemia were somewhat more common in the STS group. Of note, there were no cases of either increased creatinine or reduced GFR that met the Grade 3 threshold in either group.

The most common grade 3–4 haematological adverse events (AE) reported in STS and control participants, irrespective of attribution, were neutropaenia in 117/177 (66.1%) and 145/223 (65.0%) participant-cycles, while the most common non-haematological AE was hypokalaemia in 25/147 (17.0%) and 22/187 (11.8%) participant-cycles, respectively. As part of the NCI Adverse Event Reporting System, this study included expedited reporting of serious adverse events (SAE). Reporting was required only for participants randomised to the STS group. There were 194 toxic effects reported in this fashion. Of these, 112 were considered unrelated, 62 unlikely, 20 possibly, and none probably or definitely related to STS. Of these, 85 were non-haematological where 49 were considered unrelated, 25 unlikely, 11 possibly, and none probably or definitely related to STS. The 3 most common SAEs were neutrophil count decreased (26/194, 13.4%), platelet count decreased (23/194, 11.9%), and anaemia (21/194, 10.8%),

Survival

The final secondary aim of this study was to monitor EFS and OS to assess whether STS might influence chemotherapy effect. All 125 eligible patients were considered in this analysis at a median follow-up of 3.5 years post-study entry years (interquartile range for EFS and OS 1.4–4.5 and 1.5–4.5, respectively). As shown in Figure 2, no significant difference was detected between the control and STS groups in aggregate for EFS or OS (log-rank p=0.36 and 0.07, respectively). For the STS arm, the RHRs (95%CI) for EFS and OS risks were 1.30 (0.75, 2.26) and 2.03 (0.93, 4.44), respectively. The EFS_3 and OS_3 estimates (95%CI) for control versus STS groups were 64% (50, 74) versus 54% (40, 66) and 87% (76, 93) versus 70% (56, 80), respectively. Among the 64 controls, there were 24 events and 10 deaths; among the 61 participants assigned to STS, there were 26 events and 17 deaths. All events were relapse except for one participant in the STS group who developed a SMN. As classified by site investigators, all deaths were considered due to disease except for one attributed to cancer treatment-related sepsis in the STS group, but not related to STS.

Because of the possibility of an STS effect on survival that emerged in aggregate, a *post hoc* stratification of the sample by extent-of-disease at enrollment was performed. As shown in Figure 3A, within the group deemed to have localised disease (n=77) there was no significant difference in EFS or OS (log-rank p=0.73 and 0.88, respectively). For the STS arm, the RHRs (95%CI) for EFS and OS were 1.14 (0.54, 2.43) and 1.09 (0.35, 3.38), respectively. The EFS_3 and OS_3 (95%CI) estimates for control versus STS groups were 66% (48, 78) versus 60% (42, 74) and 89% (74, 96) versus 83% (66, 92). Among those with localised disease, there were 14 events and 6 deaths in both the control and STS groups. As shown in Figure 3B, among those deemed to have disseminated disease (n=47), there was no difference in EFS (log-rank p=0.16; RHR [95%CI] 1.80 [0.78, 4.12]), but OS was significantly lower in the STS-treated group (log-rank p=0.0090; RHR [95%CI] 4.10 [1.30, 12.97]). The EFS_3 and OS_3 (95%CI) estimates for control versus STS groups were 61% (39,

77) versus 42% (21, 61) and 84% (62, 94) versus 45% (23, 65), respectively. In those with disseminated disease, there were 10 events and 4 deaths in the control group, and 12 events and 11 deaths in the STS group.

DISCUSSION

We report the results of a multicentre RCT showing that STS significantly reduces risk for developing CIHL in children and adolescents treated for cancer. Consistent with our hypothesis, delayed post-cisplatin administration of STS in a study sample comprising a mixture of ages, diagnoses and chemotherapy regimens reduced the cumulative incidence of ASHA-defined CIHL by approximately 50%. With these results, STS becomes the first proven agent tested under these conditions and thus represents an important development in translational otoprotection research. It is notable that, to our knowledge, ACCL0431 is the first NCI-funded cooperative group clinical trial focused solely on prevention of CIHL in either children or adults. As such, the ACCL0431 experience demonstrates both the feasibility and scientific value of conducting otoprotection studies in the cooperative group setting. This study addresses a clinically important goal because of the profound, negative impact 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 CIHL and chronic tinnitus include reduction of their many downstream effects on language acquisition, learning, psychosocial development, and social functioning.[9,10]

The lack of effective otoprotectants in humans limits comparison of our results to those with other agents.[25] To date, amifostine has been studied the most but showed no benefit in two embedded COG RCTs for hepatoblastoma and germ cell tumours.[26,27] In a more recent non-randomised, comparative prospective cohort study of children/adolescents treated with cisplatin for medullobastoma, Fouladi and colleagues reported otoprotection with a more dose-intensive amifostine regimen.[28] Compared with amifostine where hypocalcemia and hypotension are common and require monitoring and management protocols, STS was substantially simpler to administer.[29] We were unable to detect any protective effect of STS on renal or haematopoietic function. Interestingly, nephrotoxicity as defined in our study was more common in the STS group but, importantly, not due to abnormal serum creatinine or GFR but rather hypophosphataemia and hypokalaemia, explanations for which are unknown. Data regarding clinical consequences and treatment of haematological or renal toxicity were not collected. Whether STS may have helped preserve cisplatin dose-intensity through avoidance of dose modifications was unable to be assessed because cancer therapy was not protocol-specified.

Survival was a secondary endpoint of this study. No statistically significant difference in EFS or OS by randomization was detected among our participants as a whole. In the stratified *post hoc* analysis by extent of disease at presentation, no difference in EFS or OS was observed for those with localised disease. However, for those with disseminated disease, lower EFS and OS were noted. There are two broad potential explanations for this finding. First, STS may be tumour protective in addition to being otoprotective, and this effect may be most pronounced among those with poorer prognosis where the incremental effect of cisplatin is important for disease control. Also, a tumour protective effect against other

agents used in combination with cisplatin cannot be excluded. The second potential explanation could relate to disease characteristics that might influence outcome but were unable to be measured directly due to the design of our study. For example, a wide variety 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 appears relatively well-balanced between the randomisation groups, we did not capture disease biology, an important outcome determinant routinely incorporated in the risk-classification of some pediatric cancers. This combined with minor imbalances of uncommon poor-prognosis malignancies could be relevant (Appendix, page 1). Among those with disseminated disease, the magnitude of difference related to STS was greater for OS than EFS, a finding also not readily explained. One could speculate that relapsed patients previously exposed to STS responded less well to retrieval therapy than controls, but this possibility cannot be assessed because data collection regarding relapse therapy and responses were beyond the scope of this trial. While relapses accounted for all but one event, our data did not suggest these occurred disproportionately among any particular diagnostic subset.

ACCL0431 was designed as a proof-of-concept study focused on the otoprotective effects of STS. 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 conducted in a cooperative group setting comprising both academic and community-based institutions of various size are significant strengths. Including diverse cancer diagnoses and risk groups offered an efficient accrual strategy and allowed STS to be tested across the age spectrum and a variety of treatment regimens. Another strength was the use of masked audiometry data by central reviewers who adjudicated the primary ototoxicity endpoint, thus reducing bias. On the other hand, this heterogeneity may have complicated our ability to understand potential differential effects of STS on survival influenced by 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. Sample size was calculated for the primary outcome and survival was monitored to detect relatively large differences between groups. In our effort to elucidate an apparent survival difference that emerged in the aggregate, retrospective application of a simple, binary classification for extent-of-disease to our diverse sample may have helped isolate an anatomic subset where STS might impact outcome, but it is unlikely to take account of all the factors that inform disease-specific risk classification. Although 21 participants (16.8%) were not evaluable for the hearing outcome, they were distributed approximately equally by randomisation and similar to other participants except for predominantly being < 5 years old. This reflects unique challenges inherent to otoprotection studies involving young children, where developmental stage and medical disability may limit cooperation for audiometry. Despite these challenges, it is notable that those < 5 years old constituted the largest age group on this trial, accounting for one-third of all participants (44/125). Administration of potentially ototoxic loop diuretics and aminoglycoside antibiotics was collected for all participants. Although quantitative pharmacological data for these and carboplatin exposure were not, it is reasonable to assume these factors were similarly balanced through randomisation.

Further, all patients completed post-treatment audiometry prior to any HCT, where myeloablative carboplatin is typically used for treatment of high-risk neuroblastoma. In ACCL0431, hearing loss was graded according to the ASHA scale, which was selected because it was considered the most sensitive among those available at the time. Since then, the SIOP-Boston scale has been developed and is considered to offer certain advantages, including no requirement for a pre-treatment baseline measurement.[4] Retrospective conversion of our results to the SIOP-Boston scale presented significant 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 agents. For example, we feel otoprotection studies should be linked, whenever possible, to disease-focused trials or protocol-specified regimens to ensure consistent diagnoses, staging and risk classification, therapy, data capture for cisplatin dose modifications, and collection of survival data as a primary focus. 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 STS and chemotherapy that could obfuscate or alter survival outcomes on key frontline trials. Given that some ACCL0431 participants may have been included because they were not eligible for a therapeutic trial, it is possible that the overall prognosis of the ACCL0431 cohort may have been different than all cisplatin-treated paediatric cancer patients. However, it does not detract from the internal validity of our study or our conclusions related to STS-related otoprotection and potential survival effect. Additionally, the study of agents requiring time-modulated administration post-cisplatin to avoid tumour protection presents challenges because interference may be a continuous rather than dichotomous effect. Finally, otoprotectants that are mechanistically distinct from the cytotoxic effects of chemotherapy or that are administered by non-systemic routes (e.g., intra-tympanic injection) may offer theoretical advantages.

In the interim, with this present report identifying STS as a commercially available agent that reduces CIHL, at least one immediate question is raised. Approximately two-thirds of children enrolled on ACCL0431 were classified as having localised disease, where no difference in either EFS or OS was detected among those treated with STS. Can STS be used safely in this subset of children? In this regard, encouraging preliminary results have been reported from SIOPEL-6, an international randomised clinical trial for children with standard-risk hepatoblastoma treated using single-agent cisplatin with or without STS 20 gm/m^2 administered on the same schedule as ACCL0431 (NCT00652132). This important trial employs an alternative design involving only one cancer diagnosis treated with a protocol-specified regimen of single-agent cisplatin. While hearing outcomes on that study are not expected until late 2017, a recent survival analysis involving 109 patients revealed no difference in 2-year EFS or OS for STS versus controls (89.0% versus 86.3% and 97.7% versus 91.4%, respectively).[30]

Only after final results are available from SIOPEL-6 to enlighten the interpretation of ACCL0431 will it become possible to develop firm recommendations concerning a potential future role for STS in clinical practice or future randomised trials. It seems likely the two

trials will prove complementary and provide a more complete understanding of the effects of STS than either study alone. Thoughtful discussion within the community of stakeholders involving paediatric oncologists, otolaryngologists, audiologists, parents, and survivors living with CIHL will be required. Whether or not consensus can soon be reached on the question of using STS for carefully-defined patient subsets, it seems clear that completion of ACCL0431 signals a new era in which historical acceptance of CIHL as an inevitable consequence of curative cancer treatment has given way to more encouraging possibilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Evidence before This Study

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

Added Value of This Study

To our knowledge, ACCL0431 is the first cooperative oncology group-sponsored, multicentre RCT focused solely on prevention of CIHL in children and adolescents treated for cancer using various disease-specific chemotherapy regimens. Our findings establish that STS significantly reduces the incidence of CIHL among children and adolescents. This benefit appears to be greatest among children less than five years old, who are most susceptible to CIHL. A secondary study aim was to monitor event-free survival and overall survival (OS) for potential effects of STS on tumour response to treatment. We found there was no apparent effect related to STS among participants with localised disease, but among those with disseminated disease OS was significantly lower.

Implications of All the Available Evidence

To our knowledge, STS is the first proven agent tested under these conditions to reduce risk for CIHL, thus representing an important development in translational otoprotection research. At the same time, the significantly lower OS observed among participants with disseminated disease who received STS necessitates caution when considering an appropriate future role for STS in clinical practice and research. Recommendations for this will be informed by the results of the ongoing SIOPEL-6 study involving only subjects with standard-risk hepatoblastoma treated on a protocol-specified regimen of single-agent cisplatin. Additional research and thoughtful consideration is needed to

understand what role STS and other potential agents should have in preventing CIHL among certain subsets of at-risk patients.

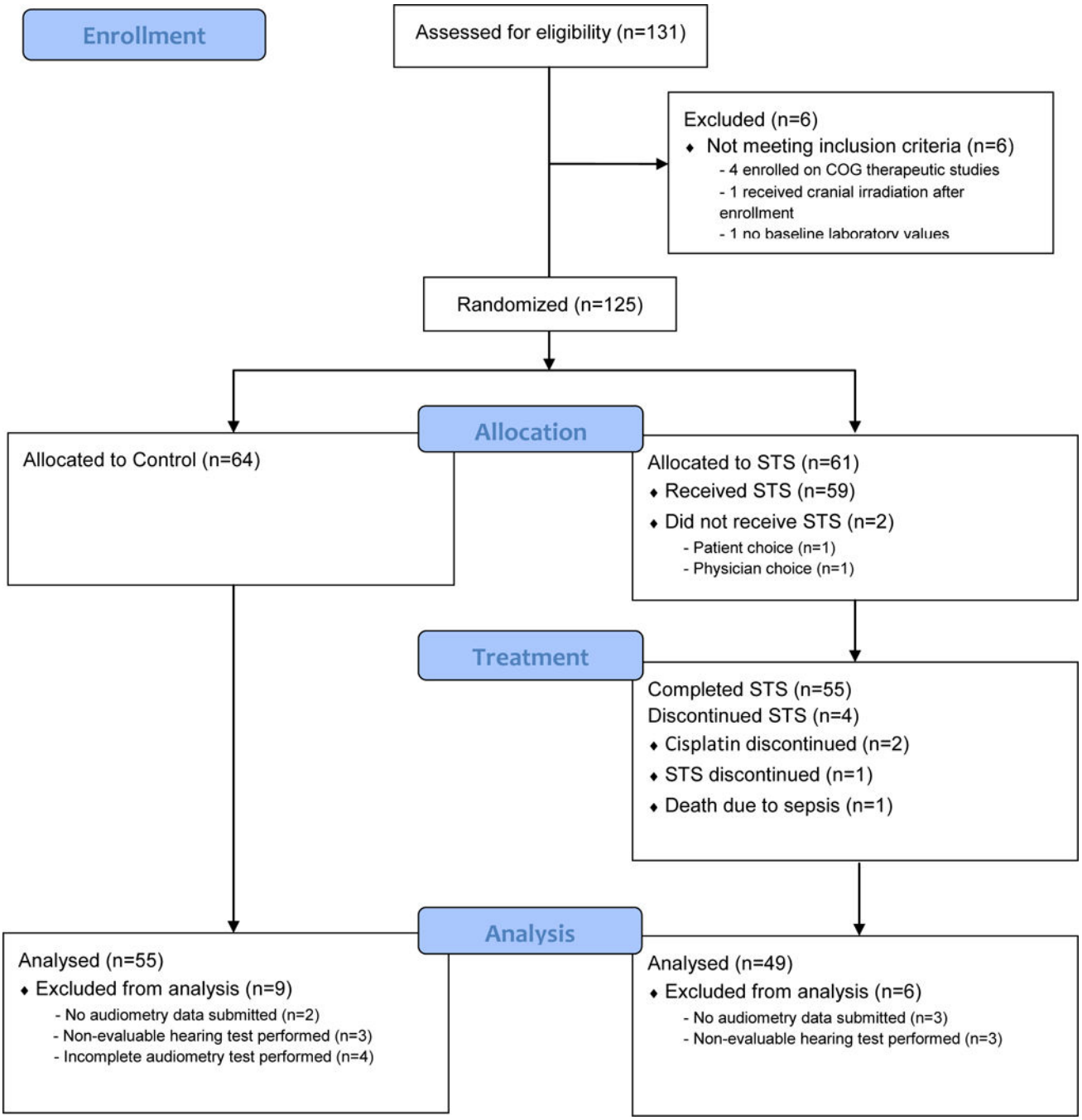

Figure 1.
Trial Profile

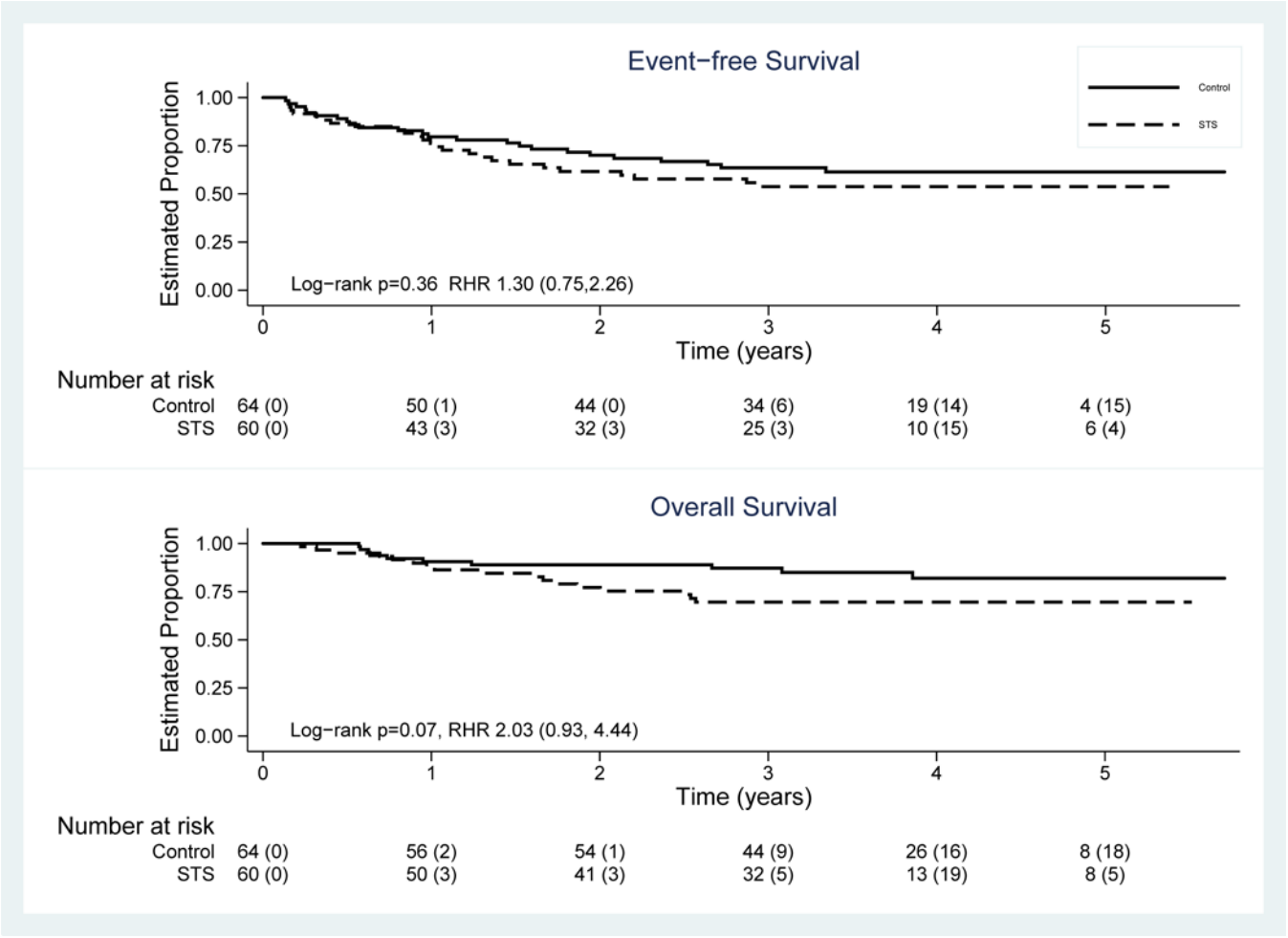

Figure 2. Event-free and Overall Survival by Randomisation for All Participants (n=125)

RHR=relative hazard ratio (95% Confidence Interval); STS=sodium thiosulfate. Parentheses indicate number censored.

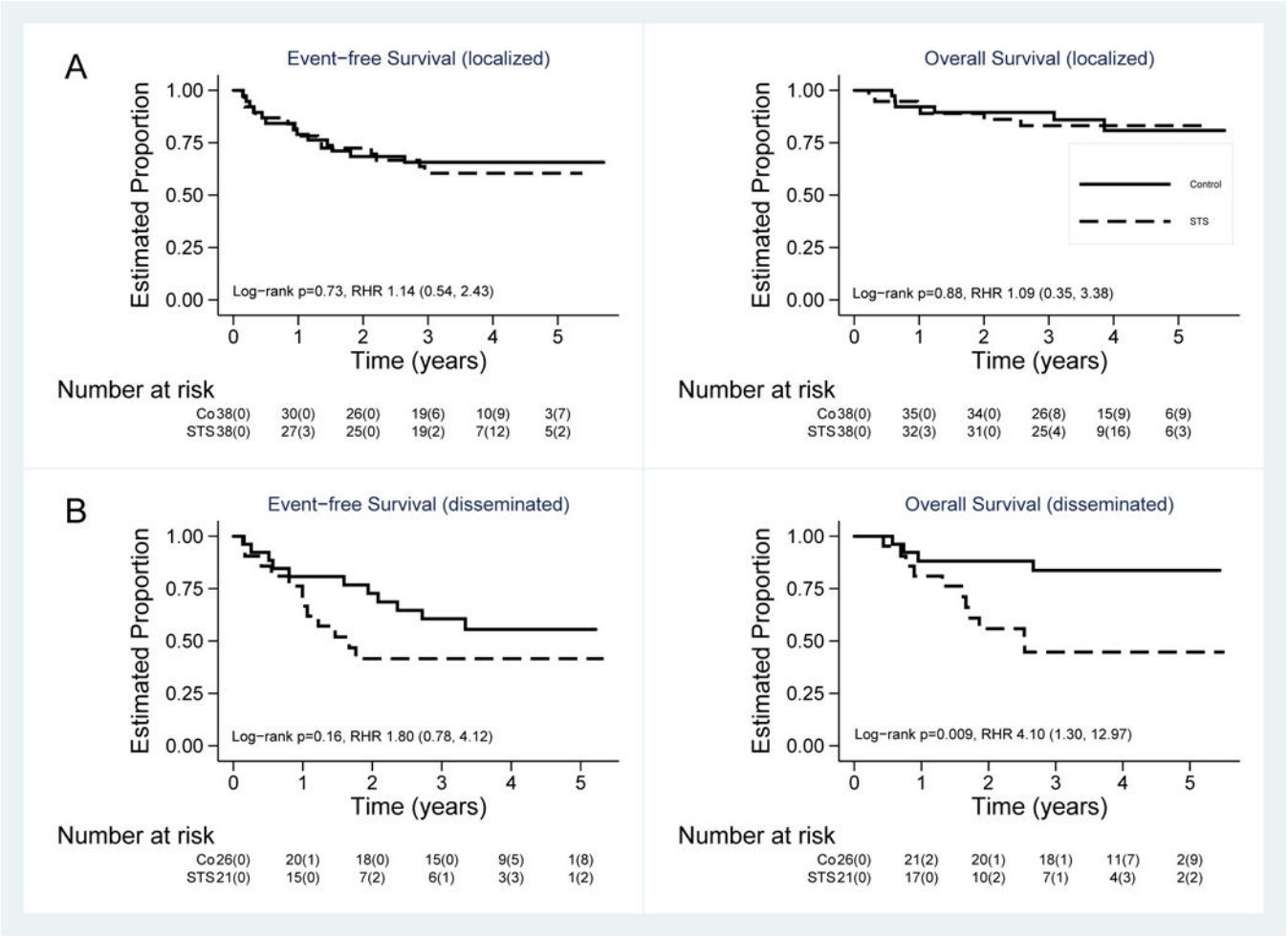

Figure 3. Event-free and Overall Survival by Randomisation and Extent of Disease (n=124)[1]

(A) Participants with localised disease (n=77).

(B) Participants with disseminated disease (n=47).

Co=control; RHR=relative hazard ratio (95% Confidence Interval); STS=sodium thiosulfate.

Parentheses indicate number censored.

[1]Extent of disease unknown for one participant

Table 1

Baseline Characteristics

Characteristic	Treatment			
	Control		STS	
	n	%	n	%
Number eligible	64	–	61	–
Age (years)				
<5	22	34.4	22	36.1
5–9	13	20.3	7	11.5
10–14	14	21.9	16	26.2
15–18	15	23.4	16	26.2
Sex				
Male	41	64.1	35	57.4
Female	23	35.9	26	42.6
Race				
White	39	60.9	42	68.9
Black	10	15.6	5	8.2
Asian	2	3.1	1	1.6
Hawaiian/Pacific Islander	1	1.6	1	1.6
American Indian/Aleutian/Eskimo	0	0	1	1.6
Other	8	12.5	11	18.1
Unknown	4	6.3	0	0
Ethnicity				
Non-Hispanic	46	71.9	41	67.2
Hispanic	15	23.4	18	29.5
Unknown	3	4.7	2	3.3
Diagnosis				
Germ cell tumour	16	25.0	16	26.2
Hepatoblastoma	5	7.8	2	3.2
Medulloblastoma/CNS PNET	14	21.9	12	19.7
Neuroblastoma	12	18.8	14	23.0
Osteosarcoma	15	23.4	14	23.0
Other	2	3.1	3	4.9
Extent of disease[1]				
Localised	38	59.4	39	63.9
Disseminated	26	40.6	21	34.4
Unknown	0	0	1	1.6

[1] Determined *post hoc*.

Table 2

Mean Change in Frequency-specific Hearing Thresholds by Randomisation

Frequency (Hz)	Change in Hearing Threshold[1] (dB)						p	Difference in Mean Change Between Groups (dB)
	Control			STS				
	Mean	n	SD	Mean	n	SD		
500	−1.1	45	8.6	−1.5	38	5.8	0.34	0.4
1,000	−0.3	47	9.0	−0.7	37	4.6	0.36	0.4
2,000	0.6	47	12.7	−1.2	38	4.9	0.42	1.8
4,000	9.6	47	20.5	1.1	38	7.1	0.11	8.5
8,000	17.0	42	24.7	9.7	37	17.3	0.18	7.3

[1] A negative value indicates a better mean hearing threshold compared to the baseline evaluation and a positive value indicates a poorer mean hearing threshold.

Table 3

Components of Reported Haematological Toxicity by Randomised Group[1]

Component	Cisplatin Cycle 1		Cisplatin Cycle 2		Cisplatin Cycle 3		Cisplatin Cycle 4		Cisplatin Cycle 5		Cisplatin Cycle 6	
	STS[2] (n=55)	Ctrl[3] (n=61)	STS (n=51)	Ctrl (n=57)	STS (n=34)	Ctrl (n=46)	STS (n=27)	Ctrl (n=33)	STS (n=8)	Ctrl (n=16)	STS (n=2)	Ctrl (n=10)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutrophil count decreased	36 (65.5)	41 (67.2)	34 (66.7)	37 (64.9)	22 (64.7)	32 (69.6)	18 (66.7)	18 (54.5)	6 (75.0)	11 (68.8)	1 (50.0)	6 (60.0)
Platelet count decreased	23 (41.8)	27 (44.3)	28 (54.9)	24 (42.1)	20 (58.8)	22 (47.8)	16 (59.3)	19 (57.6)	6 (75.0)	8 (50.0)	1 (50.0)	6 (60.0)
Anaemia	14 (25.5)	21 (34.4)	20 (39.2)	23 (40.4)	15 (44.1)	17 (37.0)	12 (44.4)	17 (51.5)	7 (87.5)	10 (62.5)	1 (50.0)	7 (70.0)

[1] Grade 3 or higher, CTCAE version 4.0

[2] STS = STS Group

[3] Ctrl = Control Group

Table 4

Components of Reported Nephrotoxicity by Randomised Group[1]

Component	Cisplatin Cycle 1		Cisplatin Cycle 2		Cisplatin Cycle 3		Cisplatin Cycle 4		Cisplatin Cycle 5		Cisplatin Cycle 6	
	STS[2] (n=47)	Ctrl[3] (n=55)	STS (n=44)	Ctrl (n=51)	STS (n=27)	Ctrl (n=39)	STS (n=23)	Ctrl (n=27)	STS (n=6)	Ctrl (n=9)	STS (n=0)	Ctrl (n=6)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Acidosis		1 ·8 (1)			1 (3 7)		1 (4.3)					
Creatinine												
Glomerular Filtration Rate												
Hypokalaemia	6 (12.8)	7 (12.7)	9 (20.5)	8 (15.7)	7 (25.9)	5 (12.8)	2 (8.7)	1 (3.7)	1 (16.7)			1 (16.7)
Hypomagnesaemia			1 (2.3)	2 (3.9)	1 (3.7)				1 (16.7)			
Hypophosphataemia	3 (6.4)	2 (3.6)	2 (4.5)	3 (5.9)	5 (18.5)	1 (2.6)	4 (17.4)	1 (3.7)	1 (16.7)			

[1] Grade 3 or higher, CTCAE version 4.0

[2] STS = STS Group

[3] Ctrl = Control Group