

OTOTOXIC EFFECTS OF ANTINEOPLASTIC DRUGS: A SYSTEMATIC REVIEW

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Abstract

Introduction: *When scientific evidence is reviewed, platinum-based chemotherapeutics are essential in cancer treatment at various levels and are the most referenced ototoxic drugs.*

Aim: *This study aims to give scientific data based on a PRISMA systematic literature review to standardize information on the ototoxic effects of antineoplastic medicines.*

Methods: *A combination based on the Medical Subject Heading Terms (MeSH) was utilized to choose studies. The databases Medline (Pubmed), LILACS, SciELO, SCOPUS, WEB OF SCIENCE, and BIREME were used without regard to language, period, or region. The quality of the papers was evaluated, and articles with a minimum score of 6 on the modified literature scale were included. The selected studies had descriptive, cohort, and cross-sectional designs connected to the research purpose.*

Results: *The results of this systematic review included three papers. The ototoxicity caused by cisplatin alone ranged from 45% to 83.3%, while that caused by carboplatin usage ranged from 16.6% to 75%. The cumulative dosages of these antineoplastic drugs, both alone and in combination, varied significantly. After therapy, there were noticeable changes in hearing, particularly at high frequencies.*

Conclusion: *Auditory alterations were observed following the administration of platinum-based antineoplastic medicines; nevertheless, there was significant variation in the frequency of ototoxicity and the cumulative dose of the drugs administered.*

Keywords: *antineoplastic drugs, cisplatin, exposure, hearing, ototoxicity*

INTRODUCTION

Cancer is a public health issue, and the International Cancer Research Agency (ICRA), which is linked with the World Health Organization (WHO), predicts that the incidence of cancer will rise by up to 63% in the next 20 years, affecting more than 29 million new individuals by 2040.^{1,2} Antineoplastic chemotherapy is one of the systemic cancer treatments that aim to treat malignant neoplasms and consists of the use of chemical substances alone or in combination, standing out as the preferred treatment for both the hematopoietic system and solid tumors, which may show regional or distant metastases. Antineoplastic or chemotherapeutic medications interfere with cell survival, proliferation, and migration mechanisms, yet they act non-specific, causing injury to both malignant and benign cells. Chemotherapy, like other cancer treatment modalities, can cause side effects for patients, including ototoxicity.^{3,4}

Ototoxicity is described as a transitory or permanent disturbance of auditory and vestibular function caused by therapeutic substances, appearing as hearing loss, tinnitus, or vertigo. It is associated with a subset of antineoplastic therapies in cancer patients, including platinum-based chemotherapy, radiation, or surgery involving the ear and vestibulocochlear nerve, as well as supportive care agents such as aminoglycoside antibiotics and loop diuretics, which may also contribute to ototoxicity.⁵⁻⁸

Platinum-based chemotherapy drugs are the most frequently cited ototoxic agents when analyzing scientific evidence, with the outer hair cells of the cochlea being the most affected structures,⁸ resulting in hearing loss and impaired social communication.⁹ Vincristine, doxorubicin, gemcitabine, cyclophosphamide, farmorubicin, oxaliplatin, carboplatin, and cisplatin, are examples of ototoxic antineoplastic medications that are commonly used in combination with two to four other drugs.¹⁰⁻¹² Cisplatin is the most often utilized of these medications, and its effects on the cochlea might include sensorineural, bilateral, symmetrical, and irreversible hearing loss.³ The rate of hearing loss in chemotherapy patients varies widely in the literature due to factors such as frequency of assessment, patient age, medication dosage, drug administration method, and criteria used to detect hearing loss.¹³ Other factors that can directly influence chemotherapy-induced ototoxicity include tissue susceptibility to the drug, drug accumulation in the organ, inhibition of normal physiological functions, direct toxic effects on sensory terminal organs, ototoxic synergism, the use of other concomitant ototoxic drugs, and radiation treatment.⁸ Hearing loss caused by antineoplastic therapy with ototoxic medicines affects patients of all ages. Hence these patients must be monitored with audiological examinations before, during, and after treatment.¹⁰

Based on the previous, the current study aims to give scientific data based on a systematic review of the literature (PRISMA) on the ototoxic effects of antineoplastic medications, to understand the effects and dose required for antineoplastic drug ototoxicity.

Methods

Protocol and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) criteria.¹⁴ The Population, Intervention, Comparison, Outcome, and Study (PICOS) technique was used to organize and organize the research. The population of interest or health problem (patients), the intervention is antineoplastic agents, the comparison is drugs, the outcome is ototoxicity, and the study refers to the types of studies included, which were: a descriptive study, cross-sectional study, observational study, case reports, case-control studies, controlled clinical trials, and cohort studies.

Search Strategy

The search was conducted in multiple electronic databases, including Medline, lilacs, scopus, web of science, bireme, and scielo. Subsequently, the identified keywords were used to search the same databases for relevant studies. The search was conducted without restriction of language, period, and location. The manual bibliographic search of identified studies was also done in the last step of the literature search.

At first, the following Boolean operators and combination of terms were proposed for the searches: (ototoxicity) AND (antineoplastic) AND (adults) AND (Childhood) AND (adolescent) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR singleblind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial” [tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh: noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]).

Table 1. Classification of references obtained from Pubmed, Scielo, Lilacs, Web of Science, Bireme, and Scopus Databases

Database	Result	Excluded	Reason	Selected
Pubmed	7	4	Excluded by title (2); excluded by abstracts (1); excluded by repetition (1).	3
Lilacs	0	0	-	0
Scielo	0	0	-	0
Web of Science	0	0	-	0
Bireme	0	0	-	0
Scopus	0	0	-	0

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were the designs of the studies with potential for selection: cross-sectional, case-control, cohort, case reports, intervention studies, and controlled clinical trials. Studies were included without restriction on language, period, and location. The exclusion criteria of the studies are articles that are Studies published in the form of letters to the editor, guidelines, literature reviews, narrative reviews, systematic reviews, meta-analyses, and abstracts were excluded. Studies that did not describe the specificities chosen by the researchers as an objective for this research or that were unclear were also excluded. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria.

Risk of Bias

The quality of the methods used in the included studies was independently assessed by the reviewers, according to the PRISMA recommendation.¹⁴ The assessment prioritized the clear description of the information. At this point, the review was carried out blindly, masking the names of the authors and journals, avoiding any potential bias and conflict of interest.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following parameters were taken into account: publication year, type of study, aims and objectives of the study, study findings and conclusion, frequency of ototoxicity, cumulative doses, age at diagnosis, mean time between the last dose of cisplatin and the hearing assessment, time of audiological monitoring. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Results

Initially, 7 publications were chosen with the possibility of being included in this study, with 6 surviving the following exclusion by repetition. The titles were examined, and 2 publications were eliminated for failing to meet the inclusion criteria suggested by these writers, leaving 4 articles. As a result, 1 item was rejected because the abstract left 3 publications to be read in full, all of which were included in the research (Figure 1). Table 1 presents an overview of the main findings of the selected studies.

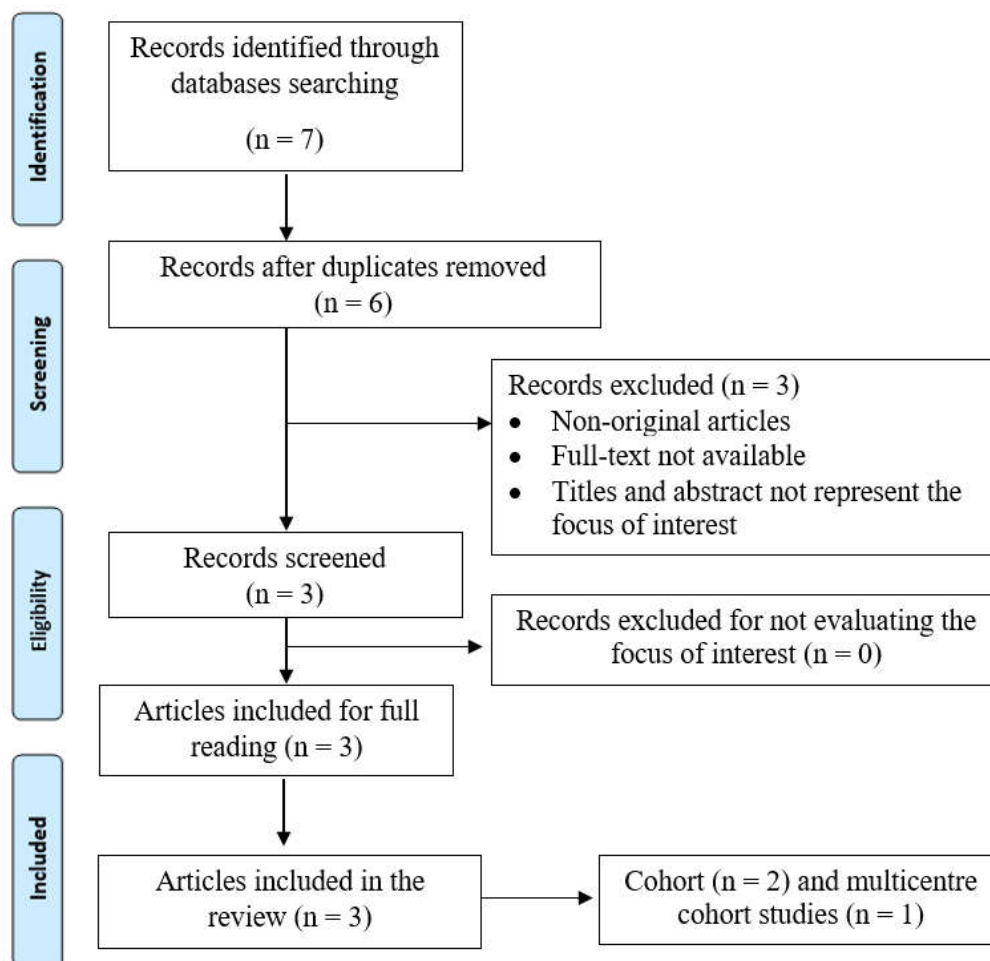


Figure 1. PRISMA Flow diagram

Table 2. Summary of selected articles

Author / year / place	Objective	n	Tests	Hearing loss classification	Results	Conclusion
Einarsson et al., ¹⁵ 2010, Sweden	Look into long-term hearing impairment in people with platinum-based chemotherapy as children or adolescents.	15	PTA (0.125, 0.25, 0.5, 1, 2, 3, 4, 6 e 8 kHz) Tympanometry Speech audiometry Measurement of the handicap level (Hearing measurement scale (HMS))	Brock et al. (1991)	The findings reveal that hearing loss increased following the termination of treatment in participants with ototoxicity, particularly lower frequencies. Hearing thresholds up to 55 dB HL deteriorated the most for frequencies above 2 kHz.	This study concluded that children and adolescents receiving platinum-based chemotherapy should have regular follow-up audiometric examinations for many years after treatment has ended. Furthermore, self-reported hearing impairment tests should be performed during and after treatment.
Clemens et al., ¹⁶ 2016, Netherlands	To assess the frequency and predictors of ototoxicity in a large multicenter cohort of child cancer survivors who received platinum but not cranial irradiation as treatment.	451	PTA (0.25, 0.5, 1, 2, 4 e 8 kHz)	Münster (Schmidt et al., 2007)	Ototoxicity was reported in 42% of individuals treated with cisplatin, 17% treated with carboplatin, and 75% treated with both medications. Ototoxicity was related to the lowest age at diagnosis, the largest cumulative dose of cisplatin, and concomitant furosemide treatment.	Treatment with a higher total cumulative dose of cisplatin, younger age of diagnosis, and concurrent use of furosemide are all related to an increased risk of ototoxicity in children treated with platinum.
Clemens et al., ¹⁷ 2017, Netherlands	To investigate the reversibility of ototoxicity following treatment discontinuation in a group of participants treated with platinum who had hearing loss at the end of cancer therapy.	168	PTA (0.25, 0.5, 1, 2, 4 e 8 kHz): age ≥5 years	Münster (Schmidt et al., 2007)	After completing chemotherapy, 61 (36.3%) of the 168 patients experienced hearing loss, and none of these subjects improved in hearing ability until 28.8 years later.	Ototoxicity following platinum treatment may be irreversible, necessitating monitoring and long-term clinical hearing care.

Notes: PTA, Pure tone audiometry; VRA, Visual reinforcement audiometry.

Individuals were treated with cisplatin and carboplatin, alone or in combination, without cranial radiation in all included studies. Cisplatin cumulative doses ranged from 45 to 950 mg/m²; carboplatin cumulative doses ranged from 104 - 9436 mg/m², and when used in combination, cisplatin cumulative doses ranged from 80 to 570 mg/m² and carboplatin cumulative doses ranged from 400 to 6043 mg/m² (Table 2).

Table 3. Cumulative doses of cisplatin and carboplatin and medications used concomitantly with chemotherapy

Authors (year)	Cumulative dose			Concomitant medications
	Cisplatin (n)	Carboplatin (n)	Cisplatin + Carboplatin (n)	
Einarsson et al. ¹⁵ (2010)	NHG: varied from 180 to 690 mg/m ² (n=5) HLG: ranged from 360 to 500 mg/m ² (n = 8)	-	HLG: cisplatin = 320 mg/m ² , carboplatin = 3000 mg/m ² (n = 1)	NCI
Clemens et al. ¹⁶ (2016)	Ranged from 45 to 950 mg/m ² (n = 276)	Ranged from 104 to 9436 mg/m ² (n = 112)	Cisplatin = ranged from 80 to 570 mg/m ² , carboplatin = ranged from 400 to 6043 mg/m ² (n = 63)	Vancomycin, gentamicin, tobramycin, furosemide (n = 285)
Clemens et al. ¹⁷ (2017)	Ranged from 180 to 900 mg/m ² (n = 46)	Ranged from 1288 to 3230 mg/m ² (n = 2)	Cisplatin = ranged from 300 to 570 mg/m ² , carboplatin = ranged from 992 to 3938 mg/m ² (n = 13)	NI

Notes: N, sample number; NHG, normal hearing group; HLG, hearing loss group; NI, no information; mg/m²: milligram per square meter.

Discussion

All trials included in this study reported ototoxicity related to the use of antineoplastic drugs in treating patients, with cisplatin causing the highest ototoxicity, ranging from 45%¹⁶ to 83.3%¹⁵ when administered alone. These figures are more remarkable than previous research, which revealed that the incidence of cisplatin-caused ototoxicity in children ranged from 22% to 70%.¹⁸⁻²⁰ A recent study of the hearing of 200 children with cancer found that chemotherapy with cisplatin caused hearing loss in 41.9% of the right ears and 47.3% of the left ears, with an 11.7 times greater risk of hearing loss in the right ear and a 17.6 times greater risk in the left ear compared to patients who were not treated with cisplatin.¹³

Carboplatin ototoxicity was discovered in a study of 60 children with retinoblastoma who were given carboplatin in combination with systemic vincristine. Twelve children (20%) had ototoxicity at some time after the initiation of treatment; ototoxicity was reversible in two of them but irreversible in ten (17%).^{21,22} However, no hearing damage was identified in another study in which carboplatin was not taken with other ototoxic medications. Carboplatin has anticancer activity comparable to cisplatin but with less ototoxicity; however, it may be associated with sensorineural hearing loss.²² The cumulative dose of cisplatin larger than 400 mg/m² stands out as having the highest probability of developing platinum-induced hearing loss.²³ However, dosages above 200 mg/m² have already been found to be ototoxic. Carboplatin does not appear to be a substantial risk factor for ototoxicity at conventional doses, even in individuals who have previously received cisplatin.¹⁰

Cisplatin ototoxicity causes bilateral and symmetrical sensorineural hearing loss, more significant at high frequencies (4 - 8 kHz), and tinnitus.²⁴⁻²⁶ In a study of cancer survivors treated with cisplatin and combinations, participation occurred from 1 kHz forward, with a significant rise from 6 kHz onward. The degree of hearing loss is dosage dependent,^{25,27} and is related to the frequency and technique of evaluation.²⁷ According to the findings of the most recent study¹⁷, hearing loss caused by platinum-based antineoplastic agents is irreversible in the long run because none of the subjects who developed hearing loss after treatment with antineoplastic agents showed progressive improvement in hearing function up to 28.8 years after treatment was stopped.

One research in this systematic review found that being diagnosed younger is related to a higher risk of ototoxicity. Li et al.²³ discovered that children under the age of five at the time of therapy were 21 times more likely than individuals aged 15-20 years to develop moderately severe high-frequency hearing loss. As a result, children receiving antineoplastic therapy should routinely undergo long-term audiological monitoring.²¹

Another component described in scientific research implies that genetics may be a part of ototoxicity; however, the findings are still conflicting and preliminary. Individuals at elevated risk of hearing loss can be identified by screening for genetic predisposition to cisplatin ototoxicity. Pharmacogenetic studies that look into genetic variants have yielded conflicting outcomes, which could be attributed to patient population diversity and differential therapies.^{18,28,29}

One study¹⁵ employed Brock's classification³⁰ to analyze hearing loss, while the other two^{16,17} used Münster's classification system. It is vital to remember that the different classes and their sensitivity differences can impact the computed frequency. For the classification of high-frequency ototoxicity, Brock's classification is preferable, whereas Münster's classification has higher sensitivity and specificity.¹⁶ According to Clemens et al.,¹⁶ the frequency of ototoxicity was 42% when using Münster's classification system, while when using Brock's classification criteria, the incidence of ototoxicity was 29%.¹⁵

High-frequency audiometry is regarded as a significant technique for identifying and monitoring hearing loss and detecting cisplatin ototoxicity, with critical frequencies of 12 kHz and 14 kHz.^{5,30,31} All of this scientific evidence analysis emphasizes the significance of regular audiological monitoring during and after platinum-based treatment, and it is also encouraged to perform self-reported hearing impairment during and after chemotherapy.¹⁵

Conclusion

The research chosen for this systematic review converged in their findings, demonstrating the influence of hearing abnormalities after administering platinum-based antineoplastic medicines, with cisplatin causing the most obvious ototoxicity, which can be permanent in many cases. There was significant variation in the frequency of antineoplastic medication ototoxicity and the dose necessary to cause these effects. The incidence of ototoxicity produced by cisplatin ranged from 45% to 83.3% when taken alone and from 16.6% to 75% when combined with carboplatin. Cisplatin cumulative doses ranged from 180 to 900 mg/m² in participants with hearing loss when administered alone and from 300 to 570 mg/m² when administered in combination with carboplatin, with the highest total cumulative dose of cisplatin being related to ototoxicity.

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