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Incidence and associated risk factors for platinum-induced ototoxicity in pediatric patients

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ABSTRACT

Objectives: Platinum-based chemotherapy is effective against a variety of pediatric malignancies. Unfortunately, the use of cisplatin and carboplatin can lead to permanent and progressive sensorineural hearing loss which can affect the quality of life of cancer survivors. The objectives of this study were to evaluate the incidence of platinum-induced ototoxicity in children and analyze potential risk factors.

Methods: Prospective cohort study. All pediatric patients receiving chemotherapy with cisplatin and/or carboplatin from 01/2012 until 10/2017 were included. Hearing evaluations were performed before every chemotherapy cycle, and following the end of chemotherapy, with auditory brainstem response, otoacoustic emissions and/or audiometry. Demographics, cumulative doses, cranial irradiation and exposure to other ototoxic agents were analyzed.

Results: Twenty-eight patients were included, with a mean age of 7.2 years at the beginning of chemotherapy (range 5 months–15 years 2 months); twenty-one patients received cisplatin, four received carboplatin, and three received both agents. Twelve patients had cranial irradiation and seven received another ototoxic medication. The most frequent malignancies were germ cell tumors, medulloblastoma and gliomas. Sensorineural hearing loss occurred in 28.6% of the patients with a mean follow-up period of 21.5 months (range: 1–53 months). All patients evaluated with audiometry had ≥ Chang 2b ototoxicity. Risk factors include age less than 5 years, cranial irradiation, and cisplatin cumulative dose greater than 400 mg/m^2.

Conclusion: Sensorineural hearing loss is a potential side effect of platinum-based chemotherapy. Pediatric patients receiving cisplatin chemotherapy with a cumulative dose exceeding 400 mg/m^2, cranial irradiation as well as patients younger than 5 years are at greater risk of developing hearing loss.

1. Introduction

The platinum compounds, cisplatin and carboplatin, are commonly used against a variety of pediatric malignancies. They are effective chemotherapeutic agents but their use can lead to serious side effects, such as nephrotoxicity, neurotoxicity, and ototoxicity [1]. Platinum-induced ototoxicity has been described as a bilateral, progressive, and irreversible sensorineural hearing loss. It has also been observed that patients can develop hearing loss years after completing their chemotherapy treatment [2], and can also exhibit tinnitus [3]. Hearing loss, particularly in children, can be debilitating, as it can have a negative impact on their ability to learn, develop, and interact with their peers. It has been shown that even a slight degree of hearing loss can disrupt a child's development, and psychological state [4,5]. As a result, it can lead to distressing consequences on the quality of life of childhood cancer survivors.

Various risk factors have been described for platinum-induced ototoxicity. It is believed that age at treatment (patients less than 5 years old), high cumulative doses, pre-existing renal insufficiency, pre-existing hearing loss, concomitant ototoxic medication use, and cranial irradiation play a role in its severity [6]. Because not all children with risk factors develop hearing loss, and because the same chemotherapy treatment can lead to different levels of severity, it has been suggested that there is a genetic susceptibility for this condition.

It has been observed that cisplatin can lead to cochlear cell death as a result of local inflammation, oxidative stress and formation of DNA adducts, and it appears that the generation of reactive oxygen species within the cochlea is the main mechanism of ototoxicity [7,8]. As a result, many gene variants have been evaluated as potential genetic risk factors including single-nucleotide polymorphisms for antioxidant enzymes (glutathione S-transferases, thiopurine S-methyltransferase, catechol-O-methyltransferase), megalin, copper transporters, and much

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more [9,10]. Although interesting and innovative studies have been published, for now, results from pharmacogenetic studies have not been able to elucidate a potential genetic marker determining which patients are at greater risk of developing hearing loss when receiving platinum-based chemotherapy [9,11].

The objective of this study is to evaluate the incidence of platinum-induced ototoxicity in pediatric patients, assess its severity, and analyze potential associated risk factors.

2. Material and methods

2.1. Ethics approval

All of the patients in this study are included in the Chilean Pediatric National Cancer Program (PINDA) which includes diagnosis, treatment, palliative care, follow-up and quality of life evaluations for children with cancer. The parents of all children provide consent for all of the above mentioned. Ethics approval for this study was obtained from the research ethics committee at the Complejo Asistencial Dr. Sótero Del Rio.

2.2. Patients

A prospective observational cohort study was carried out. All pediatric patients receiving cisplatin and/or carboplatin at the Complejo Asistencial Dr. Sótero Del Rio were included from 01/2012 until 10/2017. Pediatric patients (less than 18 years of age) with cancer requiring treatment with platinum-based chemotherapy were included. Patients were excluded from analysis if hearing evaluations were incomplete, or patients were deceased before completing their chemotherapy treatments. Data analyzed include patient demographics, type of malignancy, cisplatin and carboplatin cumulative doses, cranial irradiation, ototoxic medication use, follow-up time and hearing evaluations.

2.3. Hearing evaluation

Audiologic assessment was performed with pure-tone audiometry. For patients younger than 3 years or who could not cooperate in audiometry testing, distortion product otoacoustic emissions (DPOAEs) and/or auditory brainstem response (ABR) testing were performed. Both air and bone conduction thresholds were calculated for the frequencies 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz; bone conduction thresholds were used in order to compare audiograms. DPOAEs were obtained for the following frequencies: 597,7; 703,1; 843.8; 996.1; 1183,6; 1418; 1687.5; 2003,9; 2378.9; 2824,2; 3363.3; 3996,1; 4757.8; 5660,2; 6726,6; 8003,9; 9515.6 and 11308.6 Hz. For ABR testing, a click stimulus with alternating split polarity and stimulus rate of 27.5/sec was used (Vivosonic-integrity equipment). For all of these evaluations, patients served as their own controls for detecting changes in hearing levels. Otoscopy and immittance were always performed prior to any hearing evaluation. Hearing assessments were performed before, during and after chemotherapy.

2.4. Ototoxicity criteria

For determining hearing loss, its severity and clinically significant hearing loss, the Chang criteria was used for audiometry testing [12]. If middle ear pathology was detected or conductive hearing loss was present, grading was based on bone conduction thresholds. Only in cases when it was not possible to obtain bone conduction thresholds was the audiogram considered not evaluable. If the patient had DPOAEs initially and at a later point in time, audiometry testing, detection of incipient hearing loss was determined. DPOAE signal-to-noise ratio of less than 6 dB was considered abnormal at any frequency tested for the purposes of this study (with normal middle ear function). Because ABR latencies and amplitudes have been described to change with age and development, results were classified as normal or abnormal by the audiologist. If the ABR was considered as abnormal, thresholds and changes in amplitude and latencies were compared to previous ABRs. Ototoxicity grading was not applied to DPOAE or ABR results because there are no accepted criteria for ototoxic change with these tests at the moment.

2.5. Statistics

Descriptive data are provided as means and standard deviations for numeric variables and percentages for categorical variables. The Mann-Whitney *U* test was used for continuous variables. A P value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographics

Thirty patients were initially included in the study; however, two patients passed away during the chemotherapy treatment, therefore twenty-eight patients were finally included, with a mean age of 7.2 years at the beginning of chemotherapy (range 5 months–15 years 2 months). The most frequent malignancies were germ cell tumors, medulloblastoma and gliomas. Twenty-one patients received cisplatin, four received carboplatin, and three received both agents. The cumulative dose for cisplatin was 459.5 mg/m^2 (range 150–800 mg/m^2) and for carboplatin, 3651 mg/m^2 (range 1050–9800 mg/m^2). (Table 1). Twelve patients received cranial irradiation and seven received another ototoxic medication during the oncology regimen (furosemide, gentamicin or amikacin) (Table 2).

3.2. Hearing evaluations

All of the patients had normal hearing before beginning the chemotherapy treatment. Nineteen patients underwent hearing assessments with pure tone audiometry while eleven patients underwent ABR testing; twenty patients had DPOAE testing. At the end of the chemotherapy, sensorineural hearing loss was observed in 28.6% (8/28) of the patients with a mean follow-up period of 21.5 months (range: 1–53 months). For the patients that were evaluated with audiometry, all of the patients that developed hearing loss had ≥ Chang 2b ototoxicity. Average threshold shifts for all of the patients at the end of

Table 1
Patient demographics.

Characteristics	n (%)	Mean (range)
Sex		
Male	17 (60.7)	
Female	11 (39.3)	
Age at chemotherapy		7.2 yrs (5 months–15 yrs 2 months)
Type of malignancy		
Germ cell tumor	10 (35.7)	
Medulloblastoma	7 (25)	
Glioma	4 (14.3)	
Neuroblastoma	3 (10.7)	
Wilms tumor	2 (7.1)	
Other[a]	2 (7.1)	
Treatment		
Cisplatin	21 (75)	459.5 mg/m^2 (150–800 mg/m^2)
Carboplatin	4 (14.3)	3651 mg/m^2 (1050–9800 mg/m^2)
Cisplatin and Carboplatin	3 (10.7)	
Cranial irradiation	12 (42.9)	

[a] Other: hepatoblastoma (n = 1), osteosarcoma (n = 1).