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Medical interventions for the prevention of platinum-induced hearing loss in children with cancer.

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Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

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ABSTRACT

Background

Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin or a combination of these, is used to treat a variety of paediatric malignancies. One of the most important adverse effects is the occurrence of hearing loss or ototoxicity. In an effort to prevent this ototoxicity, different otoprotective medical interventions have been studied. This review is the second update of a previously published Cochrane review.

Objectives

To assess the efficacy of medical interventions to prevent hearing loss and to determine possible effects of these interventions on anti-tumour efficacy, toxicities other than hearing loss and quality of life in children with cancer treated with platinum-based therapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 6), MEDLINE (PubMed) (1945 to 8 July 2016) and EMBASE (Ovid) (1980 to 8 July 2016). In addition, we handsearched reference lists of relevant articles and we assessed the conference proceedings of the International Society for Paediatric Oncology (2006 up to and including 2015), the American Society of Pediatric Hematology/Oncology (2007 up to and including 2016) and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (2010 up to and including 2015). We scanned the International Standard Randomized Controlled Trial Number (ISRCTN) Register (www.isrctn.com) and the National Institute of Health Register (www.clinicaltrials.gov) for ongoing trials (both searched on 12 July 2016).

Selection criteria

Randomized controlled trials (RCTs) or controlled clinical trials (CCTs) evaluating platinum-based therapy together with an otoprotective medical intervention versus platinum-based therapy with placebo, no additional treatment or another protective medical intervention in children with cancer.

Data collection and analysis

Two review authors independently performed the study selection, data extraction, risk of bias assessment and GRADE assessment of included studies, including adverse effects. We performed analyses according to the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

We identified two RCTs and one CCT (total number of participants 149) evaluating the use of amifostine versus no additional treatment in the original version of the review; the updates identified no additional studies. Two studies included children with osteosarcoma, and the other study included children with hepatoblastoma. Children received cisplatin only or a combination of cisplatin and carboplatin, either intra-arterially or intravenously. Pooling of results of the included studies was not possible. However, in the individual studies there was no significant difference in symptomatic ototoxicity only (that is, grade 2 or higher) and combined asymptomatic and symptomatic ototoxicity (that is, grade 1 or higher) between children treated with or without amifostine. Only one study, including children with osteosarcoma treated with intra-arterial cisplatin, provided information on tumour response, defined as the number of participants with a good or partial remission. The available data analysis (data were missing for one participant), best case scenario analysis and worst case scenario analysis all showed a difference in favour of amifostine, but this difference was significant only in the worst case scenario analysis ($P = 0.04$). There was no information on survival for any of the included studies. Only one study, including children with osteosarcoma treated with intra-arterial cisplatin, provided data on the number of participants with adverse effects other than ototoxicity grade 3 or higher. There was a significant difference in favour of the control group in the occurrence of vomiting grade 3 or 4 (risk ratio (RR) 9.04; 95% confidence interval (CI) 1.99 to 41.12; $P = 0.004$). There was no significant difference between treatment groups for cardiotoxicity and renal toxicity grade 3 or 4. None of the studies evaluated quality of life. The quality of evidence for the different outcomes was low. We found no eligible studies for possible otoprotective medical interventions other than amifostine and other types of malignancies.

Authors' conclusions

At the moment there is no evidence from individual studies in children with osteosarcoma or hepatoblastoma treated with different platinum analogues and dosage schedules that underscores the use of amifostine as an otoprotective intervention as compared to no additional treatment. Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. Based on the currently available evidence, we are unable to give recommendations for clinical practice. We identified no eligible studies for other possible otoprotective medical interventions and other types of malignancies, so no conclusions can be made about their efficacy in preventing ototoxicity in children treated with platinum-based therapy. More high quality research is needed.

PLAIN LANGUAGE SUMMARY

Drugs to prevent hearing loss in children receiving platinum chemotherapy for cancer

Review question

We reviewed the evidence of the effectiveness of any medical intervention to prevent hearing loss in children with cancer treated with platinum-based therapy (that is, including the anti-cancer drugs cisplatin, carboplatin, oxaliplatin, or a combination of these). We also looked at anti-cancer effectiveness, side effects other than hearing loss and quality of life.

Background

Platinum-based chemotherapy, including cisplatin, carboplatin, oxaliplatin, or a combination of these, is used in the treatment of different types of childhood cancer. Unfortunately, one of the most important side effects of platinum chemotherapy is hearing loss. This can occur not only during treatment but also years after the end of treatment. Although it is not life-threatening the loss of hearing, especially during the first three years of life, may lead to difficulties with school performance and psychosocial functioning. Prevention of platinum-induced hearing loss is thus very important and might improve the quality of life of children undergoing cancer treatment and those who have survived treatment with platinum-based chemotherapy.

Study characteristics

The evidence is current to July 2016.

We found two randomized studies (clinical studies where people are randomly put into one of two or more treatment groups) and one controlled study (clinical studies where people are put into one of two or more treatment groups but this is not done in a random way) (149 participants), all comparing amifostine with no additional treatment. Two studies included children with osteosarcoma (a type of bone cancer), the other study included children with hepatoblastoma (a type of liver cancer). Combining the results of the included studies was not possible.

Key results

At the moment there is no evidence from individual studies showing that the use of amifostine prevents hearing loss. Only one study reported results on cancer response and side effects, so we could make no definitive conclusions. None of the studies assessed survival and quality of life. We identified no adequate studies for other possible drugs to prevent hearing loss and for other types of cancer. Before definitive conclusions can be made about the usefulness of possible drugs to prevent hearing loss (either amifostine or another drug) in children treated with platinum chemotherapy more high quality research is needed.

Quality of the evidence

The quality of the evidence was low.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Amifostine compared to no otoprotective intervention for children with cancer treated with platinum-based therapy						
Patient or population: children with cancer treated with platinum-based therapy Settings: paediatric oncology departments Intervention: amifostine Comparison: no otoprotective intervention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No otoprotective inter-vention	Amifostine				
Ototoxicity (that is, hearing loss or tinnitus, or both)						
Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (combined asymptomatic and symptomatic disease) Exact test method not reported	769 per 1000 ¹	992 per 1000 (723 to 1000)	RR 1.29 (0.94 to 1.77)	28 (1 study)	⊕⊕○○ low ^{2,3}	Length of follow-up was not mentioned When only looking at symptomatic disease there was also no significant difference between treatment groups (RR 0.87; 95% CI 0.14 to 5.32; GRADE assessment identical to combined asymptomatic and symptomatic disease analysis)

<p>Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease)</p> <p>Objective and subjective audiometric evaluations were performed, no further information provided</p>	<p>789 per 1000¹</p>	<p>821 per 1000 (600 to 1000)</p>	<p>RR 1.04 (0.76 to 1.44)</p>	<p>36 (1 study⁴)</p>	<p>⊕⊕○○ low^{3,5}</p>	<p>Length of follow-up was not mentioned</p> <p>For 3 of the 39 children included in the study (all in the amifostine group) there were no data on ototoxicity. The RR reported here results from the 'available data' analysis. Intention-to-treat analyses (that is, best case and worst case scenarios) also showed no significant difference between the treatment groups</p> <p>When only looking at symptomatic disease there was also no significant difference between treatment groups (available data analysis: RR 0.87; 95% CI 0.14 to 5.32; intention-to-treat analyses (that is, best case and worst case scenarios) also showed no significant difference between treatment groups)</p> <p>The GRADE assess-</p>
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						ment for the worst and best case scenarios and the symptomatic disease only analysis was identical to that of the 'available data' analysis for the combined asymptomatic and symptomatic disease analysis
Ototoxicity according to modified Brock criteria with intravenous platinum (combined asymptomatic and symptomatic disease) Audiograms were performed, but no further information provided	556 per 1000 ¹	594 per 1000 (411 to 861)	RR 1.07 (0.74 to 1.55)	82 (1 study)	⊕⊕○○ low ^{3,6}	Length of follow-up was not mentioned It should be noted that these 82 children were part of a larger study group; they were considered in a special interim analysis of the incidence of toxicity. The total number of eligible participants was unclear and as a result we were unable to perform an intention-to-treat analysis. Also, we were unable to check if the ototoxicity results were available for at least 50% of the eligible participants. In the 'Methods' section we stated that if that was not the case, we would not report the results

						due to the associated high risk of attrition bias. However, we decided to give this study the benefit of the doubt When only looking at symptomatic disease there was also no significant difference between treatment groups (RR 1.00; 95% CI 0.57 to 1.75; GRADE assessment identical to combined asymptomatic and symptomatic disease analysis)
Tumour response						
Tumour response with intra-arterial platinum (good and partial remission)	583 per 1000¹	933 per 1000 (566 to 1000)	RR 1.6 (0.97 to 2.63)	27 (1 study)	⊕⊕○○ low^{2,3}	Length of follow-up was not mentioned For 1 of the 28 children included in the study (in the control group) there were no data on tumour response. The RR reported here results from the available data analysis. Intention-to-treat analyses also showed no significant difference between the treatment groups in the best case scenario, but in the

						worst case scenario there was a significant difference in favour of amifostine The studies using intra- venous platinum did not report on this outcome
Survival						
Survival (overall and event-free) - not reported	See comment	See comment	Not estimable	-	See comment	No information on overall and event-free survival
Adverse effects other than ototoxicity						
Renal toxicity/vomiting/ cardiotoxicity (all grade ≥ 3 according to NCI CTC v2 criteria) with intra-arterial platinum	See comment	See comment	See comment	28 (1 study)	See comment	Length of follow-up was not mentioned Renal toxicity: no significant difference between treatment groups (Fischer's exact test $P = 0.21$; low quality evidence ^{2,3}) Vomiting: significant difference in favour of the control group (RR 9.04; 95% CI 1.99 to 41.12; low quality evidence ^{2,3}) Cardiotoxicity: none of the participants in this study experienced cardiac toxicity grade 3 or 4 (low quality evidence ^{2,3})

						The studies using intravenous platinum did not provide adequate data on adverse effects
Quality of life						
Quality of life - not reported	See comment	See comment	Not estimable	-	See comment	No information on quality of life
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; NCI CTC v2: National Cancer Institute Common Toxicity Criteria version 2; RR: risk ratio.</p>						
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						

¹ The assumed risk was based on the prevalence in the control group of the included study.

² Presence of selection bias, performance bias, detection bias and other bias was unclear; low risk of attrition bias and reporting bias (downgraded 1 level).

³ As this was a small study with a total number of events fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro software ([GRADEpro](#))), we downgraded 1 level.

⁴ This was a controlled clinical trial.

⁵ High risk of selection bias, performance bias, attrition bias and reporting bias; unclear risk of detection bias and other bias (downgraded 1 level).

⁶ High risk of attrition and reporting bias; unclear risk of selection bias, performance bias and other bias; low risk of detection bias (downgraded 1 level).

BACKGROUND

Description of the condition

Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin, or a combination of these, is used to treat a variety of paediatric malignancies. Unfortunately one of the most important adverse effects is the occurrence of hearing loss (ototoxicity). It usually manifests as bilateral, symmetrical, sensorineural hearing loss first affecting the higher frequencies (6000 Hz or higher) (McHaney 1983), and is often accompanied by tinnitus (Reddel 1982).

There is a wide variation in the reported frequency of platinum-induced hearing loss, but one Cochrane systematic review described the frequency to be as high as 90.1% (Van As 2016a). The hearing loss not only develops during platinum-based therapy but also years after completion of the therapy (Bertolini 2004; Knight 2005). This might be explained by the prolonged retention of platinum in the body; up to 20 years after treatment circulating platinum is still detectable in the plasma (Gietema 2000). Platinum-induced hearing loss seems to be irreversible and worsening of hearing loss occurs during follow-up (McHaney 1983; Bertolini 2004).

Different risk factors have been identified, such as the type of platinum analogue used. Cisplatin seems to cause substantially more hearing loss than carboplatin and the highest incidence of hearing loss has been found in people who received both cisplatin and carboplatin (Bertolini 2004; Dean 2008). The ototoxicity of oxaliplatin as compared to the other platinum analogues is not as well established but oxaliplatin seems to be the least ototoxic (Eloxatin SPC). Furthermore, the incidence of platinum-induced hearing loss seems to be dose-dependent, increasing with higher cumulative doses (McHaney 1983; Schell 1989; Bertolini 2004; Li 2004), and with higher individual doses (Reddel 1982; Li 2004). Also, bolus injections have been reported to be more ototoxic than longer infusion durations (Reddel 1982), although Cochrane systematic reviews did not confirm this (Van As 2014a; Van As 2016b). Additional risk factors are cranial radiotherapy (Schell 1989), younger age (Schell 1989; Li 2004), genetic variants (Ross 2009; Grewal 2010) and other host-specific factors (Veal 2001), impaired renal function at the time of platinum treatment (Skinner 2004), and other ototoxic drugs such as aminoglycosides (Skinner 2004; Cancer in Children 2005) and furosemide (Gallagher 1979).

Description of the intervention

In an effort to prevent or reduce platinum-induced hearing loss, extensive research has been devoted to the identification of medical interventions capable of ameliorating this adverse effect. Cisplatin interacts with cochlear tissues such as the outer hair cells of the organ of Corti, stria vascularis, spiral ligament and spiral ganglionic

cells to generate a reactive oxygen species (ROS) response while also depleting the antioxidant enzyme system that would scavenge and neutralize this increase in superoxides. Cisplatin accumulates in the cochlear tissue, integrates into DNA and causes inefficient and dysfunctional protein and enzyme synthesis. The cochlea, because of its unique anatomical position and isolation, is practically a closed system and is therefore unable to flush out the accumulated toxins with the rapid pace of their generation. This results in ROS overload and a decreased antioxidant system leading to irreversible cell injury (Rybak 2007; Rybak 2009). Thus, antioxidants such as amifostine (Gallegos-Castorena 2007; Fouladi 2008) and sodium thiosulfate (Freyer 2009) might be good treatment options against platinum-induced hearing loss. Furthermore, other medical interventions such as neurotrophins, A1 adenosine receptors and dexamethasone have been studied (Rybak 2009).

Why it is important to do this review

Although platinum-induced hearing loss is not life-threatening, loss of hearing, especially during the first three years of life and even when only borderline to mild, can have important implications. It can negatively impact speech and language development, which may lead to difficulties with school performance and psychosocial functioning (Gregg 2004; Skinner 2004; Dean 2008).

Prevention of platinum-induced hearing loss is thus very important and might improve the quality of life of childhood cancer patients and survivors treated with platinum-based therapy.

This is the second update of the first systematic review evaluating all medical interventions for the prevention of platinum-induced hearing loss in children with cancer (Van As 2012; Van As 2014b).

OBJECTIVES

To assess the efficacy of medical interventions to prevent hearing loss and to determine possible effects of these interventions on anti-tumour efficacy, toxicities other than hearing loss and quality of life in children with cancer treated with platinum-based therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) or controlled clinical trials (CCTs) evaluating platinum-based therapy together with a protective medical intervention versus platinum-based therapy with

placebo, no additional treatment or another protective medical intervention in children with cancer.

Types of participants

Children (aged 0 to 18 years at diagnosis) with any type of childhood malignancy. Studies including both children and adults were only eligible for inclusion in this review if the majority of participants were children (that is, either more than 90% children or the maximal age did not exceed 22 years).

Types of interventions

Platinum-based therapy together with a protective medical intervention versus platinum-based therapy with placebo, no additional treatment or another protective medical intervention.

Treatment other than with cisplatin, carboplatin, oxaliplatin, or a combination of these and the investigated protective medical intervention should be the same in both treatment groups, including radiotherapy to the head or neck, or both. In both treatment groups, the same platinum analogue(s) should have been given with the same infusion duration and individual dose. In the design of the study, it should have been the intention to treat both treatment groups with the same cumulative dose of cisplatin, carboplatin, oxaliplatin, or a combination of these.

Types of outcome measures

Primary outcomes

1. Hearing loss (as defined by the authors of the original studies).
2. Tinnitus (as defined by the authors of the original studies).

Secondary outcomes

1. Tumour response (complete and partial remission as defined by the authors of the original study).
2. Survival (overall survival and event-free survival as defined by the authors of the original study).
3. Adverse effects other than hearing loss and tinnitus (grade 3 or higher according to the criteria used by the authors of the original study).
4. Quality of life (as defined by the authors of the original study).

Search methods for identification of studies

We did not impose language restrictions. Cochrane Childhood Cancer ran the searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE; the review authors ran all other searches.

Electronic searches

We searched the following electronic databases: CENTRAL; 2016, Issue 6), MEDLINE in PubMed (from 1945 to 8 July 2016) and EMBASE in Ovid (from 1980 to 8 July 2016).

The appendices show the search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE or EMBASE, either published or unpublished, by searching the reference lists of relevant articles and review articles. We assessed the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2006 up to and including 2015), the American Society of Pediatric Hematology/Oncology (ASPHO) (from 2007 up to and including 2016) and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (from 2010 up to and including 2015) ([Appendix 4](#) shows search strategies). We scanned the International Standard Randomized Controlled Trial Number (ISRCTN) Register (www.isrctn.com) and the National Institutes of Health (NIH) Register for ongoing trials (www.clinicaltrials.gov) (searched on 12 July 2016; [Appendix 5](#) shows search strategies).

Data collection and analysis

Selection of studies

After employing the search strategy, two review authors independently identified studies meeting the inclusion criteria for this review. We resolved discrepancies between authors by discussion and needed no third-party arbitration. We obtained in full any study that seemed to meet the inclusion criteria on the grounds of the title or abstract, or both, for closer inspection. We clearly stated the details of the reasons for exclusion of any study considered for the review. We have included a flow diagram of the selection of studies.

Data extraction and management

Two review authors independently performed data extraction using standardized forms. We extracted data on the characteristics of participants (such as age, stage of disease and renal function), interventions (such as route of delivery, dose and timing of the protective medical intervention, information on the received anti-neoplastic treatment and possible other ototoxic drugs such as aminoglycosides and furosemide), outcome measures and length of follow-up. We resolved discrepancies between authors by discussion and needed no third-party arbitration.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies (that is, selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias). We used the risk of bias items as described in the module of Cochrane Childhood Cancer ([Module CCG](#)), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved discrepancies between authors by discussion and needed no third-party arbitration. The risk of bias in the included studies was taken into account in the interpretation of the review's results.

Measures of treatment effect

We analysed dichotomous variables using risk ratios (RR) and presented all results with the corresponding 95% confidence interval (CI).

Dealing with missing data

During study selection there were no relevant data missing. We attempted to contact the study authors with regard to missing data for data extraction and risk of bias assessment. The primary author of [Katzenstein 2009](#) told us that they were in the process of writing a final manuscript. Some of our requested data might be in there but at the time he was unable to provide us with the additional data. During the update of this review this manuscript was not yet available. We did not receive additional information from [Gallegos-Castorena 2007](#) and [Petrilli 2002](#). We extracted the data by the allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. If this was not possible, we stated this and performed an as treated or available data analysis.

Assessment of heterogeneity

Since pooling of results was not possible, the assessment of heterogeneity (both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is, the I^2 statistic ([Higgins 2011](#))) was not applicable.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the [Assessment of risk of bias in included studies](#) section, we planned to assess reporting bias by constructing a funnel plot when there were a sufficient number of included studies (that is, at least 10 studies included in a meta-analysis) because otherwise the power of the test is too low to distinguish chance from real asymmetry ([Higgins 2011](#)). Since pooling of results was not possible, this was not applicable.

Data synthesis

We entered data into the Review Manager 5 software as provided by Cochrane ([RevMan 2014](#)); we performed analyses according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We included outcome measures only if it was the intention of the study to perform the necessary assessments in all randomized participants (so not optional, or only performed in some centres). When the results of a particular outcome measure were available for less than 50% of the participants of a study, due to the associated high risk of attrition bias, we did not report the results of this outcome measure. We performed pooling of results only if both treatment groups were comparable, including the definition of ototoxicity that was used. We summarized studies for which pooling of results was not possible descriptively. We used a fixed-effect model throughout the review. For outcomes where only one study was available, we were unable to calculate an RR if one of the treatment groups experienced no events and used the Fischer's exact test instead. We calculated all RRs, 95% CIs and P values mentioned in the results in Review Manager 5 ([RevMan 2014](#)), with the exception of the Fischer's exact P value (calculated in statcalc.exe).

For each comparison we prepared a 'Summary of findings' table using the GRADEpro software ([GRADEpro](#)), in which we presented the following outcomes: ototoxicity (that is, hearing loss or tinnitus, or both), tumour response, survival (overall and event-free), adverse effects other than ototoxicity (grade 3 or higher) and quality of life. Two review authors independently assessed the quality of the evidence for each outcome using the five GRADE considerations: study limitations, inconsistency, indirectness, imprecision and publication bias.

Subgroup analysis and investigation of heterogeneity

We planned to analyse data separately for participants treated with cisplatin, carboplatin, oxaliplatin or combinations of these platinum analogues. However, since pooling of results was not possible, subgroup analyses were not applicable.

Sensitivity analysis

Since pooling of results was not possible, sensitivity analyses for risk of bias items (that is, excluding studies with a high risk of bias and studies for which the risk of bias was unclear, and comparing the results of studies with a low risk of bias with the results of all available studies) were not applicable.

RESULTS

Description of studies

Results of the search

We ran searches of the electronic databases CENTRAL, MEDLINE (PubMed) and EMBASE (Ovid) in December 2011 for the original version of this review. This search yielded 573 references. Following initial screening of the titles, abstracts, or both, we excluded 551 references that clearly did not meet all criteria required for considering studies for this review. We assessed the 22 remaining references in full, of which three fulfilled all the criteria for considering studies for this review and were thus eligible for inclusion. One reference described an ongoing study and we excluded the remaining 18 references for the reasons described in the [Characteristics of excluded studies](#) table. Scanning the reference lists of included articles and reviews and the conference proceedings did not identify any additional eligible studies. By scanning the ongoing trials databases, we identified one additional ongoing trial.

For the first update, we ran searches of CENTRAL, MEDLINE (PubMed) and EMBASE (Ovid) in March 2014 yielding 138 references, which were added to the search results from December 2011. Initial screening of the titles, abstracts, or both, excluded all 138 references as they clearly did not meet the inclusion criteria.

Scanning the reference lists of relevant articles, the conference proceedings and the ongoing trials registers did not identify any additional eligible studies. At the time of this update no publications of the ongoing trials identified in the original version of the review were available.

For the second update we ran searches of CENTRAL, MEDLINE (PubMed) and EMBASE (Ovid) in July 2016 yielding 79 references (60 references after we removed duplicates). Initial screening of titles, abstracts, or both excluded 57 references as they clearly did not meet the inclusion criteria. We assessed the three remaining references in full; two were conference proceedings describing the two ongoing studies identified in the original version of the review (which were moved from the 'Characteristics of ongoing studies' table to the [Characteristics of studies awaiting classification](#) table), the other publication did not meet the inclusion criteria (see [Characteristics of excluded studies](#) table). Scanning the reference lists of relevant articles, conference proceedings and ongoing trials registers did not identify any additional eligible studies.

In summary, the review included three studies. We also identified two studies awaiting classification. See [Figure 1](#) for a flow diagram of the selection of studies for this systematic review.

Figure 1. Flow diagram of selection of studies.

Included studies

The characteristics of the included studies are summarized below. For more detailed information, see the [Characteristics of included studies](#) table.

We identified two RCTs ([Gallegos-Castorena 2007](#); [Katzenstein 2009](#)) and one CCT ([Petrilli 2002](#)), all evaluating amifostine as a possible otoprotective intervention. The total number of participants included in these studies was 149: 72 participants received amifostine whereas 77 participants received no otoprotective intervention. Please note that the presented participants in [Katzenstein 2009](#) were considered in a special interim analysis of the incidence of toxicity; the total number of eligible participants was unclear. Participants were aged between 0 and 22 years. In all studies amifostine was given as a 740 mg/m² dose in a 15-minute infusion immediately prior to the platinum doses; for more detailed information, see the [Characteristics of included studies](#) table. In two studies participants were diagnosed with an osteosarcoma ([Petrilli 2002](#); [Gallegos-Castorena 2007](#)); in the other study the participants were diagnosed with hepatoblastoma ([Katzenstein 2009](#)). In one study participants received cisplatin ([Gallegos-Castorena 2007](#)), in one study participants received a combination of cisplatin and carboplatin ([Petrilli 2002](#)), and in one study partici-

pants received either cisplatin or a combination of cisplatin and carboplatin depending on the stage of disease and randomization ([Katzenstein 2009](#)). For detailed information on the cumulative platinum doses, individual platinum doses, platinum infusion durations, route of delivery and other agents included in the chemotherapeutic protocols see the [Characteristics of included studies](#) table. Regarding other ototoxic drugs, in two studies participants received anthracyclines (that is, doxorubicin) ([Petrilli 2002](#); [Gallegos-Castorena 2007](#)), and in one study some of the participants received vincristine ([Katzenstein 2009](#)); no study stated if participants received gentamycin or furosemide. In two studies participants did not have prior hearing dysfunction and pre-treatment renal impairment ([Petrilli 2002](#); [Katzenstein 2009](#)), whereas in the other study this was unclear. In none of the studies did participants receive prior platinum treatment, prior radiotherapy to the head and neck region, or prior cranial surgery. None of the studies reported genetic variants of platinum ototoxicity. Finally, none of the studies reported the length of follow-up.

Risk of bias in included studies

See the 'Risk of bias' section of the [Characteristics of included studies](#) table and [Figure 2](#) for the exact scores per study and the support for the judgements made.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gallegos-Castorena 2007	?	?	?	?	+	+	?
Katzenstein 2009	?	?	?	+	-	-	?
Petrilli 2002	-	-	-	?	-	-	?

Allocation

For evaluating selection bias, we assessed random sequence generation and allocation concealment. Both these items, and thus the risk of selection bias, were unclear in two studies ([Gallegos-Castorena 2007](#); [Katzenstein 2009](#)). In the other study there was a high risk of selection bias; there was no randomization since this was a CCT ([Petrilli 2002](#)).

Blinding

For evaluating performance bias, we assessed blinding of participants and personnel. In two studies the risk of performance bias was unclear ([Gallegos-Castorena 2007](#); [Katzenstein 2009](#)). In the other study the risk of performance bias was high; participants treated with amifostine were consecutive participants so blinding was not possible ([Petrilli 2002](#)).

For evaluating detection bias we evaluated blinding of outcome assessors for all separate outcomes. For ototoxicity the risk of detection bias was low in one study ([Katzenstein 2009](#)), and unclear in two studies ([Petrilli 2002](#); [Gallegos-Castorena 2007](#)). Only one study evaluated response rate and adverse effects; the risk of detection bias was unclear for both these outcomes ([Gallegos-Castorena 2007](#)).

Incomplete outcome data

For evaluating attrition bias, we assessed incomplete outcome data for all separate outcomes. In one study the risk of attrition bias was low for all outcomes, that is, ototoxicity, response rate and adverse effects ([Gallegos-Castorena 2007](#)). In the other two studies the risk of attrition bias was high for the reported outcome, that is, ototoxicity ([Petrilli 2002](#); [Katzenstein 2009](#)).

Selective reporting

For evaluating reporting bias, we assessed selective reporting. In one study the risk of reporting bias was low ([Gallegos-Castorena 2007](#)). In the other two studies the risk of reporting bias was high ([Petrilli 2002](#); [Katzenstein 2009](#)).

Other potential sources of bias

For evaluating other potential sources of bias, we assessed the following items: block randomization in unblinded trials, baseline imbalance between treatment groups related to outcome (prior ototoxic treatment, age, sex, prior hearing loss), difference in ototoxic drugs other than platinum analogue between treatment groups (furosemide, gentamycin, anthracyclines, vincristine), difference in cumulative platinum dose between treatment groups,

difference in length of follow-up between treatment groups, difference in impaired renal function at the time of platinum treatment between treatment groups, and if an insensitive instrument was used to evaluate ototoxicity. In all three studies the risk of other potential sources of bias was unclear. For a more detailed description of all different items see the 'Risk of bias' section of the [Characteristics of included studies](#) table.

Effects of interventions

See: [Summary of findings for the main comparison Amifostine compared to no otoprotective intervention for children with cancer treated with platinum-based therapy](#)

Not all articles allowed data extraction for all endpoints (see the [Characteristics of included studies](#) table for a more detailed description of the extractable end points from each article). We calculated all RRs, 95% CIs and P values mentioned below in Review Manager 5 ([RevMan 2014](#)), with the exception of the Fischer's exact P value (calculated in statcalc.exe).

Ototoxicity (that is, hearing loss or tinnitus, or both)

We extracted data on ototoxicity from all three eligible trials ([Petrilli 2002](#); [Gallegos-Castorena 2007](#); [Katzenstein 2009](#)). Unfortunately it was not possible to pool the results of this outcome. Two studies used a comparable definition but in one study participants received their platinum treatment intra-arterially ([Gallegos-Castorena 2007](#)), and in the other it was given intravenously ([Petrilli 2002](#)). Due to the potential influence of this difference on the occurrence of ototoxicity, pooling was not possible. The other study initially used the same definition as the other two trials but during the study it was decided that using that definition substantially underestimated the true incidence of significant hearing loss and it was decided to use another definition instead ([Katzenstein 2009](#)). The authors were unable to provide results using the initial definition and therefore pooling was not possible. For the definitions used in the different studies see [Table 1](#) (for [Petrilli 2002](#); [Gallegos-Castorena 2007](#)) and [Table 2](#) (for [Katzenstein 2009](#)).

We extracted data on ototoxicity (defined as National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2 or NCI CTC v2) with the use of intra-arterial platinum chemotherapy from one study with 28 participants ([Gallegos-Castorena 2007](#)). All 15 participants randomized to amifostine had asymptomatic or symptomatic ototoxicity (that is, grade 1 and higher); and 10 out of 13 participants in the control group. The analysis showed no significant difference between the treatment groups (RR 1.29; 95% CI 0.94 to 1.77; $P = 0.11$; see [Figure 3](#); low quality evidence). There were two cases of symptomatic ototoxicity (that is, grade 2 and higher) among 15 participants randomized to amifostine and

two cases among the 13 participants in the control group. The analysis showed no significant difference between the treatment groups (RR 0.87; 95% CI 0.14 to 5.32; $P = 0.88$; see Figure 4; low quality evidence). It should be noted that both analyses included the participants who experienced symptomatic ototoxicity.

Figure 3. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.1 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (combined asymptomatic and symptomatic disease).

Figure 4. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.4 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (symptomatic disease).

We extracted data on ototoxicity (defined as NCI CTC v2) with the use of intravenous platinum chemotherapy from one study with 39 participants (Petrilli 2002). For three of the 20 participants in the amifostine group no ototoxicity data were available. The available data analysis of asymptomatic or symptomatic ototoxicity (that is, grade 1 and higher) showed no significant difference between the treatment groups (RR 1.04; 95% CI 0.76 to 1.44; $P = 0.80$; see Figure 5; low quality evidence); there were 14 cases among the 17 available participants in the amifostine group and 15 cases among the 19 control participants. Intention-to-treat analyses (data not shown) also showed no significant difference between the treatment groups: the RR for the worst case scenario (that is, 17 cases among 20 participants in the amifostine group) was 1.08 (95% CI 0.80 to 1.45; $P = 0.63$; low quality evidence), while the RR for the best case scenario (that is, 14 cases among 20 participants in the amifostine group) was 0.89 (95% CI 0.61 to

1.28; $P = 0.52$; low quality evidence). The available data analysis of symptomatic ototoxicity (that is, grade 2 or higher) showed no significant difference between the treatment groups (RR 1.32; 95% CI 0.83 to 2.10; $P = 0.24$; see Figure 6; low quality evidence); there were 13 cases among the 17 available participants in the amifostine group and 11 cases among the 19 control participants. Intention-to-treat analyses (data not shown) also showed no significant difference between the treatment groups: the RR for the worst case scenario (that is, 16 cases among 20 participants in the amifostine group) was 1.38 (95% CI 0.89 to 2.15; $P = 0.15$; low quality evidence), while the RR for the best case scenario (that is, 13 cases among 20 participants in the amifostine group) was 1.12 (95% CI 0.68 to 1.85; $P = 0.65$; low quality evidence). It should be noted that both analyses included the participants who experienced symptomatic ototoxicity.

Figure 5. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.2 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease).

Figure 6. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.5 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (symptomatic disease).

We extracted data on ototoxicity (defined as modified Brock criteria) with the use of intravenous platinum chemotherapy from one study; the presented interim analysis included 82 participants (Katzenstein 2009). It should be noted that these 82 children were part of a larger study group; they were considered in a special interim analysis of the incidence of toxicity. The total number of eligible participants was unclear and as a result we were unable to perform an intention-to-treat analysis. Also, we were unable to check if the ototoxicity results were available for at least 50% of the eligible participants. In the [Methods](#) section we stated that if that was not the case we would not report the results due to the associated high risk of attrition bias; however, we decided to give this study the benefit of the doubt. There were 22 cases of asymptomatic or

symptomatic ototoxicity (that is, grade 1a and higher) among 37 participants randomized to amifostine and 25 cases among the 45 participants in the control group. The analysis showed no significant difference between the treatment groups (RR 1.07; 95% CI 0.74 to 1.55; P = 0.72; see [Figure 7](#); low quality evidence). There were 14 cases of symptomatic ototoxicity (that is, grade 2a and higher) among 37 participants randomized to amifostine and 17 cases among the 45 participants in the control group. The analysis showed no significant difference between treatment groups (RR 1.00; 95% CI 0.57 to 1.75; P = 1.00; see [Figure 8](#); low quality evidence). It should be noted that both analyses included the participants who experienced symptomatic ototoxicity.

Figure 7. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.3 Ototoxicity according to modified Brock criteria (combined asymptomatic and symptomatic disease).

Figure 8. Forest plot of comparison: I Amifostine versus no otoprotective intervention, outcome: I.6 Ototoxicity according to modified Brock criteria (symptomatic disease).

Tumour response

Please note that due to the nature of this outcome (that is, the number of participants with a remission) a high event rate is favourable. Therefore, in the figures of the analyses 'favours control' is on the left and 'favours amifostine' is on the right, as opposed to the figures of the other analyses.

One study with 28 participants provided data on tumour response (defined as number of participants with a complete, good or partial response) with the use of intra-arterial platinum chemotherapy (Gallegos-Castorena 2007). For one of the 13 participants in the control group there were no response data. The available data analysis of tumour response showed no significant difference between the treatment groups (RR 1.60; 95% CI 0.97 to 2.63; P = 0.06; low quality evidence); there were 14 remissions among the 15 participants randomized to amifostine and seven remissions in the 12 control participants. The intention-to-treat analysis (data not shown) for the best case scenario (that is, eight remissions among 13 participants in the control group) also showed no significant difference between the treatment groups (RR 1.52; 95% CI 0.97 to 2.38; P = 0.07; low quality evidence), while the intention-to-treat analysis (data not shown) for the worst case scenario (that is, seven remissions among 13 participants in the control group) showed a significant difference in favour of the amifostine group (RR 1.73; 95% CI 1.03 to 2.92; P = 0.04; low quality evidence). Petrilli 2002 and Katzenstein 2009 provided no information on tumour response.

Survival

Gallegos-Castorena 2007 and Petrilli 2002 provided no information on survival (that is, event-free survival and overall survival). Katzenstein 2009 did not provide survival data for the 82 participants included in the interim analysis presented in this manuscript.

Adverse effects other than hearing loss and tinnitus (grade 3 or higher)

Since all participants receiving chemotherapy will experience adverse effects, we decided to analyse only the severe and life-threatening effects. We defined these as grade 3 or higher.

In Gallegos-Castorena 2007 (using intra-arterial platinum chemotherapy) there was a significant difference in favour of the control group in the occurrence of vomiting grade 3 or 4. All 15 participants in the amifostine group and one of 13 participants in the control group experienced vomiting grade 3 or 4 (RR 9.04; 95% CI 1.99 to 41.12; P = 0.004). None of the participants in this study experienced cardiac toxicity grade 3 or 4. We were unable to calculate an RR for renal toxicity grade 3 or 4 since one group experienced no events, but there was no significant difference between treatment groups; none of the participants in the amifostine group and two of 13 participants in the control group experienced renal toxicity grade 3 or 4 (Fischer's exact test P = 0.21). The quality of evidence was low for all assessed adverse effects. They also provided data on amifostine-related toxicity although without stating the exact grading. However, in this review only toxicities evaluated in both treatment groups were eligible so we did not include these toxicities.

The adverse effects other than hearing loss and tinnitus (grade 3 or higher) that Petrilli 2002 and Katzenstein 2009 reported could not be included in this review. Petrilli 2002 provided data for both treatment groups but as the number of infusions with toxicity present not as the number of participants with toxicity. As a result, we could not adequately analyse these data. They provided data on amifostine infusion-related toxicity, although without stating the exact grading for most toxicities, in (part of) the amifostine group. However, in this review only toxicities evaluated in both treatment groups were eligible, so we did not include these toxicities. Katzenstein 2009 provided data on adverse effects in both treatment groups but as the number of courses with tox-

icity present and not as the number of participants with toxicity. Furthermore, it was not clear if the presented data regarded only the 82 participants included in the interim analysis presented in this manuscript. As a result, we could not adequately analyse these adverse effects data.

Quality of life

None of the studies evaluated quality of life (Petrilli 2002; Gallegos-Castorena 2007; Katzenstein 2009).

DISCUSSION

Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin, or a combination of these, is used to treat a variety of paediatric malignancies. Unfortunately, one of the most important adverse effects is the occurrence of hearing loss or ototoxicity (McHaney 1983). Although it is not life-threatening, loss of hearing, especially during the first three years of life and even when only borderline to mild, can have important implications. It can negatively impact speech and language development, which may lead to difficulties with school performance and psychosocial functioning (Gregg 2004; Skinner 2004; Gurney 2007; Dean 2008). Prevention of platinum-induced hearing loss is thus very important. This is the second update of the first systematic review evaluating all medical interventions for the prevention of platinum-induced hearing loss in children with cancer (Van As 2012; Van As 2014b).

To ascertain the efficacy of an otoprotective medical intervention adequately the best study design, provided that the design and execution are correct, is an RCT in which the only difference between the intervention group and control group is the use of the otoprotective medical intervention. CCTs can also provide reliable information, keeping in mind their limitations, but we did not include other study designs (including historical control groups) in this review due to the high risk of bias associated with such designs.

We identified three studies evaluating the use of amifostine versus no otoprotective intervention, two RCTs and one CCT; the update identified no new studies. Two studies included children with osteosarcoma, the other study included children with hepatoblastoma. Participants received cisplatin only or a combination of cisplatin and carboplatin, either administered intra-arterially or intravenously. For other possible otoprotective medical interventions and other types of malignancies we found no eligible studies.

Unfortunately, as is explained in the results, pooling of the results of the included studies was not possible. However, in all individual studies there was no significant difference in symptomatic ototoxicity only (that is, NCI CTC v2 or modified Brock criteria grade

2 or higher) and combined asymptomatic and symptomatic toxicity (that is, NCI CTC v2 or modified Brock criteria grade 1 or higher) between participants treated with or without amifostine. None of the included studies provided a description of the exact tests that were used to evaluate ototoxicity so we cannot comment on their appropriateness (for example, if age-specific tests were used or if participants were checked for otitis media, which is common in this age group (Brock 1991)). An important question regarding any otoprotective medical intervention during platinum treatment is whether the otoprotective drug could decrease the ototoxicity by platinum agents without reducing the anti-tumour efficacy (that is, the tumour response and survival) and without negative effects on toxicities other than ototoxicity. Only one study provided information on tumour response, defined as the number of participants with a complete, good or partial remission (Gallegos-Castorena 2007). This study included children with osteosarcoma treated with intra-arterial cisplatin. The available data analysis (there were no response data available for one participant in the control group), best case scenario analysis and worst case scenario analysis all showed a difference in favour of the amifostine group but only in the worst case scenario analysis (that is, the participant with missing data did not have a remission) was this difference significant ($P = 0.04$). There was no information on survival for any of the included study populations. However, Katzenstein 2009 did provide data on event-free survival, defined as the period from the date chemotherapy was started until evidence of an event (progressive disease, death, diagnosis of a second malignant neoplasm) or date of last contact, whichever occurred first, for 184 participants enrolled in this study (instead of only the 82 participants included in the toxicity interim analysis); these 184 participants were not the complete study group. There was no significant difference between the treatment groups ($P = 0.22$). Only one study, including children with osteosarcoma treated with intra-arterial cisplatin, provided data on the number of participants with adverse effects other than ototoxicity grade 3 or higher (Gallegos-Castorena 2007). There was a significant difference in favour of the control group in the occurrence of vomiting grade 3 or 4 (RR 9.04; 95% CI 1.99 to 41.12; $P = 0.004$). None of the participants in this study experienced cardiac toxicity grade 3 or 4. There was no significant difference between the treatment groups for renal toxicity grade 3 or 4. Finally, none of the studies evaluated quality of life (see [Summary of findings for the main comparison](#)).

In this review we tried to perform intention-to-treat analyses since they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000). However, for Katzenstein 2009 an intention-to-treat analysis was not possible; the presented toxicity interim analysis included 82 participants who were part of a larger study group and the total number of eligible participants was unclear. Therefore, we performed an 'available data' analysis for this study. Also, we were unable to check if the ototoxicity results of this study were available for at least 50% of the eligible

participants. In the [Methods](#) section we stated that if that was not the case we would not report the results due to the associated high risk of attrition bias. However, we decided to give this study the benefit of the doubt.

'No evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. The reason that no significant difference between treatment groups was identified could be the fact that the number of participants included in these studies was too small to detect a difference (that is, low power). Also, hearing loss not only develops during platinum-based therapy but also years after completion of the therapy ([Bertolini 2004](#); [Knight 2005](#)), so the length of follow-up could have been too short to detect a difference between the treatment groups. Unfortunately none of the included studies mentioned the length of follow-up.

Furthermore, although according to the protocol for the included studies participants in both treatment groups should have received the same platinum dosage schedule, none of the included studies reported the exact cumulative platinum dose received by the participants in both treatment arms. One study stated that the actually received doses did not differ significantly between treatment groups ([Petrilli 2002](#)), but in the other studies it was unclear if the participants in the amifostine and control groups received similar cumulative platinum doses. If participants in the control group received a higher cumulative platinum dose than participants treated with amifostine this could have led to an overestimation of the otoprotective effect of amifostine (and vice versa). This uncertainty should also be kept in mind when interpreting the results of the secondary outcomes (response rate and adverse effects). The same is true for impaired renal function at the time of platinum treatment, and the use of other ototoxic drugs such as aminoglycosides (anthracyclines, gentamycin), vincristine and furosemide ([Gallagher 1979](#); [Skinner 2004](#); [Cancer in Children 2005](#); [Meyer 2009](#)). It was unclear if there were important imbalances between the treatment groups regarding these factors.

The quality of the evidence was low for all evaluated outcomes; we downgraded one level each for both imprecision and study limitations. Often bias could not be ruled out due to lack of reporting. However, at this time this is the best available evidence, based on RCTs and CCTs, evaluating amifostine as an otoprotective medical intervention in children treated with platinum chemotherapy.

This systematic review used a very broad search strategy for identifying eligible studies. Thus, although it is unlikely that we missed eligible studies, it is never possible to completely rule out reporting bias. The search strategy included search terms for ototoxicity and as a result it is possible that for outcomes other than hearing loss and tinnitus more studies are available than the one identified in this review.

We are awaiting the final results of the currently awaiting classification studies evaluating cisplatin chemotherapy with or without sodium thiosulfate in children with different types of tumours,

such as childhood liver cancer, germ cell tumour, medulloblastoma, neuroblastoma and osteosarcoma ([Freyer 2014](#); [Maibach 2014](#)). We are also awaiting the final publication of the study by [Katzenstein 2009](#).

AUTHORS' CONCLUSIONS

Implications for practice

At the moment there is no evidence from the individual studies (two randomized controlled trials (RCTs) and one controlled clinical trial (CCT)) in children with osteosarcoma and hepatoblastoma treated with different platinum analogues and dosage schedules which underscores the use of amifostine as an otoprotective intervention as compared to no additional treatment. Since pooling of results was not possible, and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. Based on the currently available evidence we are unable to give recommendations for clinical practice.

For other possible otoprotective medical interventions and other types of malignancies we identified no RCTs or CCTs, so no conclusions can be made about their efficacy in preventing ototoxicity in children treated with platinum-based therapy. Based on the currently available evidence we are unable to give recommendations for clinical practice.

Implications for research

Before definitive conclusions can be made about the efficacy of possible otoprotective medical interventions in children (either amifostine or another intervention) treated with platinum-based therapy, more high quality research is needed. Future trials should preferably be RCTs. They should be performed in homogeneous study populations (with regard to, for example, tumour diagnosis) and have a long-term follow-up. Also, valid outcome definitions (including ototoxicity, anti-tumour efficacy, adverse effects and quality of life) should be used. Appropriate age-specific hearing tests should be used to assess ototoxicity, and it should be described how exactly these tests were performed. Possible risk factors for ototoxicity should be taken into account. The number of included participants should be sufficient to obtain the power needed for the results to be reliable.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gallegos-Castorena 2007

Methods	Randomized controlled trial; method of randomization not clear Performed in Mexico; participants were diagnosed with osteosarcoma between March 1999 and December 2002	
Participants	28 children (mean age 11.6 years (range 7 to 15); 14 boys and 14 girls) with osteosarcoma (stage nm, but in 5 participants metastatic disease, no significant differences in stage of disease between treatment groups; primary disease) treated with surgery (procedure and location nm) and chemotherapy (that is, intra-arterial cisplatin (cumulative dose nm, but according to protocol participants should have received 600 mg/m ² ; individual platinum dose 150 mg/m ² ; infusion duration nm) and doxorubicin (cumulative dose nm, but according to protocol participants should have received 150 mg/m ²)). Other ototoxic drugs: anthracyclines yes (see doxorubicin earlier), vincristine no, gentamycin nm, furosemide nm. No prior platinum treatment. No prior radiotherapy to head or neck, or both. No prior cranial surgery. Prior hearing dysfunction nm (baseline tests were performed, but results nm). Pre-treatment renal impairment nm (baseline tests were performed, but results nm)	
Interventions	Amifostine (740 mg/m ² /dose (cumulative dose nm, but according to protocol 2960 mg/m ²); intravenous infusion under sedation over 15 minutes immediately prior to each cisplatin dose) (n = 15) versus no otoprotective intervention (n = 13)	
Outcomes	<i>Ototoxicity</i> (according to WHO criteria; it was stated that for the evaluated parameters they did not differ from the NCI system; see also Table 1); audiometry/tympanometry was performed (exact instrument used nm) <i>Response rate</i> (complete/good remission defined as > 90% necrosis after tumourectomy; partial remission defined as 60% to 90% necrosis after tumourectomy) <i>Adverse effects grade 3 or higher</i> (according to WHO criteria; it was stated that for the evaluated parameters they did not differ from the NCI system)	
Notes	Length of follow-up nm Age and gender in intervention and control group nm, but it was stated that the groups were not statistically different Cumulative cisplatin dose per treatment group nm Genetic variants nm All participants received ondansetron 4 mg/m ² /dose 3 times a day and dexamethasone 6 mg/m ² /day to prevent nausea and vomiting Influence of funders unclear (funding nm)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	It was stated that participants were randomly assigned to amifostine or no additional treatment, but no further information on the methods of randomization was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that participants were randomly assigned to amifostine or no additional treatment, but no further information on the methods of randomization was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors was provided (for all reported outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	In all participants all reported outcomes were evaluated, with the exception of response rate, but there was only 1 participant from the control group missing (no histological examination)
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes are reported
Other bias	Unclear risk	<i>Block randomization in unblinded trials:</i> unclear (information on both method of randomization and blinding was not provided) <i>Baseline imbalance between treatment groups related to outcome (prior ototoxic treatment, age, sex, prior hearing loss, or a combination)</i> : prior ototoxic treatment nm, age and sex were balanced, prior hearing loss unclear (baseline tests were performed, but results nm) <i>Difference in ototoxic drugs other than platinum analogue between treatment groups (furosemide, gentamycin, anthracyclines, vincristine):</i> cumulative anthracycline dose unclear, but according to protocol participants in both treatment groups should have received the same dose; furosemide and gentamycin nm; vincristine not given

		<p><i>Difference in cumulative platinum dose between treatment groups:</i> cumulative dose unclear, but according to protocol participants in both treatment groups should have received the same dose</p> <p><i>Difference in length of follow-up between treatment groups:</i> unclear (length of follow-up nm)</p> <p><i>Difference in impaired renal function at time of platinum treatment between treatment groups:</i> unclear</p> <p><i>An insensitive instrument was used to evaluate ototoxicity:</i> unclear (exact test method nm)</p>
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Katzstein 2009

Methods	<p>Randomized controlled trial; method of randomization not clear</p> <p>Unclear where this study was performed; unclear when participants were diagnosed (study was opened in March 1999)</p>
Participants	<p>82 children (age range 0 to 11 years; 44 boys and 38 girls) with hepatoblastoma (21 stage I non-pure fetal histology or II, 61 stage III or IV; participants with stage I pure fetal histology were not eligible for this study; unclear if there were significant differences in stage of disease between treatment groups; primary disease) treated with surgery (procedure and location nm) and chemotherapy. Stage I and II participants received 4 cycles of intravenous cisplatin, 5-FU and vincristine (C5V); participants with stage III or IV were either randomized to 6 cycles of C5V or 6 cycles of intravenous cisplatin and carboplatin (CC) (see notes). Cumulative platinum doses not mentioned, but total intended platinum dose in stage I/II participants was cisplatin 400 mg/m² (12 mg/kg if < 1 year of age); individual platinum dose 100 mg/m²; infusion duration 4 hours. In stage III/IV participants treated with C5V the total intended platinum dose was cisplatin 600 mg/m² (18 mg/kg if < 1 year of age); individual platinum dose 100 mg/m²; infusion duration 4 hours and in stage III/IV participants treated with CC the total intended platinum dose was cisplatin 600 mg/m² (18 mg/kg if < 1 year of age); individual platinum dose 100 mg/m²; infusion duration 4 hours and the total intended carboplatin dose was 3640 mg/m² (120 mg/kg if < 10 kg body weight); individual platinum dose 700 mg/m²; infusion duration 1 hour. In case of C5V: cumulative 5-FU doses were nm, but according to protocol participants should have received 600 mg/m² per cycle (so total 2400 mg/m² in stage I/II participants and total 3600 mg/m² in stage III/IV participants); cumulative vincristine doses nm, but according to protocol participants should have received 4.5 mg/m² per cycle (so total in stage I/II participants 18 mg/m² and total in stage III/IV participants 27 mg/m²). Other ototoxic drugs: anthracyclines no, vincristine yes for some participants (see above), gentamycin nm, furosemide nm. No prior platinum treatment. No prior radiotherapy to head or neck, or both. No prior cranial surgery. No prior hearing dysfunction (on audiogram or auditory brainstem responses before therapy). No pre-treatment renal impairment (that is, adequate organ function documented at time of study enrolment)</p>

Interventions	Amifostine (740 mg/m ² /dose (cumulative dose nm, according to the text of the article amifostine was given immediately before cisplatin, but in the abstract it was mentioned that it was given prior to each administration of a platinum agent, that is, both before cisplatin and carboplatin); intravenous infusion given over 15 minutes immediately prior to cisplatin) (n = 37) versus no otoprotective intervention (n = 45) In the amifostine group 7 participants received CC and 30 participants received C5V; in the control group 11 participants received CC and 34 participants received C5V
Outcomes	<i>Ototoxicity</i> (according to modified Brock criteria: see notes and Table 2); audiograms were performed, further information nm
Notes	These 82 children were part of a larger study group. They were considered in a special interim analysis of the incidence of toxicity. The total number of eligible participants was unclear Stage III and IV randomization to CC was suspended in January 2002 when the projected improvement in long-term outcome associated with CC was excluded statistically as possible outcome of this trial In November 2003 it was decided that using the CTC criteria substantially underestimated the true incidence of significant hearing loss (4% grade 3 or 4 ototoxicity); it was decided that the subgroup of 82 participants should be evaluated using modified Brock criteria Length of follow-up nm Age and gender in intervention and control group nm, it was not stated if the groups were statistically different or not Cumulative cisplatin/carboplatin dose per treatment group nm Genetic variants nm All participants received granulocyte colony stimulating factor Influence of funders unclear (funders were mentioned)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that participants were randomly assigned to amifostine or no additional treatment, but no further information on the methods of randomization was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that participants were randomly assigned to amifostine or no additional treatment, but no further information on the methods of randomization was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding of participants and personnel was provided

Blinding of outcome assessment (detection bias) All outcomes	Low risk	For the reported outcome (that is, hearing loss) outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	The participants reported in this manuscript were only a subgroup of all included participants (unclear how many participants were originally included in this study)
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it) . However, response was nm, while in the methods section alpha fetaprotein levels and imaging were mentioned. Also, the definition of hearing loss was adjusted during the study and only results for the last definition were reported
Other bias	Unclear risk	<p><i>Block randomization in unblinded trials:</i> unclear (information on both method of randomization and blinding of participants and care providers was not provided)</p> <p><i>Baseline imbalance between treatment groups related to outcome (prior ototoxic treatment, age, sex, prior hearing loss, or a combination)</i> : prior ototoxic treatment nm, age and sex nm in different treatment groups, no prior hearing loss</p> <p><i>Difference in ototoxic drugs other than platinum analogue between treatment groups (furosemide, gentamycin, anthracyclines, vincristine):</i> furosemide and gentamycin nm; anthracyclines not given; vincristine unclear if balanced in different treatment groups</p> <p><i>Difference in cumulative platinum dose between treatment groups:</i> unclear if balanced between treatment groups</p> <p><i>Difference in length of follow-up between treatment groups:</i> unclear (length of follow-up nm)</p> <p><i>Difference in impaired renal function at time of platinum treatment between treatment groups:</i> unclear</p> <p><i>An insensitive instrument was used to evaluate ototoxicity:</i> unclear (audiograms were performed, but no further information provided)</p>

Methods	Controlled clinical trial (39 consecutive participants registered in the same protocol: the first 18 participants and the final participant did not receive an otoprotective intervention, whereas the 20 participants inbetween did); Brazilian Bone Tumor Study Group Protocol IV Performed in Brazil; participants were diagnosed with osteosarcoma between June 1996 and December 1997	
Participants	39 children (mean age 14.4 years (range 5 to 22); 27 males and 12 females) with osteosarcoma (stage nm, participants were either metastatic or not, no significant differences in stage of disease between treatment groups; primary disease) treated with surgery (procedure and location nm) and intravenous chemotherapy (that is, cisplatin (cumulative dose nm, but according to protocol participants should have received 500 mg/m ² ; individual dose 100 mg/m ² ; infusion duration nm), carboplatin (cumulative dose nm, but according to protocol participants should have received 2500 mg/m ² ; individual dose 500 mg/m ² ; infusion duration nm), doxorubicin (cumulative dose nm, but according to protocol participants should have received 360 mg/m ²) and ifosfamide (cumulative dose nm, but according to protocol participants should have received 45 g/m ²); for all 4 chemotherapeutic agents the actual received doses were not statistically significant different than the protocol doses). Other ototoxic drugs: anthracyclines yes (see doxorubicin earlier), vincristine no, gentamycin nm, furosemide nm. No prior platinum treatment. No prior radiotherapy to head or neck, or both. No prior cranial surgery. No prior hearing dysfunction (baseline tests were performed and without normal hearing participants were not eligible for this study). No pre-treatment renal impairment (baseline tests were performed and without normal audiometric evaluations at diagnosis participants were not eligible for this study)	
Interventions	Amifostine (740 mg/m ² /dose (cumulative dose nm, but according to protocol 7400 mg/m ²); 15-minute infusion (intra-arterial or intravenous nm) immediately prior to every cisplatin and carboplatin dose) (n = 20) versus no otoprotective intervention (n = 19)	
Outcomes	<i>Ototoxicity</i> (according to NCI CTC version 2 criteria: see also Table 1); objective and subjective audiometric evaluations were performed, no further information provided	
Notes	Length of follow-up nm Age and gender in intervention and control group nm, but it was stated that the groups were not statistically different Cumulative cisplatin and carboplatin dose per treatment group nm (for more information see information under header Participants) Genetic variants nm All participants received ondansetron 0.15 mg/kg per dose 3 times a day, dexamethasone 6 mg/m ² /day, metoclopramide 1 mg/kg/day and dimenhydrinate 2 mg/kg/day to prevent nausea and vomiting Influence of funders unclear (funding nm) This was a pilot study for a larger randomized study	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Controlled clinical trial, so no randomization performed
Allocation concealment (selection bias)	High risk	Controlled clinical trial, so no randomization performed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants with amifostine were consecutive participants, so blinding was not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors was provided (for all reported outcomes)
Incomplete outcome data (attrition bias) All outcomes	High risk	3 out of 20 participants in the intervention group missing for almost all outcomes (1 incomplete outcome data, 1 lost to follow-up, 1 nm)
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it), but not all expected outcomes were reported (for example response rate and hypocalcaemia were missing, while for hypocalcaemia it was even stated in the discussion of this article that this is 1 of the most common adverse effects of amifostine)
Other bias	Unclear risk	<i>Block randomization in unblinded trials:</i> not applicable, this is not a randomized trial <i>Baseline imbalance between treatment groups related to outcome (prior ototoxic treatment, age, sex, prior hearing loss or a combination):</i> prior ototoxic treatment nm, age and sex were balanced, no prior hearing loss <i>Difference in ototoxic drugs other than platinum analogue between treatment groups (furosemide, gentamycin, anthracyclines, vincristine):</i> cumulative anthracycline dose unclear, but according to protocol participants in both treatment groups should have received the same dose and the actual received doses were not statistically significant different than the protocol doses; furosemide and gentamycin nm; vincristine not given <i>Difference in cumulative platinum dose be-</i>

		<p><i>tween treatment groups: cumulative dose unclear, but according to protocol participants in both treatment groups should have received the same dose and the actual received doses were not statistically significantly different than the protocol doses</i></p> <p><i>Difference in length of follow-up between treatment groups: unclear (length of follow-up nm)</i></p> <p><i>Difference in impaired renal function at time of platinum treatment between treatment groups: unclear</i></p> <p><i>An insensitive instrument was used to evaluate ototoxicity: unclear (objective and subjective audiometric evaluations were performed, no further information provided)</i></p>
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5-FU: 5-fluorouracil; C5V: 5-fluorouracil plus vincristine; CC: cisplatin and carboplatin; CTC: Common Toxicity Criteria; n: number; NCI: National Cancer Institute; nm: not mentioned; WHO: World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Doolittle 2001	Study with historical controls; both children and adults (maximum age 67 years) included (children not presented separately)
Elsendoorn 2001	Same study as Weijl 2004 (describing the first 27 participants)
Fouladi 2008	Study with historical controls; both children and adults (maximum age 20.16 years) included (children not presented separately); difference in cranial radiotherapy between treatment groups
Geoerger 2005	No otoprotective intervention evaluated
Grau 1996	Both children and adults (maximum age 73 years) included (children not presented separately); unclear if other treatment was the same in the different treatment groups
Gurney 2014	Not RCT or CCT
Kingston 1986	No otoprotective intervention evaluated
Knight 2008	Not RCT or CCT, but a case report; no otoprotective intervention
Ladenstein 2010	Ototoxicity not evaluated

(Continued)

Mahoney 1982	Same study as Mahoney 1983
Mahoney 1983	Not RCT or CCT; no otoprotective intervention evaluated
Marina 2005	Study with historical controls; unclear if same cumulative platinum dose, infusion duration, individual dose and other treatment in the different treatment groups
McHaney 1983	Not RCT or CCT; no otoprotective intervention evaluated
Meyer 2009	Not RCT or CCT, but a review (no additional studies identified)
Piel 1974	No otoprotective intervention evaluated
Skinner 2006	Not RCT or CCT, but a commentary (no additional studies identified)
Spunt 2007	Not RCT or CCT; both children and adults (maximal age 21 years) included (children not presented separately)
Sullivan 2009	Not RCT or CCT, but an editorial (no additional studies identified)
Weijl 2004	Both children and adults (maximum age 69 years) included (children not presented separately); significant difference in individual platinum dose between the different treatment groups, unclear if platinum infusion duration and other treatment was the same in the different treatment groups

CCT: controlled clinical trial; RCT: randomized controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Freyer 2014](#)

Methods	Method of randomization not clear
Participants	126 children (aged 1 to 18 years with normal audiometry; sex not mentioned) with hepatoblastoma, germ cell tumour, medulloblastoma, neuroblastoma, osteosarcoma or other malignancies
Interventions	Cisplatin-containing chemotherapy with or without sodium thiosulfate; 16 g/m ² sodium thiosulfate was given intravenously over 15 minutes 6 hours after each cisplatin dose; participants not treated with sodium thiosulfate were observed; cisplatin was planned to be given with a cumulative dose of ≥ 200 mg/m ² and an infusion duration of ≤ 6 hours
Outcomes	Hearing loss was assessed using standard audiometry for age according to American Speech-Language-Hearing Association criteria at 4 weeks post the final cisplatin dose; 105 participants were available for analysis; the proportion of hearing loss for sodium thiosulfate and observation was 28.6% in the sodium thiosulfate group and 55.4% in the observation group ($P = 0.006$) Event-free survival at median post-diagnosis follow-up of 2.1 years in all 126 children was 60.1% in the sodium thiosulfate group and 70% in the observation group ($P = 0.53$)

Freyer 2014 (Continued)

	Overall survival at median post-diagnosis follow-up of 2.1 years in all 126 children was 74.5% in the sodium thiosulfate group and 88.8% in the observation group ($P = 0.05$) Post-hoc subset analyses by extent of disease (localized and disseminated) were performed; survival was significantly lower in the sodium thiosulfate group versus observation in the participants with disseminated disease
Notes	This study was not published in full text as of 11 July 2016, but was presented at the American Society of Clinical Oncology conference in 2014

Maibach 2014

Methods	Method of randomization not clear
Participants	People with newly diagnosed standard risk hepatoblastoma
Interventions	Cisplatin-containing chemotherapy with or without sodium thiosulfate; 20 g/m ² sodium thiosulfate was given intravenously over 15 minutes exactly 6 hours after each cisplatin dose; participants not treated with sodium thiosulfate were observed; cisplatin 80 mg/m ² was administered intravenously over 6 hours (6 cycles); in case of lack of response after 2 cycles sodium thiosulfate was stopped and chemotherapy changed to cisplatin and doxorubicin
Outcomes	Absolute hearing threshold at the age of ≥ 3.5 years as measured by pure tone audiometry (no results presented) Interim efficacy results on tumour response were evaluated after every 20 participants by the Independent Data Monitoring Committee, which recommended continuing the trial after 20, 40 and 60 participants
Notes	This study was not published in full text as of 11 July 2016, but was presented at the American Society of Clinical Oncology conference in 2014

DATA AND ANALYSES

Comparison 1. Amifostine versus no otoprotective intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (combined asymptomatic and symptomatic disease)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.94, 1.77]
2 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease)	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.44]
3 Ototoxicity according to modified Brock criteria (combined asymptomatic and symptomatic disease)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.74, 1.55]
4 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (symptomatic disease)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.14, 5.32]
5 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (symptomatic disease)	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.83, 2.10]
6 Ototoxicity according to modified Brock criteria (symptomatic disease)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.57, 1.75]
7 Tumour response (good remission and partial remission)	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.97, 2.63]
8 Adverse effects other than ototoxicity (vomiting $\geq$ grade 3)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	9.04 [1.99, 41.12]

Analysis 1.1. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 1 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (combined asymptomatic and symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 1 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (combined asymptomatic and symptomatic disease)

Analysis 1.2. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 2 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 2 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease)

Analysis 1.3. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 3 Ototoxicity according to modified Brock criteria (combined asymptomatic and symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 3 Ototoxicity according to modified Brock criteria (combined asymptomatic and symptomatic disease)

Analysis 1.4. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 4 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 4 Ototoxicity according to NCI CTC v2 criteria with intra-arterial platinum (symptomatic disease)

Analysis 1.5. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 5 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 5 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (symptomatic disease)

Analysis 1.6. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 6 Ototoxicity according to modified Brock criteria (symptomatic disease).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 6 Ototoxicity according to modified Brock criteria (symptomatic disease)

Analysis 1.7. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 7 Tumour response (good remission and partial remission).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 7 Tumour response (good remission and partial remission)

Analysis 1.8. Comparison 1 Amifostine versus no otoprotective intervention, Outcome 8 Adverse effects other than ototoxicity (vomiting $\geq$ grade 3).

Review: Medical interventions for the prevention of platinum-induced hearing loss in children with cancer

Comparison: 1 Amifostine versus no otoprotective intervention

Outcome: 8 Adverse effects other than ototoxicity (vomiting $\geq$ grade 3)

ADDITIONAL TABLES

Table 1. NCI CTC version 2 'Inner ear and hearing' *

Grade	Description
0	Normal
1	Hearing loss on audiometry only
2	Tinnitus or hearing loss, not requiring hearing aid or treatment
3	Tinnitus or hearing loss, correctable with hearing aid or treatment
4	Severe uni- or bilateral hearing loss (deafness), not correctable

NCI CTC: National Cancer Institute Common Toxicity Criteria.

* from [NCI CTC v2](#).

Table 2. Modified Brock criteria for the classification of hearing loss*

Grade of hearing loss	Description	Potential clinical effects on hearing
0	≤ 20 dB at 1, 2 and 4 kHz	None
1a	> 40 dB at any frequency from 6 kHz to 12 kHz	Measurable
1b	> 20 dB but ≤ 40 dB at any frequency from 3 kHz to 5 kHz	Measurable
2a	> 40 dB at any frequency from 3 kHz to 5 kHz	Noticeable
2b	> 20 dB but ≤ 40 dB at 2 kHz	Noticeable
3	> 40 dB at 2 kHz	Correctable with hearing aids
4	> 40 dB at 1 kHz	Speech comprehension deficits even with hearing aids

dB: decibel; kHz: kilohertz.

* from [Katzenstein 2009](#).

APPENDICES

Appendix I. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Hearing loss**, we used the following text words in the original version of the review and the first update:

Deafness OR hearing loss OR Loss, Hearing OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR hear* OR audiologic OR audiometry OR audiometr* OR audiogram OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

For the second update, we optimized this search strategy by excluding “hear*”.

2. For **Cisplatin**, we used the following text words:

Cisplatin OR cis-Diamminedichloroplatinum(II) OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR Platinol OR Platidiam OR Platino OR NSC-119875 OR Biocisplatin OR CDDP OR CACP OR cisplatin* OR abioplatin OR neoplatin OR cis-DDP

3. For **Carboplatin**, we used the following text words:

Carboplatin OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR CBDCA OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Paraplatin OR Carboplat OR Paraplatine OR Bristol-Myers Squibb Brand of Carboplatin OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR carboplatin* OR Platinum OR Platinum Compounds OR platinum*

4. For **Oxaliplatin and other platinum compounds**, we used the following text words:

Oxaliplatin OR oxaliplatin* OR oxaliplatine OR platinum(II)-1,2-cyclohexanediamine oxalate OR 1,2-diaminocyclohexane platinum oxalate OR oxalato-(1,2-cyclohexanediamine)platinum II OR cis-oxalato-(trans-1)-1,2-diaminocyclohexane-platinum(II) OR Eloxatine OR Eloxatin OR oxaliplatin, (SP-4-2-(1S-trans))-isomer OR oxaliplatin, (SP-4-3-(cis))-isomer OR ACT 078 OR ACT-078 OR oxaliplatin, (SP-4-2-(1R-trans))-isomer OR 63121-00-6 OR 61825-94-3 OR dacotin OR dacplat OR jm-83 OR l-ohp OR oxalato-platinum OR rp 54780 OR sr-96669 OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds

5. For **Children**, the following we used the following text words in the original version of the review and the first update:

Infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

For the second update, we used the following text words:

infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR school OR school* OR prematur* OR preterm*

Final search 1 AND (2 OR 3 OR 4) AND 5

The search was performed in title, abstract or keywords

*=zero or more characters

Appendix 2. Search strategy for PubMed

1. For **Hearing loss**, we used the following MeSH headings and text words in the original version of the review and the first update:

Deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR hear* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacusis OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

For the second update, we optimized this search strategy by excluding “hear*”.

2. For **Cisplatin**, the following MeSH headings and text words were used:

Cisplatin OR cis-Diamminedichloroplatinum(II) OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR Platinol OR Platidiam OR Platino OR NSC-119875 OR Biocisplatinum OR CDDP OR CACP OR cisplatin* OR abiplatin OR neoplatin OR cis-DDP

3. For **Carboplatin**, we used the following MeSH headings and text words:

Carboplatin OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR CBDCA OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Paraplatin OR Carboplat OR Paraplatine OR Bristol-Myers Squibb Brand of Carboplatin OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR carboplatin*

4. For **Oxaliplatin and other platinum compounds**, we used the following MeSH headings and text words:

Oxaliplatin OR oxaliplatin* OR 1,2-diamminocyclohexane(trans-1)oxalatoplatinum(II) OR oxaliplatine OR platinum(II)-1,2-cyclohexanediamine oxalate OR 1,2-diaminocyclohexane platinum oxalate OR oxalato-(1,2-cyclohexanediamine)platinum II OR cis-oxalato-(trans-1)-1,2-diaminocyclohexane-platinum(II) OR Eloxatine OR Eloxatin OR oxaliplatin, (SP-4-2-(1S-trans))-isomer OR oxaliplatin, (SP-4-3-(cis))-isomer OR ACT 078 OR ACT-078 OR oxaliplatin, (SP-4-2-(1R-trans))-isomer OR 63121-00-6 OR 61825-94-3 OR dacotin OR dacplat OR jm-83 OR l-ohp OR oxalatoplatinum OR rp 54780 OR sr-96669 OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds [mh]

5. For **Children**, we used the following MeSH headings and text words in the original version of the review and the first update:

Infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR

puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

For the second update, we used the following MeSH headings and text words:

infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm* (Leclercq 2013)

6. For **RCTs/CCTs**, we used the following MeSH headings and text words in the original version of the review and the first update:

(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh]

For the second update, we used the following MeSH headings and text words:

(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]) (Higgins 2011)

Final search 1 AND (2 OR 3 OR 4) AND 5 AND 6

[pt = publication type; tiab = title, abstract; sh = subject heading; mh = MeSH term; *=zero or more characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for EMBASE (Ovid)

1. For **Hearing loss**, we used the following Emtree terms and text words in the original version of the review and the first update:

1. exp hearing impairment/
2. (deafness or deaf\$ or hearing impairment or hearing impairments or hearing impairment\$).mp.
3. hearing loss.mp. or exp hearing loss/
4. exp hearing disorder/
5. (hearing disorder or hearing disorders).mp.
6. hear\$.mp.
7. auditory.mp.
8. exp audiology/ or audiologic\$.mp.
9. exp audiometry/
10. (audiometry or audiometr\$ or audiogram).mp.
11. exp audiography/
12. (ototoxicology or ototoxic\$ or ototoxicity).mp.
13. exp OTOTOXICITY/
14. exp HYPOACUSIS/
15. (hypoacusis or hypoacuses or hypoacus\$).mp.
16. cochleotoxicity.mp.
17. or/1-16

For the second update, we optimized this search strategy by excluding “hear\$”.

2. For **Cisplatin**, we used the following Emtree terms and text words:

1. exp CISPLATIN DERIVATIVE/ or exp CISPLATIN/ or cisplatin.mp.
2. cis-Diamminedichloroplatinum.mp.
3. Platinum Diamminodichloride.mp.
4. (cis-Platinum or cis Platinum or Dichlorodiammineplatinum or cis-Diamminedichloroplatinum or cis Diamminedichloroplatinum or cis-Dichlorodiammineplatinum).mp.
5. (Platinol or Platidiam or Platino or NSC-119875 or Biocisplatinum or CDDP or CACP).mp.
6. (cisplatin\$ or abiplatin or neoplatin or cis-DDP).mp.
7. or/1-6

3. For **Carboplatin**, we used the following Emtree terms and text words:

1. carboplatin.mp. or exp CARBOPLATIN/

2. (CBDCA or Carbosin or Carbotec or Ercar).mp.
3. (JM-8 or JM 8 or JM8).mp.
4. (NSC-241240 or NSC 241240 or NSC241240).mp.
5. (Neocarbo or Paraplatin or Carboplat or Paraplatine).mp.
6. (Platinwas or Ribocarbo or Blastocarb or nealorin).mp.
7. (carboplatin\$ or Platinum or Platinum Compounds or platinum\$).mp.
8. or/1-7
4. For **Oxaliplatin and other platinum compounds**, we used the following Emtree terms and text words:
 1. Oxaliplatin.mp. or exp OXALIPLATIN/
 2. (oxaliplatin\$ or oxaliplatine).mp.
 3. 1,2-diaminocyclohexane platinum oxalate.mp. or exp platinum 1,2 diaminocyclohexane/
 4. (Eloxatine or Eloxatin).mp.
 5. ("ACT 078" or ACT-078).mp.
 6. (dacotin or dacplat or jm-83 or l-ohp or oxalatoplatinum or rp 54780 or sr-96669).mp.
 7. (oxalato 1,2 cyclohexanediamine platinum or platinum 1,2 cyclohexanediamine oxalate or platinum 1,2 diaminocyclohexane oxalate or platinum oxalate 1,2 diaminocyclohexane).mp.
 8. transplastin.mp.
 9. Organoplatinum Compounds.mp. or exp platinum complex/
 10. 61825-94-3.rn.
 11. or/1-10
5. For **Children**, we used the following Emtree terms and text words in the original version of the review and the first update:
 1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
 2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
 3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
 4. or/1-3
 5. (infant\$ or newborn\$ or (new adj born\$) or baby or baby\$ or babies or neonate\$ or perinat\$ or postnat\$).mp.
 6. (child\$ or (school adj child\$) or schoolchild\$ or (school adj age\$) or schoolage\$ or (pre adj school\$) or preschool\$).mp.
 7. (kid or kids or toddler\$ or adoles\$ or teen\$ or boy\$ or girl\$).mp.
 8. (minors\$ or (under adj ag\$) or underage\$ or juvenil\$ or youth\$).mp.
 9. (puber\$ or pubescen\$ or prepubescen\$ or prepubert\$).mp.
 10. (pediatric\$ or paediatric\$ or peadiatric\$).mp.
 11. (school or schools or (high adj school\$) or highschool\$ or (primary adj school\$) or (nursery adj school\$) or (elementary adj school) or (secondary adj school\$) or kindergar\$).mp.
 12. or/5-11
 13. 4 or 12
- For the second update, we used the following Emtree terms and text words:
 1. infan\$.mp.
 2. (newborn\$ or new-born\$).mp.
 3. (perinat\$ or neonat\$).mp.
 4. baby/
 5. (baby or baby\$ or babies).mp.
 6. toddler\$.mp.
 7. (minors or minors\$).mp.
 8. (boy or boys or boyfriend or boyhood).mp.
 9. girl\$.mp.
 10. (kid or kids).mp.
 11. child/
 12. (child or child\$ or children\$).mp.
 13. school child/
 14. (schoolchild\$ or schoolchild).mp.
 15. (school child or school child\$).ti,ab.
 16. (adolescen\$ or youth\$ or teen\$).mp.
 17. (juvenil\$ or under\$age\$).mp.

18. pubescen\$.mp.
19. exp pediatrics/
20. (pediatric\$ or paediatric\$ or peadiatric\$).mp.
21. (school or school\$).mp.
22. (prematu\$ or preterm\$).mp.
23. or/1-22
6. For **RCTs/CCTs**, we used the following Emtree terms and text words in the original version of the review and the first update:
 1. Randomized Controlled Trial/
 2. Controlled Clinical Trial/
 3. randomized.ti,ab.
 4. placebo.ti,ab.
 5. randomly.ti,ab.
 6. trial.ti,ab.
 7. groups.ti,ab.
 8. drug therapy.sh.
 9. or/1-8
 10. Human/
 11. 9 and 10

For the second update, we used the following Emtree terms and text words:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. (randomized or randomised).ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. animals/ not human/
11. 9 not 10

Final search: 1 AND (2 OR 3 OR 4) AND 5 AND 6

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; \$=one or more characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 4. Search strategy for conference proceedings

As the 2014 editions of the International Society for Paediatric Oncology (SIOP) and the American Society of Pediatric Hematology/Oncology (ASPHO) conference proceedings were already included in the search of the electronic databases no separate search strategy was needed. For all other editions the pdf files were assessed using these terms: cisplatin, carboplatin, oxaliplatin, platinum, platidium, CDDP, CACP, DDP, CBDCA, eloxatin, dacotin, dacplat, carbosin, carbotec, ercar, neocarbo, platin, carboplat, ribocarbo, blastocarb, nealorin. The conference proceedings of the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer were only available on paper, so no search strategy could be used.

Appendix 5. Search strategy for ongoing trials registers

For the **International Standard Randomized Controlled Trial Number (ISRCTN) Register** (www.isrctn.com), we used the following search strategy:

(cisplatin OR carboplatin OR oxaliplatin OR platinum OR CDDP OR CACP OR DDP OR CBDCA OR platin) AND (deaf OR hearing OR audi OR ototoxic) AND (child OR pediatric OR paediatric OR infant OR neonate OR adolescent). We used the advanced search option for studies with date applied between 17-3-2014 and 12-7-2016 (earlier results were already included in the previous versions of this review).

For the **National Institutes of Health (NIH) Register** (www.clinicaltrials.gov), we used the following search strategy:

(cisplatin OR carboplatin OR oxaliplatin OR platinum OR CDDP OR CACP OR DDP OR CBDCA OR platin) AND (deaf OR hearing OR audi OR ototoxic) AND (child OR pediatric OR paediatric OR infant OR neonate OR adolescent) in combination with the interventional studies (at study type). We used the advanced search option for studies first received between 17-3-2014 and 12-7-2016 (earlier results were already included in the previous versions of this review).

WHAT'S NEW

Date	Event	Description
16 April 2019	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 7, 2011

Review first published: Issue 5, 2012

Date	Event	Description
8 July 2016	New citation required but conclusions have not changed	Unfortunately, no new studies could be included in this second update of the review. As a result the conclusions have not changed
8 July 2016	New search has been performed	The search for eligible studies was updated to July 2016.
2 April 2014	New citation required but conclusions have not changed	Unfortunately, no new studies could be included in this update of the review. As a result the conclusions have not changed. However, as opposed to the original version of the review we have now included a summary of findings table
2 April 2014	New search has been performed	The search for eligible studies was updated to March 2014.

CONTRIBUTIONS OF AUTHORS

JvA: identified the studies meeting the inclusion criteria. He performed the data extraction, risk of bias assessment and GRADE assessment of the included studies. He analysed the data and interpreted the results. He wrote and revised the manuscript.

HvdB: provided a clinical perspective. He critically reviewed the manuscript.

EvD: developed the search strategy in collaboration with Cochrane Childhood Cancer. She identified the studies meeting the inclusion criteria. She searched for unpublished and ongoing studies. She performed the data extraction, risk of bias assessment and GRADE assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that “Children (aged 0 to 18 years at diagnosis) with any type of childhood malignancy” were eligible for inclusion; in order not to exclude relevant data we have added the following: “Studies including both children and adults were only eligible for inclusion in this review if the majority of participants were children (that is, either more than 90% children or the maximal age did not exceed 22 years)”.

In the update we included a 'Summary of findings' table.

For the second update the Information Specialist of Cochrane Childhood Cancer optimized the search strategy as described in the appendices.

We made all changes in consultation with Cochrane Childhood Cancer.

INDEX TERMS

Medical Subject Headings (MeSH)

Amifostine [*therapeutic use]; Antineoplastic Agents [*adverse effects]; Bone Neoplasms [drug therapy]; Carboplatin [*adverse effects]; Cisplatin [*adverse effects]; Controlled Clinical Trials as Topic; Hearing Loss [*chemically induced; *prevention & control]; Hepatoblastoma [drug therapy]; Liver Neoplasms [drug therapy]; Neoplasms [*drug therapy]; Osteosarcoma [drug therapy]; Protective Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn; Young Adult