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Original Article

Cisplatin and ototoxicity in childhood: the perspective of supporting otoprotective agentes

Cisplatina e ototoxicidade na infância: perspectiva de substâncias otoprotetoras coadjuvantes

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Abstract

Cisplatin is an antineoplastic medicine used in the treatment for various types of cancer. Among its side effects is ototoxicity, which may result in a bilateral and irreversible hearing loss. The ototoxic effect in the pediatric population has a bigger impact as it compromises language acquisition. The discovery of drugs with otoprotective effects and the optimal way to administer them have become significant challenges in minimizing the impact of cisplatin regarding auditory function. The objective was to understand otoprotective drugs and their relevance in the preventive treatment to cisplatin-induced ototoxicity in childhood. An integrative review was conducted by consulting databases including PubMed, Bireme, MedLine, LILACS, SciELO, and ClinicalTrials.gov. The search strategy was performed by crossing descriptors (DeCS and MeSH) and free terms. Studies published in English, Spanish, and Portuguese were selected, with no publication year restrictions. Subsequently, articles were selected according to inclusion and exclusion criteria. A total of 736 articles were found in PubMed, 431 in Bireme, 425 in MedLine, 6 in LILACS, 0 in SciELO, and 4 in ClinicalTrials.gov. After document analysis, 12 articles were selected for full analysis. Evidence was found for 8 substances with potential otoprotective effects when used with cisplatin, which tend to minimize the impact of cisplatin regarding auditory function. The substances found were: Amifostine, Dexamethasone, Genistein, Ginkgo Biloba, Lycopene, N-acetylcysteine, Polydatin also Sodium Thiosulfate. In general, these drugs are applied before, during, or after cisplatin infusion, depending on the chosen drug, via intravenous, oral, or transtympanic injections, acting as antioxidant therapy. The biochemical effects of these substances are relevant to their potential otoprotective properties, including the inactivation of oxygen free radicals and electrophilic platinum species. The use of these substances can reduce ototoxicity, decreasing cisplatin-induced hearing loss and improving the confort of life, especially for children.

Keywords: antineoplastic, prevention, ototoxicity, children.

Resumo

Cisplatina é um antineoplásico utilizado para o tratamento de diversos tipos de câncer. Dentre os efeitos colaterais está a ototoxicidadeque pode acarretar a perda auditiva bilateral e irreversível. O efeito ototóxico na população pediátrica tem impacto maior ao comprometer a aquisição da linguagem. A descoberta de drogas com efeito otoprotetor e a melhor forma de administrá-las tornaram-se grandes desafios para minimizar o impacto da cisplatina a respeito da função auditiva. O objetivo foi conhecer as drogas otoprotetoras e sua relevância no tratamento preventivo da ototoxicidade mediada pelo uso da cisplatina na infância. A revisão integrativa foi realizada através da consulta as bases de dados Pubmed, Bireme, MedLine, LILACS, SciELO e ClinicalTrials.gov. A estratégia de busca foi realizada ao cruzar os descritores (DeCS e MeSH) e os termos livres. Foram selecionados estudos publicados em inglês, espanhol e português, não havendo restrição do ano de publicação. Posteriormente, os artigos foram selecionados de acordo com os critérios de inclusão e exclusão. Foram encontrados 736 artigos na Pubmed, 431 na Bireme, 425 na MedLine, 6 na LILACS, 0 na SciELO e 4 na ClinicalTrials.gov. Após a análise dos documentos foram selecionados 12 artigos para análise na íntegra. Foram encontradas evidências de 8 substâncias com potencial efeito otoprotetor quando usadas com a cisplatina, as quais tendem a minimizar o impacto do efeito da cisplatina sobre a função auditiva. As substâncias encontradas foram: Amifostina, Dexametasona, Genisteína, Ginkgo Biloba, Licopeno, N-acetilcisteína, Polidatinae Tiossulfato de Sódio. Em geral, essas drogas são aplicadas antes, durante ou depois da infusão de cisplatina, a depender da droga escolhida, com administração de maneira intravenosa, via oral ou por injeções transtimpânicas, agindo como terapia antioxidante. Os efeitos bioquímicos dessas substâncias

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são relevantes para os seus potenciaisotoprotetores, incluindo a inativação de radicais livres de oxigênio e espécies eletrofílicas de platina. O uso dessas substâncias pode reduzir a ototoxicidade, diminuindo a perda auditiva induzida pela cisplatina e aumentando o conforto de vida, especialmente para crianças.

Palavras-chave: antineoplásicos, prevenção, ototoxicidade, criança.

1. Introduction

Cisplatin, although discovered more than 40 years ago, remains one of the most widely used chemotherapeutic agents in the treatment for cancer in both adults and children (Brock et al., 2012; Warrier et al., 2012). It has shown activity against most pediatric solid tumors, including brain tumors, neuroblastoma, osteosarcoma, and germinal cell tumors (Packer et al., 1994).

The toxicity of cisplatin can happen in various systems, including oto, neuro, nephro and myelotoxicity (O'Dwyer et al., 2000). Ototoxicity is attributed for the production for toxic levels of reactive oxygen species (ROS) in the cochlea, resulting in hair cells damage, injury to the vascular stria, and spiral ganglion cells. It ranges from 4% to 90% and depends on factors such as the age of the patient population, concurrent agents used, such as aminoglycosides, cumulative dose, and administration techniques (Landier, 2016).

Hearing loss is typically bilateral, irreversible, initially affecting high frequencies and progressing to lower frequencies with cumulative drug dosage (Neuwelt et al., 1998; Skinner et al., 1990), often accompanied by tinnitus (Hyppolito and Oliveira, 2005). In most cases, hearing deficiency is underestimated, as patients only complain in specific situations, such as in noisy environments. Losing the hearing implies limiting one of the most crucial forms of connecting with the world and, particularly, with other individuals. Any degree for hearing loss at any age results in impairment of the message content to the Central Nervous System (CNS) and deserves full attention; moreover, when it happens with the pediatric population, it can compromise language acquisition (Liberman et al., 2012).

Approximately 60% of young people treated with cisplatin develop hearing loss, which has negative effects on speech, language, and development (Knight et al., 2005, 2007; Tropitzsch et al., 2014). In young people, the risk is higher, and there are significant long-term implications, particularly if the children are pre-lingual, in the early stages of language development, or have other functional deficiencies such as visual deficits or cognitive dysfunction (Knight et al., 2005).

One of the major concerns regarding the concurrent use of otoprotective substances is the potential reduction in cisplatin's antitumor effect (Yoo, 2014). To prevent that undesirable effect, various administration methods have been tested with animal models. In recent years, efforts have been made to identify substances and viable administration methods because the expected benefits include preserving auditory function and the possibility of increasing the total dose of cisplatin, which is often limited due to its potential dose-dependent ototoxic effect (Rybak et al., 2007).

Currently, Amifostine is the medication of choice for otoprotection, and when administered before cisplatin, it eliminates free radicals. Evidence suggests that its intravenous administration with multiple daily doses can enhance its otoprotective effects (Fouladi et al., 2008; Gurney et al., 2014; Hyppolito et al., 2005).

Therefore, the aim of this study was to identify, through an integrative review, the substances with otoprotective effects and the method of their use as a support in cisplatin chemotherapy.

2. Material and Methods

The present study is an integrative literature review in which data was systematically and methodically collected to better understand the topic of drugs with otoprotective effects and their significance in the preventive treatment for cisplatin-induced ototoxicity in childhood.

The integrative review was conducted through electronic searches on the Pubmed and Bireme platforms, as well as in the following databases: MedLine, LILACS, SciELO, and ClinicalTrials.gov. The search strategy involved combining the DeCS and MeSH descriptors with free terms, which are terms not found in DeCS or MeSH but are relevant to the research. The guiding research question was "What are the substances with otoprotective effects and their methods of use as supporting in cisplatin chemotherapy?"

In order to identify relevant articles related to the proposed question, a search strategy was developed using descriptors grouped together. Boolean operators "AND" and "OR" were used to enhance the search strategy. Due to the difficulty in finding studies with information that would address the intended objective, and to broaden the search, the names of medications already used as otoprotectors were included. So, the search strategy used was: (cisplatin) AND (child OR children OR childhood) AND ((ototoxicity OR otoprotection OR hearing loss) OR (sodium thiosulfate OR acetylcysteine OR ginkgo biloba OR dexamethasone OR small interfering RNA OR cimetidine OR methionine)).

Studies published in English, Spanish, and Portuguese were selected, with no restriction on the year of publication, considering articles published up to 2022. Subsequently, articles were selected according to inclusion and exclusion criteria. Included were original articles, literature reviews, systematic reviews, experimental studies, clinical trials, or case reports that addressed the objective proposed in the title, abstract, or body of the article. Excluded were articles duplicated in the databases, editorials, reports, as well as those not accessible in open access.

The main data from each article were collected and entered into a database using the MendeleyTM Desktop 1.13.3® 2010 program for subsequent analysis and discussion. For a better presentation of the results, it was decided to consider the following variables from the

selected articles: author/year/location, drug, study title, study type, level of recommendation/scientific evidence, and conclusion. Regarding the level for scientific evidence, the classification used was that of the Oxford Centre for Evidence-Based Medicine (CEBM, 2009).

3. Results

3.1. Characterization of studies

After the search, 736 articles were found in PubMed, 431 articles in Bireme, 425 articles in MedLine, 6 articles in LILACS, 0 articles in

SciELO, and 4 articles in ClinicalTrials.gov, totaling1,602 articles. After reviewing the titles, abstracts, and removing duplicates, 12 articles were obtained for full-text analysis, as shown in Figure 1.

In the results stratification, the analysis was divided into 2 tables, with Table 1 presenting data such as title, objective, author, location, and year of the study of the analyzed articles, while Table 2 presents the found evidence.

3.2. Synthesis of the integrative review

Table 2 refers to the synthesis of the studies found regarding otoprotective drugs, type of study conducted, level ofscientific evidence of the articles, and the study conclusions.

4. Discussion

According to the research by Gurney et al. (2014), cisplatin is a platinum-based chemotherapy agent used in the treatment for brain tumors and solid childhood tumors. Conversely, Hyppolito et al. (2005) reported that the use of cisplatin has led has an enlargement in side effects, particularly in the central nervous system (CNS), kidneys, and ototoxicity. Cisplatin causes bilateral and symmetric sensorineural hearing loss at frequencies of 4 to 8 kHz, along with the symptom of tinnitus.

Moreover, a significant portion of pediatrictumors occur before the age of 10. As a result, cisplatin-induced hearing loss often occurs during the period of speech and language acquisition and development. Therefore, in addition to causing neurocognitive deficits, sensorineural hearing loss also can lead to long-term academic and social impairment in surviving children (Gurney et al., 2014).

The cause for cisplatin-induced hearing loss is not clear; however, the most significant mechanisms involve increased generation to reactive oxygen species and the reduction of the antioxidant enzyme system of the cochlea. When this imbalance occurs within the cochlear cells, they are damaged and die, resulting in hearing loss (Tan et al., 2022).

The degree for hearing loss caused by cisplatin is typically associated with the amount of the substance, the route of administration, cranial radiation, and the patient's

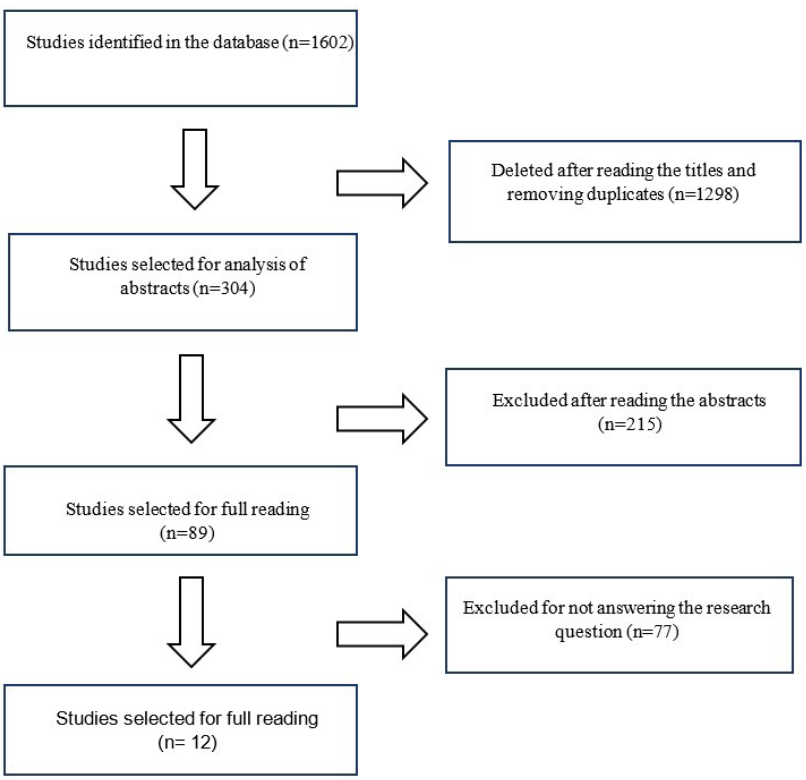

Figure 1. Selection of scientific articles from the database search.
Source: Research data (2023).

Table 1. Presentation of Research results.

Study	Title	Objective	Author/Local
1	Sodium Thiosulfate for Protection Against Cisplatin-Induced Hearing Loss.	To investigate whether the late administration for Sodium Thiosulfate would reduce the incidence and severity of cisplatin-induced hearing loss.	Brock et al. (2018), United Kingdom.
2	The chemopreventive effect of Ginkgo Biloba 761 extract against cisplatin-induced ototoxicity: a pilot study.	To elucidate the role of Ginkgo Biloba 761 in preventing damage to outer hair cells caused by cisplatin therapy in cancer patients through Distortion Product Otoacoustic Emissions.	Dias et al. (2015), Brazil.
3	Are Ginkgo Biloba and Lycopene effective against cisplatin-induced ototoxicity?	Investigate the protective effects of Lycopene and Ginkgo Biloba on cisplatin-induced ototoxicity and compare their advantages to each other	Esen et al. (2018), Turkiye.
4	Amifostine protects against cisplatin-induced ototoxicity in children with medium-risk medulloblastoma.	To investigate the ability of Amifostine to protect children receiving a high-dose cisplatin-based regimen against severe ototoxicity, defined as ototoxicity ≥ grade 3 that requires hearing aids in at least one ear, next to one year the start of treatment.	Fouladi et al. (2008), Tennessee.
5	Effects of Sodium Thiosulfate vs. Observation on the Development of Cisplatin-Induced Hearing Loss in Children with Cancer: Results from the ACCL0431 Pediatric Oncology Group Randomized Clinical Trial.	Compare the proportional incidence of post-treatment cisplatin-induced hearing loss between those randomized to receive or not receive Sodium Thiosulfate.	Freyer et al. (2017), California.
6	Evaluation of Amifostine for Protection Against Severe Cisplatin-Induced Hearing Loss in Children Treated for Medium or High-Risk Medulloblastoma.	Evaluation for Amifostine for Protection Against Severe Cisplatin-Induced Hearing Loss in Children Treated to Medium or High-Risk Medulloblastoma.	Gurney et al. (2014), Tennessee.
7	Amifostine Otoprotection Against Cisplatin Ototoxic Effects: Study in Albino Guinea Pigs Using Distortion Product Otoacoustic Emissions and Scanning Electron Microscopy.	Assessing the Potential Otoprotective Effect of Amifostine in Cisplatin Treatment through Distortion Product Otoacoustic Emissions (DPOAE) and Scanning Electron Microscopy (SEM).	Hyppolito et al. (2005), Brazil.
8	Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma. A report from the Intergroup Hepatoblastoma Study P9645 as part of the Children's Oncology Group.	To determine whether Amifostine is effective in reducing toxicities associated with the administration of platinum-containing regimens to young people with hepatoblastoma.	Katzenstein et al. (2009), California.
9	Polidatina activates the Nrf2/HO-1 signaling pathway to protect against cisplatin-induced hearing loss in guinea pigs.	Exploring the effects of Polidatina on cisplatin-induced hearing loss and attempting to unravel the underlying mechanism.	Li et al. (2022), China.
10	Amifostine doesn't protect against cisplatin ototoxicity at high doses combined with etoposide and bleomycin in pediatric germ cell tumors.	To determine if pretreatment with Amifostine reduced the significant ototoxicity associated with drugs while maintaining its survival advantage.	Marina et al. (2005), California.
11	Transtympanic injections of N-acetylcysteine and Dexamethasone for the prevention of cisplatin-induced ototoxicity: a double-blind randomized clinical trial.	Comparing the positive effects of intratympanic injection for N-acetylcysteine and Dexamethasone in preventing cisplatin-induced ototoxicity.	Sarafraz et al. (2018), Iran.
12	Effect of Genistein on cisplatin-induced ototoxicity and oxidative stress.	Evaluate the otoprotective effect of Genistein against cisplatin in rats.	Tan et al. (2022), Turkiye.

Source: Research data (2023).

Table 2. Evidence on otoprotective drugs.

Study	Drug	Typeofstudy	Level os scientificevidence	Conclusion
1	Sodium Thiosulfate	Cohortstudy	2B	Sodium thiosulfate following cisplatin chemotherapy resulted in a lower incidence for cisplatin-induced hearing loss in young people with hepatoblastoma.
2	Ginkgo Biloba	Cohortstudy	2B	Ginkgo Biloba, when administered at 240 mg per day, demonstrated otoprotective effects against cisplatin-induced damage.
3	Ginkgo Biloba e Lycopene	Cohortstudy	2B	There is a protective effect of Ginkgo Biloba and Lycopene in a cisplatin-dependent ototoxic rat model.
4	Amifostine	Cohortstudy	2B	Amifostine administered before and during cisplatin infusion can significantly reduce the risk for ototoxicity in patients with medulloblastoma.
3	Sodium Thiosulfate	Cohortstudy	2B	The studied drug provides protection against cisplatin-induced hearing loss in young people and is not associated with severe adverse events attributed to its use.
6	Amifostine	Cohortstudy	2B	Amifostine provides protection against severe cisplatin-induced hearing loss in patients with moderate-risk medulloblastoma.
7	Amifostine	Control case study	3A	Amifostine demonstrates clear signs of otoprotection against the ototoxic effects produced by cisplatin in albino guinea pigs.
8	Amifostine	Cohortstudy	2B	In this study, Amifostine failed to significantly reduce the incidence of platinum-induced toxicity in patients with hepatoblastoma.
9	Polydatin	Cohortstudy	2B	Polidatina, as a natural extract from traditional Chinese medicine, may alleviate cisplatin-induced hearing loss.
10	Amifostine	Cohortstudy	2B	Amifostine didn't protect against cisplatin-associated ototoxicity at high doses combined with etoposide and bleomycin.
11	N-acetylcysteine and Dexamethasone	Cohortstudy	2B	N-acetylcysteine injections as an antioxidant agent appear to be an effective otoprotective strategy for preventing cisplatin-induced ototoxicity.
12	Genistein	Cohortstudy	2B	Genistein exhibited positive effects against ototoxicity due to its antioxidant effect.

Source: Research data (2023).

age. The first site where ototoxicity strikes is the outer hair cells for the basal and middle turns for the cochlea. Therefore, the side effects of hearing loss can interfere with tumor treatment, often necessitating a reduction in the dose, frequency, and duration of cisplatin therapy (Dias et al., 2015).

Audiological assessments, including otoscopy, pure-tone audiometry, tympanometry, otoacoustic emissions (OAE), and auditory brainstem response (ABR), are necessary before, during, and after treatment to measure and compare hearing. These examinations are conducted and analyzed by audiologists, professionals responsible for diagnosing disorders related to the auditory system (Brock et al., 2018; Freyer et al., 2017).

The use of small-molecule drugs and the application of enhanced delivery methods are the primary strategies to combat cisplatin-induced ototoxicity. Antioxidant therapy has become paramount in treatments, reducing hearing loss and its side effects (Li et al., 2022).

When administered before cisplatin, Amifostine functions as a cytoprotectant, rapidly converted by alkaline phosphatase into an active sulfhydryl compound called WR1065, which reduces thiols and eliminates free radicals. Evidence suggests that intravenous administration with multiple daily doses can potentiate its otoprotective effects (Fouladi et al., 2008; Gurney et al., 2014; Hyppolito et al., 2005).

According to Fouladi et al. (2008), Gurney et al. (2014), and Hyppolito et al. (2005), Amifostine provides a clinically significant benefit in reducing severe cisplatin-induced hearing loss in participants undergoing treatment for moderate-risk tumors. However, Katzenstein et al. (2009) and Marina et al. (2005) report that the use of Amifostine in conjunction with platinum therapy had no impact on

their outcomes, meaning it did not provide protection against its ototoxicity.

Sodium Thiosulfate is an antioxidant containing thiol, which is rapidly excreted by the kidneys after intravenous administration. The biochemical effects of this substance are relevant to its otoprotective potential, including the inactivation of oxygen free radicals and electrophilic platinum species. Furthermore, the administration for Sodium Thiosulfate is recommended 4 to 8 hours next to cisplatin, providing its otoprotective effect and reducing the cytotoxicity of the main substance (Freyer et al., 2017).

According to the research conducted by Dias et al. (2015), Ginkgo Biloba is a well-known extract with antioxidant effects that prevent the ototoxic effects to cisplatin. The extract scavenges oxygen free radicals, thereby blocking oxidative stress and apoptosis of hair cells. In the study conducted by these researchers, no side effects were observed after taking the Ginkgo Biloba tablet, confirming that this substance does not interfere with the antitumoral activity of cisplatin.

Lycopene is a substance administered through gavage that protects hair cells against apoptosis, as it possesses anti-inflammatory properties related for cisplatin. When combined with Ginkgo Biloba extract, they become more effective, as Ginkgo Biloba extract is more efficient in protecting high frequencies, while Lycopene is more effective in protecting low frequencies, resulting in a more comprehensive cellular protective effect (Esen et al., 2018).

Polidatin (PD) is a natural active compound extracted from a Chinese medicinal plant, which has antioxidant and anti-inflammatory effects. PD is a precursor to resveratrol, a substance with antioxidant capacity in the inner ear. Furthermore, compared to resveratrol, PD is more readily absorbed orally and exhibits better antioxidant effects. Therefore, according to research conducted, PD, when used in conjunction with cisplatin, results in a reduction in hearing loss (Li et al., 2022).

Dexamethasone is among the drugs used in inner ear diseases, reducing the production for reactive oxygen species. However, when used through transtympanic injections as an otoprotective substance for cisplatin, it leads to several side effects, such as hyperglycemia, peptic ulcer, hypertension, and osteoporosis, in addition to reducing the effectiveness of the chemotherapy agent (Sarafraz et al., 2018).

In the study conducted by Sarafraz et al. (2018), it is reported that transtympanic injections of N-acetylcysteine are safe and cost-effective antioxidant agents. Their use can reduce cisplatin-induced hearing impairment and eliminate the need for hearing aids or cochlear implants, especially in children. This will lead to an improvement in the quality of life for patients and the expected functioning of chemotherapy medications.

Genistein (GST), a phytochemical found in soy, is antioxidant, anti-inflammatory, and an inhibitor for epigenetic changes in preclinical models. When cisplatin was accompanied by GST in tumor treatments, there was a significant improvement in the hearing of evaluated patients, significantly reducing all toxicity parameters. Therefore, it was proven that GST can protect against cisplatin ototoxicity by increasing antioxidant enzyme levels (Tan et al., 2022).

Early interventions with otoprotectors and auditory monitoring are necessary, particularly due to the fact that children are the most susceptible to ototoxicity and, consequently, hearing loss. As a result, the learning and development period for social skills and communicative abilities such as language and speech will be preserved, thereby enhancing the quality of life (Santos et al., 2020).

5. Conclusion

The literature analysis identified 8 substances with the potential for otoprotective effects when used preventatively in patients undergoing cisplatin treatment. Their use can reduce the percentage of ototoxicity, mitigating treatment-induced hearing loss and eliminating the need for hearing aids or cochlear implants, especially in children.

Thus, these substances have the potential to enhance the quality for life for patients while still allowing chemotherapy medications to function as intended and provide excellent survival rates. Therefore, this research becomes relevant in supporting professional practice in preventing hearing loss in young people.

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