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. 2020 February ; 4(2): 141–150. doi:10.1016/S2352-4642(19)30336-0.

Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline

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DRF, PRB, PDR, and LS were responsible for the study concepts and design. PDR and LS acquired and analysed the data. All authors interpreted the data, drafted the manuscript and revised it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

See **Online** for appendix

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Abstract

Despite ototoxicity being a prevalent consequence of cisplatin chemotherapy, little guidance exists on interventions to prevent this permanent and progressive adverse event. To develop a clinical practice guideline for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer, we convened an international, multidisciplinary panel of experts and patient advocates to update a systematic review of randomised trials for the prevention of cisplatin-induced ototoxicity. The systematic review identified 27 eligible adult and paediatric trials that evaluated amifostine, sodium diethyldithiocarbamate or disulfiram, systemic sodium thiosulfate, intratympanic therapies, and cisplatin infusion duration. Regarding systemic sodium thiosulfate, the panel made a strong recommendation for administration in non-metastatic hepatoblastoma, a weak recommendation for administration in other non-metastatic cancers, and a weak recommendation against its routine use in metastatic cancers. Amifostine, sodium diethyldithiocarbamate, and intratympanic therapy should not be routinely used. Cisplatin infusion duration should not be altered as a means to reduce ototoxicity. Further research to determine the safety of sodium thiosulfate in patients with metastatic cancer is encouraged.

Introduction

The prognosis for children with cancer has improved over time and currently, more than 80% of paediatric patients with cancer will be cured.[1] However, late effects of therapy are common and negatively affect quality of life and long-term survival.[2] A well described and prevalent consequence of cisplatin chemotherapy is ototoxicity,[3,4] which results from the death of cochlear outer hair cells.[5] Cisplatin-induced ototoxicity is permanent[6] and

progressive.[7] The consequences of hearing loss in children are myriad and are especially impactful for patients who are treated when very young. These consequences include impairment of speech and language acquisition, psychosocial and cognitive development, and educational and vocational achievement.[8–10]

Approaches that can reduce cisplatin-induced ototoxicity without decreasing survival are important to patients, parents, and clinicians. Although a clinical practice guideline is available for ototoxicity surveillance,[11] a guideline focused on interventions to reduce ototoxicity is not available for health-care professionals in paediatric oncology. Consequently, our objective was to create a clinical practice guideline for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer.

Methods

The panel members for this guideline were multidisciplinary and multinational, with representation from paediatric oncology, audiology, otolaryngology, nursing, pharmacy, and a guideline methodologist (appendix p 1), as well as two patient advocates. Panel members were primarily selected on the basis of relevant publications, geographic representation, and expertise. Panel members declared conflicts of interest and none had a conflict that precluded panel participation (appendix p 2).

We used standard processes for creating evidence-based clinical practice guidelines.[12]

The guideline addressed a key clinical question: what adjuvant interventions should be offered in conjunction with cisplatin to prevent ototoxicity in children and adolescents with cancer? The target population includes children and adolescents aged 0–18 years who are receiving cisplatin for cancer. This age range was chosen because most studies categorise paediatric patients in this way. However, these recommendations might also be applicable to older adolescents and young adults. The target users are paediatric oncologists, medical oncologists, audiologists, otolaryngologists, nurse practitioners, physician assis tants, nurses, pharmacists, and other health-care professionals who care for children receiving cisplatin or who manage ototoxicity in paediatric patients with cancer. This guideline is targeted to high-income countries.

The evidence foundation for this clinical practice guideline consisted of randomised trials because they are, in general, less susceptible to bias than observational studies.[13] Because of the paucity of paediatric randomised trials, we included randomised trials done in both adults and children. However, the panel considered whether the data were directly related to children when formulating recommendations and evaluating the level of evidence. Panel members classified outcomes as critical, important, or not important to creating recommendations by consensus. High-frequency and lowfrequency hearing loss, event-free survival, and overall survival were considered critical; tinnitus was considered important.

A rapid review of interventions to prevent cisplatin-induced ototoxicity was previously published without methodological details or synthesis.[14] For this guideline, the search was updated, methodological details were added, and synthesis was done. The literature search was done with the assistance of a library scientist. We searched for randomised trials

indexed from Jan 1, 1980, to May 14, 2019 in MEDLINE, MEDLINE inprocess, MEDLINE e-publications ahead of print, Embase, and the Cochrane Central Register of Controlled Trials (appendix pp 3–8 shows the full search strategy).

We included studies if they met the eligibility criteria that we defined a priori: (1) participants were human; (2) the manuscript was a fully published randomised or quasi-randomised trial; (3) the study evaluated an intervention (including different durations of cisplatin infusion) for the purpose of reducing ototoxicity; and (4) all participants were planned to receive cisplatin for cancer. The eligibility criterion of evaluating an intervention for the purpose of reducing ototoxicity required the study to specify a planned schedule for ototoxicity monitoring that included audiological evaluation. We specified two exclusion criteria: (1) the intervention was not for the purpose of reducing ototoxicity; and (2) the study used a systematically different cancer treatment (another drug or a different total cisplatin dose) or supportive care (except for the oto protectant or cisplatin infusion duration under evaluation). We excluded studies comparing different schedules of cisplatin administration such as fractionated or multiday dosing (other than the duration of cisplatin infusion) because of the difficulty in reliably identifying studies in which cisplatin dose was the same in each study group.

Outcomes considered critical or important were abstracted. The approach to ototoxicity classification was heterogeneous between studies and we have presented the approach used in each study if available. Any ototoxicity and severe ototoxicity were abstracted, where severe ototoxicity was defined as at least grade 3 toxicity when the study used an ototoxicity classification system ranging from 0 (least ototoxicity) to 4 (worst ototoxicity). We also abstracted decibels (dB) of hearing loss at 4 kHz and 8 kHz, chosen on the basis of clinical relevance. Both event-free and overall survival data were also abstracted. We used the Cochrane Collaboration's tool for assessing bias in randomised trials and planned to explore publication bias by visual inspection of funnel plots when at least ten studies were available for synthesis.[15] Funnel plots are a graphical display of the effect measure on the x-axis and precision on the y-axis. Identification of asymmetry with an absence of studies in the left or right lower quadrant might indicate publication bias. Two investigators (PDR and LS) screened study titles and abstracts, reviewed full articles for eligibility and abstracted data independently. Any disagreements were resolved by consensus.

We described agreement between reviewers for study inclusion using the κ statistic, where strength of agreement was defined as slight (κ=0·00–0·20), fair (κ=0·21–0·40), moderate (κ=0·41–0·60), substantial (κ=0·61–0·80), or almost perfect (κ=0·81–1·00).[16]

We synthesised data when there were at least two studies with outcome data for a comparison. For the outcomes of any ototoxicity and severe ototoxicity, we presented effects as the risk ratio (RR) with their corresponding 95% CI. Treatment effects were estimated by the Mantel-Haenszel approach and weighted by the inverse variance. For the outcome of dB of hearing loss, we presented effects as the weighted mean di?erence with their corresponding 95% CI. We used a random effects model for all analyses because we anticipated heterogeneity in effects. Event-free and overall survival were described and not synthesised. Synthesis was done using Review Manager 5.3 (Cochrane Collaboration,

Nordic Cochrane Centre, Denmark). All tests of significance were two-sided and statistical significance was defined as $p<0·05$.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to generate recommendations and assign level of evidence.[17] With this approach, recommendations can be either strong or weak. A strong recommendation means that the benefits clearly outweigh the risks (or vice versa), and consequently, in general, patients should receive (or not receive) the recommended intervention. Conversely, a weak recommendation means that the benefits and risks of the intervention are uncertain or are closely matched, and consequently, preferences and values will influence intervention administration. We considered efficacy, safety, resources, and logistical challenges in formulating recommendations. The level of evidence reflects the degree of certainty in effect estimates as applied to our target population and considers trial design, precision, consistency, and directness. Where recommendations address multiple outcomes with varied quality of evidence, the level of evidence we have assigned reflects the outcome with the lowest quality of evidence.

We developed evidence tables using synthesised and non-synthesised results. Based on these tables, recommendations were drafted and debated in a series of discussions with panel members. Given the challenges in achieving consensus regarding the sodium thiosulfate recommendations, additional steps were taken in this deliberation. For this discussion, the data were first presented, and panel members were given an opportunity to clarify their understanding of the data. Panel members then voted on the number of patient groups for which recommendations would be generated. The options presented were two groups (non-metastatic hepatoblastoma and all other cancers including metastatic cancers) or three groups (non-metastatic hepatoblastoma, non-metastatic cancers other than hepatoblastoma, and metastatic cancers). The reason for this deliberation was that one of the two studies that informed the evidence base (ACCL0431)[18] included a post-hoc stratification by non-metastatic and metastatic cancers, and the panel had to decide whether they would accept the stratified results. Once this decision had been made, each member declared his or her vote within each patient group sequentially. After the vote, consensus recommendations were sought that reflected the divergent perspectives of the panel members.

Once a consensus on the draft recommendations was achieved, draft versions of the clinical practice guideline were circulated until all authors agreed with its content. We did not send the final version to external experts but relied on the peer-review process during manuscript submission as an efficient and rigorous approach to external review. We plan to update the guideline in 5 years or sooner if important new information is published.

Recommendations and explanations

Evidence base

27 publications met the eligibility criteria (figure). Agreement among reviewers for study inclusion was perfect ($\kappa=1·0$). Interventions were divided into three broad categories: systemically administered agents, locally administered agents (all were intra tympanic), and different durations of cisplatin infusion. Studies of systemically administered agents

evaluated amifostine (five studies), sodium diethyldithiocarbamate or its oxidised product disulfiram (three), sodium thiosulfate (two), and other agents (nine). Six studies of intratympanically administered agents evaluated dexamethasone, acetylcysteine, and sodium thiosulfate. Two studies evaluated the duration of cisplatin infusion. None of the studies included in our review evaluated the intervention in patients with pre-existing hearing loss or established ototoxicity.

Table 1 provides the characteristics of included trials stratified by intervention evaluated; details of each study are presented in appendix pp 9–10. In general, ototoxicity was measured between completion of the intervention and up to 6 months later. The exception was SIOPEL 6, in which ototoxicity was measured at a median of 3 years from randomisation.[19] Six studies were solely paediatric trials. Too few studies were available to generate funnel plots and thus, publication bias was not assessed. Recommendations were not generated for the nine systemic otoprotective interventions that were each evaluated in only one study. Those interventions were vitamin E alone;[20]a combination of vitamin C, vitamin E, and selenium;[21] pantoprazole;[22]aspirin and omeprazole;[23]*Ginko biloba* extract;[24]calcium gluconate;[25]low-dose dopamine infusion;[26]systemic acetylcysteine;[27]and glutathione.[28] Two studies with methodological concerns showed beneficial effects associated with the intervention. One study randomly assigned 15 adult patients to either receive *Ginkgo biloba* extract or placebo and found that hearing as measured using distortion product otoacoustic emissions was better with *Ginkgo biloba* extract (p=0·03).[24] A second study of vitamin E randomly assigned 108 adults to either receive vitamin E or placebo but only 23 patients were included in the analysis. Significant worsening in hearing was observed in the placebo group but not in the vitamin E group.[20]

Table 2 shows synthesised results for interventions evaluated in more than one study, table 3 presents recommendations and remarks in addition to strength of the recommendation and the level of evidence, and the panel shows identified knowledge gaps.

Recommendation 1: do not use amifostine for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Our first recommendation was a strong recommendation based on evidence of high quality (table 3). Amifostine is a reducing agent that is dephosphorylated to its active thiol metabolite; it binds to cytotoxic cisplatin metabolites and scavenges free radicals. Among the five randomised trials of amifostine,[29–33]two were paediatric studies that enrolled patients with hepatoblastoma (aged 0–11 years)[32] and osteosarcoma (aged 7–15 years;[29] table 1). Amifostine did not significantly reduce ototoxicity in any of these studies. When the data were pooled, amifostine did not reduce any ototoxicity (RR 0·96 [95% CI 0·71–1·29]) or severe ototoxicity (0·85 [0·34–2·12]). None of these studies identified a negative effect of amifostine on survival.[31]

In formulating the strong recommendation against routine use of amifostine, the panel considered the absence of benefit combined with amifostine-related toxicities. Toxicities included hypocalcaemia, nausea, and hypotension.[31,32] Direct data were available in paediatric patients, increasing the quality of the evidence.

Recommendation 2: do not use sodium diethyldithiocarbamate for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Our second recommendation was a strong recommendation based on evidence of low quality (table 3). Diethyldithiocarbamate is a heavy-metal chelating thiol compound.[34] The trials included in the analysis evaluated sodium diethyldithiocarbamate (two studies) or its oxidised product, disulfiram (one). All these studies included only adult patients (table 1).[34–36] None of the trials found that administration reduced ototoxicity, and the one study of disulfiram found that the intervention was associated with more ototoxicity ($p<0{\cdot}005$).[35] Table 2 shows that sodium diethyldithiocarbamate was not associated with less severe ototoxicity (RR 0·73 [95% CI 0·08–6·44]).

The panel made a strong recommendation against routine use of sodium diethyldithiocarbamate for cisplatin-induced ototoxicity because of the absence of efficacy and because of drug-related toxicities, including hyperglycaemia, hypertension, dehydration, and taste alteration.[34] Evidence quality was low because all studies were done in adults and because the efficacy estimate was imprecise.

Recommendation 3: use sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic hepatoblastoma

Our third recommendation was a strong recommendation based on evidence of high quality (table 3). Sodium thiosulfate is a thiol-containing reducing agent and free-radical scavenger. Two trials, one conducted by the International Childhood Liver Tumor Strategy Group (SIOPEL 6)[19] and the other by the Children's Oncology Group (ACCL0431),[18]compared the addition of sodium thiosulfate with usual care (table 1). SIOPEL 6 enrolled 109 children with standard-risk hepatoblastoma (aged 1 month to 8·2 years) and administered six cycles of cisplatin. The sodium thiosulfate dose of 20 g/m^2 was administered 6 h after each cisplatin dose. The number of patients with any hearing loss was 18 (33%) of 55 with sodium thiosulfate versus 29 (63%) of 46 without sodium thiosulfate ($p=0{\cdot}002$). Survival outcomes were favourable. The 3-year event-free survival was 82% (95% CI 69–90) with sodium thiosulfate versus 79% (65–88) without sodium thiosulfate. 3-year overall survival was 98% (88–100) with sodium thiosulfate versus 92% (81–97) without sodium thiosulfate.

In contrast to SIOPEL 6, ACCL0431 enrolled 125 children with multiple cancer types, prognostic groupings, and treatments.[18] The main cancer types represented in this trial were germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, and osteosarcoma. In a post-hoc analysis, localised versus disseminated disease was classified by site investigators. In ACCL0431, the study authors used the term disseminated to describe patients with brain tumours with positive cerebrospinal fluid. To improve consistency in language, the term metastatic is used in this guideline instead of disseminated. The recommendations refer to patients with non-metastatic disease rather than localised disease to emphasise that patients with regional disease were categorised as localised in ACCL0431. Six enrolled children had a diagnosis of non-metastatic hepatoblastoma. In ACCL0431, the sodium thiosulfate dose of 16 g/m^2 was administered 6 h after each cisplatin dose. Of the 104 patents with evaluable audiological results, the number with hearing loss was 14 (29%) of 49 with sodium thiosulfate versus 31 (56%) of 55 without sodium thiosulfate ($p=0{\cdot}0002$). For all patients in

ACCL0431, the 3-year event-free survival was 54% (95% CI 40–66) with sodium thiosulfate versus 64% (50–74) without sodium thiosulfate (p=0·36). The 3-year overall survival was 70% (56–80) with sodium thiosulfate versus 87% (76–93) without sodium thiosulfate (p=0·07).

The strong recommendation to administer sodium thiosulfate in patients with non-metastatic hepatoblastoma reflects the value placed on hearing protection and high-quality evidence. In making this recommendation, the panel valued the observation that sodium thiosulfate did not reduce survival in the trial conducted specifically in children with non-metastatic hepatoblastoma (SIOPEL 6). The panel was reassured by the absence of effect on survival for patients with non-metastatic cancers enrolled on ACCL0431 (see recommendation 4). The data are most applicable to patients with non-metastatic hepatoblastoma receiving six cycles of cisplatin (as in SIOPEL 6) and thus, the strong recommendation might not be applicable to patients receiving fewer than six cycles of cisplatin.

Recommendation 4: consider sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic cancers other than hepatoblastoma

Our fourth recommendation was a weak recommendation based on evidence of low quality (table 3). The panel accepted the post-hoc stratified analysis in ACCL0431 and chose to make recommendations for three patient groups: patients with non-metastatic hepatoblastoma, patients with non-metastatic cancers other than hepatoblastoma, and patients with metastatic cancers. Among the 77 patients with non-metastatic cancers enrolled in ACCL0431, the 3-year event-free survival was 60% (95% CI 42–74) with sodium thiosulfate versus 66% (48–78) without sodium thiosulfate (p=0·73) and the 3-year overall survival was 83% (66–92) with sodium thiosulfate versus 89% (74–96) without sodium thiosulfate (p=0·88).

The panel was more certain about hearing protection because this effect should not differ between cancer types. Although sodium thiosulfate did not reduce survival in children with non-metastatic cancers in ACCL0431, the panel appreciated that this estimate was susceptible to bias given the post-hoc classification of non-metastatic disease, sub-group analysis (which can be associated with spurious results),[37] and potential for confounding. Thus, inability to evaluate consistency, imprecision, and trial design all contributed to the evidence being of low quality. These factors resulted in a weak recommendation for sodium thiosulfate administration in children with non-metastatic cancers other than hepatoblastoma. More research is needed to confirm the efficacy and safety of sodium thiosulfate in this population of children with cancer.

Of note, the two trials (SIOPEL 6 and ACCL0431) used different doses of sodium thiosulfate—16 g/m^2 and 20 g/m^2. Thus, either dose could be used but should be administered 6 h after cisplatin. Future research should consider identifying the optimal sodium thiosulfate dosing for this patient population.

Recommendation 5: we suggest sodium thiosulfate not be used routinely for the prevention of cisplatin-induced ototoxicity for children and adolescents with metastatic cancers

Our fifth recommendation was a weak recommendation based on evidence of low quality (table 3). The ACCL0431 trial included 47 patients with a post-hoc designation of metastatic cancers. Among this group, the 3-year event-free survival was 42% (95% CI 21–61) with sodium thiosulfate versus 61% (39–77) without sodium thiosulfate (p=0·16). The 3-year overall survival was 45% (23–65) with sodium thiosulfate versus 84% (62–94) without sodium thiosulfate (p=0·009).

In making a weak recommendation against routine use of sodium thiosulfate for patients with metastatic cancers, the panel considered the reduction in survival associated with sodium thiosulfate observed in children with metastatic cancers in ACCL0431. However, the panel appreciated that this estimate was susceptible to bias given the post-hoc classification of metastatic disease, subgroup analysis (which can be associated with spurious results),[37] and potential for confounding. Thus, inability to evaluate consistency, imprecision, and trial design all contributed to the evidence being of lowquality. The weak (rather than strong) recommendation against its routine use in this population was influenced by patient representatives on the panel who advocated for the importance of discussing sodium thiosulfate as an option with patients and families. Given the low-quality evidence, some families might favour administration when balancing their own personal preferences and values, which might be affected by their personal financial resources. The panel also recognised that there will be clinical scenarios in which the benefits of sodium thiosulfate administration probably outweigh the risks, such as in a child with blindness. Further, the panel was concerned that a strong recommendation against the use of sodium thiosulfate might limit the investment required to study this drug further in the future. The panel strongly encourages research of sodium thiosulfate in patients with poor prognosis and metastatic cancers so that a negative effect on survival can either be refuted or confirmed.

Recommendation 6: do not use intratympanic middle ear therapy for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Recommendation 6 was a strong recommendation based on evidence of low quality (table 3). There is great interest in studying local interventions for cisplatin-induced ototoxicity because this approach might eliminate concerns about interference with systemic chemotherapy activity. The overall goal is to deliver medication directly to the cochlea and limit systemic exposure. All included trials administered the agent intratympanically, relying on diffusion from the middle ear compartment through the cochlear round window into the perilymph to achieve this goal. Six randomised trials investigated intratympanic therapy.[38–43] Five studies compared intratympanic therapy with usual care in exclusively adult populations, whereas the sixth study compared two intratympanic therapies in a mixed-age population. All studies randomly assigned each ear of the same individual to a study group.

Two studies evaluated intratympanic acetylcysteine, which is an antioxidant and a free radical scavenger.[44] One study of 11 patients did not show a benefit of intratympanic acetylcysteine.[39] A second study of 20 evaluable patients found significant worsening in

thresholds at 8 kHz in control ears but not in ears treated with acetylcysteine.[40]Two studies evaluated dexamethasone,[38,41] which might reduce the generation of cisplatin-induced reactive oxygen species and inflammation.[45] One of these trials evaluated 20 patients and found significantly worse thresholds in control ears compared with ears treated with dexa methasone at both 6 kHz (p=0·0002) and 8 kHz (p=0·009).[41]The second trial,[38]with 26 patients, did not show a significant diffference between ears by American Speech-Language-Hearing Association ototoxicity criteria. However, significant worsening in thresholds at 6 kHz in the control ears but not in the ears treated with dexamethasone was observed.[38] When synthesised (table 2), mean differences were not significantly different for either acetylcysteine or dexamethasone versus usual care. Another study randomly assigned 120 ears in 60 patients to either intratympanic acetylcysteine or intratympanic dexamethasone.[42] The age range of participants was 6–60 years, but the number of paediatric patients enrolled was not stated. This study suggested that acetylcysteine might be better than dexamethasone because zero ears treated with acetylcysteine had tinnitus, versus 20 ears treated with dexamethasone. The study also showed significant worsening in thresholds compared with baseline at 8 kHz in ears treated with dexamethasone but not in ears treated with acetylcysteine. A different study randomly assigned 13 patients receiving concurrent chemotherapy and radiotherapy to receive three administrations of intratympanic sodium thiosulfate gel into either the left or right ear.[43] This study was closed early because of poor accrual without showing significant differences in ototoxicity between groups. Only three participants received all three planned sodium thiosulfate treatments, emphasising feasibility concerns. In all studies of intratympanic therapy, differences in thresholds between groups were not considered clinically significant by the panel, even when statistically significant differences were shown.

In making a strong recommendation against intratympanic therapy for cisplatin-induced ototoxicity, the panel noted that although benefits of intratympanic therapy were observed in small single trials, results were inconsistent, and most effects were not considered clinically important. Further, there were few direct data in paediatric patients and many concerns were raised regarding feasibility of repeated administration in this population.

In general, it might be challenging to achieve consistent drug exposure to the cochlea using intratympanic therapy because of multiple factors, including variable clearance through the Eustachian tube and inflammation that could affect the extent of diffusion across the round window.[46] Nonetheless, the panel believes that local therapy is an important area of future research (panel).[47,48] More effective approaches to achieve consistent delivery of medication into the cochlea are of particular interest. For example, gel formulation installation into the middle ear might result in more sustained concentrations and more consistent delivery across the round window.[49] Alternatively, administration directly into the cochlea is being explored, including microneedle array infusion devices placed at the round window[48] and otomagnetic administration of nanocapsules containing the drug.[47] Future research will be required to evaluate both the efficacy and safety of these approaches.

Recommendation 7: do not alter cisplatin infusion duration, as a means in itself, to reduce ototoxicity in children and adolescents with cancer

Our seventh recommendation was a strong recommendation based on evidence of low quality (table 3). Only two studies were identified that compared different durations of cisplatin infusion and specified a planned schedule for ototoxicity monitoring that included audiological evaluation. These studies compared continuous infusion of cisplatin over 24 h versus bolus infusion over 1 h[50] and versus bolus infusion over 20 minutes.[51] Synthesis was only possible for any ototoxicity in which no benefit was observed, although the confidence interval was wide, resulting in downgrading of evidence quality. Further, the panel was concerned that many studies that compared different infusion durations were focused on outcomes other than hearing. Together, these issues reduced the ability to determine if infusion duration is associated with ototoxicity risk. Thus, the duration of cisplatin infusion should not be altered, as a means in itself, to reduce ototoxicity. However, if sodium thiosulfate is to be introduced as an otoprotectant, then the cisplatin infusion will need to be 6 h or less, as was required in the SIOPEL 6 and ACCL0431 trials.

Discussion

In this clinical practice guideline, developed by an international and multidisciplinary group, the panel made a strong recommendation for sodium thiosulfate administration for patients with non-metastatic hepatoblastoma, a weak recommendation for sodium thiosulfate administration for patients with other non-metastatic cancers, and a weak recommendation against the administration of sodium thiosulfate for patients with metastatic cancers. The panel made strong recommendations against the use of amifostine, sodium diethyldithiocarbamate, and intratympanic therapy to reduce cisplatin-induced ototoxicity. The duration of cisplatin infusion should not be altered, as a means in itself, to reduce ototoxicity.

Achieving consensus for the recommendations related to sodium thiosulfate administration was challenging. Thus, additional methodological steps were applied to 8 the guideline development process to ensure inclusion of the perspectives of all panel members. The participation of patient representatives on this panel was crucial, because recommendations had to be balanced between more certain hearing preservation and less certain potential to negatively influence survival. Given the high-quality evidence for an otoprotective effect of sodium thiosulfate, the panel wanted to promote sodium thiosulfate use and protect the hearing of the largest number of children in situations with the most certainty about its efficacy without a negative effect on survival. However, the panel also wanted to limit the use of sodium thiosulfate in situations where harm might be possible. The panel identified an urgent need to obtain more data about sodium thiosulfate use in patients with poor prognosis and metastatic cancers so that its use can be optimised.

Of note, in both randomised trials of sodium thiosulfate (SIOPEL 6 and ACCL0431),[18,19] administration was protocol-specified to be a 15 min infusion starting 6 h after completion of each cisplatin infusion. The duration of each cisplatin infusion itself could be no longer than 6 h. Thus, if sodium thiosulfate is planned to be used, it should be administered in a similar fashion as used in these two trials.

None of the identified studies focused on patients who had already developed some degree of cisplatin-induced ototoxicity or had pre-existing hearing loss; the efficacy of sodium thiosulfate in preventing further deterioration of hearing among patients with pre-existing hearing loss is unknown. Therefore, an important knowledge gap is the optimal approach to preserve hearing in this subset of patients. Similarly, the safety, particularly concerning survival, of cisplatin dose reduction or platinum substitution with the view to mitigate further hearing deterioration in these patients requires evidence-based evaluation.

In summary, we present a guideline for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer. Further research to determine the safety of sodium thiosulfate in patients with metastatic cancers and to evaluate different approaches for local otoprotectant therapy is encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Pediatric Oncology Group of Ontario provided funding but did not influence the content of this manuscript or the decision to submit for publication. LS is supported by a Canada Research Chair in Pediatric Oncology Supportive Care.

Declaration of interests

DRF has received financial support from Sensorion for his consulting time and expertise, and his hospital has received research support from Otonomy for site participation in a clinical trial. PRB has received consulting fees from Fennec Pharma. KWC has received financial support from Otonomy for travel expenses to attend an event to discuss a multi-institutional trial of a possible otoprotectant. MS was a principal investigator for a clinical trial and has published a commentary on ototoxicity. All other authors declare no competing interests.

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Key messages

- On the basis of a systematic review of the evidence, an international and multidisciplinary panel developed a clinical practice guideline addressing the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer
- The guideline panel made a strong recommendation for sodium thiosulfate administration for patients with non-metastatic hepatoblastoma, a weak recommendation for sodium thiosulfate administration for patients with other non-metastatic cancers, and a weak recommendation against the administration of sodium thiosulfate for patients with metastatic cancers
- The panel made strong recommendations against the use of amifostine, sodium diethyldithiocarbamate, and intratympanic therapy to reduce cisplatin-induced ototoxicity
- Further research todetermine the safety of sodium thiosulfate in patients with metastatic cancers and to evaluate different approaches for local otoprotectant therapy is encouraged

Panel:

Knowledge gaps in prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

- To evaluate the effectiveness and cancer outcomes associated with sodium thiosulfate administration when used in clinical practice, particularly for patients with poor prognosis and metastatic cancers, and for those with genetic susceptibility to cisplatin-induced ototoxicity
- To determine the optimal dosefor sodium thiosulfate administration
- To develop and evaluate approaches to improve delivery of otoprotective agents to the cochlea, including intracochlear therapy
- To identify effective and safe interventions to preserve hearing among children and adolescents who have already developed cisplatin-induced ototoxicity, with a plan for further cisplatin administration
- To determine therisk of tinnitus, vertigo, and other patient-reported ototoxicity-related outcomes and to identify the effect of sodium thiosulfate and other proposed otoprotectants to reduce these outcomes
- To evaluate compliance withthis clinical practice guideline for cisplatin-induced ototoxicity and to determine the effect of guideline-concordant care
- To create decision aidsto facilitate patient and parent decision making in the setting of weak recommendations

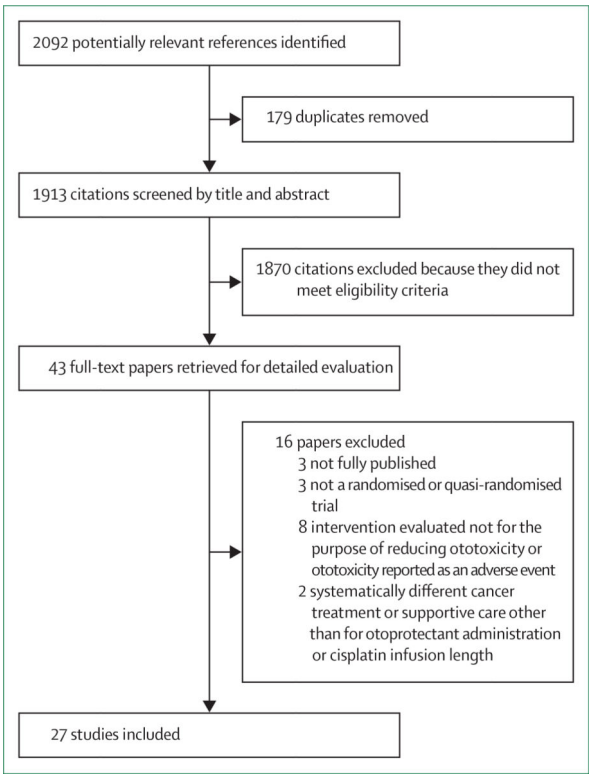

Figure:
Flow diagram showing study identification, selection and reasons for exclusion

Table 1:

Characteristics of included randomised trials by type of intervention

	Amifostine (n=5)	Sodium diethyldithiocarbonate (n=3)	Systemic sodium thiosulfate (n=2)	Other systemic (n=9)	Intratympanic acetylcysteine (n=3)*	Intratympanic dexamethasone (n=3)*	Intratympanic sodium thiosulfate (n=1)	Duration of cisplatin infusion (n=2)
Study population								
Adults	3	3	0	8	2	2	1	1
Children	2	0	2	1	0	0	0	1
Both	0	0	0	0	1	1	0	0
Type of cancer								
Single cancer type or site	5	1	1	1	1	0	1	2
More than one type or site	0	2	1	8	2	1	0	0
Not reported	0	0	0	0	0	2	0	0
Stage of cancer								
Only non-metastatic	0	0	1	0	0	0	0	0
Metastatic included	4	3	1	3	2	0	1	2
Not reported	1	0	0	6	1	3	0	0
Control group type								
Usual care	5	2	2	3	2	2	1	0
Placebo	0	1	0	5	0	0	0	0
Other	0	0	0	1	1	1	0	2
Risk of bias adequacy†								
Sequence generation	0	0	1	1	0	1	1	0
Allocation concealment	0	1	1	1	0	0	1	0
Participants and personnel masked	0	1	0	5	1	1	0	0
Outcome assessors masked	0	1	2	6	2	2	1	0
Absence of attrition bias	4	1	1	4	0	1	0	1
Free of selective reporting	4	1	2	3	3	3	0	1

27 studies were included.

* One study compared intratympanic acetylcysteine versus intratympanic dexamethasone and is thus represented in two columns.

† Number of studies adjudicated to have these attributes and therefore to have a reduced risk of bias.

Table 2:

Data synthesis of trials for cisplatin-induced ototoxicity prevention

	Studies (n)	Patients (n)	Effect size*	95% CI	I^2 (%)	p value
Amifostine *vs* no treatment						
Any ototoxicity	5	465	RR 0·96	0·71 to 1·29	49%	0·78
Severe ototoxicity	4	223	RR 0·85	0·34 to 2·12	0%	0·72
Sodium diethyldithiocarbamate *vs* no treatment						
Severe ototoxicity	2	255	RR 0·73	0·08 to 6·44	56%	0·77
Sodium thiosulfate *vs* no treatment						
Any ototoxicity	2	205	RR 0·51	0·37 to 0·71	0%	<0·0001
Intratympanic acetylcysteine *vs* no treatment						
Threshold at 4 kHz	2	62	MD −2·7	−14·9 to 9·5	0%	0·66
Threshold at 8 kHz	2	62	MD −1·6	−14·8 to 11·6	0%	0·81
Intratympanic dexamethasone *vs* no treatment						
Threshold at 4 kHz	2	92	MD −0·7	−5·8 to 4·5	0%	0·80
Threshold at 8 kHz	2	92	MD −8·7	−18·1 to 0·7	34%	0·07
Continuous cisplatin infusion *vs* bolus cisplatin infusion						
Any ototoxicity	2	78	RR 1·60	0·62 to 4·13	0%	0·33

RR=risk ratio. MD=mean difference.

*RR less than 1 and MD less than 0 favour intervention.

Table 3:

Summary of cisplatin-induced ototoxicity prevention recommendations for children and adolescents with cancer

	Recommendation	Recommendation strength	Evidence quality	Remarks
Recommendation 1	Do not use amifostine for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	High quality	Benefits of amifostine were not observed in single studies or when trials were synthesised; direct data were available for paediatric patients, thus increasing the quality of the evidence; toxicities of amifostine were considered in making this recommendation
Recommendation 2	Do not use sodium diethyldithiocarbamate for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	Low quality	Benefits of diethyldithiocarbamate were not observed in single studies or when trials were synthesised; evidence quality was low because all studies were done in adults and estimates were imprecise; toxicities of sodium diethyldithiocarbamate contributed to the strong recommendation against routine administration
Recommendation 3	Use sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic hepatoblastoma	Strong	High quality	Evidence was rated as high quality for consistency, precision, trial quality, and availability of direct data; in making this recommendation, the panel valued the observation that sodium thiosulfate did not reduce survival in the trial conducted specifically in this patient population (SIOPEL 6); the panel was reassured by the absence of effect on survival for patients with non-metastatic cancers in the trial that included multiple cancer types (ACCL0431)
Recommendation 4	Consider sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic cancers other than hepatoblastoma	Weak	Low quality	The panel was more certain about hearing protection because this effect should not differ based on cancer type; although sodium thiosulfate did not reduce survival in children with non-metastatic cancers in the one trial that included multiple cancer types (ACCL0431), the panel appreciated this estimate was susceptible to bias given the post-hoc classification of non-metastatic disease, sub-group analysis, and potential for confounding; thus, inability to evaluate consistency, imprecision, and trial design all contributed to this evidence being considered low quality
Recommendation 5	We suggest sodium thiosulfate not be used routinely for the prevention of cisplatin-induced ototoxicity for children and adolescents with metastatic cancers	Weak	Low quality	In making a weak recommendation against routine use of sodium thiosulfate for patients with metastatic cancers, the panel considered the reduction in survival associated with sodium thiosulfate observed in children with metastatic cancers in the one trial that included multiple cancer types (ACCL0431); however, the panel appreciated this estimate was susceptible to bias given the post-hoc classification of metastatic disease, subgroup analysis, and potential for confounding; thus, inability to evaluate consistency, imprecision, and trial design all contributed to this evidence being considered low quality; the weak (rather than strong) recommendation was influenced by patient representatives who advocated for the importance of discussing sodium thiosulfate as an option with patients and families; given the low-quality evidence, some families might favour administration when balancing their own personal preferences and values
Recommendation 6	Do not use intratympanic middle ear therapy for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	Low quality	Although benefits of intratympanic therapy were observed in small single trials, results were inconsistent, and most effects were not considered clinically important; in general, achieving consistent drug exposure to the cochlea using intratympanic therapy is challenging; direct data were scarce in paediatric patients and concerns were raised regarding feasibility of repeated administration in this population
Recommendation 7	Do not alter cisplatin infusion duration, as a means in itself, to reduce ototoxicity in children and adolescents with cancer	Strong	Low quality	Studies comparing different durations of cisplatin infusion often focused on outcomes other than hearing; only two studies targeted ototoxicity and estimates were imprecise; thus, there was considerable uncertainty about the effect of infusion duration on ototoxicity risk