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Journal

Pediatric Blood & Cancer, 67(11)

ISSN

1545-5009

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Publication Date

2020-11-01

DOI

10.1002/pbc.28647

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Pediatr Blood Cancer. 2020 November ; 67(11): e28647. doi:10.1002/pbc.28647.

Assessment of provider perspectives on otoprotection research for children and adolescents:a Children's Oncology Group Cancer Control & Supportive Care Committee survey

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Abstract

BACKGROUND: Cisplatin-induced hearing loss (CIHL) is a common and debilitating toxicity for childhood cancer survivors. Understandingprovider perspectives is crucial to developing otoprotectionstudies that are both informative and feasible. Two international trials (ACCL0431, SIOPEL6) investigated the drug sodium thiosulfate (STS) as an otoprotectant, but definitive interpretation of the findings of these trials has been challenging. Adoption of STS has therefore been uneven and provider perspectives on its role unknown.

PROCEDURE: TheChildren's Oncology Group (COG) Cancer Control and Supportive Care Neurotoxicity Subcommittee therefore conducted asurvey of providers at COG institutionsto determine perspectives on pediatric otoprotectionpractices and researchsurrounding three major themes: (1) prevalence of routine use of STS with cisplatin-based regimens, (2) application of audiometry to cisplatin therapy, and (3) preferred modalities for otoprotection research.

RESULTS: Survey respondents (45%, 44/98surveyed institutions) were of diverse institutional sizes, practice settings, and geographical locations primarily in United States and Canada. Overall, respondents considered CIHL an important toxicity and indicated strong enthusiasm for future

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Conflicts of Interest Statement: E Orgel served on an advisory board for Servier Pharmaceuticals outside the scope of this work. No other authors report any disclosures.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

studies (98%, 40/41). Results indicated that while STS was the current or planned standard of care in a minority of responding institutions (36%, 16/44), most sites were receptive to its inclusion in appropriate study designs. Application of audiometry for ototoxicity monitoring varied widely across sites. For otoprotection research, systemic agents were preferred (68%, 28/41) as compared to intratympanic approaches.

CONCLUSION: These results suggest that pediatric otoprotection trials remain of interest to providers; the emphasis of these trials should remain on systemic and not intratympanic therapy.

Keywords

Cisplatin; hearing loss; ototoxicity; otoprotection; sodium thiosulfate

INTRODUCTION

The chemotherapy agent cisplatin is the therapeutic backbone for nearly 40% of newly diagnosed non-hematologic tumors in children and adolescents.[1]More than 5,000 pediatric patients are treated with cisplatin each year.[2] While effective for cure, cisplatin damagesthe auditory sensory structures of the cochleaand causes permanent and progressive cisplatin-induced hearing loss (CIHL) in up to 80% of children receiving platinum-intensive therapy.[3–6]CIHL impacts the quality of life in survivors due to neurocognitive deficits, difficulty with socialization, and poorer long-term academic and work achievement.[7–11]

Recently, sodium thiosulfate (STS) was evaluated for potential to prevent CIHL in two international, contemporaneous, Phase III randomized trials, the Children's Oncology Group (COG) ACCL0431[12]and the International Childhood Liver Tumors Strategy Group (SIOPEL) SIOPEL-6.[13] In comparing the randomized groups, both trialsdocumented a significant, approximately 50% reduction in the proportional incidence of hearing loss among those who received STS. Results concerning potential impact of STS on cisplatin efficacy differ somewhat by study. Briefly, SIOPEL-6 indicated no impactof STS on event free survival (EFS) or overall survival (OS) in young children treated for standard-risk hepatoblastoma using one protocol-specified cisplatin regimen. In contrast, ACCL0431 enrolled a heterogeneousmix of patients with multiple cancer types and stages receiving variouscisplatin regimens; in a *post hoc*stratified survival analysis by extent of disease, lower EFS and OSwere found in those receiving STS and classified as having disseminated disease, but not in those with localized disease.Definitive interpretation of these combined results has proven challenging due to key design differences between the two studies.[14]Consequently, theresults of ACCL0431 and SIOPEL-6 are considered complementary andhave been used in combination to informthoughtful discussion regarding the efficacy, safety, and role of STS in pediatric cancer care and in otoprotection research.[13,15–18]However, to our knowledge, provider perspectiveson these issues have not been assessed in light of thesestudies and are currently unknown.

To determine an approach tootoprotection research that is both scientifically appropriate and feasible, it is necessary to have an informed understanding of provider practices and viewpoints regarding STS and other potential otoprotectants.Within the COG, the Cancer Control and Supportive Care (CCL) Committeeconducts research focused on the "reduction

of acute and delayed treatment-related toxicities in children with cancer."[19]To investigate issues most pressing to thosetreating patients across the spectrum of academic and community-based sites, the CCL Committee created a "Responsible Individual Network" (RI Network) to obtain input from clinical oncology providers.[19–21]Using this representative network, the CCL Neurotoxicity Subcommittee conducted a survey to understand provider perspectives within three domains relevant to otoprotectionresearch in the cooperative group setting: (1) prevalence of routine use of STS with cisplatin-based regimens, (2) application of audiometry to cisplatin therapy, and (3) preferred modalities for otoprotection research.

METHODS

Survey design

The COG CCL Committee developed an anonymous, electronic survey to explore views on otoprotection use, ototoxicity monitoring, and potentialresearch. The survey was piloted with COG CCL Committee leadership and revised according to feedback prior to wider dissemination. The survey (see Supplemental Data) included answer formatswith dichotomized yes/no responses as well as multiple-choice matrices and optional free-text fields for additional comment.The survey introduction referenced both aforementionedSTStrials and the goal to understand the implications of the results for standard of care (SOC) and otoprotectionresearch. Questions regarding STS were prefaced with references to both trials. Questions regarding physiological and behavioral audiometry techniques were prefaced with lay-language descriptions of each technique.The electronic survey was distributed to the CCL RI network via emailbetween February and August 2019 with three email reminders to maximize response rate. Respondents with incomplete surveys (skipped questions) were included and results were therefore presented for each question inclusive of the denominator to indicate the answer pool. Statistical analyses incorporated tests of proportions and non-parametric comparisons (Wilcoxon) using STATA SE version 15 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of responding institutions

Survey responses were received from 44of 98 CCL RI sites (45%). These included institutions located in the United States (n= 23 states), Canada (n=8 sites), and New Zealand (n=1 site). Estimated patient volume varied by institution with a median of 17 pediatric patients treated with cisplatin-containing regimens per year (range 3–50);25% (11/44) treated <10 patients/year, 39% (17/44) treated 10–19 patients/year, and 36% (16/44) treated ≥20 patients/year.

Prevalence of routine use of STS

A minority of respondents (36%, 16/44) indicated their institutions had current or future plans to routinely incorporate STS into any cisplatin-based therapy as SOC. Among these sites, criteria for use of STS varied (Table 1). STS was reported as used variably across different tumor types and in patients with localized and disseminated tumors (Figure 1). The

broadest support for routine use of STS was for patients with localized hepatoblastoma(81%, 13/16), and to a lesser extent in treatment ofmedulloblastoma and osteosarcoma (56% for both, 9/16). Of institutions indicating they had no plans to use STS as SOC (64%, 28/44), 82% (23/28) provided free-text responses of their views on current barriers to routine usage of STS (Table 1). There was no difference in use of STS by institutional patient volume (median of 13 versus 12 patients/year, p=0.685).

Application of audiometry to cisplatin therapy

Allinstitutions (100%, 41/41) routinely assessCIHL at baseline, during treatment, and/or after completion of therapy. However, audiometry assessment schedules and modes of testing vary widely among sites. A minority of sites assess hearing before every dose of cisplatin (27%, 11/41) while most sites evaluate hearing prior to autologous hematopoietic cell transplantation (66%, 27/41%). Sites were asked whether they would factor results of extended behavioral and physiological audiometry into clinical decision-making changes; the minority replied they would do so for high-frequency audiometry (HFA)at frequencies >8,000 Hz (17%, 7/41), distortion-product otoacoustic emission (DPOAE)at “speech frequencies” (33%, 13/40), and/or speech audiometry to complement conventional audiograms (40%, 16/40). Most sites reported they were “not sure” how to use these audiometry results to guide clinical decision making (Figure 2). Patient age did not influence frequency of audiometry testing protocols for most institutions (78%, 32/41). Enrollment in a research trial did not alter planned audiometry for nearly all institutions (90%, 37/41).

Preferred modalities for otoprotection research

All but oneinstitution (98%, 40/41) supported continued otoprotectionresearchinto systemic agents for localized tumors. The primary concern from the single opposing site was the limitations of otoprotective agents currently available for study. Sites were asked about a potential control arm for a future randomized trial in localized tumors. Among sites not routinely using STS, most were supportive of usingSTS as the control arm (96% [26/27]). Among sites routinely using STS for at least some patient subsets, fewer were amenable toan observation-only arm (67% [10/15), p=0.009). When asked about the preferred modality of a prospective investigative agent, 68% (28/41) preferred systemic otoprotectionwhile 32% (13/41) favored an intratympanic approach. Centers open to investigating anintratympanicapproach treated more patients per year than those favoring systemic agents (median 25 versus 10 patients/year, p=0.025). Reasonsin favor of pursuing intra-tympanicotoprotectionincluded eliminating concerns over tumor protection and the challenging side effect profile of systemic agents. Conversely, barriers to intratympanic regimens included concerns for sedation, procedural invasiveness, the availability of otolaryngologists, and logistical challenges of coordinating the procedure.

DISCUSSION

This survey of pediatric oncology providers in the COG CCL RI network was undertaken to determine current clinical practice patterns for use of STS, application of audiometry among children and adolescents receiving cisplatin, and how providers are prioritizing engagement in otoprotection research. These three themes are essential to understand how findings from

the recent otoprotection trials are being applied to clinical practice in order to guide the focus and implementation of future trials. Though the survey was conducted within the COG, respondents included a wide range of program sizes and geographic locations. The cohort was thus largely representative of pediatric oncology practice settings in the United States and Canada.

Two international randomized clinical trials, ACCL0431 and SIOPEL-6, have demonstrated efficacy of STS in preventing CIHL in children with cancer. Bothsignificantly reduced the prevalence of hearing loss from approximately 55–60% among children in the control arm to approximately 29–33% in those whoreceived STS [12, 13]. Despite this,survey data showedthat a majority of responding institutions currently do not use, and have no plans to use,STS with cisplatin-containing regimens as standard of care.Respondents described a perceived need foradditional data validatingthe efficacy and safety of STS. Specifically, respondents questioned whether current trial results can be generalized across all cisplatin-based treatment regimens, including among different tumor types and stages. These concerns likely stem from the differing results of ACCL0431 and SIOPEL-6regardingsurvival by randomized group (STS versus control). The primary endpointof the ACCL0431 study was hearing loss; EFS and OS were therefore monitoredonly to detect unanticipated large differences. As such, the study enrolled multiple tumor types,comprised oftumors of any disease extent and staging, and included a wide variety of cisplatin-containing regimens. At completion of the STS trial, an unplanned *post hoc* analysis examined EFS and OS stratified by extent of disease (localized versus disseminated).Participants classifiedas having localized disease demonstrated no survival difference by randomized group, whereas those with disseminated disease demonstrated no difference in EFS but a significant four-fold increase in risk for lower OS if they had received STS (log-rank p=0.0090).[12]However, as a *post hoc* analysis, it is unknown if this difference in OS reflects an imbalance of unmeasured biological risk factors between the randomized groups. In contrast, SIOPEL-6 enrolled only children with localized/standard-risk hepatoblastomareceiving the same regimen and found no difference in tumor necrosis, EFS, and OS by randomized arm.[13] While caution must be used in interpreting the *post hoc* analysis of ACCL0431,particularly in the context of the reassuring findings from SIOPEL-6, these study results nonetheless continue to influence current usage of STS as evidenced by this survey.Even among sites currently using STS, criteria for its use varyacross tumor types, with greatest consensus surrounding use only for treatment of localized hepatoblastoma. This pattern of use is consistent with a recently published clinical practice guideline for STS.[22] This new guideline may alleviate concerns at those sites which identified the need for consensus input intouse of STS. However, absent new clinical datafor STS within different tumor types, and especiallyin metastatic disease, these questions will likely persist for many providers. Thus, new otoprotection trials are warranted to expand and/or refine routine use of STS and other systemic otoprotectants.

The survey also identified a knowledge gap for incorporating contemporary audiometry into therapeutic decisions. Current monitoring recommendations focus on conventional audiometry[23,24]as data for HFA, DPOAE, and speech audiometry are lacking. The majority of respondents were simply unsure how to apply these results to clinical practice. As ototoxicity monitoring during cisplatin therapy remains heterogeneous, trials must

clearly specify required audiometry. However, even when audiometry is consistently employed, differences among ototoxicity grading systems in use internationally[25] complicate comparison of findings between trials.[12,13] Earlyinternational input into a consensus ototoxicity endpoint will improve inter-trial comparisons and create a foundation for advances in otoprotection. Planned research must address not only agent and route, but also the application of audiometry to cisplatin therapy.Opportunity exists within intervention trials to better understand clinical applications of expanded audiometry and “pre-clinical” physiologic changes, such as found with DPOAE.

It is notable that enthusiasm in otoprotection trials within the COGcooperative group setting is high. Nearly all surveyed institutions (98%) were supportive of continued research into pediatric otoprotection. In this survey, providers expressed two clear preferences regarding such research. First,and as exemplified by the SIOPEL-6 study, it was important to respondents that the design ofotoprotection trials involving systemic agents with potential for chemotherapy interferencemustinclude the ability to assess tumor response and survival as definitively as possible. Second, there was a lack of enthusiasm for theintratympanic approach of administering otoprotectantsdesigned to abrogate the risk of tumor protection posed by systemic modalities.[26]Pending demonstration of feasibility in a cooperative group setting, research in the immediate future should continue to focus on appropriately designed studies of systemic otoprotection.

This study has several strengths and some limitations. Strengths include use of the diverse and well-established CCL RI network, which afforded input from a range of academic and community practice institutions. Results are thus likely representative of real-world practice settings in the United States and Canada. Additionally, this survey assessed usage of STS, an agent with demonstrated efficacy that is currently the subject of new drug applications under review by both the Food and Drug Administration and European Medicines Agency for otoprotection in patients receiving cisplatin for localized tumors[27]. Limitations of this study include a somewhat low response rate despite multiple reminders which may increase the response bias inherent to survey-based research. However, the diverse representation of institutional types, practice settings, and geographical regions among the responses we did receive mitigates these concerns.It will also be important to reevaluate changing international perspectives and practice patterns following the regulatory determinations. With increasing emphasis on quality of life in cancer research in the United States and Europe,[28,29] this survey provides a strong indicator of the continued significance of CIHL as an important long-term toxicity to be addressed by the COG and other cooperative groups.

For children treated with cisplatin, STS is being adopted primarily for use in certain, mostly localized, tumors, albeit with considerable variation among sites. Otoprotectionresearch in cooperative group settings should include consensus audiometry guidance and endpoints; pending feasibility data for intratympanic approaches, trials should currently focus on systemic agents.CIHL remains an important toxicity to address within the pediatric oncology community with strong enthusiasm for continued otoprotection research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding source: This work was supported by research funding from the National Institute of Deafness and other Communication Disorders at the National Institutes of Health (1K23DC014291, Orgel) and the Children's Oncology Group, the National Cancer Institute at the National Institutes of Health via U10 CA180886 and U10 CA180899 and NCORP grants U10 CA095861 and UG1CA 189955, and the St. Baldrick's Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviation

CCL	Cancer Control and Supportive Care Committee
CIHL	Cisplatin-induced hearing loss
COG	Children's Oncology Group
DPOAE	Distortion-product otoacoustic emissions
HFA	High-frequency audiometry
RI	Responsible individual (liaison)
SIOPEL	International Childhood Liver Tumors Strategy Group
SOC	Standard of care
STS	Sodium thiosulfate

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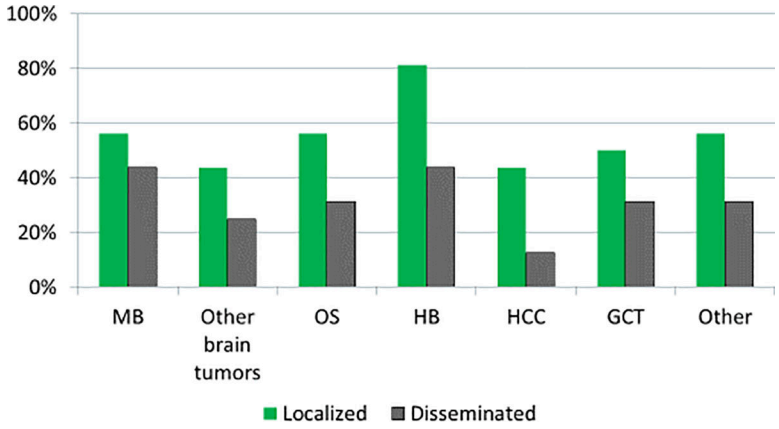

Figure 1: Proportion of institutions using sodium thiosulfate by tumor type and stage.

Planned usage of sodium thiosulfate (STS) for routine otoprotection across tumor types and by disease stage at presentation. MB = medulloblastoma. OS = osteosarcoma. HB= hepatoblastoma. HCC = hepatocellular carcinoma. GCT = germ cell tumor. Other = other cisplatin-treated tumors.

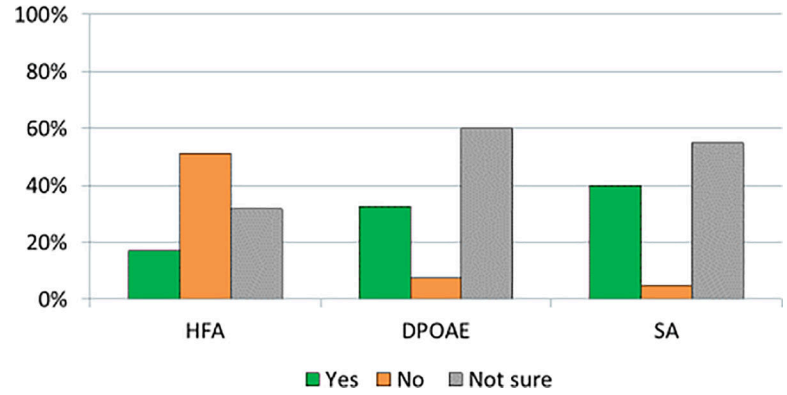

Figure 2: Proportion of institutions incorporating expanded audiometry into clinical decision making

Depiction of how responding sites currently factor into clinical decision making for cisplatin dosing the results from expanded audiometric testing such as high frequency audiometry (HFA, >8,000 Hz), distortion-product otoacoustic emissions (DPOAE), and speech audiometry (SA).

Table 1:

Descriptive responses of barriers and criteria for routine incorporation of STS for otoprotection

Barriers to routine use of STS	Criteria used to determine routine use of STS
• Need for additional efficacy and/or safety data for STS	• Tumor stage at diagnosis • Biologic risk of tumor recurrence
• Competing efforts to investigate reduction of therapy for low-risk tumors (and if/how to incorporate STS into them)	• Patient age • Pre-existing hearing loss • Risk of ototoxicity from the regimen
• Lack of regulatory approval for the indication of otoprotection	
• Absence of consensus guidelines recommending its use	