Prevention and treatment of platinum ototoxicity in adults: A systematic review

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Abstract

Background: Ototoxicity is a common disabling side effect of platinum-based chemotherapy. This study aimed to systematically assess the evidence on the management of platinum-induced ototoxicity in adult cancer patients. **Methods:** Three databases were searched up to November 1, 2022. Original studies were included if they reported on a pharmacologic or non-pharmacologic intervention to prevent or treat platinum ototoxicity in adults. The articles' quality was assessed with two grading scales. **Results:** Eighteen randomized controlled trials and five quasi-experimental studies with 1673 patients were analyzed. Eleven interventions were identified, nine pharmacological and two non-pharmacological. Six of the interventions (sodium thiosulfate, corticoids, sertraline, statins, multivitamins, and D-methionine) showed mild benefit preventing cisplatin-induced ototoxicity. The data must be carefully analyzed due to the low quality and underreporting of side effects. **Conclusions:** Current interventions have mild benefits preventing cisplatin-induced ototoxicity in adult cancer patients. High-quality research is required to clarify the significance of these findings.

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Conclusions: Current interventions have mild benefits preventing cisplatin-induced ototoxicity in adult cancer patients. High-quality research is required to clarify the significance of these findings.

Keywords: Cisplatin-induced ototoxicity, platinum chemotherapy, chemotherapy-related adverse events, hearing loss, otoprotection.

Key Messages

1. Chemotherapy ototoxicity is a well known adverse effect that has few treatment options and that has not been sufficiently studied in the adult population.
2. Tinnitus and vertigo are distressing symptoms overlooked in cisplatin-induced ototoxicity research.
3. Pharmacological interventions to prevent cisplatin induced hearing loss are controversial given their mild efficacy and potential side effects. Future investigations of sodium thiosulfate for preventing cisplatin-induced ototoxicity are warranted.

Introduction

Platinum chemotherapy agents are the cornerstone of several oncologic and hematologic protocol treatments given their high effectiveness, cost, and accessibility (Dillard et. al, 2022). These benefits are tied to unwanted side effects. Ototoxicity is a well-known adverse effect of platinum compounds, such as cisplatin and carboplatin, that may cause permanent hearing loss, tinnitus, or vestibular disturbances in 40–80% of treated adult patients, which is globally estimated to be half a million cases per year (Dillard et. al, 2022, Frisina et al., 2016). Ototoxicity type and degree vary depending on sex, age, genetic predisposition, changes in protein expressions, previous neuro-otological symptoms, chemotherapy interval of administration, dose regimen (up to 100% of patients have been found to be affected in a dose range between 150–225 mg/m2), concomitant radiotherapy treatments, or even the patient's stress level (Kirkim et al., 2015, Charif et al., 2019, Coling et al., 2007, Bielefeld et al., 2021, Chan et al., 2018, Miaskowski et al., 2018). Current knowledge has shown platinum-induced ototoxicity is a multifactorial process where free radical oxygen species and inflammation induce endogenous antioxidants depletion and increase lipid peroxidation, causing rupture of the outer hair cell stereocilia in the organ of Corti (Gentilin et al, 2019, Tang et al., 2021). This process may have an acute or progressive onset, as cisplatin is retained in the cochlea indefinitely, activating the apoptotic pathway in the marginal cells on the stria vascularis region that maintains the endolymph composition (Breglio et al., 2017). Depending on the hearing loss frequency and the severity of speech impairment, more than ten grading systems have been proposed to better characterize patients´ affection(Waissbluth et al., 2017). Moreover, accurate prediction models of posttreatment hearing alterations with good performance (eg. sensitivity of 80% and specificity of 75%) and follow-up screening audiometric test analysis have been proposed to diagnose platinum ototoxicity (Shuette et al., 2020, Frisina et al., 2016, Ardeshirrouhanifard et al., 2022). However, there is a paucity of safe and effective pharmacological or non-pharmacological options to prevent or treat platinum-induced ototoxicity in adults, without inhibiting antitumor effects. Numerous studies on animals have been conducted with relative success and a guideline to treat cisplatin-induced ototoxicity in children has been published (Freyer et al., 2020), albeit the evidence concerning the adult population is sparse, non-pharmacologic treatments have not been systematically researched, and the use of otoprotecting strategies for other chemotherapy agents besides platinums is anecdotal (Desilets et al., 2020). Even so, ototoxicity prevention and treatment is a major research priority due to the symptom burden and diminishing quality of life patients experience (Miaskowski et al., 2018). Thus, we conducted a comprehensive systematic literature review on pharmacological or non-pharmacological interventions to prevent or treat platinum-induced ototoxicity in adult cancer patients.

Methodology

Objective

The primary aim was to systematically review the effectiveness and safety of pharmacological or non-pharmacological interventions used to prevent or treat platinum-induced ototoxicity in adult cancer patients. Even though ototoxicity is a less common adverse effect of other chemotherapy agents, we consider that studies could report ototoxicity interventions for multiple chemotherapy regimens. So our secondary aim was to assess pharmacological or non-pharmacological interventions for ototoxicity caused by other chemotherapy agents in adult cancer patients.

Search Strategy

We developed a search strategy using Medical Subject Headings (MeSH) related to chemotherapy-induced ototoxicity. We searched three databases (Medline, CINHAL, and PubMed) using the following search string:*(Ototoxicity OR Drug-Induced Ototoxicity OR Drug-Related Otological Toxicities OR Drug-Induced Cochleotoxicity OR Drug Induced Cochlear Toxicity OR Drug Induced Vestibulotoxicity OR vertigo OR tinnitus) AND (Antineoplastic Agent OR Anticancer Agent OR Antineoplastic Drug OR Antineoplastic OR Antitumor Drug OR Cancer Chemotherapy Agent OR Antitumor Agent OR Cancer Chemotherapy Drug OR Chemotherapeutic Anticancer Agents OR Chemotherapeutic Anticancer Drug OR Combined Antineoplastic Agents OR Antineoplastic Combined Chemotherapy Regimens)* . The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42022376324). The search results were downloaded into Endnote software to remove duplicates. The debugged search was uploaded to Rayyan where two reviewers (JEC and NM) screened abstracts and selected relevant titles with a 0.43 inter-rater agreement. In the event of a conflict of views, a consensus was reached through discussion. Further to ensure consistency in eligibility criteria the full texts were reviewed by the seven authors. There was a vote in case of disagreement. References from selected articles were also included. We report the results following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(Page et al. 2021)(Figure 1.).

Study Selection

Eligible studies had to be 1) original investigations published in a peer-reviewed journal before November 1, 2022; 2) include human patients over 18 years old; 3) report an intervention as prophylaxis or treatment for ototoxicity induced by any chemotherapy agent; 4) be published in English; 5) use an experimental or quasi-experimental research design, and 6) report treatment outcomes, either their safety or efficacy. Ototoxicity induced by chemotherapy was considered as hearing loss, tinnitus, or vestibular disturbances after chemotherapy treatment. Gray literature, editorials, commentaries, case series with ten or fewer patients, case studies, and protocols were excluded from the review.

Data extraction

Three reviewers (EQ, JEC, and LB) independently extracted data into a Microsoft Excel spreadsheet. Data extracted included the year of publication, country, study design, number of participants, inclusion/exclusion criteria, sample characteristics, type of cancer, patient's functionality, chemotherapy agent, dose average, number of cycles, concomitant radiotherapy exposure, audiometric measurements, kind of ototoxicity, type of intervention, comparator, time of follow-up, and efficacy and safety outcomes. To ensure consistency, extracted data were compared between reviewers, and disagreements were discussed until a consensus was reached.

Quality Appraisal

Four reviewers (LC, SG, NM, and MFI) independently assessed each included study for the risk of bias. A third reviewer arbitrated possible differences. Randomized controlled trials (RCT) were evaluated using the Cochrane Collaboration's Risk-of-Bias Tool 2 and non-randomized studies were assessed with the Newcastle Ottawa Scale (Higgins et al., 2021, Wells et al., 2016). No study was disregarded for its quality.

Data Synthesis and Analysis

The synthesis of results was performed using the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews (Popay et al., 2006). The outcomes regarding platinum ototoxicity symptom ease were reported using means (or difference in means) $\pm$ standard deviations or means with confidence intervals (CIs) and p values. Epidemiological statistics were reported according to the original articles. The data is presented regarding the efficacy and safety of each intervention. Furthermore, to improve intervention comparisons, the summary information underlines the intention of the intervention (prevention/treatment), the type of assessed ototoxicity (hearing loss, tinnitus, and/or vestibular disturbances), and if other ototoxic treatments

were associated with the platinum treatment (e.g. radiotherapy with Gray dose). All authors were involved in analyzing and interpreting the results and vouch for their completeness and accuracy.

Results

The search rendered 4590 studies, 742 duplicates were removed, and 3442 were deemed ineligible after screening titles and abstracts. The reference review resulted in the addition of one article. The resulting 35 full texts were screened, of which twenty-three studies were selected for data extraction and analysis (Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Madasu et al., 1997, Planting et al., 1999, Ekborn et al., 2004, Zuur et al., 2007, Yıldırım et al., 2010, Riga et al., 2013, Yoo et al., 2014, Marshak et al., 2014, Ishikawa et al., 2015, Crabb et al., 2017, Nasr et al., 2018, Delarestaghi et al., 2018, Rolland et al., 2019, Duinkerken et al., 2021, Fernandez et al., 2021, Moreno et al., 2022, Weijl et al., 2004, Villani et al., 2016, Scasso et al., 2017, Campbell et al., 2022). Figure 1 depicts the PRISMA complete screening process. Publication dates were 1995–2022, with studies conducted in 14 different countries, with 5 studies from the United States, 4 from the Netherlands, 2 from Canada and Italy, and one study from Sweden, Turkey, Greece, Spain, Israel, Japan, United Kingdom, Egypt, Iran, and India. Studies consisted of 18 controlled trials (Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Planting et al. 1999, Zuur et al. 2007, Yıldırım et al. 2010, Riga et al. 2013, Yoo et al. 2014, Marshak et al. 2014, Crabb et al. 2017, Nasr et al. 2018, Delarestaghi et al. 2018, Rolland et al. 2019, Duinkerken et al. 2021, Moreno et al. 2022, Weijl et al. 2004, Villani et al. 2016, Campbell et al. 2022) and 5 quasi-experimental studies (Madasu et al. 1997, Ekborn et al. 2004, Ishikawa et al. 2015, Fernandez et al. 2021, Scasso et al. 2017). The median number of patients per study was 73 and ranged from 11 to 277. Of note, only four RCT had a low risk of bias, seven had some concern of bias, and seven had a high risk of bias. Across the 18 RCT, the most common sources of bias were related to the outcome measurement and the selection of results. In the quasi-experimental studies quality assessment, two studies were of high quality and three were rated as having poor methodological quality. The source of bias came from the comparability and outcome evaluations. Table 1 and Table 2 presents the quality assessment for all of the studies. In total 11 interventions were used for cisplatin-ototoxicity, 9 pharmacological interventions were assessed in 19 studies(Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Madasu et al. 1997, Planting et al. 1999, Ekborn et al. 2004, Zuur et al. 2007, Yıldırım et al. 2010, Riga et al. 2013, Yoo et al. 2014, Marshak et al. 2014, Ishikawa et al. 2015, Crabb et al. 2017, Nasr et al. 2018, Delarestaghi et al. 2018, Rolland et al. 2019, Duinkerken et al. 2021, Fernandez et al. 2021, Moreno et al. 2022) and 2 non-pharmacological interventions assessed in 4 studies(Weijl et al. 2004, Villani et al. 2016, Scasso et al. 2017, Campbell et al. 2022). All of the studies assessed platinum-ototoxicity prevention, except for one that evaluated ototoxicity treatment (Nasr et al. 2018). Although we searched for platinum-induced ototoxicity, all studies assessed cisplatin and none of the studies included other platinum agents or other types of chemotherapy agents. All of the studies interpreted cisplatin-induced ototoxicity (CiO) outcome as hearing loss, five studies also considered tinnitus (Planting et al., 1999, Madasu et al., 1997, Ishikawa et al., 2015, Yoo et al., 2014, Scasso et al., 2017), and only two included vestibular disturbances(Madasu et al., 1997, Ishikawa et al., 2015). All of the studies used an audiometry test to examine ototoxicity. The study's characteristics for the pharmacologic and nonpharmacologic interventions appear in Table 3 and Table 4, respectively.

Table 1. Assessment of the risk of bias in clinical trials.

Study	Bias Arising From the Randomization Process	Bias caused by Deviations From Intended Interventions	Bias caused by Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the results	Overall risk of bias
Gandara et al.	Some concerns	Some concerns	Low	High	Some concerns	High
Somlo et al.	High	High	Low	High	Low	High
Kemp et al.	Low	Low	Low	Low	Low	Low

Study	Bias Arising From the Randomization Process	Bias caused by Deviations From Intended Interventions	Bias caused by Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the results	Overall risk of bias
Planting et al.	Low	Some concerns	Low	Low	Low	Some Concerns
Weijl et al.	Some concerns	Some concerns	Low	Low	Low	Some Concerns
Zuur et al.	Some concerns	Low	Low	Low	Low	Some Concerns
Yıldırım et al.	Some concerns	Some concerns	Low	Low	Low	Some Concerns
Riga et al.	High	Some concerns	Some concerns	Low	Low	High
Marshak et al.	Low	Low	Low	Low	Low	Low
Yoo et al.	High	Some concerns	High	Low	Low	High
Villani et al.	Low	Low	Low	Low	Some concerns	Some Concerns
Crabb et al.	Low	Some concerns	Low	Low	Low	Some Concerns
Delarestaghi et al.	Some concerns	Some concerns	Low	High	Low	High risk
Nasr et al.	High	Some concerns	Low	Low	Low	High risk
Rolland et al.	Low	Low	Low	Low	Low	Low
Duinkerken et al.	High	Low	Low	High	Low	High
Campbell et al.	Low	Some concerns	Low	Low	Low	Some Concerns
Moreno et al.	Low	Low	Low	Low	Low	Low

Quality tool used: Cochrane risk-of-bias tool for randomized trials Version 2

Table 2. Quality assessment of Cohorts and Cases-Control studies.

Study	Type of study	Selection	Comparability	Outcome/exposure	Overall
Madasu et al.	Cohort	2 (*)	1 (*)	0 (*)	Poor Quality
Scasso et al.	Case and controls	3 (*)	0 (*)	1 (*)	Poor Quality
Fernandez et al.	Cohort	3 (*)	1 (*)	3 (*)	High Quality
Ishikawa et al.	Cohort	3 (*)	1 (*)	3 (*)	High Quality
Ekborn et al.	Cohort	2 (*)	0 (*)	1 (*)	Poor Quality

Quality tool used: Newcastle - Ottawa quality assessment scale

Patient characteristics

Study populations included adults 18 to 82 years. Almost all studies include both female and male participants. Several types of cancers were accepted for participation, for instance, four studies included all types of cancers. The most prevalent type was head and neck cancer in 11 studies(Planting et al., 1999, Madasu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019, Yoo et al., 2014, Riga et al. 2013, Crabb et al., 2017, Fernandez et al., 2021, Campbell et al. 2022). Other types were ovarian, bladder, germ cell, gastric, lung, breast, sarcoma, thymus, mesothelioma, esophagus, melanoma, and cancer of unknown origin. Most of the studies recruited patients about to begin chemotherapy, with no prior history of auditory surgery, affection, or disease, and good performance status. Cisplatin dose ranged between 75 to 517 milligrams per square meter (mg/m2), an average of 138 mg/m2. Study exclusion criteria varied, with some studies excluding patients with metastasis in the central nervous system, hepatic or renal insufficiency, hearing asymmetry, hearing aid users, and concomitant neuropathy or radiotherapy. In regards to this last condition, there was great heterogeneity between studies, 10 studies demanded or allowed concomitant radiotherapy (Planting et al., 1999, Madasu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019, Yoo et al., 2014, Fernandez et al., 2021, Scasso et al. 2017, Campbell et al. 2022) while 13 considered radiotherapy as an exclusion criterion. For those studies that reported follow-up time, the mean was 6,4 months.

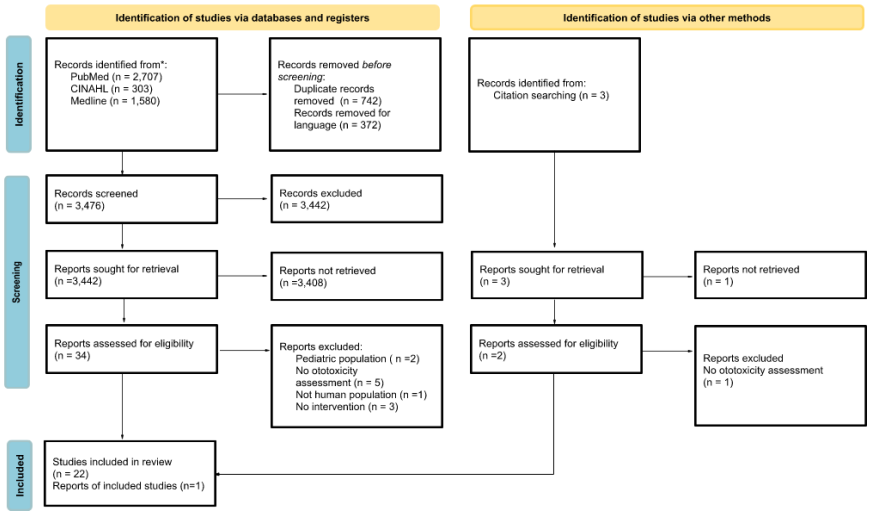

Figure 1. PRISMA flow chart to illustrate the flow of studies through the review and the selection process.

Pharmacological interventions

Diethyldithiocarbamate

A randomized placebo-controlled multicenter used diethyldithiocarbamate for chemoprotection against CiO in patients with lung or ovarian cancer. Patients who received diethyldithiocarbamate received lower cumulative doses of cisplatin, were more likely to be withdrawn from treatment early due to chemotherapy-related toxicities, and had a trend for a greater reduction in auditory acuity at 3000 Hz (P = 0.095)(Gandara et al., 1995).

Dopamine

In a randomized, placebo-controlled, double-blind trial, the protective effect of low-dose dopamine given as a continuous infusion in cisplatin toxicity was evaluated. No differences were observed in favor of the dopamine group when audiogram results were analyzed at 2,000, 4,000, or 8,000 Hz (P =0.27, 0.14, and 0.49, respectively)(Somlo et al., 1995).

Amifostine

Three studies assessed amifostine in CiO prevention. None of them found favorable results with amifostine as a pretreatment strategy. The first study was a randomized trial of patients with advanced ovarian cancer, the amifostine group required less dose reduction or discontinuation of cisplatin and reported a 43% reduction in ototoxicity incidence, however, this difference did not reach a statistical difference (P = 0.095)(Kemp et al., 1996). The second randomized trial used a weekly course of amifostine in patients with head and neck cancer, 21% of the patients received concomitant radiotherapy. There was no difference in hearing or tinnitus occurrence (P = 0.24)(Planting et al., 1999). Lastly, in a prospective cohort of 15 patients with different types of cancer, 11 out of 12 patients displayed auditory symptoms despite amifostine treatment (Ekborn et al., 2004). Amifostine treatment was poorly tolerated, all three studies report patients experienced nausea and/or vomiting, hypotension, flushing, sneezing, dizziness, sleepiness, hiccups, anxiety, palpitations, and chills(Kemp et al., 1996, Planting et al., 1999, Ekborn et al., 2004).

Sodium Thiosulfate

Five articles researched sodium thiosulfate for CiO prevention (Madasu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019). The first one was a prospective cohort of 70 patients with head and neck cancer, who received cisplatin, radiotherapy (dose not specified), and systemic sodium thiosulfate. The baseline audiometric analysis comparison to the audiometry after the fourth cisplatin infusion did not appear to confer sodium thiosulfate a protection hearing effect. Tinnitus or vestibular loss were not reported, nor were adverse reactions (Madasu et al., 1995). A similar prospective cohort of 18 patients with the same kind of cancer and receiving 60-70 Gray of radiotherapy assessed sodium thiosulfate otoprotection. The sodium thiosulfate group had significant hearing loss at ultra-high frequencies of 10 and 12 kHz (p = 0.028, 0.039, respectively), whereas the group not receiving sodium thiosulfate had significant hearing loss at high frequencies of 8 and 10 kHz (p = 0.016, 0.027, respectively). During follow-up, one patient presented with subjective tinnitus. Vertigo episodes and adverse reactions were not reported for any patient (Ishikawa et al. 2015). Later a pilot non-randomized control trial using transtympanic sodium thiosulfate in 12 adults for cisplatin and radiotherapy (maximum cochlear dose 30 Gray) was performed. The pure-tone average shift at 8 -12.5 kHz was 18.4 dB less in treated ears compared to untreated ears (p=0.068)(Duinkerken et al., 2021). This positive finding was further explored in a randomized control trial that tested intravenous sodium thiosulfate for CiO in 158 patients. All patients received concomitant radiotherapy (mean dose 70 Gray). In both treatment arms, the incidence of CiO did not deviate (P =0.14), but the intervention group had 10% less hearing loss at frequencies vital for speech perception (P = 0.001). No difference in adverse reactions between groups was observed (Zuur et al., 2007). Finally, a second randomized control trial tested trans-tympanic injections of sodium thiosulfate for CiO prevention in 13 patients with head and neck cancer. Although all of the patients received radiotherapy no dose information was provided. After 18 months of follow-up, the average hearing loss was 1.3 dB less for treated ears compared to control ears. Although not statistically (p = 0.61) nor clinically significant, the difference was in favor of the treated ears for all frequencies between 3 and 10 kHz. Injections caused dizziness in 3 patients, vertigo in one patient, and pain in 4 patients (Rolland et al., 2019).

N-acetylcysteine

Three randomized placebo-controlled trials have explored if N-acetylcysteine can avert CiO administered intratympanic(Riga et al., 2013, Yoo et al., 2014) or orally (Yıldırım et al., 2010). A RCT used intratympanic N-acetylcysteine at 10% in 20 patients with different types of tumors. They found that treated ears with N-acetylcysteine had no significant changes in auditory thresholds while the control ears had a significant decrease in auditory thresholds at the 8000 Hz frequency band (P = 0.008) with cisplatin (Riga et al., 2013). Another RCT assessed the effectiveness of intratympanic N-acetylcysteine at 2% to prevent hearing and tinnitus due to cisplatin in 11 patients with head and neck cancer receiving concomitant radiotherapy. No benefit in hearing preservation or tinnitus incidence was found (Yoo et al. 2014). The concentration difference of N-acetylcysteine may have influenced the disparity of the results as the occurrence of side effects. For instance, the highest concentration of N-acetylcysteine was associated with pain application among almost

all patients (Riga et al., 2013), while the trial with a lower concentration of N-acetylcysteine did not report adverse reactions (Yoo et al., 2014). The third RCT compared the protective hearing effect of placebo, oral N-acetylcysteine, and salicylate in 54 patients with solid organ tumors receiving cisplatin. Audiometry and auditory brainstem parameters showed no significant difference between placebo and salicylate. On the other hand, the N-acetylcysteine group did have a reduction in cisplatin hearing ototoxicity at 10,000 and 12,000 Hz ($p<0.005$) compared to placebo. Nonetheless, safety outcomes between study interventions were not reported (Yıldırım et al., 2010).

Corticoids

Three investigations have evaluated the role of intratympanic corticosteroids to prevent CiO (Marshak et al., 2014, Moreno et al., 2022, Nasr et al., 2018). Two studies used dexamethasone and one methylprednisolone. In a controlled trial, prior to each cisplatin treatment session, intratympanic dexamethasone was injected 0.7 to 1.0 ml (10mg/ml) into randomly assigned ears. A significant attenuation in the hearing loss at 6000 Hz ($P<0.02$) and decreased outer hair dysfunction in the range of 4000 to 8000 Hz ($P<0$ .04) was observed in the intervention group (Marshak et al., 2014). These positive findings of intratympanic dexamethasone protecting the hearing capacity were corroborated by a second randomized controlled phase IIIB trial. Dexamethasone was administered via a passive diffusion device to an ear and the contralateral ear was used as the control. Audiometric analysis showed a higher hearing threshold in the study group than in the control group with significant differences at frequencies of 500, 1000, and 6000 Hz ($p < 0.05$)(Moreno et al. 2022). Safety outcomes for both trials reported slight pain and mild vertigo during the application, otological infections, and permanent tympanic perforation in 34.8% of the patients (Marshak et al., 2014, Moreno et al., 2022). Lastly, 0.3ml (40mg/ml) of intratympanic methylprednisolone was also assessed for CiO treatment in a prospective cohort of 20 patients with any type of cancer. Intratympanic corticosteroid injections appeared to have minimal therapeutic effect diminishing cisplatin-induced hearing loss at 6000 and 8000 Hz. The adverse effects of this trial were not reported (Nasr et al., 2018).

Aspirin

A phase II double-blind placebo RCT recruited 94 patients to receive aspirin 975 mg twice daily, before and after their cisplatin dose. Patients in the aspirin arm were more commonly affected by aspirin renal toxicity(17.8% vs 10.2%) and no protective hearing effect was observed ($p= 0.233$)(Crabb et al., 2017).

Sertraline

A double-blind placebo RCT assessed if oral sertraline (50 mg/day) can contribute to preserving the hearing threshold among patients with lymphoma and gastric cancer exposed to cisplatin. The two groups were distributed homogeneously. The ototoxicity grade for the sertraline group was lower compared to the placebo group ($p<0.001$). The level of distortion product otoacoustic emissions was unchanged among 57.1% in the sertraline group versus 17.1% in the placebo group ($p=0.000$). However, 11.4% of the patients in the sertraline group reported severe nausea and vomiting (Delarestaghi et al., 2018).

Statins

Previous studies in mice have demonstrated statins reduce CiO. Their effect was tested on 277 adults (546 ears) treated with cisplatin and concurrent radiotherapy for head and neck cancer in an observational study. Of the 6 types of statins tested in this observational study, 44% of patients took atorvastatin. The mixed-effect model analysis showed atorvastatin was significantly associated with reduced cisplatin hearing loss (P [?] 0.01) (OR = 0.47; 95% CI, 0.30–0.78). No significant correlation was found between high-frequency hearing loss and atorvastatin dose. Adverse effects were not reported (Fernandez et al., 2021).

Table 3. Characteristics of the studies assessing pharmacological interventions.

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Gandara et al. 1995	RCT 214	Lung cancer Ovarian cancer	100 mg/m2	Clinical grading scale & audiometry	Diethyldithiocarbamate	Not reported	Patients in the intervention group had a greater but not significant reduction in auditory acuity at 3000 Hz(P = 0.095).	No difference between groups
Somlo et al. 1995	RCT 42	Sarcoma Breast	125 mg/m2	Audiometry	Dopamine infusion 2 ug/kg/min over 48 hours	1 month	No differences were observed in favor of the dopamine group when audiogram results were analyzed at 2,000, 4,000, or 8,000 Hz (P =0.27, 0.14, and 0.49, respectively).	Not reported

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Kemp et al. 1996	RCT 242	Ovarian	100 mg/m2	Audiometry	Amifostine 910 mg/m2	41 months	Amifostine had a 43% reduction in the incidence of ototoxicity (P = 0.108) Ototoxicity required cisplatin dose reduction or discontinuation 16% in the control arm vs 9% in the amifostine arm.	Nausea and/or vomiting, hypotension, flushing, sneezing, dizziness, sleepiness, hiccups, and chills.
Madasu et al. 1997	Prospective Cohort 70	Head and neck	150 mg/m2	Audiometry	Sodium Thiosulfate	22 days	Sodium thiosulfate did not appear to confer protection. There were no cases of debilitating tinnitus or vestibular loss.	Not reported

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Planting et al. 1999	RCT 74	Head and neck	70 mg/m2	Audiometry	Amifostine 740 mg/m2	6 months	Hearing loss was only seen at the high-frequencies (4000 and 8000 Hz). No difference in hearing or tinnitus occurrence (P = 0.24).	Hypotension, dizziness, flushing, anxiety, palpitations, sneezing.
Ekborn et al. 2004	Prospective Cohort 15	Melanoma Esophagus Cancer.	125 - 150 mg/m2	Audiometry	Amifostine 50 mg/mL	Not reported	92% of patients (11 of 12) had auditory symptoms. Ototoxicity was unacceptable despite amifostine treatment.	Nausea and vomiting, ototoxicity, neurotoxicity, oliguria, and hypotension.
Zuur et al. 2007	RCT 158	Head and neck	150 mg/m2	Audiometry	Intravenous Sodium Thiosulfate 9 g/m2 (30 minutes) followed by 12 g/m2 (2 hours)	3 months	Approximately 10% less hearing loss at frequencies vital for speech perception (P = 0.001).	No difference between groups

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Yıldırım et al. 2010	RCT 54	Solid organ tumors	Not reported	Audiometry & auditory brainstem response	N-acetylcysteine 600 mg/day or salicylate 300 mg/day	2 months	Cisplatin-ototoxicity could be reduced in N-acetylcysteine group in 10,000 and 12,000 Hz ($p<0.005$) compared to placebo.	Not reported
Riga et al. 2013	RCT 20	Gastric Melanoma Head and neck Ewing Sarcoma Small cell lung cancer	50 - 100 mg/m2	Audiometry	Transtympanic N-acetylcysteine (10%)	Not reported	In treated ears no significant changes in auditory thresholds were recorded. In the control ears cisplatin induced a significant decrease of auditory thresholds at the 8000 Hz frequency band ($P = 0.008$).	Almost all patients had pain after application but it decreased gradually. One patient had an ear infection.
Yoo et al. 2014	RCT 11	Head and neck	100 mg/m2	Audiometry	Transtympanic L-N-Acetylcysteine (2%) 200mg/ml	2 months	The difference in hearing preservation did not reach significance.	Not reported

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Marshak et al. 2014	RCT 26	Any cancer	517 mg/m2	Audiometry and DPOAE	Intratympanic Dexamethasone (10 mg/ml solution).	Not reported	Significant increase in the pure tone threshold for 6000 Hz was observed in the control (P<0.02) but not in the study group. Groups' comparison showed a difference in the DPOAE average signal-to-noise ratio (P<0.04).	Slight pain and short mild vertigo during application
Ishikawa et al. 2015	Prospective Cohort 18	Head and neck	100 - 180 mg/m2	Audiometry	Sodium Thiosulfate 14 g/m2/4 h	2 months	Intra-arterial cisplatin with sodium thiosulfate caused relatively less severe cisplatin ototoxicity than usual intra-venous cisplatin chemoradiation.	Not reported

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Crabb et al. 2017	RCT 94	Bladder Germ cell Head and neck Lung	200 mg/m2	Audiometry	Aspirin 975 mg three times a day for 4 -5 days	3 months	Aspirin did not protect patients receiving cisplatin. Patients demonstrated mean combined hearing loss of 49 dB vs 36 dB(p=0.233).	Renal toxicity affected more patients in the aspirin arm (17.8% vs 10.2%), the rest of toxicities were similar between arms.
Nasr et al. 2018	Non-randomized clinical trial	Any cancer	Average cumulative cisplatin dose 546.3 ± 111.58 mg	Audiometry	Intratympanic methylprednisolone 40 mg/ml	After cisplatin dose reached 400 mg.	Significant increases in the average pure-tone thresholds at 6000 Hz were found in both the study and control groups (P = <0.001 and <0.001, respectively) at 6000 and 8000 Hz.	Not reported

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Delarestaghi et al. 2018	RCT 79	Lymphoma Gastric	75 mg/m2	Audiometry & otoacoustic emissions	Sertraline 25 - 50 mg/d	3 months	Level of distortion product otoacoustic emissions was unchanged 57.1% and 17.1% in the sertraline and placebo groups, respectively(p=0.000).	11.4% had severe nausea and vomiting in the sertraline group
Rolland et al. 2019	RCT 13	Head and neck	100 mg/m2	Audiometry and Bone conduction audiograms	Transtympanic sodium thiosulfate (dose 0.1 ml).	18 months	The average loss of hearing was 1.3 dB less for treated ears compared to control ears (p = 0.61) 3 and 10 Hz.	3 patients reported dizziness and 1 patient had vertigo. Pain in the middle ear was noted for 4 patients.
Duinkerken et al. 2021	Single-blind placebo controlled study. 12	Lung Head and neck Mesothelioma Thymus carcinoma	75 - 100 mg/m2	Audiometry	Transtympanic Sodium Thiosulfate 0.5% 2.0 ml	3 months	Shift pure-tone average at 8 -12.5 Hz was 18.4 dB less in treated ears compared to untreated ears (p=0.068).	Vertigo, pain and tinnitus

Author	Type of study & number of patients	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Fernandez et al. 2021	observational study 277	Head and neck	200 mg/m2	Audiometry	Various statins at different doses	3 months	Atorvastatin use was significantly associated with reduced cisplatin-induced hearing loss (P [?] 0.01) (OR = 0.47; 95% CI, 0.30–0.78).	Not reported
Moreno et al. 2022	RCT 23	Lung Bladder Unknown origin	70 -100 mg/m2	Audiometry	Intratympanic dexamethasone 8mg	2 months	Audiometric analysis showed a higher hearing threshold in the study group at frequencies of 500, 1000, and 6000 Hz: 4.9 dB, 5.5 dB, and 16 dB ($p < 0.05$).	Infections 8.6% and permanent perforation 34.8%.

RCT: Randomized control trial Hz: Hertz dB: decibel DPOAE: Distortion Product Otoacoustic Emissions

Table 4. Characteristics of the studies assessing non-pharmacological interventions.

Author	Type of study	Type of Cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse Reactions
Weijl et al. 2004	RCT 50	Any cancer	100mg/m2	Audiometry	1000mg Vitamin C, 400mg Vitamin E, 100mg selenium	12 months	Patients with the highest micronutrient antioxidant score had less loss of high-tone hearing (conduction threshold at 8.0 Hz 2.8 vs. 14.4 dB; p=0.028).	Not reported
Villani et al. 2016	RCT 108	Solid malignancies	Not reported	Audiometry and evoked brainstem responses	400mg Vitamin E per day	3 months	A significant hearing loss in the control group at both 2000 Hz and 8000 Hz. Conversely, audiograms did not show significant changes in the active group at 2000, 4000, and 8000 Hz.	Not reported

Author	Type of study	Type of Cancer	Cisplatin dose	Ototoxicity assess-ment	Intervention	Follow-up time	Outcome	Adverse Reac-tions
Scasso et al. 2017	Case-control study 26	Any cancer	100 mg/m2	Audiometry	Coenzyme Q10 + Multivitamins	4 months	A higher hearing impairment in the control patients occurred in 6 out of 8 patients (75.0%). Otherwise, only 2 out of 18 patients (11.1%) who took the supplement daily were affected (P $<$ 0.01).	Not reported
Campbell et al. 2022	RCT 27	Head and neck Genitourinary Esophagus	50 mg/m2	Audiometry	D-methionine (100 mg/kg) fraction-ated into two doses	5 cycles of cisplatin	Placebo group showed a threshold shifts from baseline to post-treatment at 10 Hz (-13.65 dB p =0.008), 11.2 Hz (-16.15dB p=0.008) and 12.5 Hz (-11.46dB p=0.03). The inter-vention group showed no significant threshold shifts.	No differences between groups

RCT: Randomized control trial Hz: Hertz dB: decibel

Non-pharmacological interventions

Multivitamins

Three investigations evaluated multivitamin supplementation in CiO(Weijl et al., 2004, Villani et al., 2016, Scasso et al., 2017). A multivitamin beverage that contained vitamin C, vitamin E, and selenium was used as CiO profilaxis in a RCT. At 12 months they did not find any difference between the occurrence of nephrotoxicity and ototoxicity induced by cisplatin. However, patients with the highest micronutrient antioxidant values at the start of chemotherapy had significantly less loss of high-tone hearing than patients with low values (conduction threshold at 8.0 kHz 2.8 vs. 14.4 dB; p=0.028)(Weijl et al., 2004). Another RCT compared the protective effect of vitamin E supplementation for 3 months against placebo in CiO. At 1 month the control group had significant hearing loss at both 2000 Hz (right ear: p=0.05; left ear: p=0.04) and 8000 HZ (right ear: p=0.04; left ear: p=0.03) when compared with baseline values. Audiograms did not show significant changes in the active group at 2000, 4000, and 8000 Hz. Evoked brainstem responses remained unchanged in both groups. The planned follow-up evaluations weren't completed because of a 37% patient drop-out (Villani et al., 2016). Ultimately a case-control study tested if dietary supplementation with coenzyme Q10 plus multivitamins could preemptively reduce reactive oxygen species and consequently CiO. They found that patients on dietary supplementation, 7 days before and 21 days after chemotherapy, had a significantly lower amount of reactive oxygen metabolite derivatives ($P < 0.05$) and a stable range of blood antioxidants ($P < 0.05$) compared to the control group. Moreover, the intervention group showed lesser augmentation on the hearing threshold level at 8000 Hz frequency 6.9 $\pm$ 11.8 dB compared to the control group 20.0 $\pm$ 16.2 dB ($P < 0.05$). Similarly, tinnitus incidence was higher in the control group (62.5% vs 11.1% $P < 0.05$). In this study, 69% of patients received concomitant head radiation (dose not specified)(Scasso et al., 2017). None of the studies reported adverse effects due to vitamin supplementation, only the patient´s dislikeness for the taste of the supplementation product.

D-methionine

A RCT assessed the otoprotective effect of D-methionine in CiO in 27 patients receiving chemoradiotherapy for head and neck, genitourinary, and esophagus cancer. Radiotherapy was used on 37% of the patients, the delivered dose was not stated. While the placebo group showed significant hearing threshold decline from baseline to post-treatment at 10 kHz (-13.65 dB p =0.008), 11.2 kHz (-16.15dB p=0.008), and 12.5 kHz (-11.46dB p=0.03), the intervention group showed no significant hearing threshold shift. There was no difference in side effects between the groups (Campbell et al., 2022).

Discussion

This systematic review is a comprehensive synthesis of all the interventions that have been used in adult patients to mitigate cisplatin-induced ototoxicity. Previous systematic reviews have described the evidence on potential therapeutic targets based on animal models (Mukherjea et al., 2020), have noted the effectiveness of a particular intervention (Duval et al., 2012), or have focused on the pediatric population (Freyer et al., 2020). This is the first systematic review in the adult population with CiO that broadly recopilates the evidence on pharmacological and non-pharmacological interventions. Our study approach allowed us to search for ototoxicity caused by other types of platinum and chemotherapy agents, albeit the retrieved studies only focused on cisplatin ototoxicity. In total eleven interventions (nine pharmacological and two non-pharmacological) for CiO in adults were identified. Based on the authors' information, this review analyzes the most interventions to date. All of the interventions have been tested as a preemptively otoprotective strategy and only one (corticosteroids) has been assessed in one study as a treatment strategy once the hearing deficit is established due to cisplatin administration (Nasr et al., 2018). This finding may be relevant to explain the ineffective results of some interventions. The action of free radical oxygen species may take time to occur as cisplatin accumulates in the cochlea, meantime the prophylactic effect of the otoprotective intervention may be lost, not coinciding with the nadir damage on the ear function(Breglio et al., 2017, Tang et al., 2021).

We encounter four pharmacological and two non-pharmacological interventions with positive results that merit future investigation. Of the pharmacological interventions, sodium thiosulfate, corticoids, sertraline, and statins showed a preserving hearing effect. Nevertheless, the current evidence on these interventions has limiting aspects to consider. A considerable number and severity of side effects were reported in the intratympanic corticoids trial, a single trial has been conducted with sertraline and statins, and the statins trial had a heterogeneous intervention which limits the confidence of the results. Although the studies showed a partial benefit, sodium thiosulfate appears as the most promising intervention to prevent CiO in adults undergoing cisplatin therapy. These results are similar to what has been found in high-quality RCT in the pediatric population, where sodium thiosulfate reduced the incidence of cisplatin-induced hearing loss among children with standard-risk hepatoblastoma, without jeopardizing overall or event-free survival (Brock et al., 2018). A recent systematic review and meta-analysis, based on four studies with mixed pediatric and adult populations, confirms the otoprotective effect of sodium thiosulfate (Chen et al., 2021). On the other hand, the two non-pharmacological interventions that showed positive results were multivitamins and D-methionine. As with the pharmacological interventions, this too has limiting considerations. The multivitamins regimens tested vary widely among the studies, and the evidence regarding D-methionine consists of a unique pilot trial. None of the studies testing non-pharmacological interventions had a good quality rating. However, the safety profile of these dietary supplements seems to be superior and could make them a good option depending on future trials. Moreover, the low number of participants reduces the chances of detecting significant adverse events and increases the likelihood of Type II errors. (Faber et al., 2014).

Additionally, our results highlighted the focus and gaps of CiO research. Even though tinnitus and vertigo are symptoms that may considerably affect patients' quality of life, even more than the mild hearing loss that occurs above the frequency range of human speech (0.25 – 8 kHz) that may go undetected (Chauhan et al., 2011), few studies in our review documented them. Moreover, none showed that any kind of intervention could prevent or palliate these symptoms. It is not clear why the studies did not take the whole spectrum of CiO symptoms into account, given that cisplatin-induced tinnitus is reported to be prevalent with high cumulative cisplatin doses($p=0.007$) and in older populations ($p=0.007$)(Frisina et al., 2016). Investigators have also found cisplatin-induced tinnitus is significantly correlated with reduced hearing per frequency (0.25-12 kHz, $p< 0.0001$) and vertigo (OR = 6.47; $p< 0.0001$)(El Charif et al., 2019), which means it is uncommon for patients to experience hearing loss without tinnitus and vertigo. This suggests that these symptoms are likely underdiagnosed or overlooked in oncology, hematology, or palliative care consultations. Currently, four clinical trials in adult patients with CiO risk are underway to evaluate sodium thiosulfate and mannitol, rosuvastatin, and intratympanic N-acetylcysteine (Dizon et al., Kasem et al., Sajeniouk et al., Cavelier et al.). Only one of them considers the apparition of tinnitus in their outcomes. Therefore, future high-quality randomized clinical trials should consider the shortcomings and successes of existing evidence to improve their internal validity.

Limitations

There are a number of limitations to our review. Relevant articles might be missed because the search was conducted only in three databases, in one language, and excluded grey literature. One article about the protective effect of ginkgo biloba extract on CiO was retrieved by the manual research on clinicaltrial.gov, but wasn't available in its full-text format. The conclusions of our review are based on studies with small and heterogeneous samples, who were followed on different time ranges, and whose analysis had low quality, so our results should be taken as preliminary findings that need to be corroborated in the future. None of the trials took into account patients' quality of life or reported outcomes to assess the intervention's benefit. So a comprehensive understanding of the effectiveness of any intervention is missing. Finally, the safety outcomes of the interventions were not mentioned in 10 out of 23 studies. Since most of the interventions contain mild benefits and uncertain risks, underreporting of side effects limits the power of our conclusions.

Conclusions

Ototoxicity is a known side effect of platinum-based chemotherapeutics. Eleven pharmacological and non-pharmacological strategies have been proposed to address this issue in the adult cancer population. This

review summarizes the effectiveness of each intervention for the prevention and treatment of hearing loss associated with cisplatin. Current studies' results are limited by their suboptimal methodological quality and underreporting of safety outcomes. High-quality randomized clinical trials are warranted to clarify the significance of these preliminary findings. Future research should ensure to include patients' reported outcomes and overlooked otic symptoms like tinnitus and vertigo.

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