HHS Public Access

Author manuscript

Lancet Child Adolesc Health. Author manuscript; available in PMC 2020 September 28.

Published in final edited form as:

Lancet Child Adolesc Health. 2019 August ; 3(8): 578–584. doi:10.1016/S2352-4642(19)30115-4.

Interventions for cisplatin-induced hearing loss in children and adolescents with cancer

David R Freyer,
Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA, USA

Departments of Pediatrics and Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Penelope Brock,
Department of Haematology and Oncology, Great Ormond Street Hospital, London, UK

Kristin Knight,
Division of Pediatric Audiology, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR, USA

Gregory Reaman,
Division of Oncology, Children's National Health System, Department of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington DC, USA

Sandra Cabral,
Pediatric Oncology Group of Ontario, Toronto, ON, Canada

Paula D Robinson,
Pediatric Oncology Group of Ontario, Toronto, ON, Canada

Lillian Sung
Division of Haematology and Oncology, The Hospital for Sick Children, Toronto, ON, Canada

Abstract

The identification of preventive interventions that are safe and effective for cisplatin-induced ototoxicity is important, especially in children because hearing loss can impair speech-language acquisition development. Previous randomised trials assessed systemic drugs such as amifostine, sodium diethyldithiocarbamate or disulfiram, and sodium thiosulfate. Amifostine, sodium diethyldithiocarbamate, and disulfiram did not show hearing preservation. Paediatric trials assessing sodium thiosulfate showed efficacy in terms of hearing protection. The SIOPEL 6 trial consisted solely of patients with localised hepatoblastoma and no effects on survival were shown.

Correspondence to: Prof Lillian Sung, Division of Haematology and Oncology, The Hospital for Sick Children, Toronto, ON, M5G 1X8, Canada lillian.sung@sickkids.ca.

Contributors

DRF contributed to the interpretation of relevant literature and the design, writing, and editing of the manuscript. PB contributed to the discussion around the aim of the paper, review, criticism, and writing the discussion and background literature. KK reviewed and contributed to the manuscript draft and approval of final manuscript. GR contributed to the review of relevant literature, writing, and editing of the manuscript. SC contributed to the data collection. PDR and LS contributed to the literature search, study design, data collection, data analysis, data interpretation, and manuscript writing and editing.

In the ACCL0431 trial, which included heterogeneous patients, a post-hoc analysis showed significantly worse overall survival among patients who had disseminated disease receiving sodium thiosulfate than among controls, but not among those with localised disease. Intratympanically administered drugs have mainly been assessed in adults and include N-acetylcysteine and dexamethasone. Inconsistent effects of these drugs were identified but these studies were limited by design, small sample size, and statistical approach. Future studies of systemic drugs will need to consider the measurement of disease outcomes through study design and sample size, and ototoxicity endpoints should be harmonised to enhance comparability between trials.

Introduction

Children with cancer are increasingly cured because of advances in cancer treatments, risk stratification, risk-adjusted therapy, and supportive care.[1] However, survivors are at considerable risk of late effects of therapy,[2] and ototoxicity is a well described consequence of cisplatin chemo therapy.[3,4] Cisplatin-induced hearing loss is permanent,[5] progressive,[6] and caused by the death of the cochlear outer hair cells.[7] Cisplatin-induced hearing loss is important because it not only affects quality of life but also has downstream effects on access to speech and spoken language development in childhood. Language and communication are fundamental for psychosocial development, cognition, learning, and literacy.[8,9] Consequently, the identification of drugs that can reduce chemotherapy-induced ototoxicity without affecting anticancer activity is of great importance. No drugs have been approved by the US Food and Drug Administration or the European Medicines Agency for the prevention of cisplatin-induced ototoxicity. Many animal models of ototoxicity exist, including guinea pig, chinchilla, and mouse models, but because findings might not be applicable to patients[10] we focused on data from human studies. In this Rapid Review, we aimed to assess which interventions are effective for preventing cisplatin-induced ototoxicity in children and adolescents with cancer.

Current evidence

Because randomised studies generally have a lower risk of bias compared with observational studies,[11] we searched for randomised trials of interventions to reduce cisplatin-induced ototoxicity in adults and children. We then identified trials that included children to assess the generalisability of results to paediatric patients. We focused on hearing outcomes and survival endpoints. However, we recognised that because of differences between adults and children in cancer types and their natural histories, chemotherapy regimens, and treatment efficacy, adult data will not be generalisable to the paediatric population for the assessment of the interaction of otoprotectants with chemotherapy and effects on survival.

We identified 24 randomised trials, of which 18 were done in adults,[12–29] five were done in children,[30–34] and one included adults and children.[35] These studies were broadly categorised according to the use of systemic drugs versus local (intratympanic) drugs. Systemic drugs that were assessed in more than one trial were amifostine (n=5); sodium diethyldithiocarbamate (also known as ditiocarb sodium) or its metabolite disulfiram (n=3);

and sodium thiosulfate (n=2). Nine other interventions were assessed individually in single studies. Intra-tympanically administered agents were assessed in five trials and included N-acetylcysteine versus usual care (n=2), dexamethasone versus usual care (n=2), and N-acetylcysteine versus dexamethasone (n=1; table 1).

Amifostine

Amifostine is a thiophosphate-reducing drug that has been studied widely as a cytoprotectant. The drug is dephosphorylated to its active thiol metabolite, which binds to cytotoxic cisplatin metabolites and scavenges free radicals. The five randomised trials of amifostine that we found[17,19,27,31,34] included two paediatric studies that enrolled children with hepatoblastoma[34] and osteosarcoma[31] (table 2). All control groups were usual care in these studies and none were placebo-controlled. Table 2 outlines the proportion of patients with any ototoxicity and those with severe ototoxicity defined as grades 3 or 4 if the ototoxicity classification scheme used a 0–4 grading scale. Of note, one of the paediatric studies[34] had planned to collect ototoxicity endpoints using routine toxicity reporting via the Common Terminology Criteria for Adverse Events. However, because routine reporting substantially underestimated the incidence of ototoxicity, the authors did a blinded review of submitted audiological results. None of the studies showed a statistically significant preservation of hearing that was associated with amifostine administration.

Cancer outcomes were not consistently reported across the five studies, but no negative effects associated with amifostine administration were identified in any of the studies, including the two paediatric trials. Among the two paediatric studies, the study of patients with hepatoblastoma included patients with localised and metastatic disease and did not show a difference in event-free survival (p=0·22).[34] Conversely, the study of patients with osteosarcoma (including both localised and metastatic disease) found that the response to chemo therapy defined as percent necrosis (>90%, 60–90%, and <60%) was significantly better with amifostine than with usual care (p=0·043); event-free and overall survival were not reported.[31] The other three studies in adult populations did not identify differences in tumour response to chemotherapy, relapse rates, or survival.

Sodium diethyldithiocarbamate or disulfiram

Diethyldithiocarbamate is a thiol compound used principally as a heavy metal-chelating drug that has been investigated as a protectant against cisplatin-induced toxicity. The drug is thought to be protective against toxicity through the chelation and removal of tissue-bound cisplatin.[20] The three randomised trials consisted of two studies of sodium diethyldithiocarbamate and one study of its metabolite, disulfiram; all three included only adult patients (table 2).[20,22,23] None of the studies showed hearing preservation associated with the intervention and, in fact, one study found ototoxicity to be significantly worse with disulfiram administration than with usual care (p<0·005).[22] No differences in response rate, time to progression, or median survival were reported in any of these studies.

Sodium thiosulfate

Sodium thiosulfate is a thiol-containing reducing drug and free radical scavenger. Two multicentre, open-label, randomised trials compared sodium thiosulfate with usual care,

which were done by the International Childhood Liver Tumors Strategy Group (SIOPEL 6)[30] in 2018 and the Children's Oncology Group in 2017 (ACCL0431; table 2).[33] SIOPEL 6 enrolled a homogeneous group of children with localised hepatoblastoma who were administered six cycles of cisplatin. Sodium thiosulfate (20 g/m^2) was administered 6 h after each cisplatin dose, on the basis of preclinical studies that showed no interference with chemotherapy with temporal separation of 4–8 h.[36] 109 patients were randomly assigned to sodium thiosulfate (n=57) or usual care (n=52). The primary outcome was ototoxicity, classified using the Brock scale, at the end of therapy, or when patients were aged 3·5 years or older. 18 (33%) of 55 patients had any hearing loss with sodium thiosulfate versus 29 (63%) of 46 in the control group (p=0·002). The 3-year event-free survival was 82% (95% CI 69–90) with sodium thiosulfate versus 79% (65–88) in the control group and the 3-year overall survival was 98% (88–100) with sodium thiosulfate and 92% (81–97) in the control group. Thus, this study showed that hearing protection was associated with sodium thiosulfate administration, with no effect on event-free survival or overall survival, in a group of children that was homogenous in terms of cancer type, stage, risk category (localised disease), and treatment.

By contrast with SIOPEL 6, ACCL0431[33] enrolled a heterogeneous group of children with various cancer diagnoses and treatments, of whom 47 (38%) of 125 had disseminated disease (as classified by site investigators post-hoc).[33] ACCL0431 administered sodium thiosulfate (16 g/m^2) 6 h after each cisplatin dose. 125 patients were randomly assigned to sodium thiosulfate (n=61) or usual care (n=64). The primary outcome was ototoxicity classified using the American Speech-Language-Hearing Association criteria at 4 weeks after the final dose of cisplatin. 14 (29%) of 49 patients had hearing loss with sodium thiosulfate versus 31 (56%) of 55 in the control group (p=0·0002). The 3-year event-free survival was 54% (95% CI 40–66) with sodium thiosulfate versus 64% (50–74) in the control group and the 3-year overall survival was 70% (56–80) with sodium thiosulfate versus 87% (76–93%) in the control group. Because of these concerning estimates, a post-hoc classification was done and the analysis was stratified by patients with localised versus disseminated disease. Among the 77 patients who were classified as having localised disease, the 3-year event-free survival was 60% (42–74) for sodium thiosulfate versus 66% (48–78; p=0·73) in the control group, and the 3-year overall survival was 83% (66–92) versus 89% (74–96; p=0·88), respectively. However, among the 47 (38%) patients who were classified as having disseminated disease, the 3-year event-free survival was 42% (21–61) with sodium thiosulfate versus 61% (39–77; p=0·16) in the control group and the 3-year overall survival was 45% (23–65) versus 84% (62–94; p=0·009), respectively. Given the heterogeneous cohort, adjusting for biological prognostic factors was not possible. Notably, the 3-year overall survival of 45% in the sodium thiosulfate group was closer to the expected survival reported in similarly treated children with disseminated disease than to the 84% in the control group.[37–40] Plausible explanations for this finding include unmeasured confounders such as tumour biology and histology, differences in anti-tumour therapy, bias in the post-hoc classification of disseminated disease, random chance, or a true effect of sodium thiosulfate.

Other systemic interventions

Nine interventions were assessed in individual studies, namely vitamin E alone;[12] a combination of antioxidant micronutrients (vitamin C, vitamin E, and selenium);[16] pantoprazole;[32] aspirin and omeprazole;[13] Gingko biloba extract;[24] calcium gluconate;[18] low-dose dopamine infusion;[21] systemic N-acetylcysteine;[28] and glutathione.[29] The study of Ginkgo biloba extract randomly assigned 15 adult patients and found that, using distortion-product otoacoustic emissions, a benefit of the intervention was observed for hearing loss (p=0·03).[24] In the trial of vitamin E, 108 adults were randomly assigned but only 23 (21%) patients were included in the analysis because of study dropouts (n=40), cumulative cisplatin dose less than 300 mg/m^2 (n=27), or too few study visits (n=18). The results described a significant decline in hearing loss with the control group but not with the intervention group, thus implying a benefit of the intervention.[12] Conversely, the study of antioxidant micronutrients did not show preservation of hearing in the intervention group.[16] None of the other studies described a benefit of the intervention in terms of hearing loss.

Most of the studies did not describe cancer outcomes.[12,13,16,18,21,28] Studies that did describe cancer outcomes found similar histological responses and survival[29,32] or lack of interference with cisplatin antitumour activity.[24]

Intratympanic N-acetylcysteine

Local instillation of a drug into the middle ear for otoprotection is attractive, since use of the technique addresses possible concerns of interference with systemic chemotherapy activity. N-acetylcysteine is an antioxidant and might be effective through the scavenging of free radicals.[41] Two studies of adult patients compared N-acetylcysteine given intratympanically versus no treatment. One study randomly assigned 22 ears[15] in 11 patients and the second randomly assigned 48 ears in 24 patients, with 20 of them being assessable[26] (table 3). One study described a larger change in hearing thresholds at 8 kHz in the control ears compared with in the intervention ears,[26] thus implying a benefit of the intratympanic N-acetylcysteine; the second study did not observe differences in hearing thresholds.[15] A third study randomly assigned 120 ears in 60 patients to either intratympanic N-acetylcysteine or intratympanic dexamethasone.[35] Children were included in this study and the median age was 32 years (range 6–60 years). However, the specific number of children that was included and their results were not described. Using the Tinnitus Handicap Inventory questionnaire, tinnitus was reported in none of the patients treated with N-acetylcysteine and in 20 patients treated with dexamethasone. In the N-acetylcysteine ears, no significant change occurred in hearing thresholds from baseline at 8 kHz compared with the dexamethasone ears, in which a significant decline was noted at this frequency. These findings suggested that there was a benefit of N-acetylcysteine. Local side-effects in these three studies were either non-existent or mild with transient pain.

In these trials, concerns about small sample size, statistical approaches (lack of direct comparison of ears using paired tests), and the open-label design with the potential for bias limit conclusions of efficacy. Because of the small number of children included, the feasibility of the intratympanic administration of a drug is unknown in the paediatric population, particularly for very young children.

Intratympanic dexamethasone

The second intratympanically administered drug that has been studied in randomised trials is dexamethasone. The drug might be effective by limiting the generation of cisplatin-induced reactive oxygen species and associated inflammation.[42] In addition to the trial that compared intratympanic N-acetylcysteine with dexamethasone, two trials compared intratympanic dexamethasone with no treatment (table 3), both of which enrolled adult patients. One trial randomly assigned 40 ears in 20 patients[25] and found significantly higher hearing thresholds in control ears than in intervention ears at 6 kHz (p=0·0002) and 8 kHz (p=0·009). The second trial randomly assigned 52 ears in 26 patients and found no significant difference by the American Speech-Language-Hearing Association criteria, although noted a significant increase in thresholds at 6 kHz in the control ears but not in the intervention ears, thus implying a benefit of dexamethasone.[14] Neither of these studies described local adverse effects associated with intratympanic administration. Studies of intratympanic dexamethasone are similarly limited to those of intratympanic N-acetylcysteine by sample size, statistical approach, and study design.

Conclusions and future directions

Three interventional trials, including non-randomised studies, are registered with ClinicalTrials.gov that have not been completed (table 4). ClinicalTrials.gov also lists several studies that have been terminated, withdrawn, or have unknown status of the following interventions: intratympanic dexamethasone, transtympanic Ringer's lactate, topical Ringer's lactate, sodium thiosulfate eardrops, and aspirin. This list raises the issue of trial feasibility and the importance of designing studies that can be successfully completed and disseminated.

To enhance the evidence base for children receiving cisplatin chemotherapy, trials of systemic drugs need to be designed such that disease control can be adequately assessed. This design is particularly crucial for otoprotectants whose mechanism of action is non-specific and could interfere with cisplatin antitumour activity, as considered on the basis of either theoretical concerns or data from preclinical studies. These trials are needed in both good and poor prognosis cancers and in patients with localised and disseminated disease. Such trials would ideally involve international co-operation such that sufficient sample sizes of homogeneous patients can be achieved expeditiously. For otoprotectants with theoretical or empirical concerns for cisplatin interference, the preferred study design might be limited to a single cancer type and treatment regimen so that inclusion criteria, response criteria, and treatment details can be specified and accessioned (such as in SIOPEL 6). For otoprotectants without these mechanistic concerns, a study design enrolling a heterogenous sample might be appropriate and efficient (such as in ACCL0431).

Importantly, in the future, localised administration might not be limited to intratympanic delivery, which relies on diffusion through the round window to the inner ear, but might be expanded by new technologies to include administration directly into the inner ear.[43,44] In terms of intratympanic or inner ear treatment, we need to understand the feasibility of single and repeated administration in children, particularly in the setting of short-term anaesthesia for young children, as well as the efficacy of such interventions to prevent hearing loss.

Overall, tools should be considered that facilitate decision making for families and clinicians. These data need to be incorporated into clinical practice guidelines that focus on interventions to prevent cisplatin-induced ototoxicity to improve clinical care. Finally, we found that systems for classifying hearing loss differed across studies. This heterogeneity limits the ability to compare interventions across studies. Thus, future efforts should harmonise ototoxicity endpoints that are reported in clinical trials.

Acknowledgments

KK (consultant on R01 [5R01CA137488-23]) and LS (co-principal investigator on UG1 [1UG1CA189955-01] and PI R25 [1R25CA168526-01A1]) have received NIH grants.

Declaration of interests

DRF reports research support paid to a hospital for site participation in a clinical trial of an intratympanic drug to prevent cisplatin-induced hearing loss from Otonomy and reimbursed time paid to a hospital for content expertise for the development of a potential clinical trial of a new oral drug for the prevention of cisplatin-induced hearing loss from Sensorium. PB reports serving as a consultant for Fennec Pharma since November, 2016. All other authors declare no competing interests.

References

1. Public Health Agency of Canada. Cancer in young people in Canada: a report from the Enhanced Childhood Cancer Surveillance System. 2017 https://www.canada.ca/en/health-canada/services/publications/science-research-data/cancer-young-people-canadasurveillance-2017.html (accessed Dec 27, 2018).
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006; 355: 1572–82. [PubMed: 17035650]
3. Brock PR, Knight KR, Freyer DR, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol 2012; 30: 2408–17. [PubMed: 22547603]
4. Knight KR, Chen L, Freyer D, et al. Group-wide, prospective study of ototoxicity assessment in children receiving cisplatin chemotherapy (ACCL05C1): a report from the Children's Oncology Group. J Clin Oncol 2017; 35: 440–45. [PubMed: 27937095]
5. Clemens E, de Vries AC, Am Zehnhoff-Dinnesen A, et al. Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors. Pediatr Hematol Oncol 2017; 34: 120–29. [PubMed: 28590156]
6. Waissbluth S, Chuang A, Del Valle A, Cordova M. Long term platinum-induced ototoxicity in pediatric patients. Int J Pediatr Otorhinolaryngol 2018; 107: 75–79. [PubMed: 29501316]
7. Laurell G, Bagger-Sjoback D. Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol 1991; 20: 158–67. [PubMed: 1870163]
8. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. Pediatrics 2007; 120: e1229–36. [PubMed: 17974716]
9. Schreiber JE, Gurney JG, Palmer SL, et al. Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. Neuro Oncol 2014; 16: 1129–36. [PubMed: 24497405]
10. Yorgason JG, Luxford W, Kalinec F. In vitro and in vivo models of drug ototoxicity: studying the mechanisms of a clinical problem. Expert Opin Drug Metab Toxicol 2011; 7: 1521–34. [PubMed: 21999330]
11. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002; 359: 248–52. [PubMed: 11812579]

12. Villani V, Zucchella C, Cristalli G, et al. Vitamin E neuroprotection against cisplatin ototoxicity: preliminary results from a randomized, placebo-controlled trial. Head Neck 2016; 38 (suppl 1): E2118–21. [PubMed: 26849799]
13. Crabb SJ, Martin K, Abab J, et al. COAST (cisplatin ototoxicity attenuated by aspirin trial): a phase II double-blind, randomised controlled trial to establish if aspirin reduces cisplatin induced hearing-loss. Eur J Cancer 2017 12; 87: 75–83.
14. Marshak T, Steiner M, Kaminer M, Levy L, Shupak A. Prevention of cisplatin-induced hearing loss by intratympanic dexamethasone: a randomized controlled study. Otolaryngol Head Neck Surg 2014; 150: 983–90. [PubMed: 24618499]
15. Yoo J, Hamilton SJ, Angel D, et al. Cisplatin otoprotection using transtympanic L-N-acetylcysteine: a pilot randomized study in head and neck cancer patients. Laryngoscope 2014; 124: e87–94. [PubMed: 23946126]
16. Weijl NI, Elsendoorn TJ, Lentjes EG, et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer 2004; 40: 1713–23. [PubMed: 15251161]
17. Rick O, Beyer J, Schwella N, Schubart H, Schleicher J, Siegert W. Assessment of amifostine as protection from chemotherapy-induced toxicities after conventional-dose and high-dose chemotherapy in patients with germ cell tumor. Ann Oncol 2001; 12: 1151–55. [PubMed: 11583199]
18. Grau JJ, Estape J, Cuchi MA, Firvida JL, Blanch JL, Ascaso C. Calcium supplementation and ototoxicity in patients receiving cisplatin. Br J Clin Pharmacol 1996; 42: 233–35. [PubMed: 8864323]
19. Kemp G, Rose P, Lurain J, et al. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol 1996; 14: 2101–12. [PubMed: 8683243]
20. Gandara DR, Nahhas WA, Adelson MD, et al. Randomized placebo-controlled multicenter evaluation of diethyldithiocarbamate for chemoprotection against cisplatin-induced toxicities. J Clin Oncol 1995; 13: 490–96. [PubMed: 7844610]
21. Somlo G, Doroshow JH, Lev-Ran A, et al. Effect of low-dose prophylactic dopamine on high-dose cisplatin-induced electrolyte wasting, ototoxicity, and epidermal growth factor excretion: a randomized, placebo-controlled, double-blind trial. J Clin Oncol 1995; 13: 1231–37. [PubMed: 7738626]
22. Verma S, Stewart DJ, Maroun JA, Nair RC. A randomized phase II study of cisplatin alone versus cisplatin plus disulfiram. Am J Clin Oncol 1990; 13: 119–24. [PubMed: 2180271]
23. Paredes J, Hong WK, Felder TB, et al. Prospective randomized trial of high-dose cisplatin and fluorouracil infusion with or without sodium diethyldithiocarbamate in recurrent and/or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 1988; 6: 955–62. [PubMed: 2836565]
24. Dias MA, Sampaio AL, Venosa AR, Meneses Ede A, Oliveira CA. The chemopreventive effect of Ginkgo biloba extract 761 against cisplatin ototoxicity: a pilot study. Int Tinnitus J 2015; 19: 12–19. [PubMed: 27186927]
25. Nasr W, Abdelhady M, Abd Elbary M, Nada E. Treatment of cisplatin-induced ototoxicity by intra-tympanic corticosteroid injection. Indian J Otol 2018; 24: 33–37.
26. Riga MG, Chelis L, Kakolyris S, et al. Transtympanic injections of N-acetylcysteine for the prevention of cisplatin-induced ototoxicity: a feasible method with promising efficacy. Am J Clin Oncol 2013; 36: 1–6. [PubMed: 22134515]
27. Planting AST, Catimel G, De Mulder PHM, et al. Randomized study of a short course of weekly cisplatin with or without amifostine in advanced head and neck cancer. Ann Oncol 1999; 10: 693–700. [PubMed: 10442192]
28. Yildirim M, Inancli HM, Samanci B, Oktay MF, Enoz M, Topcu I. Preventing cisplatin induced ototoxicity by N-acetylcysteine and salicylate. Kulak Burun Bogaz Ihtis Derg 2010; 20: 173–83. [PubMed: 20626325]

29. Schmidinger M, Budinsky AC, Wenzel C, et al. Glutathione in the prevention of cisplatin induced toxicities: a prospectively randomized pilot trial in patients with head and neck cancer and non small cell lung cancer. Wien Klin Wochenschr 2000; 112: 617–23. [PubMed: 11008323]
30. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med 2018; 378: 2376–85. [PubMed: 29924955]
31. Gallegos-Castorena S, Martinez-Avalos A, Mohar-Betancourt A, Guerrero-Avendano G, Zapata-Tarres M, Medina-Sanson A. Toxicity prevention with amifostine in pediatric osteosarcoma patients treated with cisplatin and doxorubicin. Pediatr Hematol Oncol 2007; 24: 403–08. [PubMed: 17710657]
32. Fox E, Levin K, Zhu Y, et al. Pantoprazole, an inhibitor of the organic cation transporter 2, does not ameliorate cisplatin-related ototoxicity or nephrotoxicity in children and adolescents with newly diagnosed osteosarcoma treated with methotrexate, doxorubicin, and cisplatin. Oncologist 2018; 23: 762–79. [PubMed: 29445029]
33. Freyer DR, Chen L, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017; 18: 63–74. [PubMed: 27914822]
34. Katzenstein HM, Chang KW, Krailo M, et al. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the intergroup hepatoblastoma study p96 as a part of the Children's Oncology Group. Cancer 2009; 115: 5828–35. [PubMed: 19813275]
35. Sarafraz Z, Ahmadi A, Daneshi A. Transtympanic injections of N-acetylcysteine and dexamethasone for prevention of cisplatin-induced ototoxicity: double blind randomized clinical trial. Int Tinnitus J 2018; 22: 40–45. [PubMed: 29993216]
36. Harned TM, Kalous O, Neuwelt A, et al. Sodium thiosulfate administered six hours after cisplatin does not compromise antineuroblastoma activity. Clin Cancer Res 2008; 14: 533–40. [PubMed: 18223229]
37. Frazier AL, Hale JP, Rodriguez-Galindo C, et al. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United Kingdom and United States. J Clin Oncol 2015; 33: 195–201. [PubMed: 25452439]
38. von Bueren AO, Kortmann RD, von Hoff K, et al. Treatment of children and adolescents with metastatic medulloblastoma and prognostic relevance of clinical and biologic parameters. J Clin Oncol 2016; 34: 4151–60. [PubMed: 27863192]
39. Kager L, Zoubek A, Potschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol 2003; 21: 2011–18. [PubMed: 12743156]
40. Boye K, Del Prever AB, Eriksson M, et al. High-dose chemotherapy with stem cell rescue in the primary treatment of metastatic and pelvic osteosarcoma: final results of the ISG/SSG II study. Pediatr Blood Cancer 2014; 61: 840–45. [PubMed: 24254749]
41. Thomas Dickey D, Muldoon LL, Kraemer DF, Neuwelt EA. Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res 2004; 193: 25–30. [PubMed: 15219317]
42. Nagura M, Iwasaki S, Wu R, Mizuta K, Umemura K, Hoshino T. Effects of corticosteroid, contrast medium and ATP on focal microcirculatory disorders of the cochlea. Eur J Pharmacol 1999; 366: 47–53. [PubMed: 10064151]
43. Ramaswamy B, Roy S, Apolo AB, Shapiro B, Depireux DA. Magnetic nanoparticle mediated steroid delivery mitigates cisplatin induced hearing loss. Front Cell Neurosci 2017; 11: 268. [PubMed: 28955202]
44. Aksit A, Arteaga DN, Arriaga M, et al. In-vitro perforation of the round window membrane via direct 3-D printed microneedles. Biomed Microdevices 2018; 20: 47. [PubMed: 29884927]

Key messages

- Interventions investigated for cisplatin-induced ototoxicity include systemic agents such as amifostine (assessed in five trials), sodium diethyldithiocarbamate or disulfiram (three trials), and sodium thiosfulate (two trials), as well as intratympanically administered agents such as N-acetylcysteine (three trials) and dexamethasone (three trials)
- Amifostine, diethyldithiocarbamate, and disulfiram studies did not show hearing preservation in previous trials (mostly done in adults)
- Sodium thiosulfate was effective in preserving hearing among paediatric patients treated with cisplatin but with different potential influence on survival observed: one study consisting solely of patients with localised hepatoblastoma showed no effects of sodium thiosulfate on survival and one study that included heterogeneous patients showed significantly worse overall survival among those classified in a post-hoc analysis as having disseminated disease, but not among those classified as having localised disease
- Inconsistent effects of intratympanic administration were identified and these studies were limited by design, small sample size, and statistical approach
- Future studies of systemic drugs will need to consider measurement of disease outcomes through study design and sample size
- Development of a clinical practice guideline that is focused on the prevention of cisplatin-induced ototoxicity is an important future step

Search strategy and selection criteria

We did a literature search for randomised trials indexed from Jan 1, 1980 to Dec 11, 2018, in MEDLINE, MEDLINE in-process, MEDLINE Epubs Ahead of Print, and Embase. The search strategy included Medical Subject Heading terms and text words that identified adult or paediatric patients receiving cisplatin for cancer who were randomly assigned to an intervention to reduce cisplatin-induced ototoxicity. The complete search strategies are provided in the appendix. We restricted the review to randomised trials because they are generally at lower risk of bias compared with observational studies. Studies published in any language were assessed. We restricted the review to fully published randomised trials (eg, conference abstracts were excluded). Additionally, trials were excluded in which there were systematically different cancer treatments or supportive care other than otoprotectant administration between trial groups.

Table 1:

Summary of randomised trials to reduce cisplatin-induced ototoxicity

	Amifostine (n=5)	Sodium diethyldithiocarbamate (n=3)	Sodium thiosulfate (n=2)	Other systemic drug (n=9)	Intratympanic N-acetyl cysteine (n=3)*	Intratympanic dexamethasone (n=3)*
Study population						
Adults	3	3	0	8	2	2
Children	2	0	2	1	0	0
Both	0	0	0	0	1	1
Type of cancer						
Single cancer type or site	5	2	1	1	1	0
More than one type or site	0	1	1	8	2	1
Not reported	0	0	0	0	0	2
Stage of cancer						
Only localised cancer included	0	0	1	0	0	0
Metastatic cancer included	4	3	1	3	2	0
Not reported	1	0	0	6	1	3
Control group type						
Usual care	5	2	2	3	2	2
Placebo	0	1	0	5	0	0
Other	0	0	0	1	1	1
Risk of bias adequacy						
Sequence generation	0	0	1	1	0	1
Allocation concealment	0	1	1	1	0	0
Participants and personnel masked	0	1	0	5	1	1
Outcome assessors masked	0	1	2	6	2	2
No attrition bias	4	1	1	4	0	1
Free of selective reporting	4	1	2	3	3	3

Data are n.

*A randomised trial of intratympanic N-acetyl cysteine *vs* dexamethasone is included in both intratympanic groups.

Table 2:

Results of randomised trials of systemically administered drugs

	Age group	Cancer type	Ototoxicity scale	Patients with any ototoxicity		Patients with severe ototoxicity	
				Intervention group	Control group	Intervention group	Control group
Amifostine							
Katzenstein (2009)[34]	Children (aged 0–11 years)	Hepatoblastoma (localised and metastatic)	Brock	22/37 (59%)	25/45 (56%)	4/37 (11%)	4/45 (9%)
Gallegos-Castorena (2007)[31]	Children (aged 7–15 years)	Osteosarcoma (localised and metastatic)	WHO	15/15 (100%)	10/13 (77%)	0/15 (0%)	0/13 (0%)
Rick (2001)[17]	Adult	Relapse or refractory germ cell tumours (stage not reported)	WHO	8/20 (40%)	11/20 (55%)	0/20 (0%)	2/20 (10%)
Planting (1999)[27]	Adult	Head and neck cancer (localised and metastatic)	WHO	15/36 (42%)	17/37 (46%)	3/36 (8%)	4/37 (11%)
Kemp (1996)[19]	Adult	Ovarian cancer (localised and metatstatic)	Unique	11/122 (9%)	19/120 (16%)	NA *	NA *
Sodium diethyldithiocarbamate							
Gandara (1995)[20]	Adult	Lung or ovarian cancer (localised and metastatic)	CTCAE	NA *	NA *	9/96 (9%)	6/99 (6%)
Verma (1990)[22]	Adult	Multiple cancers (localised and metastatic)	ECOG	NA *	NA *	NA *	NA *
Paredes (1988)[23]	Adult	Squamous cell head and neck cancer (localised and metastatic)	WHO	7/29 (24%)	10/31 (32%)	0/29 (0%)	3/31 (10%)
Sodium thiosulfate							
Brock (2018)[30]	Children (aged 1 month to 8 years)	Hepatoblastoma (localised)	Brock	18/55 (33%)	29/46 (63%)	2/55 (4%)	6/46 (13%)
Freyer (2017)[33]	Children (aged 1–18 years)	Multiple cancers (localised and metastatic)	ASHA	14/49 (29%)	31/55 (56%)	NA *	NA *

Data are n/N (%). CTCAE=Common Terminology Criteria for Adverse Events. ECOG=Eastern Co-operative Oncology Group. ASHA=American Speech-Language-Hearing Association.

* Not reported or not comparable to other scales.

Table 3:

Results of randomised trials of intratympanic N-acetylcysteine and dexamethasone compared with no treatment

	Number of participants	Age group	Hearing threshold at 4 kHz		Hearing threshold at 8 kHz	
			Intervention	Control	Intervention	Control
N-acetylcysteine *vs* no treatment						
Yoo (2014)[15]	11	Adult	42·3 (23·5)	49·5 (23·9)	58·2 (21·7)	58·2 (30·1)
Riga (2013)[26]	20	Adult	43·1 (24·6)	43·1 (25·1)	61·6 (25·8)	64·1 (27·6)
Dexamethasone *vs* no treatment						
Nasr (2018)[25]	20	Adult	40·0 (11·3)	40·9 (7·7)	43·2 (15·6)	55·7 (13·3)
Marshak (2014)[14]	26	Adult	37·0 (18·2)	37·0 (17·8)	43·7 (23·2)	46·3 (24·5)

Data are n or mean (SD).

Table 4:

Ongoing trials to prevent cisplatin-induced ototoxicity

	Trial description	Intervention	Planned sample size	Population	Sponsor
NCT03480971	Placebo-controlled, double blind, phase 2	Tempol piperidine nitroxide	120	Adults with head and neck cancer	Matrix Biomed
NCT01451853	Placebo-controlled, double blind, phase 2	SPI-1005 (ebselen)	80	Adults with head and neck or small cell lung cancer	Sound Pharmaceuticals
NCT02094625	Single-arm dose finding	N-acetylcysteine	60	Children with cancer	Children's Hospital Los Angeles