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Hearing loss in Mexican children treated with cisplatin

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ABSTRACT

Objective: Cisplatin is widely used to treat a variety of pediatric solid tumors. One of the most severe and debilitating adverse drug reactions experienced by patients who receive cisplatin therapy is permanent bilateral hearing loss. The aim of this study was to evaluate the incidence and risk factors for cisplatin-induced hearing loss in Mexican pediatric patients.
Methods: Detailed medical and drug histories, including use of cisplatin as well as other drugs known to cause hearing loss, were collected from patient medical records. Results of audiology tests on pediatric patients with solid tumors were collected at baseline, during treatment and at the end of cisplatin chemotherapy. Hearing loss was classified according to the Common Terminology Criteria for Adverse Events. Bivariate and multivariate analyses were performed using survival curves.
Results: Fifty-nine pediatric patients, median age 11 years (range, 3–17 years) were included in the study. The incidence of cisplatin-induced hearing loss was 56%. Individual risk factors including age (<5 years), male sex, and concomitant medications were not associated with an increased risk of cisplatin-induced hearing loss. Patients with a diagnosis of osteosarcoma and a cumulative cisplatin dose greater than 400 mg/m^2 were at higher risk of hearing loss compared with all other tumor and cumulative dose combinations (HR = 2.47 [95% CI, 1.043–5.831]).
Conclusions: Cumulative dose and tumor type are associated with an increased risk of cisplatin-induced hearing loss. Further research is required to characterize fully the interindividual variation in hearing loss in Mexican patients.

Introduction

Every year in Mexico about 4000 children are diagnosed with cancer [1], about 40% of whom have a solid tumor [2]. Fortunately, treatment of childhood cancer has improved significantly with survival rates reaching 80% at 5 years after diagnosis [3]. Regrettably, 40% of childhood cancer survivors suffer severe life-threatening or permanently disabling adverse drug reactions [4]. Cisplatin has improved survival in a variety of pediatric malignancies, but its use may result in irreversible bilateral high-frequency sensorineural hearing loss [5]. Platinum cochlear toxicity is thought to occur because of interference with signal transduction in the cochlea. Evidence indicates that cisplatin causes damage by inducing apoptosis that occurs at three sites in the cochlea: the outer hair cells in the organ of Corti, the spiral ganglion, and the stria vascularis [6]. The mechanism of this damage has not been fully elucidated, although evidence points to the generation of

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toxic levels of reactive oxygen species, which initiate cell death by the activation of caspases [7]. In general, about 50% of children treated with cisplatin develop some degree of permanent hearing loss, the incidence reaching 90% in young children with cumulative cisplatin doses above 400 mg/m^2 [8–11]. Several risk factors have been associated with cisplatin-induced hearing loss, including age younger than 5 years, higher cumulative cisplatin doses, high cisplatin doses, coadministration with aminoglycosides and loop diuretics, impaired renal function, and cranial irradiation [8–11]. Cisplatin-induced hearing loss may affect the development of speech and language, educational performance and social–emotional development [10,12]. Although this problem has been documented extensively in the literature, information regarding Latin American patients is scarce. Therefore, the aim of this retrospective cohort study was to evaluate the incidence and risk factors associated with hearing loss in Mexican pediatric cancer patients treated with cisplatin.

Materials and methods

Study design

A retrospective medical record review was performed to identify pediatric patients with cancer treated with cisplatin at the Hospital Infantil de Mexico Federico Gomez, between January 2000 and February 2010. Children who met the following criteria were included: (1) tonal audiometry before the start of chemotherapy; (2) audiological monitoring during treatment; and (3) audiometry at the end of chemotherapy. Any patient with hearing impairment before starting chemotherapy was excluded. Data collection included demographic information, cancer diagnosis, cumulative dose of cisplatin, concomitant medication, and audiograms. Approval for this study was obtained from the Institutional Review Board of the Hospital Infantil de Mexico Federico Gomez.

Audiometric evaluation

A pediatric audiologist using a sound-damped cabinet performed pure-tone audiometry. Air and bone conduction hearing thresholds were tested at 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. Hearing loss severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [13]. Children with changes in hearing threshold > 20 dB at 8 kHz in one ear (CTCAE, grade 1) or higher were considered cases.

Statistical analysis

Descriptive statistics were used, using median and range for the quantitative variables age and cumulative dose, and frequency and percentage for the qualitative variables sex, tumor type, and concomitant medications. Kaplan–Meier plots were used to estimate the time to hearing loss defined according to the CTCAE criteria. Two groups were identified depending on hearing status: the first without changes in hearing thresholds and the second with hearing loss at grade ≥ 1 according to the CTCAE criteria. To determine risk factors for cisplatin-induced hearing loss, we estimated odds ratios (OR) with 95% confidence intervals (95% CI). In addition, the ORs were adjusted for age, sex, diagnosis of osteosarcoma and cumulative cisplatin doses ≥ 400 mg/m^2 using a multiple logistic regression (MLR). Furthermore, an OR was calculated to determine the risk of cisplatin-induced hearing loss when cisplatin was given with other drugs. Calculated ORs were adjusted for age and cumulative cisplatin dose using an MLR. Several Cox proportional hazards models were constructed to assess the impact of simultaneous predictors of cisplatin-induced hearing loss. Results of this analysis are expressed as hazard ratio (HR) with 95% CI. All analyses were performed using SPSS version 20 (IBM, Chicago, IL).

Results

Fifty-nine patients met the criteria for inclusion in this study. Table 1 shows the characteristics of the patients included. The median age was 11 years with a range of 3–17 years at the time of baseline hearing evaluation. The majority of patients were treated for osteosarcoma (64.4%) and hepatoblastoma (15.3%). Half the patients were boys. The most commonly used concomitant medication was doxorubicin (67.8%) followed by vincristine (22.0%). The median cumulative dose of cisplatin was 370 mg/m^2.

Thirty-three patients had a decreased hearing threshold according to CTCAE criteria (56%). Fifty-two percent (31/59) had moderate to severe hearing loss (CTCAE ≥ 2). Thirteen patients (22%) required hearing aids at the end of treatment with cisplatin. The median time to the first significant decrease in hearing was 254 days (95% CI, 173–334 days; Fig. 1). In the risk factor analysis, age ≤ 5 years ($n = 13$; OR = 0.90 [95% CI, 0.26–3.09]), male sex (OR = 0.91 [95% CI, 0.32–2.55]), cumulative cisplatin dose > 400 mg/m^2 (OR = 1.92 [95% CI, 0.67–5.46]) or osteosarcoma diagnosis (OR = 1.69 [95% CI, 0.57–4.94]) were not associated with an increased risk of cisplatin-induced hearing loss. Similar results were observed when risk factors were analyzed in a multivariate analysis (Table 2). No increased risk was found with concomitant treatment with doxorubicin (OR = 0.46 [95% CI, 0.15–1.46]), vincristine (OR = 1.70 [95% CI, 0.38–7.58]) or amikacin (OR = 0.77 [95% CI, 0.14–4.15]). No significant association with any variable was found in multivariate analysis (Table 3). To understand better the interaction of risk factors in the development of cisplatin-induced hearing loss we constructed several Cox proportional hazards models. Interestingly, we observed that patients

Table 1
Clinical characteristics of pediatric patients with cancer treated with cisplatin ($N = 59$).

	N (%)
Sex, male	31 (52.5)
Tumor type	
Osteosarcoma	38 (64.4)
Hepatoblastoma	9 (15.3)
Germ cell tumor	4 (6.8)
Rhabdomyosarcoma	2 (3.4)
Sarcoma	2 (3.4)
Adrenal carcinoma	1 (1.7)
Wilms tumor	1 (1.7)
Neuroblastoma	1 (1.7)
Medulloblastoma	1 (1.7)
Concomitant medication	
Doxorrubicin	40 (67.8)
Vincristine	13 (22.0)
Ifosfamide	9 (15.3)
Cyclophosphamide	6 (10.2)
Etoposide	3 (5.1)
Amikacin	6 (10.2)
CTCAE[a] hearing loss	
No hearing loss	26 (44.0)
Grade 1	2 (3.5)
Grade 2	18 (30.5)
Grade 3	10 (16.9)
Grade 4	3 (5.1)
	Median (min–max)
Age, years	11.0 (3–17)
Cumulative cisplatin dose, mg/m^2	370 (170–695)

[a] CTCAE: Common Terminology Criteria for Adverse Events.