Literature Review

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Ototoxic medications used in treating childhood cancer: a systematic review

Medicações ototóxicas utilizadas no tratamento oncológico pediátrico: uma revisão sistemática

Érica Alessandra Caldas[1], Rosane da Silva Dias[1]

ABSTRACT

Objective: The aim of the present study was to perform a literature review on ototoxic medications used for the treatment of childhood cancer and determine the harm caused by such drugs to the auditory system as well as the methods used to identify this harm. **Search strategy:** The electronic databases of the Virtual Health Library (Brazilian Health Ministry), PubMed, Brazilian Digital Library of Theses and Dissertations, and Databank of Theses and Dissertations of the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES [Brazilian Coordination for the Advancement of Higher Education Personnel]) were searched for relevant national and international papers involving the pediatric population with a history of treatment for cancer published between 2007 and 2016. **Selection criteria:** Observational studies published in Portuguese, English or Spanish with abstracts available and that informed the method for assessing hearing damage. **Results:** The final sample consisted of 12 articles. Pure-tone threshold audiometry was the used in ten (84.61%) of the studies and otoacoustic emissions were investigated in 46.15%. All studies involved patients who made use of cisplatin or platinum derivatives. Only one of the studies included in the present review reported no changes in hearing in the population studied. **Conclusion:** Platinum derivatives play an important role in the treatment of cancer and are the most widely cited ototoxic agents in studies. The cochlea is the most affected site, specifically the outer hair cells. The most widely used methods for assessing altered hearing are pure-tone threshold audiometry and otoacoustic emissions.

Keywords: Neoplasms; Toxicity; Child; Hearing loss; Drug therapy

RESUMO

Objetivo: Fazer um levantamento dos medicamentos ototóxicos utilizados no tratamento do câncer pediátrico, apontar os danos das drogas para o sistema auditivo e os métodos utilizados na identificação destes danos nessa população. **Estratégia de pesquisa:** Foram utilizados periódicos nacionais e internacionais pertinentes ao assunto, acessados eletronicamente em bases de dados da Biblioteca Virtual em Saúde - MS, PubMed, Biblioteca Digital Brasileira de Teses e Dissertações, que envolvessem a população pediátrica com histórico de tratamento oncológico, publicados entre 2007 e 2016, e no Banco de Teses e Dissertações da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior. **Critérios de seleção:** Foram selecionados estudos que contemplassem os seguintes critérios: estudos observacionais nas línguas portuguesa, inglesa ou espanhola e resumos disponíveis que informassem o método de avaliação do dano auditivo. **Resultados:** A amostra final resultou em 12 artigos. Destes, a audiometria tonal limiar foi o método de avaliação auditiva mais utilizado, estando presente em 10 (84,61%) dos estudos, seguido das emissões otoacústicas (46,15%). Todos os estudos foram desenvolvidos com pacientes que fizeram uso de cisplatina ou derivados da platina e, quanto ao dano auditivo, apenas 1 dos estudos incluídos não relatou presença de alteração na população estudada. **Conclusão:** Os derivados da platina expressam papel importante no tratamento do câncer em diversos níveis e são os agentes ototóxicos mais citados em pesquisas. A cóclea é o local mais afetado, mais especificamente as células ciliadas externas. Os métodos de investigação da alteração auditiva mais utilizados são a audiometria tonal limiar e as emissões otoacústicas.

Palavras-chave: Neoplasias; Toxicidade; Criança; Perda auditiva; Tratamento farmacológico

Study carried out at the Departamento de Fonoaudiologia, Universidade Ceuma – UNICEUMA - São Luís (MA), Brasil.
[1]Universidade Ceuma - UNICEUMA – São Luís (MA), Brasil.
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Corresponding author: Érica Alessandra Caldas. E-mail: ericaacaldas@hotmail.com
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INTRODUCTION

Children account for 50% of the population in developing countries, where childhood cancer accounts for 3 to 10% of all forms of cancer. In contrast, the proportion is much lower in developed countries (around 1%)[1].

Besides cancer of the head and neck region, other types can also lead to hearing loss due to the effects of ototoxic mediations used for the treatment of such cases. According to the American Speech-Language-Hearing Association, there are currently more than 200 ototoxic medications, including certain aminoglycosides and drugs such as cisplatin and carboplatin[2].

Different classes of medications are used in the treatment of cancer, such as aminoglycosides, anti-tumor agents, antibiotics, non-steroidal anti-inflammatory drugs, diuretics and anti-hypertensive agents, some of which are considered ototoxic[3]. Medications derived from platinum are the most devastating and have the following side effects when used at cumulative doses higher than 360 mg/m^2: nausea, vomiting, nephrotoxicity, myeolsuppression and ototoxicity[4]. Hearing damage is irreversible and, when treatment is continued, the loss includes low frequencies due to the progression of the damage to the apical portion of the cochlea and inner hair cells, which can lead to a high degree of hearing impairment, including at speech frequencies[5,6].

Altered hearing due to having undergone cancer treatment with ototoxic medication affects patients of different ages and it is therefore important for these patients to be submitted to hearing tests before, during and after treatment. Knowledge on the ototoxic medications used during the treatment of cancer as well as the type of hearing assessments administered to these patients is very important. Monitoring individuals in treatment with ototoxic medications enables the early detection of hearing loss and, whenever possible, establishing a way for hearing to be preserved or minimizing the impact that hearing loss can exert on quality of life[7].

OBJECTIVES

The aim of the present review of the literature was to answer the following questions: a) what ototoxic medications used for the treatment of cancer in the pediatric population are the most widely studied in the literature? b) what harm do these drugs cause to the auditory system? c) what are the most widely employed methods for the identification of auditory harm caused by these drugs?

The results of this review could serve as a resource for health professionals by improving their understanding of ototoxicity and the hearing assessment methods used during auditory monitoring programs.

SEARCH STRATEGY

A systematic review of the literature was conducted following the methodological guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA statement). The electronic databases of the Virtual Health Library (Brazilian Health Ministry), PubMed (US National Library of Medicine), Brazilian Digital Library of Theses and Dissertations, and Databank of Theses and Dissertations of the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES [Brazilian Coordination for the Advancement of Higher Education Personnel]) were searched for relevant national and international papers.

The following search terms were employed based on the Health Sciences Descriptors: "toxicity", "hearing loss", "anti-tumor agents", "anti-tumor antibiotics", "oncology", "antimetabolites" and "child". The Boolean operator "AND" was used to combine search terms: "toxicity" AND "hearing loss"; "hearing loss" AND "anti-tumor agents"; "hearing loss" AND "anti-tumor antibiotics", "hearing loss" AND "oncology" and "hearing loss" AND "antimetabolites". As a bias control strategy, authors were contacted by email to determine the existence of studies that had not yet been published. Once the selection was completed, the bibliographic references were searched in an attempt to find other studies not identified in the databanks.

SELECTION CRITERIA

The articles were selected by two independent reviewers. The titles and abstracts were analyzed for the determination of the following eligibility criteria: observational studies that involved the pediatric population with a history of oncological treatment published in Portuguese, English or Spanish between 2007 and 2016 with an available abstract and that offered information on the auditory damage assessment method. When the determination of eligibility was not possible based on the title and abstract, the full text was submitted to analysis.

Studies for which access to the complete text was not possible, duplicate studies, laboratory studies, opinion/authority articles, case series, case reports and reviews were excluded.

DATA ANALYSIS

The data are presented in the form of a table in the results section to assist in the visualization of the main findings of the selected articles as well as information referring to the authors, year of publication, type of study, sample size, description of the sample, medication used, auditory function assessment method and results of the hearing assessment. The evaluation of systematic errors that could characterize bias in the selected studies was performed using the criteria established in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE statement)[8], which consists of 22 items addressing information that should be present in the title, abstract, introduction, methods, results and discussion sections of the articles. The STROBE initiative was developed by researchers in the fields of epidemiology, statistics and the scientific method as well as editors of scientific journals, the aim of which is to disseminate principles that should guide

the description of observational studies. The appraisal was performed qualitatively, with the classification of "+" when a criterion was present, "-" when a criterion was absent and "?" for incomplete data.

RESULTS

A total of 1365 papers were found using the search strategy described above. After the removal of duplicates, the reading of abstracts and the application of the eligibility criteria, the final sample was composed of 12 articles (Figure 1).

Table 1 displays the characteristics of the studies, such as authors, year of publication, type of study, sample size and age range of the sample. All studies had an observational design and were published between 2007[9,10] and 2016[11].

The sample size differed among the studies, ranging from 10 to 406 participants. The periods of chemotherapeutic treatment and the hearing exam were analyzed. Most exams were performed after the completion of treatment (57.14%)[9-14]. Three studies (25.0%)[9,11,15] included children up to nine years of age, whereas the others included children and adolescents.

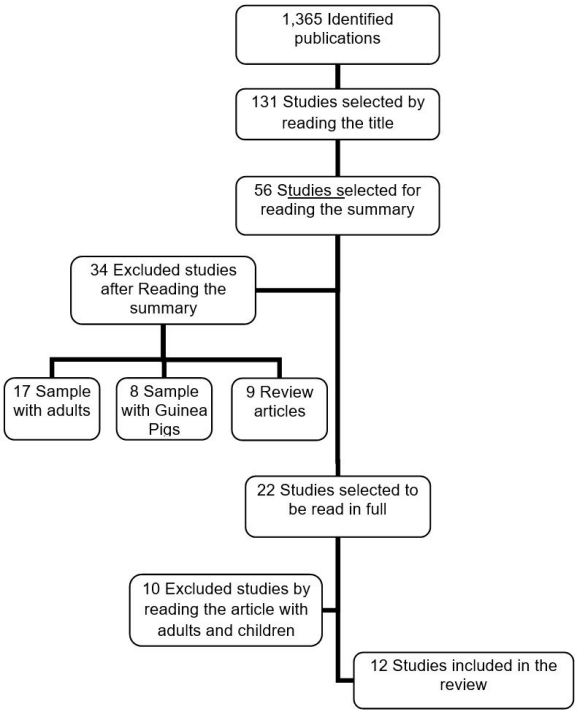

Figure 1. Flowchart of article selection process

Table 1. Characteristics of articles included in present review

AUTHOR/YEAR	TYPE OF STUDY	N	PERIOD	
			Treatment period	Exam period
Amorim et al., 2007[9]	Observational	18	9 months – 9 years	After end of treatment
Coradini et al., 2007[10]	Observational	23	Mean: 12.3 years	After end of treatment
Almeida et al., 2008[14]	Observational	10	6 months – 13 years	After end of treatment
Al-Khatib et al., 2010[16]	Observational	31	1 to 17 years	During treatment
Paulino et al., 2010[17]	Observational	44	3 years – 12 years	During treatment
Al-Noury et al., 2011[12]	Observational	26	7 – 15	After end of treatment
Weissenstein et al., 2012[18]	Observational	27	Mean: 9,84	During treatment
Qaddoumi et al., 2012[15]	Observational	60	Mean: 8.6 years	During treatment
Yancey et al., 2012[19]	Observational	102	< 18 years	During treatment
Caldas et al., 2015[20]	Observational	12	2 – 12 years	During treatment
Brinkman et al., 2015[13]	Observational	406	Mean: 8.6 years	After end of treatment
Liberman et al., 2016[11]	Observational	200	Mean: 6 years	After end of treatment

Pure-tone threshold audiometry was employed in 10 (84.61%) of the studies[10-19]. Transient otoacoustic emissions[9,10,12,16,20] and distortion product otoacoustic emissions[10,12,16,18,20] were investigated in 46.15% of the studies. The four studies[10-13] that employed tympanometry only used this assessment method to exclude patients with a middle ear condition, which is not a characteristic of ototoxicity.

With regard to the treatment protocol, the studies were developed with patients who made use of cisplatin or platinum derivatives. Two studies were conducted with patients who received platinum derivatives[9,12], five were conducted with patients who received platinum derivatives and radiotherapy[11,13,16-18], three were conducted with patients who received platinum derivatives and aminoglycoside antibiotics[10,19,20], one was conducted with patients who received platinum derivatives and a mitotic inhibitor[14] and one study was conducted with patients who received platinum derivatives, a mitotic inhibitor and radiotherapy[15]. Only one study[9] did not report the occurrence of hearing damage in the population studied. Table 2 lists the treatment protocols, hearing assessment methods and hearing damage found in the studies.

The STROBE criteria were employed for the determination of systematic errors that characterized biases in the studies. None of the studies fulfilled the criteria for items 9 or 21,

which respectively refer to the measures adopted to avoid potential sources of bias and the external validation of the results in the discussion section. Regarding the evaluation procedures for the outcome, the studies employed validated instruments for measuring this variable, but none reported the blinding of the evaluator. In the data analysis, none of the articles reported confounding variables or stratification with the use of multivariate regression. None of the studies described how the sample size was determined. Among the 12 articles included in this review, only one[11] fulfilled 11 of the 22 items and three[13,15,19] fulfilled 10 of the items. These findings are listed in Table 3.

Table 2. Description of evaluation methods, medications and hearing damage found in studies selected for review

	HEARING ASSESSMENT METHOD					PROTOCOL/ MEDICATION USED	HEARING DAMAGE		
	PTTA	TOAE	DPOAE	PTTA High Freq.	Tymp		HL	TOAE absent	DPOAE absent
Amorim et al., 2007[9]		•				Carboplatin			
Coradini et al., 2007[10]	•	•	•		•	Cisplatin and aminoglycoside antibiotic	•	•	•
Oliveira et al., 2008[14]	•			•		Cisplatin associated to vincristine and actinomicina D	•		
Al-Khatib et al., 2010[16]	•	•	•			Cisplatin and/or carboplatin and radiotherapy	•		
Paulino et al., 2010[17]	•					Cisplatin and radiotherapy	•		
Al-Noury et al., 2011[12]	•	•	•		•	Cisplatin	•	•	•
Weissenstein et al., 2012[18]	•		•			Cisplatin and radiotherapy	•		•
Qaddoumi et al., 2012[15]	•					Carboplatin, vincristine and radiotherapy	•		
Yancey et al., 2012[19]	•					Cisplatin, carboplatin and aminoglycoside antibiotic	•		
Caldas et al., 2015[20]		•	•			Cisplatin, carboplatin and aminoglycoside antibiotic		•	•
Brinkman et al., 2015[13]	•				•	Cisplatin, carboplatin and radiotherapy	•		
Liberman et al., 2016[11]	•				•	Platinum derivatives, cisplatina and radiotherapy	•		
	•				•		•		

Legend: PTTA = Pure-tone Threshold Audiometry; TOAE = Transient Otoacoustic Emissions; DPOAE = Distortion Product Otoacoustic Emissions; Tymp = Tympanometria; HL = Hearing Loss; Freq = frequency

Table 3. Systematic appraisal of errors for characterization of bias following criteria of Strengthening the Reporting of Observational Studies in Epidemiology

Author/year of publication	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Amorim et al., 2007[9]	-	+	+	-	?	+	+	+	-	+	?	?	-	-	?	?	-	-	-	-	-	-
Coradini et al., 2007[10]	-	+	+	-	+	?	?	?	-	-	+	?	?	+	?	-	-	+	-	?	-	-
Almeida et al., 2008[14]	?	+	+	-	?	?	-	-	-	-	-	-	?	-	-	?	-	+	-	?	-	-
Al-Khatib et al., 2010[16]	?	+	+	+	+	+	-	?	-	-	-	-	?	+	+	-	-	+	?	?	-	-
Paulino et al., 2010[17]	-	?	+	-	?	+	+	+	-	-	+	?	-	-	+	?	-	+	?	?	-	-
Al-Noury et al., 2011[12]	-	+	+	-	+	+	?	?	-	-	-	-	+	+	+	-	-	+	+	?	-	-
Weissenstein et al., 2012[18]	?	?	+	?	+	?	?	+	-	-	+	?	-	-	+	?	-	+	?	?	-	-
Qaddoumi et al., 2012[15]	?	+	?	+	+	+	+	+	-	-	+	?	+	+	+	?	-	+	-	?	-	-
Yancey et al., 2012[19]	+	?	+	+	+	?	?	+	-	-	+	?	+	-	+	?	?	+	+	?	-	+
Caldas et al., 2015[20]	?	?	+	-	+	+	?	+	-	-	+	-	?	?	+	?	-	+	?	?	-	+
Brinkman et al., 2015[13]	?	+	+	+	+	+	-	+	-	-	+	?	?	-	+	?	-	+	-	?	-	+
Liberman et al., 2016[11]	?	?	+	?	+	+	?	+	-	-	+	?	+	+	+	+	?	+	?	+	-	-

Legend: "+" data are presented, "-" data are missing and "?" data are incomplete 1. Title and abstract; 2. Background and rationale; 3. Objectives; 4. Study design; 5. Setting; 6. Methods/Participants; 7. Variables; 8. Data sources/measurement; 9. Bias; 10. Study size; 11. Quantitative variables; 12. Statistical methods; 13. Results/Participants; 14. Descriptive data; 15. Outcome; 16. Main results; 17. Other analyses; 18. Discussion/Results; 19. Discussion of Limitations; 20. Interpretation of results; 21. Generalisability of results; 22. Funding

DISCUSSION

Ototoxic medications used for the treatment of cancer and the harm caused to the auditory system of the pediatric population have been highlighted in the scientific community, as knowledge of these issues and the identification of adequate auditory monitoring tests enable changing the medicinal regimen, when necessary, and, in many cases, minimizing the harm, which assists in providing a better quality of life for these patients.

Current data on the ototoxicity of cisplatin are clear, but contradictions remain with regard to carboplatin. In 2006, a study involving 25 individuals with retinoblastoma who underwent treatment with carboplatin (median dose: 2240 mg/m^2) found no effect on hearing when the drug was not used in combination with other ototoxic drugs[21]. However, authors report that carboplatin has similar anti-tumor activity to cisplatin with less severe ototoxicity, but may nonetheless be related to neurosensory hearing loss[15]. The same authors report that age at the time of the onset of treatment is significantly associated with hearing loss, with younger patients more susceptible to this outcome.

Although some studies have analyzed the effects of cisplatin and carboplatin separately, the use of combinations of the two drugs hinders a precise analysis and comparisons between studies. Aminoglycosidic antibiotics can also cause ototoxicity, which appears as ringing in the ears, high frequency hearing impairment and vestibular damage. This condition can be irreversible, especially if the use of the medication is constant and if there is negligence regarding the treatment time and dose. The medications with the greatest ototoxicity are neomycin, kanamycin, streptomycin and amikacin. These drugs have the amine group, which has anti-infection action, but has toxic effects on the kidneys and inner ear[22]. The use of these drugs can affect the hair cells of the organ of Corti and the two branches of the 8th cranial pair. Nystagmus is evident in these patients and is due to cochlear damage, causing nausea, vomiting and vertigo[23].

Amikacin has predominantly cochlear toxicity[24]. A dose of 400 mg/Kg/days for 12 days causes the complete destruction of the outer hair cells and partial injury to the inner hair cells, referring to the first and second spirals of the cochlea to be affected first[25].

Another combined form of treatment was a plastin derivative and radiotherapy[11,13,15-18]. While some authors report that the radiation had no significant impact[11,16], the authors of one study report that 13% of the sample that received radiation exhibited ototoxicity[17]. Qaddoumi et al.[15] described sex, race, age, period of the onset of treatment, cumulative dose of carboplatin and the use of radiotherapy as risk factors for hearing loss. Studies on hearing impairment as a consequence of radiotherapy have mainly involved tumors of the head and neck. The main hearing alterations caused by radiotherapy are reported to be necrosis of the outer ear canal, osteoradionecrosis of the temporal bone, otitis media, various degrees of conductive hearing impairments, otalgia, ringing in the ears and degeneration of the hair cells, which can occur up to two years after the end of treatment[26]. Moreover, stiffening of the ossicular chain and layers of the tympanic membrane may also occur[27].

The articles in the present review revealed evidence of hearing impairment during treatment as well as changes that occurred after the conclusion of treatment[18,28]. This underscores the importance of annual follow-up evaluations.

Pure-tone threshold audiometry is still considered the gold standard test for the detection of changes in the auditory system. However, this test is often unviable for children, for whom the investigation of otoacoustic emissions is more favorable. This is an objective test that is easy to administer and quite useful in the differential diagnosis of neurosensory hearing loss and the monitoring of the health of the outer hair cells in patients exposed to ototoxic drugs. Otoacoustic emissions have greater specificity and sensitivity than other methods in the evaluation of hearing function; when used for the monitoring of patients taking ototoxic drugs and for the study of cochlear function, otoacoustic emissions demonstrate altered responses prior to alterations being registered at the hearing threshold[7,29].

Distortion product otoacoustic emissions are more precise than transient otoacoustic emissions for the monitoring of specific portions of the outer hair cells, since small injured regions are represented as abnormal responses[12,24]. For sensory hearing loss that affects the outer hair cells, a correlation can be made between hearing thresholds determined by pure-tone audiometry and the results of otoacoustic emissions. Responses recorded for transient otoacoustic emissions suggest hearing thresholds lower than 30 dB[30].

The degenerative process of the organ of Corti caused by ototoxic drugs can be avoided by adequate monitoring[14]. According to the guidelines proposed by the American Speech-Language-Hearing Association, auditory assessments should occur prior to the onset of medication therapy or 24 hours after the administration of the first dose of chemotherapeutic agents and within 72 hours when treatment is with antibiotics. If the results of the exams demonstrate a reduction in or absence of a response at a frequency that previously had a positive response, a complete auditory evaluation should be performed and the treatment protocol should be reevaluated.

Besides monitoring during oncological treatment, the pediatric population that has been treated for cancer should undergo periodic evaluations for the detection of late-onset complications[31]. When the avoidance of hearing loss is not possible, the family and patient should be counseled with regard to the possible difficulties this change may signify. Family members and educators need to receive the necessary orientation in a timely fashion to ensure a better quality of life for the child, including information on the use of hearing aids, if needed.

CONCLUSION

Platinum derivatives play an important role in the treatment of cancer and are the most widely cited ototoxic agents in studies. Regarding the effect of these drugs on the auditory system, the cochlea is the most affected site, specifically the outer hair cells. The most widely used methods for assessing altered hearing are pure-tone threshold audiometry and otoacoustic emissions.

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