

Hearing changes in pediatric cancer patients treated with cisplatin

Cambios en la audición de pacientes pediátricos con cáncer tratados con cisplatino

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Abstract

Objective: To measure changes in hearing assessed by tone audiometry and otoacoustic emissions by product distortions (EOAPD) in children with cancer treated with cisplatin. **Method:** Retrospective cohort study. There were 42 files of children with cancer, who had tone audiometry (conventional frequencies and high frequencies) and EOAPD, performed after each dose of cisplatin. Hearing was compared with cisplatin amount and doses number. **Results:** Of the 42 subjects, 88.1% were patients with criteria for ototoxicity (pCCO) and 11.9% without criteria (pSCO). Antineoplastic therapy was administered in 2 (31%) and 3 (69%) doses. In the second study, there was superficial damage in medium and high tones in pCCO ($p < 0.046$). The high frequencies were affected from first dose in pCCO and second dose in pSCO; the damage was related with accumulated dose ($rs = 0.54$; $p = 0.0001$; odds ratio [OR]: 1.125; 95% confidence interval [95% CI]: 0.893-1.417) in doses of 300-325 mg/m² of body surface. EOAPD were absent in 100% of pCCO at the last dose (OR: 4.0; 95% CI: 0.733-21.838) at 300-325 mg/m² of body surface ($p = 0.034$). **Conclusions:** The use of cisplatin in children with cancer was associated with hearing damage between 2000 and 16,000 Hz from the start of treatment and at dose of 300 mg/m² of body surface.

Keywords: Cisplatin. Pediatric cancer. Otoacoustic emissions. Hearing loss. Ototoxicity.

Resumen

Objetivo: Medir los cambios en la audición evaluada por audiometría tonal y emisiones otoacústicas por productos de distorsión (EOAPD) en niños con cáncer tratados con cisplatino. **Método:** Estudio de cohorte retrospectiva. Se incluyeron 42 archivos de niños con cáncer que tenían audiometría tonal (frecuencias convencionales y altas frecuencias) y EOAPD, realizados después de cada dosis de cisplatino. Se comparó la audición con la cantidad de cisplatino y el número de dosis. **Resultados:** El 88.1% tuvieron criterios para ototoxicidad (pCCO) y el 11.9% sin criterios (pSCO). La terapia antineoplásica se administró en dos (31%) o tres dosis (69%). En el segundo estudio hubo deterioro superficial en tonos medios y agudos en pCCO ($p < 0.046$). Las altas frecuencias estuvieron afectadas desde la primera dosis en pCCO y hasta la segunda en pSCO; el daño tuvo relación con la dosis acumulada ($rs = 0.54$; $p = 0.0001$; odds ratio [OR]: 1.125; intervalo de confianza del 95% [IC 95%]: 0.893-1.417) con dosis de 300-325 mg/m² de superficie corporal. Las EOAPD estuvieron ausentes en el 100% de pCCO en la última dosis (OR: 4.0; IC 95%: 0.733-21.838) a 300-325 mg/m² de superficie corporal ($p = 0.034$). **Conclusiones:** El uso de cisplatino en niños con cáncer se relacionó con daño auditivo entre 2000 y 16,000 Hz desde el inicio del tratamiento y a dosis de 300 mg/m² de superficie corporal.

Palabras clave: Cisplatino. Cáncer pediátrico. Emisiones otoacústicas. Hipoacusia. Ototoxicidad.

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Introduction

According to the World Health Organization, the most common types of childhood cancer are leukemia, brain cancer, lymphoma, and solid tumors such as neuroblastoma and Wilms tumor¹. According to the International Agency for Research on Cancer, in 2015 there were between 344,543 and 360,114 cases of childhood cancer worldwide (178.0 per million), 29,002 of which were located in Latin America and the Caribbean². In Mexico, cancer is the second leading cause of death in children under 15 years of age, because children are surviving up to 2-6 years, the age at which cancer incidence is highest. In 2007, the National Childhood Cancer Registry was initiated, and it was reported that between 2007 and 2015 there were 24,039 new cases from Seguro Popular alone, representing an increase in incidence from 133.5 per million in 2007 to 150.1 per million in 2015. In our country, the cancer mortality rate is 8.6/100,000 children per year between 15 and 18 years of age, with an overall survival rate of 75% in institutions with more than 15 beds and at least 3 oncologists³. At Instituto Mexicano del Seguro Social, the 5-year overall survival rate was 56.1% (median time: 3.4 years) in the period from 2006 to 2012⁴, and this trend has continued³.

Due to advances in the care of patients with pediatric cancer, long-term survival has improved, so surgery, chemotherapy (CT), and radiotherapy (RT) can cause late effects in childhood cancer survivors^{3,5}, creating a growing population of survivors who will spend part of their lives at risk of chronic conditions and late mortality, with potential loss of life years or living with disability⁶. Among the disabling effects is hearing loss related to the use of CT, common in these children, since it has been detected that when treated with RT and CT they experience a high incidence rate of sensorineural hearing loss over time as a side effect, with an association found between more severe sensorineural hearing loss and the doses received⁷. In particular, RT has shown that with higher doses, the risk and severity of hearing impairment will be greater, as a delayed response to fractionated radiation. Hearing loss is permanent when irreversible damage to the inner ear occurs, and it has been proposed that the basal turn is more susceptible to radiation, although the cochlea is considered as a complete organ for dose-response analysis⁸.

Cisplatin is widely used for some frequent cancers in children, but sometimes RT and CT are combined⁹, and although there are studies indicating that the cisplatin dose outweighs the importance of the RT dose on the cochlea, it seems that prior irradiation reduces the cisplatin dose threshold for hearing loss¹⁰, so it becomes important to determine the additive ototoxic impact of CT that allows oncologists to find safer doses for the cochlea¹¹.

Cisplatin is one of the most potent antineoplastic cytostatic agents available, widely used as standard treatment against a wide range of childhood cancers, which in combined regimens allows a high cure rate¹², with the disadvantage that it crosses the cochlea and causes permanent sensorineural hearing loss, the impact of which is reflected in deficits in neurocognitive areas, causing alterations in the learning process and social contact, and behavioral problems that affect quality of life, more evident the younger the child, due to the deprivation of auditory stimulation on the central nervous system^{13,14}. Platinum resides in the ear for months or years after treatment, so 70% of children on platinum develop irreversible hearing loss, and 40% will need hearing aids at an early stage¹⁵. Like RT, higher doses of cisplatin cause greater ototoxicity, but there are doubts about the cumulative dose, which makes it difficult to develop risk-adjusted approaches for its administration and to better guide new otoprotective agents, such as sodium thiosulfate¹³, which would support the prevention of hearing loss induced by cisplatin, carboplatin, or oxaliplatin, with a positive influence on the quality of life of childhood cancer survivors¹⁶. When platinum compounds became widespread, they had a higher incidence of hearing loss, but currently it seems that the detection of damage has stabilized in survivors, and it is proposed that this may be because new treatment regimens have less ototoxic radiation, and platinum compounds are dosed more carefully¹⁷. Considering all the above, the objective of the present study was to measure the changes in hearing of children with cancer treated with cisplatin at different doses, by performing tonal audiometry with conventional and high frequencies, as well as distortion product otoacoustic emissions (DPOAEs).

Method

To achieve the objective, we conducted a retrospective cohort study by reviewing the medical records of children diagnosed with cancer who included cisplatin

as part of the CT. The selection criteria were age between 4 and 17 years, record in the medical history of the administered doses of CT, and a minimum of 2 audiological evaluations related to the administration of cisplatin in any combination. Patients with a past medical history of hearing loss before the diagnosis of cancer or the start of treatment, those with a history of RT to the head or neck, a history of acute or chronic infection, or previous ear surgery were excluded. Audiological evaluations included pure-tone threshold audiometry (0.125 Hz to 8 kHz), high-frequency tonal audiometry (10 to 16 kHz), and DPOAEs.

Ototoxicity was evaluated using the criteria of the American Speech-Language-Hearing Association (ASHA), including:

- Decrease ≥ 20 dB HL (Hearing Level) in the pure-tone threshold at a single test frequency.
- Decrease ≥ 10 dB HL in the threshold at 2 adjacent frequencies.
- Loss of response at 3 consecutive frequencies where responses were previously obtained.

The ASHA criteria detect early ototoxic changes before clinical sensorineural hearing loss exists, but they do not detect clinically significant hearing loss in oncology, so when significant sensorineural hearing loss was found, the loss was classified using the scale of grades proposed by Chang for ototoxicity, specifically developed for clinically significant platinum-induced changes. Chang's ototoxicity criteria for the severity of hearing loss are:

- 0 = thresholds ≤ 20 dB at 1, 2, and 4 kHz.
- 1a = thresholds ≥ 40 dB at 6-12 kHz.
- 1b = thresholds > 20 and < 40 dB at 4 kHz.
- 2a = ≥ 40 dB at frequencies ≥ 4 kHz.
- 2b = thresholds > 20 and < 40 dB at frequencies < 4 kHz.
- 3 = ≥ 40 dB at frequencies ≥ 2 kHz.
- 4 = thresholds ≥ 40 dB at frequencies ≥ 1 kHz^{18,19}.

According to the findings in the audiological tests for tonal threshold, patients were categorized using Brock's criteria for hearing loss:

- None: bilateral hearing loss, < 40 dB at all frequencies.
- Mild: bilateral hearing loss, > 40 dB at 8000 Hz.
- Moderate: bilateral hearing loss, > 40 dB from 6000 Hz.
- Marked: bilateral hearing loss, > 40 dB from 4000 Hz.
- Severe: bilateral hearing loss, > 40 dB from 2000 Hz^{20,21}.

Results

We reviewed a total of 140 medical records of children and adolescents with cancer at Hospital Infantil de México Federico Gómez, treated with cisplatin in combination with other drugs, of which 42 met the inclusion criteria (30%). Of these, there were 22 (52.4%) women and 20 (47.6%) men, with a mean age of 10.9 ± 3.38 years. Table 1 shows the rest of the general characteristics of the 42 cases and their division into patients with criteria for ototoxicity (PCO) ($n = 37$; 88.1%), located in grade 1a, and patients without criteria for ototoxicity (PWCO) ($n = 5$; 11.9%), corresponding to grade 0 of Chang, and the therapeutic regimen and prescribed dose of cisplatin, regardless of the number of administrations in which it was given. The predominance of women can be observed, with no significant difference in mean age ($p > 0.05$). Osteosarcoma was the most common type of cancer (78.6%). All received cisplatin as part of the treatment regimen, and 7 different CT regimens were used, with cisplatin and adriamycin being the most common combination (71.4%). The drug was administered in 3 doses in most patients (69%). The administered dose of cisplatin is also shown, in the general population and divided into PCO and PWCO.

Table 2 shows that most received the drugs in 3 doses (37 patients). Despite the small number of subjects without ototoxicity (5 patients), they showed the highest mean doses per administration in 2 and 3 doses (range: PWCO 150-300 vs PCO 146.11-155.71 mg/m² of body surface area), and it was statistically significant between groups for the first administered dose ($p = 0.025$), but not for the second ($p = 0.71$) and third doses ($p = 0.88$), as well as for the cumulative dose (range: PWCO 294.44-461.89 vs PCO 323.75-600) ($p = 0.46$). However, there was significance in the cumulative dose when separated between those who received 2 and 3 doses, between the groups with and without ototoxicity ($p = 0.0001$). In the intragroup comparison, there were no differences for the different administered doses.

Table 3 shows the auditory thresholds of the 42 patients in the study, separated into PCO and PWCO. It can be observed that the low and mid frequencies remained on average within the limits of normality in all studies (< 20 dB), although the high frequencies did show greater alterations in the third study, in the group with ototoxicity; however, an average increase can be seen in all measurements, and the ranges show that there were patients with hearing

Table 1. General characteristics, treatment regimen, and cisplatin dose of the 42 selected patients categorized by the presence or absence of ototoxicity

Characteristic	Variable	General population (n = 42)	Patients with ototoxicity (n = 37)	Patients without ototoxicity (n = 5)
Sex	Male, (%)	20 (47.6%)	20 (54.1%)	0
	Female, (%)	22 (52.4%)	17 (45.9%)	5 (100%)
Age (years)	Mean $\pm$ SD	10.9 $\pm$ 3.38	10.89 $\pm$ 3.35	11 $\pm$ 4
Diagnosis (cancer type)	Osteosarcoma	33 (78.6%)	29 (78.4%)	4 (80%)
	Medulloblastoma	3 (7.1%)	3 (8.1%)	0
	Rhabdomyosarcoma	2 (4.8%)	2 (5.4%)	0
	Germ cell tumor	2 (4.8%)	2 (5.4%)	0
	Sarcoma	1 (2.4%)	1 (2.7%)	0
	Adrenal adenoma	1 (2.4%)	0	1 (20%)
Treatment regimen	Cisplatin $\pm$ Adriamycin	30 (71.4%)	27 (73%)	3 (60%)
	Cisplatin $\pm$ Adriamycin $\pm$ Doxorubicin	2 (4.8%)	1 (2.7%)	1 (20%)
	Cisplatin $\pm$ Etoposide	2 (4.8%)	1 (2.7%)	1 (20%)
	Cisplatin $\pm$ Adriamycin $\pm$ Cyclophosphamide	2 (4.8%)	2 (5.4%)	0
	Cisplatin $\pm$ Adriamycin $\pm$ Etoposide	1 (2.4%)	1 (2.7%)	0
	Cisplatin $\pm$ Cyclophosphamide	1 (2.4%)	1 (2.7%)	0
	Cisplatin $\pm$ Etoposide $\pm$ Cyclophosphamide	1 (2.4%)	1 (2.7%)	0
	Cisplatin $\pm$ Doxorubicin	1 (2.4%)	1 (2.7%)	0
	Cisplatin $\pm$ Doxorubicin $\pm$ Vincristine	1 (2.4%)	1 (2.7%)	0
	Cisplatin $\pm$ Etoposide $\pm$ Doxorubicin	1 (2.4%)	1 (2.7%)	0
Number of combined drugs	2	34 (81.0%)	30 (81.1%)	4 (80%)
	3	8 (19.0%)	7 (18.9%)	1 (20%)
Number of doses received	2	13 (31%)	9 (24.3%)	4 (80%)
	3	29 (69%)	28 (75.7%)	1 (20%)
First dose of cisplatin (mg/m ² BSA)	Mean $\pm$ SD	155.19 $\pm$ 37.55	150.48 $\pm$ 31.27	190 $\pm$ 62.7
Second dose of cisplatin (mg/m ² BSA)	Mean $\pm$ SD	153.57 $\pm$ 34.16	152.8 $\pm$ 36.16	159 $\pm$ 12.4
Third dose of cisplatin (mg/m ² BSA)	Mean $\pm$ SD	155.5 $\pm$ 37.5	155.7 $\pm$ 38.17	150 $\pm$ 0
Cumulative cisplatin dose (mg/m ² BSA)	Mean $\pm$ SD	416.1 $\pm$ 118.8	421.16 $\pm$ 118.9	379 $\pm$ 124.56

n: number of patients; mean $\pm$ SD: mean and standard deviation; mg/m² BSA: milligrams per square meter of body surface area.

impairment in each audiological measurement. The inferential analysis in PCO showed that there was only a significant difference in the intragroup hearing level between the first and second studies in the mid ($p = 0.043$) and high frequencies ($p = 0.046$).

When separating the groups considering the number of doses (Table 4), it was found that in those who received 2 doses there was also a significant difference in the mid ($p = 0.043$) and high frequencies ($p = 0.018$) across the studies. In those who received

Table 2. Number of cisplatin doses received and amount administered in the general population and in patients with and without ototoxicity criteria

Cisplatin doses received (mg/m ² BSA)	X ± SD	General population (n = 42)		Patients with ototoxicity (n = 37)		Patients without ototoxicity (n = 5)	
		2 doses (n = 13)	3 doses (n = 29)	2 doses (n = 9)	3 doses (n = 28)	2 doses (n = 4)	3 doses (n = 1)
First dose Mean ± SD	X ± SD	151.2 ± 19.2	157 ± 43.6	146.1 ± 19.5	151.9 ± 34.4	162.5 ± 14.4	300
Second dose Mean ± SD	X ± SD	152.3 ± 18.7	154.1 ± 39.5	148.3 ± 20	154.3 ± 40.2	161.3 ± 13.1	150
Third dose Mean ± SD	X ± SD	-	155.5 ± 37.5	-	155.7 ± 38.2	-	150
Cumulative dose Mean ± SD	X ± SD	303.5 ± 34.5	466.7 ± 107.8	294.4 ± 36.8	461.9 ± 106.7	323.8 ± 18.4	600

X ± SD: mean ± standard deviation; mg/m² BSA: milligrams per square meter of body surface area; BSA: body surface area.

3 doses, a significant difference was found from the low frequencies between the first and third studies ($p = 0.003$), and between the second and third studies ($p = 0.010$); for the mid frequencies, there was only a difference in auditory thresholds between the second and third studies ($p = 0.001$); and in the high frequencies, the difference was located in all comparisons across studies (first-second, first-third, and second-third) ($p = 0.0001$).

In patients without ototoxicity, there was no intra-group difference in the thresholds of low ($p = 0.99$), mid ($p = 0.141$), or high frequencies ($p = 0.180$) between the studies of those who received 2 doses ($p > 0.05$); analysis was not applicable in the only patient with 3 doses.

Table 5 shows the auditory findings in supra-threshold frequencies (10-16 kHz), where it can be seen that from the first study the mean threshold was > 20 dB, with a constant increase in the frequencies evaluated in all PCO (2 and 3 doses). In contrast, the PWCO who received 2 doses had normal mwn thresholds, although the analysis within the data shows that there were already patients with an affectation > 20 dB in the second study (20.0 ± 3.4 dB and range 18-25); as well as the only patient who received 3 doses, who from the second study showed an abnormal threshold that increased in the third study. When comparing PCO, greater hearing damage was observed compared to PWCO, from the first study, but it was only significant in the second ($p = 0.004$) and third studies ($p = 0.008$). The intragroup comparison showed that the difference was significant for PCO between the first and second studies ($p = 0.0001$), and between the first and third studies ($p = 0.0001$), but not between the second and third studies ($p = 0.319$). Despite the constant increase in the thresholds of the PWCO, the

differences were not significant ($p > 0.06$). A correlation was found between the cumulative dose and the auditory threshold of the second study in low tones ($r_s = 0.38$; $p = 0.013$), mid tones ($r_s = 0.53$; $p = 0.0001$), and high tones ($r_s = 0.32$; $p = 0.034$).

Alterations in high frequencies were evident from the first administration of the drug in PCO, with mean losses always > 20 dB up to the third dose, although they were significant only between the first and second studies ($p = 0.0001$) and between the first and third studies ($p = 0.001$) in both patients with 2 and 3 doses, but not between the second and third studies ($p = 0.793$). In PWCO, mild alteration appeared in the second and third doses, but not significant ($p > 0.05$) (Table 5). Similarly, the comparison between PCO and PWCO was significant only in the second ($p = 0.001$) and third studies ($p = 0.006$) (Table 5). Considering damage in high frequencies, there was a difference in the third dose ($p = 0.001$) and with the cumulative dose ($p = 0.0001$), and an excellent correlation between hearing loss after the third dose with having received 3 doses ($r_s = 0.80$; $p = 0.0001$) and with the cumulative dose ($r_s = 0.54$; $p = 0.0001$), as well as greater loss with doses > 300 and 325 mg/m² of body surface area in the second dose ($p = 0.036$) and in the cumulative dose ($p = 0.009$), and also between the third study and the cumulative dose ($p = 0.006$). A risk (odds ratio [OR]) of 1.125 (95% confidence interval [95% CI]: 0.893-1.417) was documented for presenting damage in supra-threshold frequencies in the third study with cisplatin doses of 300 mg/m² of body surface area.

DPOAEs showed changes related to the administered dose of cisplatin. Table 6 shows that, in the first study, most patients had present responses in PCO (33 patients; 89.2%) and PWCO (5 patients; 100%).

Table 3. Mean hearing threshold by frequency (Low, Mid, and High) in the general population and separated by patients with and without ototoxicity

Hearing threshold by frequency	Mean $\pm$ SD/Range	General population (n = 42)	With ototoxicity (n = 37)	Without ototoxicity (n = 5)	p
Low frequencies dose 1 (dB)	Mean $\pm$ SD	13.4 $\pm$ 3.3	13.7 $\pm$ 3.2	11.4 $\pm$ 3.3	0.142
	Range	8-21	8-21	8-15	
Low frequencies dose 2 (dB)	Mean $\pm$ SD	14. $\pm$ 6.3	15.27 $\pm$ 6.5	11.6 $\pm$ 3.6	0.228
	Range	8-47	8-47	8-16	
Low frequencies dose 3 (dB)	Mean $\pm$ SD	17.7 $\pm$ 8.3	17.6 $\pm$ 8.5	19.0	0.874
	Range	7-56	7-56	-	
Mid frequencies dose 1 (dB)	Mean $\pm$ SD	14.1 $\pm$ 6.6	14.49 $\pm$ 6.9	11.4 $\pm$ 2.07	0.335
	Range	7-47	7-47	8-13	
Mid frequencies dose 2 (dB)	Mean $\pm$ SD	13.8 $\pm$ 7.6	14.68 $\pm$ 7.6	7.4 $\pm$ 3.3	0.043
	Range	4-34	5-34	4-12	
Mid frequencies dose 3 (dB)	Mean $\pm$ SD	12.2 $\pm$ 6.9	12.3 $\pm$ 7.0	8.0	0.547
	Range	3-34	3-34	-	
High frequencies dose 1 (dB)	Mean $\pm$ SD	19.17 $\pm$ 12.7	19.8 $\pm$ 13.5	14.4 $\pm$ 1.1	0.379
	Range	8-63	-	13-16	
High frequencies dose 2 (dB)	Mean $\pm$ SD	31.1 $\pm$ 18.2	33.16 $\pm$ 18.4	16 $\pm$ 1.7	0.046
	Range	10-76	10-76	15-19	
High frequencies dose 3 (dB)	Mean $\pm$ SD	44.6 $\pm$ 20.9	45.7 $\pm$ 20.3	11.0	0.104
	Range	11-91	11-91	-	

X $\pm$ SD: mean $\pm$ standard deviation.

There were changes after the second dose in PCO, in which most did not present emissions (22 patients; 60%), yet the variation was not significant ($p = 0.11$; chi-square test), and for the evaluation after the third dose, all presented absence of response (28 patients; 100%) ($p = 0.05$). In PWCO, there were no changes, as only 1 patient had no response ($p = 0.34$). The only patient who received 3 doses always presented a response in the different measurements. The presence/absence of responses in DPOAEs showed a significant difference only after the second dose of cisplatin ($p = 0.034$), with an OR of 1.973 (95% CI, 1.097-3.549) for the absence of responses with doses higher than 300 and 325 mg/m² of body surface area. In patients with 3 doses, the difference was significant, with absence of responses ($p = 0.0001$). An association was found ($r_s = 0.67$; $p = 0.036$) with the cumulative dose of 300 mg/m² of body surface area in PCO after the second dose and an OR of 4.0 for

the absence of responses (95% CI, 0.733-21.838) with the same dose ($p = 0.034$).

Discussion

One of the most important findings of this study was to identify hearing impairment in children with cancer treated with cisplatin in high and high-frequency tones (10,000-16,000 Hz) from the first dose of cisplatin, along with 1 or 2 more drugs (Tables 3 to 5). Of note, the prevalence of hearing loss at the end of treatment is considered the most important primary finding, as it reflects the toxicity of CT at the end (Tables 3 to 5). In this investigation all 37 PCO (100%) presented deterioration in high frequencies from the first dose and had damage in high-pitched tones from the second dose, according to Brock's classification (Tables 4 and 5), which is consistent with other reports¹⁵.

It has been published that hearing loss occurs in about 10% of childhood cancer survivors in general²²,

Table 4. Mean and standard deviation, and range, of hearing thresholds by frequency low (0.125-0.5 kHz); mid (1-2 kHz); High: (4-8 kHz) in the general population and separated by patients with and without ototoxicity, according to number of doses received (two or three)

Hearing threshold by frequency	Mean $\pm$ SD/Range	General population		With ototoxicity		Without ototoxicity	
		2 doses (n = 13)	3 doses (n = 29)	2 doses (n = 9)	3 doses (n = 28)	2 doses (n = 4)	3 doses (n = 1)
Low frequencies dose 1 (dB)	Mean $\pm$ SD	11.69 $\pm$ 2.18	14.2 $\pm$ 3.41	12.2 $\pm$ 1.64	14.18 $\pm$ 3.47	10.5 $\pm$ 3.0	15
	Range	8-15	8-21	10-15	8-21	8-14	-
Low frequencies dose 2 (dB)	Mean $\pm$ SD	11.69 $\pm$ 2.17	16.2 $\pm$ 7.07	12.2 $\pm$ 1.64	16.25 $\pm$ 7.2	10.5 $\pm$ 3.0	16
	Range	8-15	8-47	10-15	8-47	8-14	-
Low frequencies dose 3 (dB)	Mean $\pm$ SD	-	17.8 $\pm$ 8.4	-	17.79 $\pm$ 8.56	-	19
	Range	-	7-56	-	7-56	-	-
Mid frequencies dose 1 (dB)	Mean $\pm$ SD	11.46 $\pm$ 2.47	15.3 $\pm$ 7.55	11.6 $\pm$ 2.69	15.39 $\pm$ 7.68	11.0 $\pm$ 2.16	13
	Range	7-16	8-47	7-16	8-47	8-13	-
Mid frequencies dose 2 (dB)	Mean $\pm$ SD	8.3 $\pm$ 3.75	16.28 $\pm$ 7.6	9.0 $\pm$ 3.8	16.5 $\pm$ 7.67	6.75 $\pm$ 3.59	10
	Range	4-16	6-34	5-16	6-34	4-12	-
Mid frequencies dose 3 (dB)	Mean $\pm$ SD	-	12.5 $\pm$ 6.8	-	12.68 $\pm$ 6.89	-	8
	Range	-	3-34	-	3-34	-	-
High frequencies dose 1 (dB)	Mean $\pm$ SD	16.3 $\pm$ 4.49	20.45 $\pm$ 14.9	17.0 $\pm$ 5.3	20.7 $\pm$ 15.15	14.75 $\pm$ 0.95	13
	Range	13-28	8-63	13-28	8-63	14-16	-
High frequencies dose 2 (dB)	Mean $\pm$ SD	21.2 $\pm$ 9.46	35.5 $\pm$ 19.49	23.4 $\pm$ 10.7	36.29 $\pm$ 19.4	16.25 $\pm$ 1.89	15.00
	Range	14-45	10-76	14-45	10-76	15-19	15
High frequencies dose 3 (dB)	Mean $\pm$ SD	-	45.38 $\pm$ 20.8	-	46.6 $\pm$ 20.13	-	11.00
	Range	-	11-91	-	11-91	-	11

Mean $\pm$ SD = mean and standard deviation.**Table 5. Mean and standard deviation, and range, of suprathreshold hearing (high frequencies 10-16 kHz) in the general population and separated by patients with and without ototoxicity, according to number of doses received (two or three)**

High-frequency hearing threshold	Mean $\pm$ SD/ Range	General population		With ototoxicity		Without ototoxicity	
		2 doses (n = 13)	3 doses (n = 29)	2 doses (n = 9)	3 doses (n = 28)	2 doses (n = 4)	3 doses (n = 1)
First test (dose 1) (dB)	Mean $\pm$ SD	22.3 $\pm$ 10.7	23.8 $\pm$ 16.8	24.7 $\pm$ 12.3	24.0 $\pm$ 17.0	17.0 $\pm$ 1.6	18.0
	Range	15-53	2-71	17-53	2-71	15-19	-
Second test (dose 2) (dB)	Mean $\pm$ SD	35.9 $\pm$ 18.2	45.0 $\pm$ 19.9	43.0 $\pm$ 17.6	45.8 $\pm$ 19.9	20.0 $\pm$ 3.4	23.0
	Range	18-70	14-87	25-70	14-87	18-25	-
Third test (dose 3) (dB)	Mean $\pm$ SD	-	58.8 $\pm$ 19.8	-	60.0 $\pm$ 19.1	-	26.0
	Range	-	21-102	-	21-102	-	-

Mean $\pm$ SD = mean and standard deviation

but in our work the prevalence was much higher (88.1%), more in line with that reported by Diepstraten et al.¹⁵, who indicate that up to 70% of children on

platinum develop irreversible hearing loss, and 40% need to use hearing aids at an early stage. However, our figure may be overestimated, since all used

Table 6. Proportion of patients with presence/absence of distortion product otoacoustic emissions in the general population and separated by patients with and without ototoxicity, according to the number of doses received (two or three)

DPOAE (present/absent)	Present/absent	General population		With ototoxicity		Without ototoxicity	
		2 doses (n = 13)	3 doses (n = 29)	2 doses (n = 9)	3 doses (n = 28)	2 doses (n = 4)	3 doses (n = 1)
First test (dose 1)	Present	12	26	8	25	4	1
	Absent	1	3	1	3	0	0
Second test (dose 2)	Present	7	12	4	11	3	1
	Absent	6	17	5	17	1	0
Third test (dose 3)	Present	-	1	0	0	-	1
	Absent	-	28	0	28	-	0

DPOAE = distortion product otoacoustic emissions.

cisplatin and had audiological studies, although consistent with the report that prevalence estimates of hearing loss after cisplatin vary widely between different studies, due to additional risk factors such as the use of aminoglycosides and loop diuretics, or other antineoplastic agents that cause hearing loss²².

Some authors propose that in the evaluation of these children, the use of more than one study that assesses auditory function is convenient, due to the credibility of the results considering the age of the child at the time of performing behavioral studies. In this work, tonal and high-frequency audiometry, as well as DPOAEs, were used, because impedanceometry findings and brainstem auditory evoked potentials are not considered relevant^{15,23}.

According to other authors, we found that the cumulative dose of cisplatin was associated with hearing loss¹¹, since higher cyclical doses can increase the cochlear administration of the drug through the saturation of active and passive transport mechanisms in the cochlea, and once there, cisplatin accumulates and is retained, particularly after repeated high doses²⁴. It was interesting that a cumulative dose > 300 and 325 mg/m² of body surface area was related to the presence of lesions in high frequencies and high-pitched tones, and with the absence of response in DPOAEs ($p < 0.05$)¹⁵.

Keilty et al.⁷ found, for the development of hearing loss, an OR of 1.48 for the cisplatin dose, taking into account 100 mg/m² of body surface area ($p < 0.001$), with increases in the cumulative incidence of high-frequency hearing loss (> 4 kHz) at 5 years of age and in all frequencies after 5 years⁷. Our analysis made it

possible to show an OR of 1.125 (95% CI, 0.893-1.417) for presenting damage in high frequencies in the third study with cisplatin doses of 300 mg/m² of body surface area, and an OR of 1.973 (95% CI, 1.097-3.549) for the absence of responses in DPOAEs with doses > 300 and 325 mg/m² of body surface area at the end of treatment^{7,15}. Although we found significant differences in hearing loss between the administered doses, second and third doses, as well as in the cumulative dose, the duration of the infusions does not seem to matter¹⁶.

Bass et al.¹⁸ identified subclinical effects of hearing loss after exposure to RT in cancer patients, particularly in the high-frequency range and in DPOAEs, while hearing remained normal for conventional frequencies. Our findings are consistent with this behavior, in relation to the use of cisplatin, although without long-term follow-up (Figs. 1 and 2, and Table 6). However, it is important to follow the recommendation of follow-up for several years to monitor possible late auditory effects¹⁸, due to exposure to ototoxic drugs with CT or RT. Also, Moke et al.¹³ reported that the risk for hearing loss increased by 10-20% for every 100 mg/m² of body surface area of cumulative cisplatin dose (OR, 1.11; 95% CI, 1.01-1.23). We found a similar risk (OR, 1.125; 95% CI, 0.893-1.417) with a cisplatin dosage of 300 and 325 mg/m² of body surface area in the second dose ($p = 0.036$), while in the work of Moke et al.¹³ the loss was moderate/severe at the end of treatment with cisplatin doses, finding that for every 50 mg/m²/cycle increase, they identified an OR, 2.16 (95% CI, 1.37-3.51). In addition, we found that differences in cisplatin dosage conferred an OR of

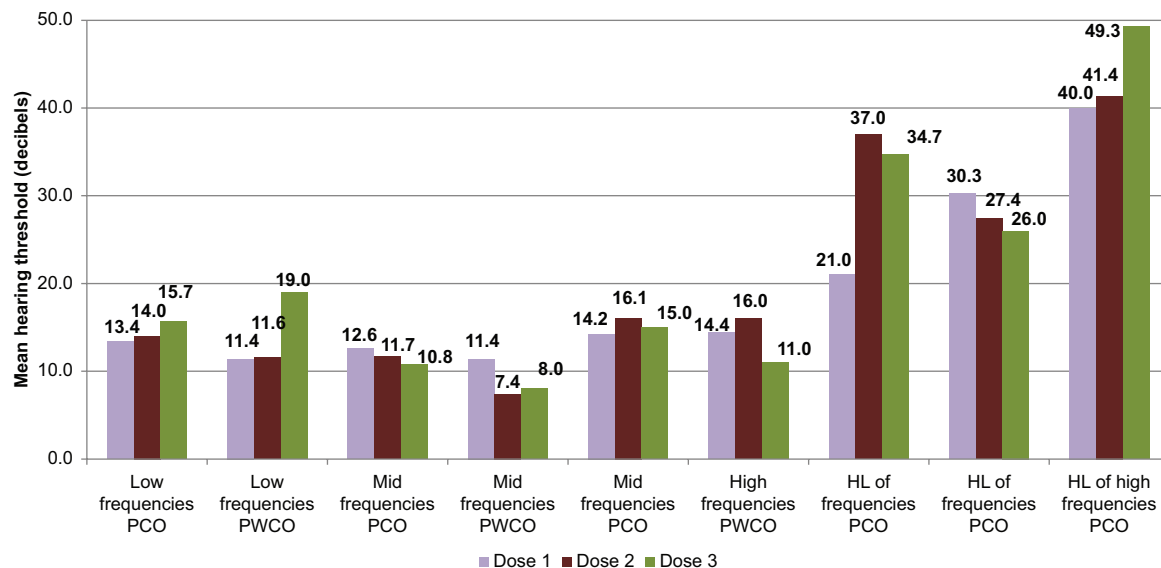


Figure 1. Behavior of auditory thresholds, with and without ototoxicity criteria, according to the number of doses. HL: hearing loss; PCO: patients with criteria for ototoxicity; PWCO: patients without criteria for ototoxicity.

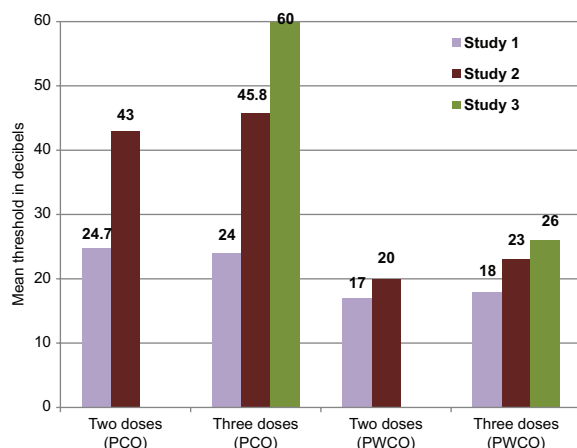


Figure 2. Behavior of supra-threshold responses, with and without ototoxicity criteria, according to the study number. PCO: patients with criteria for ototoxicity; PWCO: patients without criteria for ototoxicity.

4.0 (95% CI, 0.733-21.838) in loss of responses in DPOAEs. While it should be considered that increasing the cumulative dose of cisplatin administered ($\pm 100 \text{ mg/m}^2$ of body surface area) protected against death, it was the opposite with disease progression¹³.

Contrary to what was stated by Moke et al.¹³, it is believed that retained cisplatin is likely to only contribute to long-term toxicity, as circulating cisplatin has been detected in the plasma of survivors even decades after therapy. Therefore, further research is justified on possible interventions to reduce cisplatin-induced

hearing loss by altering the intensity of cisplatin dosage with or without the introduction of otoprotective agents, while maintaining the cytotoxicity and curative potential of the cumulative dosage, such as the use of amifostine and sodium thiosulfate in children as an otoprotective intervention¹³ or the use of dexamethasone and antioxidant nanoparticles, which effectively prevented apoptosis and the production of reactive oxygen species caused by ototoxic stimuli²⁵.

The audiological data found show that hearing loss is frequent in childhood cancer survivors. It is difficult to establish the relationship between hearing loss and other antineoplastic drugs (such as vincristine)¹³, because treatment with cisplatin was an inclusion criterion, which makes it difficult to identify the contribution of other factors. However, hearing tests are non-invasive, cheap, and easy to perform, and each child undergoes them several times during childhood for screening purposes. Therefore, our results are consistent with the need for future studies to have broader inclusion criteria and to offer hearing tests to all people who received any CT, not only those who received drugs already known to be ototoxic²². Studies with broader criteria will allow the detection of new risk factors in the constantly evolving landscape of cancer therapies²⁶.

Accurate audiological tests and timely detection of ototoxicity contribute to the early detection of hearing loss, which can indirectly lead to a better quality of

life. In addition, high-quality data were collected on the relationship between disease status, type of treatment, and audiological functioning in children with cancer during treatment, which in the future could be used to identify children who are at risk and who could benefit from otoprotective agents¹⁵.

We also consider this work relevant because some authors mention that there is a surprising lack of studies that specifically investigate the late effects in childhood cancer survivors, considering that the number of survivors has currently increased²⁷.

Conclusions

Cisplatin is a widely used antineoplastic drug in the treatment of childhood cancer, and ototoxicity is one of its most frequent adverse effects. We found 88.1% of patients with hearing impairment and up to 100% when high frequencies were included in the studied cases. Sensorineural hearing loss was documented to begin in high frequencies, but with the increase in the cumulative dose of cisplatin (≥ 300 mg/m² of body surface area), the damage continues to high-pitched and mid frequencies, compromising the language area after the second and third doses. Evaluating the auditory function of children with cancer during their treatment with cisplatin can allow the timely detection of deterioration of auditory thresholds. High-frequency tonal audiometry and DPOAEs proved to be useful, as they revealed early changes in auditory function compared to tonal audiometry at conventional frequencies, so auditory monitoring protocols in patients treated with cisplatin should include, at least, these audiological studies.

In conclusion, because the number of childhood cancer survivors has increased in recent decades, it is of utmost importance to establish screening and monitoring protocols for ototoxicity in patients treated with cisplatin and other potentially ototoxic agents to know the auditory function from the initial stages of treatment, and to be able to intervene opportunely with auditory rehabilitation, since hearing loss in this population group has repercussions on language, learning, social integration, and personality development.

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Conflicts of interests

The authors declare no conflicts of interest.

Ethical Considerations

Protection of persons and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. The relevant recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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