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REVIEW ARTICLE

Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale

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See accompanying editorial on page 2303

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ABSTRACT

Purpose
The platinum chemotherapy agents cisplatin and carboplatin are widely used in the treatment of adult and pediatric cancers. Cisplatin causes hearing loss in at least 60% of pediatric patients. Reducing cisplatin and high-dose carboplatin ototoxicity without reducing efficacy is important.

Patients and Methods
This review summarizes recommendations made at the 42nd Congress of the International Society of Pediatric Oncology (SIOP) in Boston, October 21-24, 2010, reflecting input from international basic scientists, pediatric oncologists, otolaryngologists, oncology nurses, audiologists, and neurosurgeons to develop and advance research and clinical trials for otoprotection.

Results
Platinum initially impairs hearing in the high frequencies and progresses to lower frequencies with increasing cumulative dose. Genes involved in drug transport, metabolism, and DNA repair regulate platinum toxicities. Otoprotection can be achieved by acting on several these pathways and generally involves antioxidant thiol agents. Otoprotection is a strategy being explored to decrease hearing loss while maintaining dose intensity or allowing dose escalation, but it has the potential to interfere with tumoricidal effects. Route of administration and optimal timing relative to platinum therapy are critical issues. In addition, international standards for grading and comparing ototoxicity are essential to the success of prospective pediatric trials aimed at reducing platinum-induced hearing loss.

Conclusion
Collaborative prospective basic and clinical trial research is needed to reduce the incidence of irreversible platinum-induced hearing loss, and optimize cancer control. Wide use of the new internationally agreed-on SIOP Boston ototoxicity scale in current and future otoprotection trials should help facilitate this goal.

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INTRODUCTION

Platinum drugs are effective chemotherapeutic agents commonly used in the treatment of a variety of adult and pediatric cancers.[1] Sixty percent of children treated with cisplatin develop permanent bilateral hearing loss.[2,3] Although cisplatin is more ototoxic than other platinum-based drugs, carboplatin is also ototoxic, especially when delivered at myeloablative doses for autologous bone marrow transplantation or when administered in conjunction with osmotic opening of the blood-brain barrier.[4,5] Once clinically significant toxicity is observed on audiologic monitoring, current practice suggests dose reductions or omissions, potentially reducing cure,[6] but the ototoxic damage is already done and the hearing loss is permanent.[7] In a young child, this will have a detrimental effect on speech, language, and social development.[2,3] Further research is needed to clarify the mechanisms of platinum ototoxicity, improve methods of reducing irreversible hearing loss,[2,3,8,9] and permit maintenance or escalation of platinum dose intensity to improve cancer control. The development of cotherapies aimed at

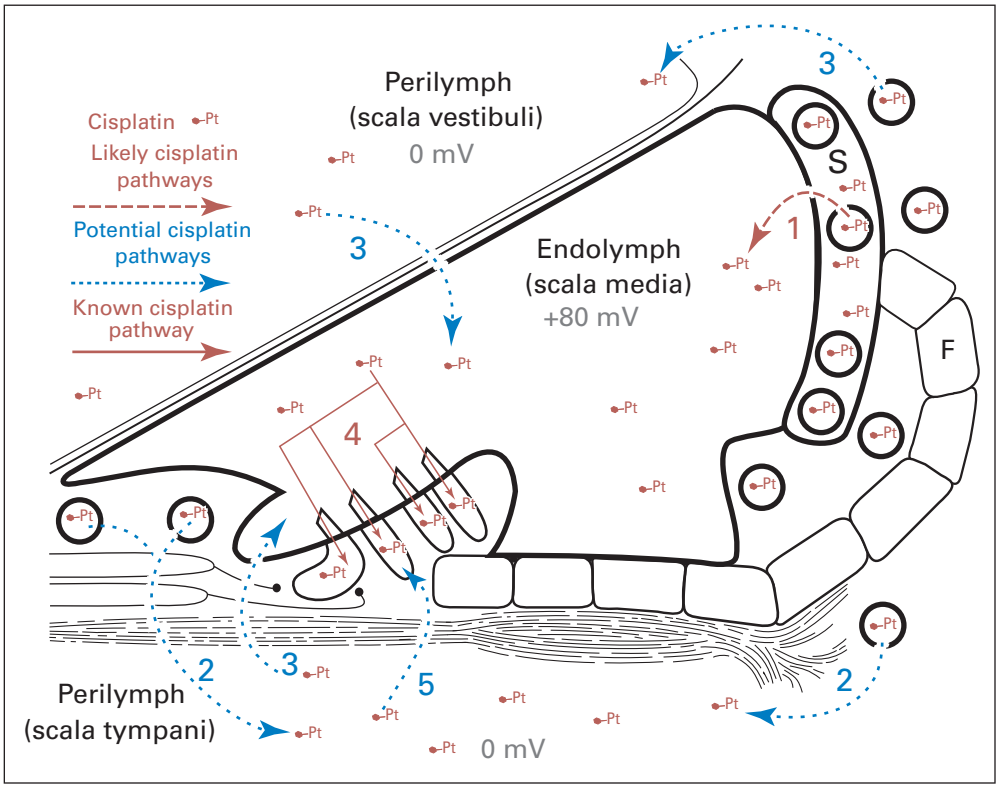


Fig 1. Model of the cochlea and cisplatin (Pt) trafficking routes. Potential pathways for systemic Pt to cross the blood-labyrinth barrier and enter hair cells include (1) a transstrial trafficking route from strial capillaries to marginal cells, followed by clearance into endolymph; (2,3) traversing the blood-labyrinth barrier into perilymph and subsequently into endolymph via transcytosis across the epithelial perilymph/endolymph barrier. (4) Once in endolymph, Pt enters hair cells across their apical membranes. (5) Pt in the scala tympani could also pass through the basilar membrane into extracellular fluids within the organ of Corti and enter hair cells across their basolateral membranes. S, stria vascularis; F, fibrocytes in spiral ligament (data adapted[35]).

preventing platinum ototoxicity requires collaboration between experts in auditory systems, cancer therapeutics, drug interactions, and clinical oncology to ensure that proposed otoprotectants do not reduce the platinum agents' potent tumoricidal activity.[10-12]

This article summarizes the work of four groups of experts (Appendix Table A1, online only) in the fields of basic science, genetics, ototoxicity monitoring, and clinical trials in otoprotection. Each of the groups included European and American experts who met through telephone conferences and prepared a working document that was presented at a symposium on chemotherapy-induced ototoxicity at the 42nd Congress of the International Society of Pediatric Oncology (SIOP) in Boston in October 2010. Attendees at the international symposium were invited to join breakout sessions following the symposium to share their expertise and contribute to a draft report. The essence of those four working group summary reports and recommendations are presented here.

MECHANISMS OF PLATINUM-INDUCED OTOTOXICITY

In preclinical studies, cisplatin has been the platinum agent most frequently investigated in guinea pigs, mice, rats, and other rodents. Induction of consistent ototoxicity with cisplatin requires a high dose with either intraperitoneal or intravenous administration; however, a single low dose is ototoxic if infused retrograde into the common carotid artery,[13,14] likely because of first-pass high-dose perfusion of the vertebral arteries feeding the cochlea.

Platinum agents induce dose-dependent death of cochlear hair cells, with outer hair cells more susceptible to cisplatin and inner hair cells more susceptible to carboplatin[15,16] in some animal models. However, in the rat, carboplatin primarily targets outer hair cells.[17] Cochlear hair cell death is first evident at the cochlear base and progresses apically with continued exposure to the drug.[15,18] Platinum agents target the DNA of proliferating cells to exert tumoricidal effects.[19,20] Inside the cell, cisplatin is activated by the replacement of one of its two chloride groups by a water molecule, and carboplatin is activated by replacement of the cyclobutane moiety. The activated monoaqua-platin binds to DNA, forming intra- and interstrand complexes that lead to inhibition of DNA synthesis, suppression of RNA transcription, cell cycle arrest, and apoptosis. In contrast to tumor cells, cochlear and proximal tubule cells proliferate slowly, and mammalian cochlear hair cells not at all. In these cells, cisplatin alkylation in mitochondria leads to release of proapoptotic factors and generation of toxic levels of reactive oxygen species (ROS), both of which can initiate cell death mechanisms through caspase activation.[21-23] Hair cell death is significantly inhibited (or at least delayed) by broad-spectrum inhibition of caspases, which are highly involved in apoptosis, thought to be a mechanism of hair cell death.[24-27] Cytosolic ROS formation has also been implicated as a major mediator of cisplatin-induced hair cell death.[28-30] Increased pools of ROS not only damage proteins and lipids but also deplete the cell's intrinsic antioxidant molecules potentiating further damage.[31,32]

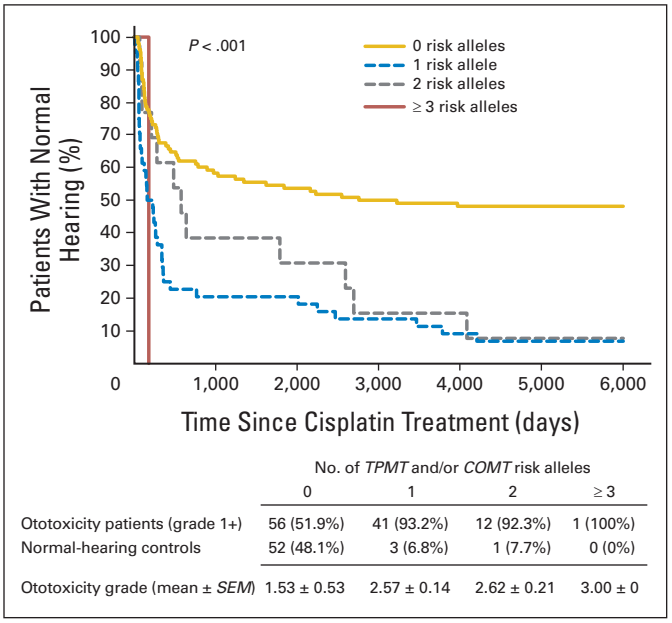
Cisplatin also induces degeneration of the stria vascularis, decreasing the number of marginal and intermediate cells as well as spiral ganglion cells.[33,34] Inner ear sensory cells reside within a blood-labyrinth barrier (BLB; Fig 1), similar to the blood-brain barrier. Any breakdown in the cellular integrity or increase in paracellular permeability (decoupling of tight junctions) between adjacent endothelial cells in the BLB rapidly induces loss of the endolymphatic potential

with consequent loss of hearing sensitivity. Although platinum is largely excluded by the blood-brain barrier,[36,37] it can be detected in cochlear tissues, indicating that it does cross the intact BLB (Fig 1),[38,39] but the trafficking mechanism remains poorly understood.[40,41] A clear understanding of BLB function is critical to studies aimed at inhibiting the entry of platinum (and other ototoxic agents) into cochlear tissues or delivering potential otoprotective molecules to the cochlea to reduce ototoxicity.

GENETICS OF OTOTOXICITY

Platinum toxicity shows significant interindividual variability since 20% or more of children are seemingly not affected, and there is some evidence to support ethnic/racial variability.[42] These observations have led to the hypothesis that genetic factors may render certain individuals more susceptible to the adverse effects of cisplatin.[43-45] The field of pharmacogenomics seeks to explore this interindividual variability in drug response and identify genetic predictors of cisplatin-induced hearing loss. A literature search of candidate genes involved in platinum-induced ototoxicity is summarized in Table 1.

In a recent study,[42] genetic variations in two specific genes, thiopurine *S*-methyltransferase (*TPMT*) and catechol-*O*-methyltransferase (*COMT*), were identified as having a strong association with cisplatin-induced ototoxicity in children (Fig 2). *TPMT* and *COMT* variants were found to be associated with severe cisplatin-induced hearing loss (combined odds ratio, 42.2; $P < .001$). Furthermore, the number of risk alleles carried by an individual was inversely related to time to deafness; those who carried at least three of four risk alleles had a rapid decline in their hearing, often with their first dose of cisplatin. The combination of *TPMT* and *COMT* genotypes could be used as a clinical test to identify individuals more likely to develop cisplatin-induced deafness with a positive predictive value of 92.9% and a negative predictive value of 48.6%.[42] Whether treatment can be adapted for an individual patient following on from these results will depend on the potential alternative treatments available and balance of risks for each child and each tumor type. Similarly, genes involved in cisplatin-DNA adduct repair (*ERCC1*, *ERCC2*) can increase the risk of cisplatin-associated toxicity but may also carry a tumor cell survival advantage. This is because there are molecular factors that not only play a role in platinum's mode of action but also interfere with the ability of the drug to induce apoptosis (Table 1).[19,47,49,50,54] Target tissues within the cochlea may show a variable genetic susceptibility to platinum, and genetic variation in the detoxification of platinum within the cochlea may contribute to the severity of ototoxicity.[47] Investigators have also been interested in genetic variation in the glutathione *S*-transferase genes with somewhat conflicting results in adults: one group identifies an association with *GSTM3*,[47] and another group identifies an association with *GSTP1*.[55] Replication of genotype-phenotype findings is needed in both candidate gene and genome-wide approaches to evaluate validity and applicability in the clinic.[56,57] All of the studies done to date are limited by the fact that they are retrospective in nature; thus, prospective evaluation of these genetic variations through future studies is urgently needed.



	No. of *TPMT* and/or *COMT* risk alleles			
	0	1	2	≥ 3
Ototoxicity patients (grade 1+)	56 (51.9%)	41 (93.2%)	12 (92.3%)	1 (100%)
Normal-hearing controls	52 (48.1%)	3 (6.8%)	1 (7.7%)	0 (0%)
Ototoxicity grade (mean ± *SEM*)	1.53 ± 0.53	2.57 ± 0.14	2.62 ± 0.21	3.00 ± 0

Fig 2. Kaplan-Meier graph of cisplatin ototoxicity and number of thiopurine *S*-methyltransferase (*TMPT*) and catechol-*O*-methyltransferase (*COMT*) risk alleles. An increasing number of *TPMT* rs12201199 and *COMT* rs9332377 risk alleles is associated with earlier onset of cisplatin-induced hearing loss ($P < .001$) and with more severe cisplatin-induced hearing loss ($P < .001$; adapted by permission from Macmillan Publishers: Nature Genetic, 2009[42]).

Table 1. Results of Published Studies in Cisplatin Pharmacogenomics Using Candidate Gene Approach

Gene/Protein	Summary of Results
Megalin	Selected for candidate gene approach because it is highly expressed in renal proximal tubular cells and marginal cells of the inner ear. Also associated with the uptake of ototoxic aminoglycosides.[46]
GSTs	Animal studies suggest GSTs are found in the cochlea and have a role in protection from ototoxicity. The *GSTM1*, *GSTT1*, and *GSTP1* genes are polymorphic in humans, and nonfunctional variants are commonly found in whites.[47]
TPMT, COMT	Two cohorts (identified through the Canadian Pharmacogenomics Network for Drug Safety) were evaluated for cisplatin toxicity.[42] They used a gene chip composed of variants in 220 drug metabolism genes and found that genetic variants of *TPMT* (odds ratio, 17) and *COMT* (odds ratio, 5.5) were significantly associated with cisplatin-induced hearing loss. The combination of *TPMT* and *COMT* genotypes could be used as a clinical test to identify those who will have cisplatin-induced deafness with a positive predictive value of 92.9% and a negative predictive value of 48.6%.[42] Mechanisms of toxicity include increased efficiency of cisplatin cross-linking, as well as a possible role of the methionine pathway through a common substrate, *S*-adenosylmethionine.[42]
ERCC1, ERCC2	*ERCC1* encodes an excision repair enzyme involved in platinum DNA adduct repair.[48] Two common single nucleotide polymorphisms in *ERCC1* are correlated with an increased risk of both toxicity and survival in adults with non–small-cell lung tumors.[49,50]
Mitochondrial gene mutations	No studies have been performed that have evaluated for associations between mitochondrial gene mutations and cisplatin-induced hearing loss. Aminoglycoside-induced deafness is thought to be associated with mutations in the mitochondrial 12S ribosomal RNA gene.[51-53]

Abbreviations: *COMT*, catechol-*O*-methyltransferase; *ERCC1*, excision repair cross-complementation group 1; *ERCC2*, excision repair cross-complementation group 2; GST, glutathione-*S*-transferase; *TPMT*, thiopurine *S*-methyltransferase.

The challenges to these studies are that false-positive findings may occur that are not reproducible because of small sample size, inadequate phenotyping, poor case-control definition and/or use of patients from different ancestries. Moreover, monogenic approaches may underestimate susceptibility to platinum ototoxicity because it is likely that multiple genetic pathways are involved in the metabolism, transport, and detoxification of platinum. Future research will require a polygenic approach and novel methodologies.[58] Cost reduction and new techniques in whole-genome sequencing should permit large-scale projects if adequate sample sizes of well-characterized phenotypes become available. Inclusion of genetic studies in pediatric treatment studies with standardized audiologic assessment is essential so that the phenotyping will be adequate to identify ototoxicity susceptibility alleles.

OTOTOXICITY GRADING

Platinum ototoxicity is sensorineural and typically bilateral, initially impairing hearing in the high frequencies and progressing to lower frequencies with increasing cumulative dose.[6,7] The risk is greatest in young children, and there are significant long-term implications, particularly if the children are prelingual or in the early stages of language development[2] or have other functional impairments such as visual deficits or cognitive dysfunction. Since high-frequency speech sounds are critical to speech intelligibility, even mild hearing loss in the high frequencies may affect academic and social-emotional development in young children.[59-63] Acquired hearing loss can be addressed with hearing assistive technology, speech-language therapy, and/or the use of communication strategies. It is essential to appreciate that although these interventions may reduce the negative consequences of the hearing loss, they do not restore normal hearing. If we are to succeed in conducting prospective pediatric clinical trials to reduce platinum ototoxicity and compare patients, disease groups, candidate genes, and otoprotective agents, it is critically important to adopt an international standard for grading and comparing ototoxicity at the end of therapy.[64]

Impact of Ototoxicity in Children

Compared with adults and adolescents, young children require greater audibility for speech recognition and comprehension. Young children do not have the language base or neurologic maturity to fill in the gaps when acoustic access is compromised.[65] Hearing loss decreases the audibility of speech and also reduces the clarity of speech.[61,62] Platinum ototoxicity initially affects high-frequency hearing. When low-frequency hearing is preserved, children continue to hear vowel sounds, intonation, nasality, and consonants that have primary energy in the lower frequencies. High-frequency hearing loss causes difficulty in distinguishing high-frequency consonants (s, sh, f, t, z, th, h, k, p) that are critical for speech intelligibility, and it significantly impairs recognition of speech in the presence of background noise.[66-68] For children developing language and vocabulary who are learning spoken language through listening, high-frequency hearing loss is communicatively and educationally significant.[65] Gurney et al[63] studied educational achievement and quality of life in 137 neuroblastoma survivors. Children with hearing loss were reported as having twice the rate of educational difficulties and need for support services or special education.

High-frequency hearing loss in older children and adolescents has an impact on ease of listening and may negatively affect educational achievement and social-emotional development.[60] Learning in a classroom environment is highly dependent on hearing and listening. Poor classroom acoustics (noise and reverberation) compound the perceptual deficits caused by hearing loss.

Ototoxicity Grades and Classification

Numerous ototoxicity criteria or grading systems have been developed and used to classify hearing loss in children, but in the clinical trial setting, uniformity is essential. There are currently two main types of ototoxicity assessment criteria: (1) those that rely on change of hearing from baseline, including WHO Common Toxicity Criteria,[69] National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE),[70] protocol criteria from Children's Cancer Group A9961 (CCG-A9961; phase III intergroup average-risk medulloblastoma protocol[71]), and the Children's Hospital Boston (CHB) scale[72]), and (2) those specifically written for children that measure absolute hearing levels, including Brock et al[7] and Chang and Chinosornvatana[73] (hereafter Brock and Chang), and the new SIOP Boston scale proposed in this article. The new scale detailed in Table 2, which all participants agreed on, combines the best elements from all the assessment criteria. This new scale will make it possible to compare clinical trial outcomes world-wide.

Classification of ototoxicity in children should be objective, sensitive, reliable, valid, functionally relevant, applicable to results obtained at any age, and simple to understand and describe. The primary intent of any scale will depend on whether its purpose is to guide treatment decisions, identify ototoxicity at the soonest possible opportunity during treatment, or report the incidence and severity of acquired hearing loss in children at the completion of treatment for comparison of clinical trials. The SIOP scale is intended to be used for patients at the end of treatment on a clinical trial (Table 2). It is sensitive to high-frequency hearing losses that result in reduced audibility of the average speech spectrum, and it uses the criteria that correspond to functional outcomes, including the need for audiologic interventions such as hearing aids and other assistive technologies.

Table 2. SIOP Boston Ototoxicity Scale

Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above

NOTE. Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea.

Abbreviations: SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss.

The scale was based on a modification of the CHB functional scale,[72] which classifies hearing loss as grade 1, 2, or 3 on the basis of change in hearing threshold of 20 dB or more compared with baseline measures. The CHB scale was validated by using the Brock scale which, in a multivariate analysis, showed that cisplatin dose was a significant predictor of hearing loss. The CHB scale was favored for its simplicity and objectivity, but two main modifications were recommended. The first was to use absolute hearing levels similar to those of Brock and Chang. The second was to add a grade 4 that was equivalent to Brock and Chang grade 3.

The reason for opting for absolute hearing levels is that, although baseline evaluation is the gold standard for ototoxicity monitoring and obtaining a baseline is recommended for all children who are treated with cisplatin, it has been recognized for many years that a complete and reliable baseline evaluation is not always possible in young children with cancer. Children are often quite sick, they may be fearful in the clinical setting, and attention or cooperation may be limited. When grading is based on change from baseline, audiograms from children without a baseline are not gradable. Furthermore, absolute hearing threshold levels after cessation of treatment, rather than change from baseline, determine whether an individual child has sufficient acoustic access to all of the speech sounds for everyday listening situations, including distance hearing and the ability to understand speech in a noisy environment.

Grade 4 was added, equivalent to Brock and Chang grade 3, to distinguish children who acquire moderate or greater ototoxic hearing loss from those with milder impairment, since there are important functional and clinical differences as the degree of hearing loss increases. A minor modification was to expand grade 3 to include hearing loss greater than 20 dB at 2,000 or 3,000 Hz, since audibility at both 2,000 and 3,000 Hz is critical for speech intelligibility, and loss at either of these frequencies is commonly used as the indication for hearing aids in children.

The SIOP Boston ototoxicity scale is being validated on existing data that include international multicenter audiologic results in very young children treated with cisplatin. Results will be directly compared with existing scales (CTCAE versions 3 and 4; Brock and Chang) to determine whether the SIOP scale better correlates with functional outcomes and offers improved simplicity and inter-rater reliability. Results will be submitted for future publication and the SIOP scale will be recommended if the study outcomes are positive.

OTOPROTECTION

Several promising otoprotective agents are in preclinical and clinical development. The challenge is how to select the best products for further investigation, how to evaluate their efficacy and safety, and how to introduce them into clinical practice.

Preclinical Studies

Activated platinum agents react preferentially with antioxidant molecules, particularly glutathione and metallothioneins.[74] In cancer cells with high levels of glutathione, platinum can be effectively bound by the glutathione, inhibiting DNA binding and reducing the chemotherapeutic efficacy in these tumors.[75] Cisplatin-induced ototoxicity is reduced in animal models by a variety of antioxidants, including N-acetyl-cysteine (NAC),[13,14,76-78] alpha-tocopherol,[79,80] lipoic acid,[81-83] sodium thiosulfate (STS),[14,17,84-87] salicylate,[88] ebselen,[82,89] D-methionine,[90] and amifostine.[86,91]

Preclinical studies have demonstrated that choice of species, dosing protocol, route of administration, and optimal timing relative to platinum therapy are critical issues.[13,14,72,87,92-94] Intravenous or intra-arterial administration of NAC is required to achieve the high concentration necessary for otoprotection, since oral administration does not provide effective concentrations.[13,14,78,87] Strategies for localized delivery of protective molecules include transtympanic or round window delivery,[77,92,95] although this method has had variable success in animal models to date, depending on the agent.[96,97] [SCAP]d-methionine has shown complete otoprotection with round window application or oral administration in animal studies.[96,98,99] As is the case with any chemoprotectant, systemic administration of otoprotectants must address whether the protective agent interferes with the tumoricidal effect of platinum. Delayed administration of a protective agent such as STS or NAC may provide hearing protection[4,5,13,14] without compromising anticancer therapy[87,100,101] (Fig 3).

Clinical Studies

Antioxidants that have been tested as otoprotectants in clinical trials in humans receiving platinum-based chemotherapy are amifostine[69-71,102] and STS.[4,5] To the best of our knowledge, the only otoprotection study completed in the cooperative oncology group setting to date is CCG-P9645, a randomized controlled trial of amifostine for prevention of cisplatin-induced hearing loss in children with newly diagnosed hepatoblastoma, conducted by the Children's Oncology Group (COG) from 1999 to 2006.[102] Amifostine did not provide otoprotection when the suggested dose and schedule were used, and it was accompanied by hypocalcemia. However, a more dose-intensive schedule of amifostine tested in a comparative cohort study[71] was reported to reduce ototoxicity in children treated with cisplatin for medulloblastoma. Both the COG, which fully accrued as of March 2012, and the International Pediatric Oncology Epithelial Liver Tumor Strategy Group (SIOPEL) are currently conducting randomized controlled trials of STS to prevent cisplatin-induced hearing loss. Further information can be found at the National Cancer Institute Physician Data Query (NCI-PDQ) Clinical Trials Web site.[103] Both of these phase III STS studies are based on phase II studies of carboplatin followed by delayed STS (Fig 3D).[4] In addition, these studies have also incorporated DNA collection from patients, which allows pharmacogenomic studies to be performed.

Emerging Agents

Several properties or characteristics constitute the ideal pediatric otoprotectant: it must be effective (reliable otoprotection), be safe (no tumor protection), have minimal adverse effects, use simple administration techniques, be suitable for use with various platinum compounds and schedules of administration, and be of sufficient interest to the pharmaceutical industry for investment in research and development.

Currently no pharmacologic agents have US Food and Drug Administration (FDA) approval to prevent or reverse platinum-induced hearing loss, although STS has orphan-drug designation as an otoprotectant. The development of amifostine, STS, NAC, D-methionine, and ebselen are summarized in Table 3. NAC is well established as being safe in humans, shows good promise as an otoprotectant, has the added benefit of providing nephroprotection from cisplatin,[11,12] and when combined with STS, it may

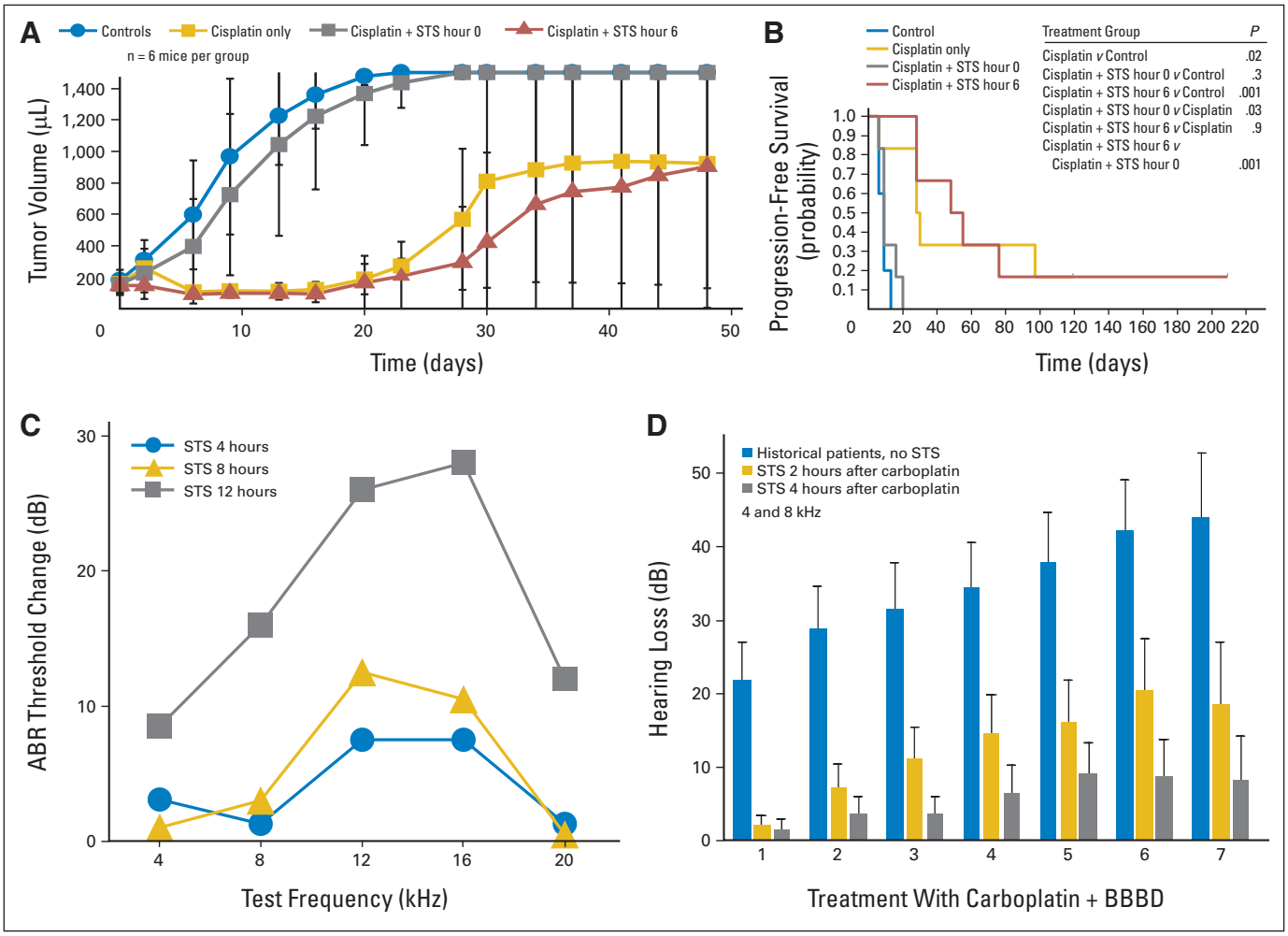


Fig 3. Chemoprotection studies. (A) Effect of sodium thiosulfate (STS) and cisplatin on subcutaneous human neuroblastoma xenograft growth. Nude mice were inoculated subcutaneously with 3.2×10^7 SMS-SAN neuroblastoma cells and were treated with no treatment (blue circles; n = 5), cisplatin 4 mg/kg intraperitoneally (IP) × 4 days (gold squares; n = 6), cisplatin 4 mg/kg per day × 4 days plus STS 3.5 g/kg per day IP × 4 days immediately (0 hours) after cisplatin (gray squares; n = 6), or cisplatin 4 mg/kg per day IP × 4 days plus STS 3.5 g/kg per day IP × 4 days at 6 hours after cisplatin (red triangles; n = 6). Tumor volumes were measured twice per week (data adapted[100]). (B) Time to tumor progression (tumor volume of > 600 µL or last measurement taken) was determined. The probability of progression-free survival for the four treatment groups was determined by using the permutated log-rank test. STS given 6 hours after cisplatin daily for 4 days did not significantly (P = .9) affect cisplatin antitumor activity in SMS-SAN xenografts in athymic *nu/nu* mice compared with cisplatin alone. However, STS given simultaneously with cisplatin daily for 4 days did significantly (P = .03) protect tumors from cisplatin (data adapted[100]). (C) Cisplatin induced changes in auditory brainstem response (ABR) threshold when STS was given at 4, 8, or 12 hours after cisplatin in a rat model. As illustrated, delay of 4 or 8 hours was highly otoprotective, whereas delay of 12 hours was not otoprotective (data adapted[14]). (D) Comparison of threshold shift against carboplatin treatment number (at 4,000 Hz) in historical comparison patients who received carboplatin without STS and in patients treated with STS delayed 2 hours or 4 hours after carboplatin. There was a significant difference between the STS treatment groups and the historical comparison control group (P = .0075; Adapted and reprinted by permission from the American Association for Cancer Research[4]). BBBD, blood-brain barrier disruption.

protect the bone marrow from carboplatin toxicity.[101] We recommend completing or initiating pediatric clinical trials with STS, NAC, D-methionine, and possibly ebselen, depending on further findings as these drugs are developed.

Another approach to otoprotection is that of anatomic or compartmental therapy, that is, delivery of D-methionine to the round window before systemic treatment with platinum-based chemotherapy.[96]

CONSIDERATIONS IN CLINICAL STUDY DESIGN FOR OTOPROTECTION

Potential characteristics of clinical trials of otoprotectants will vary according to their phase of drug development. After phase I studies to assess pharmacokinetics, pharmacodynamics, and dose-limiting toxicity, each otoprotectant must be tested in patients receiving ototoxic chemotherapy. Phase II studies will estimate dose-timing response curves and efficacy range with hearing threshold change or proportional incidence of hearing loss as the outcome measure. Randomized phase III study designs will be necessary to confirm protection against ototoxicity (n = 100 to 250 patients). Exact sample sizes will depend on the characteristics of the study agent and the statistical parameters used (eg, effect size and desired significance level). Pharmacogenomic testing that leads to only patients at high risk for ototoxicity being included in clinical trials may enable smaller sample sizes to be used for these protectant trials.

Pursuing the two major goals of efficacy (reducing ototoxicity) and safety (not compromising chemotherapeutic antitumor

Table 3. Representative Emerging Otoprotectants for Use With Platinum-Based Chemotherapy

Agent	Route	Mechanism	Comment
STS	IV	Thiol-reducing agent	In rats, STS protects against ototoxicity[14] without reducing antitumor efficacy.[101] Currently in phase III trials. Possible approaches include delayed administration, [14,87,100] two-compartment models, [4,5,104] and cochlear application.[85,96]
Amifostine	IV	Metabolized to WR-1065, a thiol-reducing agent	Most trials show no otoprotection; dose intensity may be critical; routine use of amifostine to prevent platinum-associated neurotoxicity or ototoxicity is not currently supported by the American Society of Clinical Oncology 2008 Clinical Practice Guideline.[105]
NAC	IV	Thiol-reducing agent	High dose (1,000 mg/kg) IV or intra-arterial NAC protects against cisplatin ototoxicity in the rat when given either 30 minutes prior to or 4 hours after chemotherapy and also blocks kidney toxicity and weight loss.[14,78] Delayed IV NAC does not block chemotherapy antitumor efficacy.[101]
D-methionine	PO, IV, or delivery to the round window	Glutathione modulator, free-radical scavenger	Animal studies have confirmed D-methionine protection from carboplatin- and cisplatin-induced ototoxicity.[99] Effective delivered PO,[99] systemically, or to the round window.[96] Animal studies have not shown significant antitumor interference.[106] One small-scale clinical trial showed complete otoprotection.[107] Larger-scale clinical trials will be needed.
Ebselen	PO	Glutathione peroxidase promoter	In animal studies, ebselen, a selenium-containing compound, has reduced cisplatin-induced outer hair cell loss with and without allopurinol co-administration[89] and does not appear to comprise cisplatin's antitumor efficacy.[108] To date, ebselen has not been tested in clinical trials, but trials are in the planning stages.
Ringer's solution or dexamethasone	Intratympanic injection	Agent dependent (anti-inflammatory)	Compartmental therapy via tympanostomy tubes.[92,95]

Abbreviations: IV, intravenous; NAC, N-acetylcysteine; PO, orally; STS, sodium thiosulfate.

activity) within the same clinical trial presents serious challenges in statistical design. The sample size required for proving superiority in otoprotection is usually substantially smaller than that required for demonstrating noninferiority in tumor control.[109] Study designers must choose which end point should control power calculations. Given the justifiable concern for ensuring patient safety (ie, lack of tumor protection), there may be a temptation to insist on completion of classical noninferiority trials involving sample sizes of several hundred patients. However, a classical noninferiority trial of this type is not feasible in pediatric oncology, because accrual of adequate numbers of children with cisplatin-sensitive cancers would take many years and would lock up limited clinical trials resources in the interim.[109] A trial in adults to justify the pediatric indication may not provide a definitive solution because hearing loss is not the dose-limiting cisplatin toxicity in adults that it is in children,[110] and common adult tumors treated with cisplatin are insufficiently chemotherapy-sensitive to serve as a marker for tumor protection.

A more novel approach than the traditional noninferiority study is critically needed to optimize safety in a practical way that permits effective otoprotectants to be developed and made commercially available. Lacking such innovation, the field of otoprotection and the children who stand to benefit from protective agents are condemned to the status quo—life with significant hearing loss, the associated educational and social costs, and the risk of reduced cancer control with platinum reduction or omission. One approach for these unique pediatric situations may be for regulatory agencies such as the FDA to accept a combination of preclinical studies that are unequivocal on the tumor protection question plus smaller clinical trials in children that are compelling for hearing protection and at least reassuring against tumor protection. Development of such a strategy will require a partnership of committed individuals in academic medicine, the pharmaceutical industry, and FDA.

Strategies for improving the safety and efficiency of trial designs include combining trials (eg, phase IIIA and IIIB could be designed in one trial with an interim analysis of otoprotection and a final analysis of antitumor efficacy). Safety can be enhanced by incorporating an interim futility analysis on the otoprotection question, which limits risk to future patients by identifying an ineffective agent before study completion. Another strategy is to devise a method for monitoring early tumor responses in an initial study cohort. Although this approach will likely lack statistical significance because of the small number of patients, it may serve as an early warning system to detect major, unanticipated treatment failures. Once one or more safe and effective otoprotectants have been identified, future trials of a new agent may need to incorporate an established agent, rather than observation, as the control arm.

Clinical trials of otoprotection may be conducted in the setting of single institutions, multiple collaborating institutions (a consortium), or larger cooperative oncology groups. In planning and designing future studies, it is imperative that anticipated concerns of treating pediatric oncologists about tumor protection be addressed as thoroughly as possible in the concept proposal stage by using available preclinical and clinical data, and for experienced pediatric audiologists to be involved in determining the study end points and methods.[111] Central review of the audiologic data are recommended to ensure that maximal evaluable data will be available during the analytic phase of the study.

RECOMMENDATIONS

Mechanisms to foster translation from basic science to clinical practice are needed, as is more research regarding mechanisms of platinum ototoxicity, trafficking of platinum to cochlear sensory cells, and development of clinically relevant animal models for studying ototoxicity and otoprotectants. Collaboration between the pharmacogenomic

community and basic scientists to investigate potential new pathways and biologic understanding could result in novel strategies.

New technologies and cost reduction now make relevant pharmacogenomic research possible. Identification of genotypes that are at high risk for ototoxicity and novel clinical trial design could increase the power of clinical studies and decrease the sample size needed to demonstrate effect. Cooperative groups that focus on hearing loss should collect DNA samples for research. Audiologic results are a key end point in the study of otoprotective agents, and they provide the phenotypes for pharmacogenomic ototoxicity research. It is critical that high-quality, reliable audiologic data be obtained. International standardization and wide use of the SIOP Boston ototoxicity scale (Table 2) will allow for comparison between studies and replication of results.

It is feasible to conduct otoprotection trials in the pediatric cooperative oncology group setting as with STS, but cooperative groups need to include otoprotection as a high scientific priority. Additional innovative study designs that measure otoprotection need to be generated to modify standard tumor-related phase III trials, possibly through a task force that involves key scientific disciplines and stakeholders, including pediatric oncologists, audiologists, basic and translational researchers, biostatisticians, clinical pharmacologists, pharmaceutical companies, and patient advocates (particularly parents and childhood cancer survivors). This testing paradigm could be readily applied to new otoprotectants as they become available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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