

Review articles

Effects of chemotherapy on the auditory system of children with cancer: a systematic literature review

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ABSTRACT

Purpose: to identify and analyze the effects of chemotherapy on the auditory system of children and/or adolescents with cancer treated with cisplatin and carboplatin, assessed through standardized audiological procedures.

Methods: studies in Brazilian Portuguese and in English were searched for, as available in the databases Science Direct, PubMed, LILACS, BIREME, Embase, SciELO, Web of Science and Cochrane. The descriptors were: Hearing Loss, Audiology, Child Cancer, Chemotherapy, and Child. Articles with levels 1 and 2 of scientific evidence, published in the last 20 years (1997 to 2017), were considered, of which the audiological results were analyzed, as well as the prevalence of hearing loss in children with cancer undergoing chemotherapy.

Results: 3,625 articles were found, of which only 23 were selected for analysis in the present review. Studies have shown a high incidence of sensorineural hearing loss and decrease or even loss of otoacoustic emissions in children and adolescents with cancer, even after the first dose of chemotherapy drugs, with high frequencies being the most affected.

Conclusion: there is evidence that both carboplatin and especially cisplatin from the first doses may impair the hearing of children and adolescents, mainly affecting the cochlear function, thus, the importance of long-term audiological monitoring.

Keywords: Hearing Loss; Cancer; Child; Chemotherapy; Audiology

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INTRODUCTION

Child and adolescent cancer (involving children and adolescents between zero and 19 years old) is a disease with characteristics of its own, especially concerning histopathology and clinical behavior. In general, child and adolescent cancer presents short latency periods, grows faster, and is more aggressive. However, it responds better to treatment and has good prognosis¹.

Chemotherapy is a mode of systemically treating the oncologic patient, more recent than surgery and radiotherapy, and it consists in administrating chemical substances, either alone or in combination, with the objective of destroying malignant neoplastic cells, while preserving the normal ones².

The antineoplastic therapy includes the use of various drugs, among which are the alkylating agents, which are chemical substances capable of replacing a hydrogen atom by an alkyl radical. Platinum compounds, including cisplatin, carboplatin and oxaliplatin, can penetrate the cells by diffusion and modifying the DNA molecules, which are indispensable for the cell replication process³.

Among the many collateral effects resulting from chemotherapy, ototoxicity is one that may cause lesions to the inner ear structures, resulting in hearing loss, normally, sensorineural, bilateral and symmetric, affecting first the higher frequencies^{4,5}. Producing free radicals with the use of antineoplastic therapeutic agents may change the cell wall and the cells' genetic material, including the cochlea's hair cells. Thus, basic mechanisms of these collateral effects involve the production of reactive oxygen species in the cochlea that induce these cells to death, making it impossible for the electrical signals to be adequately transmitted to the auditory nerve⁶.

It is known that platinum compound-induced hearing loss may vary from zero to 90.1%⁷. Furthermore, some studies have described that hearing loss may be triggered during the platinum-based therapy, or even develop after the treatment has finished^{5,8,9}.

Moreover, in the literature there are studies relating possible factors that contribute to the seriousness of the hearing loss. For instance, higher cisplatin dosages, as well as younger patients, can maximize the ototoxic effects of the platinum compound^{10,11}. On the other hand, it is shown that even individual dosages can impair the auditory system¹².

Although cisplatin ototoxicity has been carefully investigated, much less is known about ototoxicity

caused by carboplatin. Factors that can potentialize carboplatin ototoxicity are known to include previous exposure to cisplatin or other ototoxic medications, or high carboplatin dosages¹³.

Carboplatin, which is considered less ototoxic than cisplatin, proved to be highly toxic for the cochlea's inner hair cells and type I ganglion neurons in animals¹⁴. Conversely, another study observed that ototoxic complications from carboplatin chemotherapy were rarer and mild¹⁵.

A systematic review recently published described varied prevalence of hearing loss induced by platinum compounds (cisplatin, carboplatin or both, in different doses). However, this review focused on the description of the findings related to the prevalence of hearing loss and to symptomatology resulting from the effects of ototoxicity⁷.

Considering that there are still gaps on the knowledge about the effects of platinum compounds on the auditory pathway, it is important that studies describing the results of audiological procedures on the subject be developed, to investigate on what part of the auditory system there is more impact of the platinum agents. Thus, it would be possible to offer better guidance on the need and the form of auditory monitoring in this population. It is known that such monitoring is extremely important to detect possible auditory alterations in due time and, whenever possible, reconsider treatment possibilities^{4,9}.

Hence, this study aimed at identifying and analyzing the effects of chemotherapy on the auditory system of children and/or adolescents with cancer, treated with cisplatin and carboplatin, assessed through standardized audiological procedures.

METHODS

Research strategy

Initially, the following research question was developed and defined: What are the effects of carboplatin and cisplatin treatment on the auditory system of children and adolescents with cancer, assessed through standardized audiological procedures?

The systematic review was conducted in compliance with the recommendations by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁶. Within the PRISMA strategy, the PICO (population, intervention, comparison/control, outcome)¹⁷ was used to formulate the objective of the study:

- **Patient (P):** children or adolescents with cancer undergoing chemotherapy carboplatin and/or cisplatin treatment;
- **Intervention (I):** containing audiological assessment data (acoustic immittance, pure-tone audiometry, otoacoustic emissions – OAE – and/or brainstem auditory evoked potentials – BAEP) of individuals undergoing carboplatin and/or cisplatin chemotherapy treatment;
- **Comparison (C):** the comparison of longitudinal results (before and after chemotherapy) was considered, as well as the comparison with criteria of normality defined in the literature;
- **Outcomes (O):** either presenting or not audiological alterations, considering type, degree, configuration and/or prevalence of hearing loss.

The search was conducted on the electronic databases MEDLINE-PubMed, Science Direct, LILACS, Embase, SciELO, Web of Science and Cochrane, with the following descriptors: Hearing Loss, Audiology, Childhood Cancer, Chemotherapy, Drug Therapy, Child. The descriptors were used in English, in accordance with the Medical Subject Headings (MeSH), and in Portuguese, in accordance with the Health Sciences Descriptors (DeCS, its Portuguese acronym). These descriptors were combined with the Boolean operator “AND”.

Selection criteria

The period selected for inclusion of studies in Portuguese or English was the last 20 years (1997 to 2017). The ones included, in general, were original articles dealing with the hearing of children and adolescents with cancer submitted to cisplatin and/or carboplatin chemotherapy treatment, with levels 1 and 2 of scientific evidence according to the Oxford Centre for Evidence-based Medicine¹⁸. These articles included: systematic review of randomized controlled clinical trials or of cohort studies, randomized controlled clinical trial with narrow confidence interval, “all or nothing” therapeutic results, cohort studies and therapeutic results observation. Articles with expert opinion, case reports, case-control studies and systematic literature reviews were excluded, as well as studies including the use of otoprotective agents.

The selection of the articles was carried out by two researchers. At first, the articles obtained through the search on the databases were identified; then, the articles were selected, excluding the duplicated ones and those not related to the defined descriptors,

through the screening of titles and summaries; after this step, the eligibility was conducted with the full reading of the texts, excluding the articles not meeting the previously established criteria; lastly, the eligible articles were included in the systematic review.

Data analysis

After finishing the collection from the databases, a table was filled out with the data from each study in order to exclude repeated articles. Two independent researchers conducted the analysis of the texts found, selecting the texts that met the inclusion criteria. For an initial filtering, the title of each article was read, and then, the summary of the remaining articles. After that, the articles that remained were read in full.

From the articles that were selected after full reading, the following data were identified for posterior analysis: number, gender and age of the participants; type of tumor; audiological procedures employed; drug(s) used, cycle and dose; hearing loss criteria; follow-up; main audiological findings; evidence of ototoxicity. Conflicts in the analysis of the studies were solved by discussion between the researchers.

For the assessment of risk of bias in each study, the Cochrane¹⁹ tool was used, which encompasses the following criteria: randomization; allocation concealment; blinding of participants; blinding of outcome assessor; incomplete outcomes; selective outcome reports; and other sources of bias. Each individual criterion was considered as having low risk of bias, high risk of bias, or uncertain risk of bias (lack of information, or uncertainties referring to potential biases). The discrepancies between the authors were solved by consensus.

LITERATURE REVIEW

Results in the electronic databases

A total of 3,625 studies were found throughout the databases researched. Among these, 2,415 studies were repeated and so they were excluded.

The titles of the remaining 1,210 articles were read, leading to the exclusion of 622 due to their digressing from the topic approached in this review, so that 588 remained, whose summaries were read.

After the reading of the summaries, 186 articles of interest were left, which were fully read. Of these, 163 did not meet all the criteria for this research.

Lastly, 23 articles met all the inclusion criteria and answered the research question; hence, they were considered for analysis in this review. The flowchart

with the stages in the selection of the articles can be visualized in Figure 1. The main aspects of the selected studies are found in Figures 2 and 3.

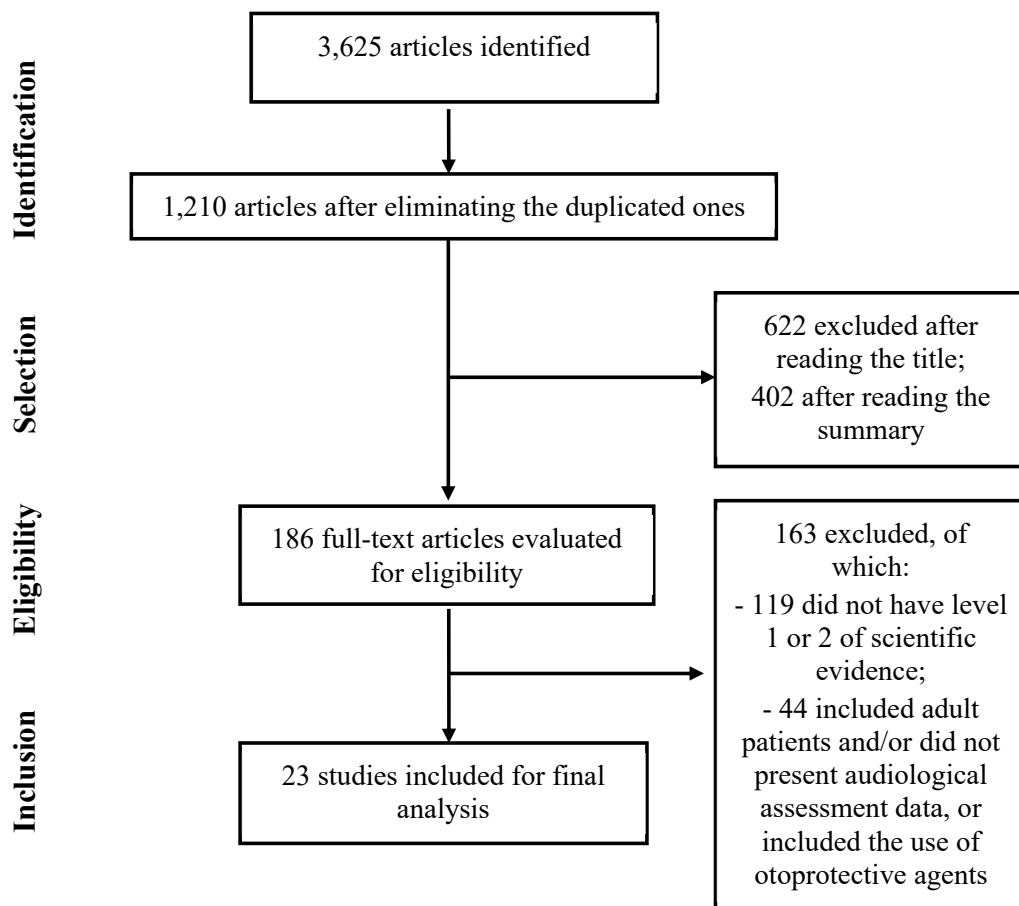


Figure 1. Flowchart of the selection stages of articles found in the literature

Reference	Sample number (final)	Age range at beginning of treatment	Treatment	Dosage (mg/m ²)	Cycles	Procedures	Hearing loss or ototoxicity criterion
Al-Khatib et al., 2010	31	0 to 17 years	Cisplatin and/or carboplatin	Cisplatin 53 - 498; Carboplatin 261-15550	NS	PTA, OAE	ASHA
Al-Noury, 2011	26	7 to 15 years	Cisplatin	60 - 120	1	PTA, TEOAE, DPOAE	> 20 dB
Amorim et al., 2007	18	9 months to 9 years	Carboplatin	560 per cycle	4 to 6	TEOAE	NS
Berg et al., 1999	28	8 to 180 months	Cisplatin	60 - 120	1 to 6	PTA, TEOAE, BAEP	NS
Bhagat et al., 2010	10	3 to 72 months	Carboplatin	TCD: 1200–2210 (322 - 617 per cycle)	3 to 4	DPOAE	OAE responses pre- and post-chemotherapy
Castelán-Martínez et al., 2014	59	3 to 17 years	Cisplatin	TCD: 170-695	NS	PTA	>20 dB at 8 kHz
Clemens et al., 2016	451	0 to 19 years	Cisplatin and/or carboplatin	TCD cisplatin:45-950; TCD carboplatin: 104-9436; TCD of both: cisplatin of 80- 570 and carboplatin of 400-6043	NS	PTA	Muenster scale grade 2b (>20 dB at 4 and 8 kHz).
Einarsson et al., 2010	15	0 to 17 years	Cisplatin and/or carboplatin	TCD cisplatin 180-480 (90-320 per cycle); TCD carboplatin: 3000 (only 1 patient)	NS	PTA	Brock
Knight et al., 2007	32	0 to 20 years	Cisplatin and/or carboplatin	TCD cisplatin: 200-700 (45-200 per cycle); TCD carboplatin: 1700-3240 (540-1700 per cycle)	NS	High-frequency PTA, DPOAE, BAEP	ASHA and Brock
Lanvers-Kaminsky et al., 2006	24	0 to 20.3 years	Cisplatin	TCD cisplatin: 200-480 (100-160 per cycle)	2 to 4	PTA, TEOAE, DPOAE, BAEP	ASHA, Brock and Muenster scale
Smits et al., 2006	25	0.5 to 41 months	Carboplatin	TCD: 560–6580	1 to 9	PTA, TEOAE, DPOAE, BAEP	OAE responses pre- and post-chemotherapy
Stavroulaki et al., 2001	12	4.6 to 14.5 years	Cisplatin	50	1	PTA, TEOAE, DPOAE	ASHA
Lambert et al., 2008	116	0 to 25 months	Carboplatin	18.6 mg/kg per cycle	1 to 6	PTA, OAE, BAEP	NS
Fetoni et al., 2016	104	0 to 17 years	Cisplatin and/or carboplatin	TCD cisplatin: 100-1000; TCD carboplatin: 800-13000; TCD of both: cisplatin of 40-900 and carboplatin of 200-8000.	NS	PTA, acoustic immittance, BAEP	SIOP Boston ototoxicity
scale	200	NE	Cisplatin	DTC em média de 647,8 a 668,1	NE	ATL, imitanciometria	NE
Lieberman et al., 2016	200	NS	Cisplatin	Mean TCD of 647.8 to 668.1	NS	PTA, acoustic immittance	NS
Einar-Jon et al., 2011	15	0 to 18 years	Cisplatin and/or carboplatin	TCD cisplatin: 58-820; TCD carboplatin: 410-5200	NS	PTA, acoustic immittance, TEOAE, DPOAE	NS
Weissenstein et al., 2012	27	4.1 to 16.1 years	Cisplatin	Mean dose: 401.9	NS	PTA, SOAE, DPOAE	>20 dB
Bertolini, 2004	120	0 to 17 years	Cisplatin and/or carboplatin	TCD cisplatin: 80-800; TCD carboplatin: 400-8000	NS	PTA, DPOAE, BAEP	>20 dB and Brock.
Bhagat et al., 2013	10	3 to 72 months	Carboplatin	1236–2210	3 to 4	TEOAE	NS
Coradini et al., 2007	23	10.4 to 16.1 years	Cisplatin	TCD cisplatin: 317-575	NS	PTA, acoustic immittance, TEOAE, DPOAE	NS
Silva et al., 2007	94	1 to 18 years	Cisplatin and/or carboplatin	Cisplatin mean dose: 78.09; carboplatin mean dose: 330.75	4 cycles in average	PTA	ASHA, POGT and BHL
Peleva et al., 2014	306	2 months to 21.4 years	Cisplatin and/or carboplatin	TCD cisplatin: 20-720; TCD carboplatin: 450-14,820	NS	PTA, acoustic immittance, TEOAE, DPOAE	ASHA
Schmidt et al., 2008	55	4 to 16.4 years	Cisplatin	Mean TCD: 391.5	NS	PTA, acoustic immittance, TEOAE, DPOAE	NS

Legend: PTA: Pure-tone audiometry; OAE: Otoacoustic emissions; TEOAE: Transient evoked otoacoustic emissions; DPOAE: Distortion-product otoacoustic emissions; SOAE: Spontaneous otoacoustic emissions; BAEP: Brainstem auditory evoked potentials; ASHA: American Speech-Language-Hearing Association; POGT: Pediatric Oncology Group Toxicity; BHL: Bilateral Hearing Loss; NS: Not specified in the article; TCD: Total cumulative dose.

Figure 2. Summary of the main methodological aspects of the selected articles

Reference	Pre-treatment hearing loss	Hearing loss right after treatment	Audiological follow-up	Ototoxicity
Al-Khatib et al., 2010	NS	42% presented bilateral HL (3 mild, 3 moderate, 7 severe to profound).	Average of 3.4 years (1.5 to 6.6 years) conducted with 21 individuals: 33% had worse bilateral threshold (4000–8000 Hz), in up to 50 dB	Yes
Al-Noury, 2011	0% (inclusion criterion)	7.6% absent OAE with HL in high frequencies	3 more individuals presented HL in high frequencies	Yes
Amorim et al., 2007	NS	100% presence of TEOAE	NS	No
Berg et al., 1999	2 with SNHL	NS	Average of 6 months (2 to 16). 26% had further changes (SNHL in high frequencies)	Yes
Bhagat et al., 2010	NS	40% presented indications of ototoxicity (amplitude decrease of the DPOAE at 7,996 Hz)	Not carried out	Yes
Castelán-Martínez et al., 2014	0% (inclusion criterion)	NS	Average of 254 days: 56% had HL, 52% with moderate to severe degree	Yes
Clemens et al., 2016	0% (inclusion criterion)	45% of ototoxicity in individuals treated with cisplatin alone; 17% of those treated with carboplatin alone; and, 75% of the ones treated with both agents	Not carried out	Yes
Einarsson et al., 2010	0%	NS	Average of 10.8 to 12.1 weeks (0.3 to 57.3). 40 presented HL (ototoxicity degree 1-3). Mean threshold for the frequencies of 3 to 8 kHz was of 66.9 and 74.8 for the best and worst ear, respectively.	Yes
Knight et al., 2007	0%	62.5% acquired bilateral ototoxicity during the treatment, and 81.3% presented bilateral amplitude decrease of the DPOAE. Of the 17 individuals with high-frequency audiometry, 94.1% had bilateral ototoxicity.	Not carried out	Yes
Lanvers-Kaminsky et al., 2006	0%	6 presented SNHL after the 1st cycle of cisplatin (cumulative doses: 120-160 mg/m ²); 4 developed ototoxicity after the 2nd; and, 2 after the 3rd cycle of cisplatin (cumulative doses: 200-320 mg/m ² , and 360 mg/m ²).	Not carried out	Yes
Smits et al., 2006	0%	0%	Average of 25 months (1 to 94). No alterations.	No
Stavroulaki et al., 2001	16% presented mild symmetric SNHL at 6 and 8 kHz. All with present OAE.	50% had worse thresholds in PTA (4 to 8 kHz); worse responses of the TEOAE (at 4 kHz) and of the DPOAE (at 3 kHz)	Not carried out	Yes
Lambert et al., 2008	5.60% of HL	NS	Average of 40 months (3-127). No alterations.	No
Fetoni et al., 2016	0%	25% of all the individuals developed HL	Average of 22 months. Progressive HL in 8.6%. 12.5% presented degree 2 or over SNHL.	Yes
Liberman et al., 2016	NS	De 41.9% to 47.3% presented HL, especially bilateral and symmetric SNHL.	Not carried out	Yes
Einar-Jon et al., 2011	Not assessed	Not assessed	Average of 9.1 years (0.8-16.5). 20% presented mild to severe HL beginning at 3 kHz	Yes
Weissenstein et al., 2012	NS	NS	Up to 6 months. 24.1% presented increase on high-frequency auditory thresholds (4-8 kHz).	Yes
Bertolini, 2004	0%	NS	Average of 112 months (30–181). Up to 2 years post-chemotherapy: 11%. Another 2 years post-chemotherapy: 44%	Yes
Bhagat et al., 2013	NS	No difference in the OAE after 3-4 cycles	Not carried out	No
Coradini et al., 2007	Not assessed	Not assessed	Average of 44 months (28-92). Alterations in 22% of the TEOAE and in 71% of the DPOAE were observed.	Yes
Silva et al., 2007	Not assessed	Not assessed	The prevalence of hearing loss was of 42.5% using ASHA, 40,4% POGT, and 12.8% using BHL.	Yes
Peleva et al., 2014	NS	48% with HL	Average of 39 months (6-125). 48% with HL	Yes
Schmidt et al., 2008	0% (inclusion criterion)	NS	Average of 15,6. 100% presented worse thresholds in the frequencies beginning at 2 kHz	Yes

Legend: PTA: Pure-tone audiometry; OAE: Otoacoustic emissions; TEOAE: Transient evoked otoacoustic emissions; DPOAE: Distortion-product otoacoustic emissions; HL: Hearing loss; SNHL: Sensorineural hearing loss; ASHA: American Speech-Language-Hearing Association; POGT: Pediatric Oncology Group Toxicity; BHL: Bilateral Hearing Loss; NS: Not specified in the article

Figure 3. Summary of the main results of the selected articles

Analysis of the selected studies

There is in the literature a concern regarding the ototoxic effects in children with cancer submitted to platinum-based chemotherapy, since the administration of these substances can impair the functioning of the structures of the auditory system. Even though only 23 studies met all the inclusion criteria, it was observed in the first stages of the research a great number of articles verifying the chemotherapy effects on hearing.

Regarding the risk of bias (Figure 4), all the studies included presented methodological flaws in at least one criterion evaluated. In all the studies, a high risk of bias

was noted in the criteria of randomization, allocation concealment, blinding of participants and blinding of outcome assessors, which may be justified by the type of population assessed and treatment conducted. As for the criterion of incomplete outcomes, all the studies presented low risk of bias, since all data loss was justified, and the outcomes lost did not influence on the effect size observed. For the criterion selective outcome reports, five studies presented uncertain risk of bias, for the information was insufficient to enable it to be judged. Nine studies presented other sources of bias, the main one being the absence of information regarding the use of concomitant medications.

Reference	Randomization	Allocation concealment	Blinding of participants	Blinding of outcome assessors	Incomplete outcomes	Selective outcome report	Other sources of bias
Al-Khatib et al., 2010	-	-	-	-	+	?	?
Al-Noury, 2011	-	-	-	-	+	+	+
Amorim et al., 2007	-	-	-	-	+	+	-
Berg et al., 1999	-	-	-	-	+	+	+
Bhagat et al., 2010	-	-	-	-	+	+	?
Castelán-Martínez et al., 2014	-	-	-	-	+	+	+
Clemens et al., 2016	-	-	-	-	+	+	+
Einarsson et al., 2010	-	-	-	-	+	+	+
Knight et al., 2007	-	-	-	-	+	+	?
Lanvers-Kaminsky et al., 2006	-	-	-	-	+	+	+
Smits et al., 2006	-	-	-	-	+	+	+
Stavroulaki et al., 2001	-	-	-	-	+	+	?
Lambert et al., 2008	-	-	-	-	+	?	+
Fetoni et al., 2016	-	-	-	-	+	+	+
Liberman et al., 2016	-	-	-	-	+	?	+
Einar-Jon et al., 2011	-	-	-	-	+	+	?
Weissenstein et al., 2012	-	-	-	-	+	+	?
Bertolini, 2004	-	-	-	-	+	?	?
Bhagat et al., 2013	-	-	-	-	+	+	?
Coradini et al., 2007	-	-	-	-	+	+	-
Silva et al., 2007	-	-	-	-	+	+	+
Peleva et al., 2014	-	-	-	-	+	?	+
Schmidt et al., 2008	-	-	-	-	+	+	+
Legend:	Low risk (+)	High risk (-)	Uncertain risk (?)				

Figure 4. Analysis of the risk of bias of the selected articles

Chemotherapy drugs and types of tumors

Concerning the drug used in chemotherapy treatment, nine studies (39.13%) assessed the effect of cisplatin alone^{12,20-27}, with doses ranging from 50 to 160 mg/m² per cycle (cycles between 1 and 6); five studies (21.74%) assessed carboplatin alone²⁸⁻³², with doses ranging from 322 to 2,210 mg/m² per cycle (cycles between 1 and 9); and, nine studies (39.13%) assessed the effects of cisplatin and/or carboplatin^{4,8,33-39}. Of the studies with cisplatin and/or carboplatin, the majority does not mention the number of cycles and/or the doses of each drug per cycle; the total cumulative dose of cisplatin ranged from 20 to 1,000 mg/m², whereas that of carboplatin ranged from 104 to 15,550 mg/m².

Regarding the types of tumors included, five studies (21.74%) were limited to studying individuals diagnosed with retinoblastoma²⁸⁻³². The other studies considered various other types of tumors, the most common being: neuroblastoma, medulloblastoma, osteosarcoma, hepatoblastoma, sarcoma, carcinoma, glioma, central nervous system tumor, and germ-cell tumor.

Methodological characteristics

The sample number varied greatly, as there were studies that assessed only 10 individuals^{31,32}, whereas another one assessed 451 individuals³⁸ (80.72 ± 109.99).

Regarding gender, only two studies^{4,30} did not mention the distribution of the participants. Most of them included children and adolescents of both genders, similarly distributed (mean number of female individuals per study: 39.8 ± 57.6; and male individuals: 35.95 ± 55.4).

The mean age at diagnosis also varied considerably between the various studies, from seven months²⁸ to 12.3 years²².

Considering that the aim of this research was to verify the effects of cisplatin and carboplatin chemotherapy on the auditory system of children and/or adolescents with cancer, the selected studies tended to be longitudinal, assessing the individuals before, during and/or after chemotherapy; the follow-up after chemotherapy ranged from one month to 127 months. Only five studies performed the assessment exclusively post-chemotherapy treatment^{4,22,27,29,36}.

Among the studies, different methods were employed to compose the audiological assessment. Since a wide age range was involved in the assessment, sometimes including very small children, the auditory

assessment method had to be adapted to the child's response possibilities; therefore, for some of the studies, objective and/or subjective procedures had to be used^{8,12,20,28,30,33,39}.

Four studies used only the pure-tone audiometry (conventional, conditioned or with visual reinforcement)^{4,26,35,38}, and only one considered high-frequency audiometric assessment³³.

The acoustic immittance, though used in many of the studies^{12,20,24,27,28,31,35}, was carried out mainly with the purpose of discarding possible middle ear alterations that could compromise the results of the other procedures, especially those of the otoacoustic emissions (OAE).

Of the 17 studies that assessed auditory functioning through the OAE, only one made use of spontaneous OAE²⁵. Three studies used transient evoked otoacoustic emissions (TEOAE)^{20,29,32}, three used distortion-product otoacoustic emissions (DPOAE)^{8,31,33}, and eight used both procedures^{12,21-24,28,36,37}; in two of the studies, it was not possible to specify the type of stimulus used^{30,34}.

The OAE, besides being an objective method, an alternative to behavioral auditory assessment, had its inclusion justified by some authors for its potential in assessing outer hair cells function in patients submitted to chemotherapy, capable of providing early evidences of cochlear damage, even before the occurrence of alterations on auditory thresholds obtained through pure-tone audiometry^{22,32,36,39}.

Some studies also included the brainstem auditory evoked potentials (BAEP)^{8,12,20,28,30,33,39}; however, the usefulness of this procedure was mostly in estimating the psychoacoustic threshold of babies and very small children, who are not able to respond to behavioral assessments. Of the seven studies that used the BAEP^{8,12,20,21,28,33,39}, only one described the findings from such assessment²⁰.

In addition to the diversity of procedures, there was also a diversity of criteria used for classifying hearing loss and/or detecting ototoxicity. Two studies considered as hearing loss auditory thresholds superior to 20 dB HL, without mentioning any other specific criterion^{24,25}. Other studies also used 20 dB HL as hearing loss criterion, besides including specific criteria to identify the presence of ototoxicity, such as: Common Terminology Criteria for Adverse Events²⁶; Brock grading system^{8,35}; ASHA's criteria referring to ototoxicity^{19,34,37}; Muenster criteria³⁸; SIOP Boston ototoxicity scale³⁹; and a comparison between diverse criteria (ASHA, Brock, Muenster, POGT, BHL)^{4,12,33}. On

the other hand, ten studies did not specify the criterion used to classify hearing loss and/or presence of ototoxicity^{20,22,23,27-32,36}.

The absence of this criterion for the classification of hearing loss due to ototoxicity may be justified by the variety of methods used in audiological assessment, since not carrying out the pure-tone audiometry makes it unfeasible to use many of these standardized criteria, as most of them are based on auditory thresholds and/or on evolution throughout time.

A recent literature review on the subject⁴⁰ assessed the most used criteria for ototoxicity, discussing their benefits and limitations. The authors observed that diverse criteria are used in the various studies, including some verified in this study: ASHA, Brock, Muenster, SIOP, among others. The authors concluded that the different ototoxicity criteria result in different prevalence and degrees of hearing loss, which may result in different medical practice. Moreover, attention was called to the need of further research on the subject, emphasizing the importance of adopting a consensual criterion to follow up chemotherapy regimens, as well as the inclusion of high-frequency audiometry (>8 kHz) and/or auditory assessment through OAE.

Results of the audiological assessment and occurrence of ototoxicity

The methodological differences between the studies (different audiological procedures, time of assessment, as well as the use of different classification criteria) resulted in a great variability between the 23 studies. Despite this, in regard to prevalence or incidence of hearing loss, it can be concluded that most of the studies (82.6%) verified the occurrence of ototoxicity in children and adolescents submitted to platinum-based medication treatment.

Of the 19 studies that verified ototoxic effects during or after the treatment with the antineoplastic agents used, nine included only cisplatin, whereas the others studied cisplatin and/or carboplatin.

Regarding cisplatin, it was noted that auditory impairment could already be verified right after the first chemotherapy dose, with absence or decrease of the OAE in 7.6% of the individuals²⁴, as well as significant changes of high-frequency auditory thresholds, and decrease in OAE, in approximately 50% of the individuals²¹.

Similarly, another study identified that 25% of the individuals already presented sensorineural hearing

loss right after the first cycle of cisplatin (cumulative doses of 120 to 160 mg/m²). Furthermore, 16.6% of the individuals developed hearing loss after the second cycle of cisplatin (cumulative doses of 200 to 320 mg/m²) and 8.3% of the individuals presented hearing loss after the third cycle of cisplatin (cumulative doses of 360 mg/m²)¹².

In addition to the immediate effect, other studies highlighted that the appearance of hearing loss may happen even after the cisplatin treatment has finished, justifying the importance of audiological monitoring even after the end of the treatment. One of the studies analyzed in this review observed that 26% of the individuals presented high-frequency sensorineural hearing loss, whose appearance began from one to 60 months after the end of the chemotherapy, regardless of individual or cumulative doses of cisplatin²⁰. Another three studies also verified percentages of alterations ranging from 24 to 100%, from 6 to 44 months after, the main hearing loss being the sensorineural, bilateral and symmetric^{22,23,25-27}.

As for the studies that assessed carboplatin and/or cisplatin, all of them verified ototoxic effects of the drug(s), there being found prevalence of auditory alterations ranging from 17 to 94%^{4,8,33-39}, including decreased amplitude of OAE and/or hearing loss of various degrees, involving mainly the high frequencies.

Two of these studies also specified the prevalence of alterations related to each drug^{38,39}. The first study verified 45% of alterations in individuals treated only with cisplatin, 17% of those treated only with carboplatin, and 75% of the ones treated with both agents³⁸. As for the second study, there was a prevalence of 25% those treated only with cisplatin; 19% of those treated only with carboplatin, and 35% of the individuals that underwent combined treatment (cisplatin and carboplatin)³⁹. Despite the differences in prevalence, it was observed that carboplatin presented a less ototoxic effect, followed by cisplatin, whereas the combined use of the two substances presented greater ototoxic power due to its synergistic effect.

Not all the studies described systematically the hearing loss characteristics in children with cancer, due to the different methodological procedures/ classification criteria employed, as previously mentioned. Nevertheless, in the studies that described these variables, it was noted that the audiological profiles were very similar after the chemotherapy treatment. There was a prevalence of sensorineural hearing loss^{12,20,21,27,39}, of mild to moderate degree, bilateral and

symmetric in most of the cases^{21,27}, affecting mainly the high frequencies^{12, 20-23,25,36}, although some studies also observed the presence of severe degree of hearing loss in some patients^{9,26,36,39}.

The high-frequency audiometry analysis (between 9 and 16 kHz), which was used in only one study, showed 94.1% of bilateral ototoxicity in this frequency range³³. Likewise, the studies revealed a decrease in the amplitude of responses to the OAE, both by transient stimuli and distortion product, the high frequencies being more sensitive to ototoxic action^{21,22,24,31,33}. The analysis of the responses to the OAE was compatible with the results presented in the pure-tone audiometry^{20,24}, which highlights that the basal regions of the cochlea are the most affected³³.

It is described in the literature that the platinum-based compounds affect first the outer hair cells at the basal region of the cochlea, which is the reason for it initially affecting frequencies over 4,000 Hz^{24,31}.

Regarding the brainstem auditory pathway analysis, the only study that described this finding (registered in seven patients) observed an increase of the wave V latency at the intensity of 20 dBnHL in an individual, suggesting a cochlear dysfunction, and an increase of the interpeak in two individuals, suggesting a neural-conduction slowdown along the auditory nerve. This is the only study of those selected for this review that highlighted the possibility of retrocochlear alteration as a result of the cisplatin²⁰.

Hence, future studies are necessary to consider the auditory pathway integrity analysis through the BAEP, and to assess the possibility of neurotoxicity resulting from the use of chemotherapy medications.

Five studies assessed only individuals with retinoblastoma, treated with carboplatin alone²⁸⁻³². Of these, only one study observed decrease in DPOAE at the frequency of 7,996 Hz in 40% of the individuals, which indicates ototoxicity³¹; in the other four studies, no ototoxic effects resulting from chemotherapy were observed^{28-30,32}. Some other studies have reported that carboplatin alone may not cause alterations in the auditory pathways^{8,36}; nonetheless, cumulative doses are potentially ototoxic³¹.

When observing the cumulative doses in these five studies²⁸⁻³², administration of high doses was not observed in the study that observed ototoxicity³¹ in comparison to the other ones^{28-30,32}. Therefore, though countless other factors may have interfered in these results, it cannot be discarded the influence that even

small doses may have on impairing the functioning of the cochlear hair cells.

In the case of children with retinoblastoma, one of the studies highlighted the priority of early detection of ototoxicity, since many children are diagnosed after presenting visual impairment. If the ototoxic potential is identified in due time, the dosage of carboplatin and/or other drugs can be changed to avoid further cochlear deterioration, considering that the negative impacts of hearing loss can be even more aggressive in a child with visual impairment²⁸.

Among the most highlighted factors of great risk of developing platinum-induced hearing loss, the diagnosis of osteosarcoma²⁶ and the cumulative cisplatin dosage can be cited^{8,20,22,27}, being this greater than 400 mg/m²²⁶, though dosages superior to 200 mg/m² have already shown to be ototoxic¹². The influence of age has also been mentioned, as well as the concomitant use of furosemide³⁸.

Considering this, it is fundamental that audiological monitoring be carried out in this population, before, during and after the treatment, emphasizing the need of long-term follow-up, as well.

Auditory monitoring can aid in decision-making related to the treatment itself and/or in determining the appropriate clinical interventions for each case, seeking to minimize possible negative impacts of hearing loss for the language, schooling and quality of life of these individuals.

Regarding the evaluative procedures, the instrument should be adapted to child's response possibilities. Nevertheless, whenever possible, conducting pure-tone threshold audiometry is desirable, as most of the time the auditory thresholds are gold standard for ototoxicity monitoring in the many criteria available.

Furthermore, the inclusion of the OAE and/or the high-frequency audiometry (>8 kHz) is fundamental, since these are clinical resources capable of showing possible auditory impairments even before any alteration is observed on the conventional pure-tone audiometry, due to the damage beginning at the basal region of the cochlea.

In this study, the possible role of genetics on determining ototoxicity was not discussed, neither was the use of otoprotective agents for hearing loss in this population. Future studies on the subject should be conducted, deepening knowledge about these specific issues.

CONCLUSION

The studies demonstrated a high incidence of sensorineural hearing loss, mainly at high frequencies, as well as absence or decrease of OAE response amplitude, suggesting important cochlear impairment, especially at the basal regions of the cochlea, which can be already triggered after the first dose of chemotherapy, to which carboplatin seems to have a smaller ototoxic effect than does cisplatin.

The effects of ototoxicity on the central auditory pathways are not yet clear, so future research should consider post-chemotherapy central auditory nervous system integrity assessment.

The development of specific protocols for the identification of hearing loss is necessary, considering the age of the individuals and, consequently, the audiological procedures to be used. Such aspect would aid in adopting specific criteria for the identification of ototoxicity, thus, facilitating the audiological monitoring, the comparison between different studies and the medical practice.

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Erratum

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