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Risk Factors for Cisplatin-Associated Ototoxicity in Pediatric Oncology Patients

Allison Yancey, MD^{1,*}, Michael S. Harris, MD², Akinbode Egbelakin, MBBS³, Jaimie Gilbert, PhD², David B. Pisoni, PhD², and Jamie Renbarger, MD^{1,3}

¹Division of Pediatric Hematology/Oncology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana

²Department of Otolaryngology—Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, Indiana

³Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Abstract

Background—Cisplatin is an effective chemotherapy agent against several pediatric malignancies. One of its side effects is irreversible sensorineural hearing damage that is highly variable with a reported incidence of 22–70%. The aim of this study was to evaluate the incidence and identify clinical predictors of cisplatin-related ototoxicity.

Procedures—We performed a retrospective chart review of 102 pediatric patients who had completed cisplatin therapy for osteosarcoma, neuroblastoma, hepatoblastoma, or germ cell tumor. Patients were diagnosed at Riley Hospital for Children between January 1995 and June 2008, were less than 18 years old at diagnosis, and had normal hearing prior to therapy. Audiograms were scored using the Brock scale (0–4), a validated grading system for cisplatin-related hearing loss.

Results—Forty-two percent of the patients experienced hearing loss and 28% had moderate to severe ototoxicity (Brock score ≥ 2). Males were at significantly greater risk for developing hearing loss than were females ($P = 0.005$, OR 4.812). Age at cancer diagnosis was inversely related to severity of ototoxicity. Patients who suffered Brock grade 3 ototoxicity had a mean age of 4.5 years versus 11.5 years and 7.2 years for grades 1 and 2, respectively ($P = 0.02$). Cumulative cisplatin dose was also identified as a risk factor for development of ototoxicity ($P = 0.03$).

Conclusions—Gender and cumulative dose are important clinical biomarkers of cisplatin ototoxicity. Severity of ototoxicity may be inversely related to age at time of exposure, with very young patients exhibiting higher grades of hearing loss following cisplatin therapy.

Keywords

cisplatin; hearing loss; ototoxicity; risk factors

INTRODUCTION

Cisplatin is an important component of pediatric chemotherapy regimens used to treat neuroblastoma, osteosarcoma, germ cell tumor, hepatoblastoma, brain tumors, and retinoblastoma. One of its common side effects is ototoxicity, manifested as bilateral sensorineural hearing loss. The reported incidence of cisplatin-related ototoxicity in children ranges from 22% to 70% [1–4]. The severity of hearing loss appears to be worse at high frequencies (4–8 kHz) and is related to the cumulative dose of cisplatin. Other factors including age, concurrent medications, administration schedule, renal function, and cranial irradiation play a less clearly defined role. The degree of hearing loss is highly variable. Some children experience loss of only high frequency hearing while others experience hearing loss at frequencies less than 4 kHz and require subsequent intervention with an assistive device. The hearing damage tends to be permanent, and although most studies have found that the degree of hearing loss remains stable overtime, there is some evidence that it may be progressive, even after cisplatin therapy has ended [2]. High frequency hearing loss renders certain consonants inaudible and may compromise speech recognition and comprehension. Given that hearing is an integral component of speech development, young children receiving cisplatin may be at risk for cognitive and psychosocial delays [4–6].

Some of the variability in reported incidences of ototoxicity is due to the inconsistencies in assessment and grading tools. Conventional grading systems, including the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), may not be appropriate for classifying cisplatin ototoxicity as the grades are determined by threshold shift, not actual hearing loss. This could lead to widely variable scoring if patients start from different baselines. Obtaining a baseline, pre-chemotherapy audiologic evaluation can be difficult in some clinical situations. Hearing loss classifications specifically designed for cisplatin-related ototoxicity exist such as the Brock criteria [7] and the more recently published Chang scale [8]. The majority of the current literature examining post-cisplatin hearing loss in children utilizes the Brock criteria. This system was designed and validated specifically for cisplatin-related ototoxicity, focusing on high frequencies, where hearing loss initially occurs following cisplatin exposure. Hearing loss grades 0–4 are assigned based on standard pure-tone audiograms and reflect absolute hearing loss as opposed to a shift from baseline. Each progressive grade corresponds to loss of critical speech tones (Supplemental Table I).

In this retrospective cohort study, we used the Brock criteria to analyze the hearing status of patients who had been previously treated with cisplatin for neuroblastoma, osteosarcoma, germ cell tumor, or hepatoblastoma at a single pediatric center. The objectives of this study were to evaluate the incidence and severity of hearing loss following cisplatin exposure and to identify clinical and demographic predictors of cisplatin ototoxicity.

METHODS

The Institutional Review Board at Indiana University-Purdue University Indianapolis approved this retrospective cohort study. Review of an internal database at the Riley Children's Cancer Center (RCCC) identified 141 pediatric patients who had received cisplatin therapy for neuroblastoma, osteosarcoma, germ cell tumor, or hepatoblastoma between January 1995 and June 2008. Patients were excluded if age at diagnosis was greater than 18 years, if baseline hearing evaluation was abnormal or if audiograms were not performed at Riley Hospital for Children (and thus were not available). Due to potential effects of tumor location and irradiation, brain tumor patients were excluded from this study. Clinical data and audiologic evaluations were extracted from paper and electronic medical records. Data collected included demographics (gender, race, and age at diagnosis),

cumulative dose of cisplatin for therapy duration (mg/m²), cisplatin dosing adjustments (if applicable), renal function, serum electrolytes, disease status, and audiologic testing. When available, data regarding the use of other potentially ototoxic medications such as vancomycin, gentamicin, amphotericin B, furosemide, and carboplatin were recorded. All patients were treated with cisplatin according to administration schedules described in open cooperative group trials or institutional standard therapy. Doses of other initial chemotherapy agents or relapse therapy were not included.

Ototoxicity Evaluation

Audiology records were reviewed retrospectively by the study audiologist and otolaryngologist. Presence and degree of hearing loss following chemotherapy was ascertained by comparing baseline pure-tone audiograms (2 months prior to initiation of therapy to 3 months after initiation of cisplatin therapy) to end-of-therapy pure-tone audiograms (obtained 5 months prior to completion of therapy to 2.8 years following completion of therapy.) All audiometric assessments were originally performed by conventional or play audiometry by clinical pediatric audiologists under standardized conditions in a sound attenuated booth as part of routine clinical monitoring for cisplatin-related hearing loss. Only children with pure tone audiograms consisting of two or more tested frequencies were included in our analysis. Age, state of illness, and side effects of treatment contribute to the difficulty in obtaining ear specific, multiple-frequency auditory thresholds in this population. However, these individuals represent an important part of the population that we felt should be included in this analysis. Brock grades were assigned based on the available audiometric data. For the purposes of the current analyses, if frequency specific data were missing, we classified thresholds as consistent (i.e., at the same level) with the available data. Given that ototoxicity damages hearing first at higher frequencies (sloping hearing loss), this errs on the side of caution in predicting better hearing/less hearing loss. If frequency specific information across all octave frequencies from 250 to 8,000 Hz was not obtained at the audiometric assessment, there was no consistent pattern for which frequencies data were able to be obtained. The audiograms were conducted by several audiologists who may differ in the order in which they present the tones/frequencies. In our opinion, the children that were able to provide only a limited amount of auditory threshold data should to be included in the analysis as they represent an important part of this population for whom we need to have better knowledge to predict outcomes.

Hearing loss severity was graded using the Brock criteria. Following a protocol established in earlier research in this area, a score achieved by the better ear was utilized [2]. Other than in the setting of ascertaining pre-chemotherapy hearing status, data from otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs) (auditory assessment alternatives for those too young or too ill to participate in pure tone audiometry) were not considered because the Brock criteria cannot be applied to these modalities, and a grading system for cisplatin ototoxicity utilizing these data does not exist.

Ototoxicity Cohorts

For the purposes of analysis, the patients were assigned to two cohort groups. One group consisted of those demonstrating hearing loss following chemotherapy as indicated by a Brock grade of 1 or greater. The second group consisted of patients who maintained normal hearing following chemotherapy, as measured by a Brock grade of 0.

Statistical Analysis

The data analysis for this study was generated using SAS software version 9.1 (SAS Institute, Inc., Cary, NC). Normality of distribution was assessed using the Kolmogorov–

Smirnov and Cramér–von Mises Test. Relationships of continuous variables with the presence/absence of ototoxicity were evaluated with the Wilcoxon's rank sum test, while categorical data were compared using the chi-squared and Fisher's exact test. The Kruskal–Wallis test was used to compare the grades of ototoxicity and continuous variables. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

The preliminary search of the RCCC database revealed 141 patients who had received cisplatin between January 1995 and June 2008. One-hundred thirty-eight children met initial study inclusion criteria. Medical records were available for 132 patients. Of these, 11 were excluded due to diagnosis made at a different institution or due to chemotherapy being administered at a regional hospital. One patient died during therapy and was not included. Review of the medical records of the remaining 121 patients led to exclusion of 19 patients due to lack of audiological records. Table I provides patient, tumor, and treatment characteristics for the 102 patients included in the final analysis.

Forty-one percent of patients received at least one additional ototoxic medication concurrently with cisplatin as part of their treatment. Cisplatin dose was changed or held due to ototoxicity in seven patients. Ten patients had abnormal creatinine or serum electrolyte levels during chemotherapy and five patients had cisplatin doses held or changed due to such lab changes. No patients had abnormal renal function laboratory results at the end of therapy.

Audiometric Analysis

Characteristics of patients with and without hearing loss (any grade) are shown in Table II. Overall, 42% (43/102) exhibited hearing loss of Brock grade 1. Twenty-eight percent (29/102) suffered moderate-to-severe ototoxicity (Brock grade 2). Nearly 12% of patients studied (12/102) were known to use hearing aids after completion of cisplatin therapy. Sixty-six percent of those had grade 3 hearing loss, 25% with grade 2, and 8% with grade 1. Differences in the hearing loss versus no hearing loss groups were found for gender and cumulative cisplatin dose. Males had significantly more hearing loss than females ($P=0.0003$, OR 4.812). The mean cumulative dose of cisplatin was greater for those who had ototoxicity versus those that did not ($429.1 \pm 78 \text{ mg/m}^2$ vs. $390.6 \pm 102 \text{ mg/m}^2$, $P=0.034$). Use of gentamicin, vancomycin, amphotericin B, or furosemide did not have a significant effect on the development of ototoxicity, although we saw a trend toward increased ototoxicity with the use of gentamicin ($P=0.07$). Patients who received carboplatin in addition to cisplatin had significantly more hearing loss than those who received cisplatin only ($P=0.02$). Presence of electrolyte or creatinine changes did not differ between the two groups. Age was not found to be a predictor for the development of ototoxicity; but of those with hearing loss, younger age correlated with more severe toxicity ($P=0.02$, Fig. 1).

DISCUSSION

We evaluated ototoxicity in 102 pediatric patients who had received cisplatin as part of their initial cancer therapy. We observed an overall incidence of hearing loss of 42% and an incidence of moderate to severe hearing loss of 28%. Cumulative cisplatin dose and male gender were found to be independent risk factors for developing ototoxicity.

Cumulative cisplatin dose has consistently been shown to be predictive of cisplatin ototoxicity. In agreement with previous studies, we found that patients with ototoxicity had received cumulative doses greater than 400 mg/m^2 . There is some evidence to suggest that

individual doses and varied dosing regimens differ in their propensity to cause ototoxicity [2,3,5,8]. When we examined incidence of hearing loss across specific tumor types, germ cell tumor patients had less hearing loss as compared to all other tumor types in the cohort ($P = 0.002$). One possible explanation may be the difference in dosing schedules. The majority of germ cell tumor regimens consist of 5 days of cisplatin at 20 mg/m²/dose, in contrast to neuroblastoma and osteosarcoma regimens consisting of a single day of 100 or 120 mg/m²/dose. While the overall cumulative dose of different regimens may be the same, the dosing schedule per course may affect toxicity profiles.

We found gender to be a predictor of hearing loss, with males being four times more likely to experience hearing loss than females. It was noted in this population that hepatoblastoma patients had the most ototoxicity and this group was predominantly male. The group with the least amount of ototoxicity (germ cell tumors) was comprised of mostly female patients. Hence we did a subgroup analysis of neuroblastoma and osteosarcoma tumor groups and we were able to again demonstrate the male ototoxic preponderance ($P = 0.041$). This is an uncommon finding with only two reports in the literature of male gender being associated with cisplatin ototoxicity [4,9]. Previous research examining predictors of cisplatin ototoxicity has not reported a difference in hearing loss between genders [2,10]. Gender-related susceptibility to thrombocytopenia and grade 4 neutropenic fever following cisplatin administration in females with non-metastatic osteosarcoma has been reported, but no differences along gender lines were noted for the presence or absence of hearing loss [11]. Huang et al. examined the half maximal inhibitory concentration (IC₅₀) as an indicator of the effectiveness of a drug at inhibiting biological function. In some cell populations for a number of chemotherapy agents, including cisplatin, female cell lines showed higher IC₅₀ than their male counterparts [12]. It is possible that phenotypic differences following cisplatin therapy, such as hearing loss, may reflect gender-related genetic differences in drug disposition and sensitivity.

Young children are at more risk of developing moderate to severe hearing loss from cisplatin than their adult counterparts [3–5,13]. Often their age at diagnosis and therapy corresponds to a critical stage of development where hearing ability dramatically affects speech, language, and social skills. In this study, moderate to severe hearing loss was seen predominately in patients younger than age 5 years at time of cancer diagnosis. Of the 43 patients with hearing loss of any grade, the mean age and cumulative dose of patients with Brock grade 3 was 4.5 ± 4.9 years (454.3 mg/m^2) versus 11.5 ± 5.3 years (437.7 mg/m^2) and 7.2 ± 4.7 years (404.1 mg/m^2) for grades 1 and 2, respectively. However, although the ototoxicity experienced by older patients is often reported as less severe in terms of grading scales, all patients may exhibit progression of hearing loss over time independent of or synergistic with exposure to other hearing insults as they age. In a long-term follow-up study, Bertolini et al. [2] found a level of grade 2 hearing loss in 11% of patients within 2 years of the end of therapy. In evaluations greater than 2 years off therapy, 44% of patients were found to have grade 2 hearing loss, supporting the possibility of progression of hearing loss with time. As such, even hearing loss that is deemed minimal or mild during cancer treatment may have implications with aging and may still affect school performance and social/emotional functioning.

Another known side effect of cisplatin is nephrotoxicity. For this cohort, renal dysfunction was defined as changes in creatinine, GFR, or electrolytes that persisted at the completion of therapy. Renal function was not found to be significantly affected by cisplatin exposure. An association between altered renal function and hearing loss after cisplatin is not well-studied. Measurements of nephrotoxicity are crude, and additional methods need to be explored in order to develop a clearer understanding of cisplatin-induced kidney injury. Although we did not find any persistent renal abnormalities (in those with or without hearing loss), these data

were incomplete for some patients and this was not a primary outcome in our analysis. Examination may also be confounded by the fact that some chemotherapy agents used in conjunction with cisplatin, such as methotrexate, are also nephrotoxic and the chemotherapeutic drug combinations vary between tumor types.

We did not find an association between disease outcome and incidence of ototoxicity. Our study was not powered to evaluate for this association and thus we cannot confirm a lack of association based on this analysis. The evaluation of a link between cisplatin efficacy and toxicity needs further exploration as a critical factor in optimizing cisplatin use.

A limitation of this study is its retrospective nature. Audiologic data was incomplete for some patients, both at baseline and post-cisplatin time points. While audiologic evaluation was fairly consistent in its performance, there were multiple evaluators collecting audiologic data over time. While this may have minimized individual bias, it also likely introduced variability in testing techniques. In order to maximize the number of patients evaluated in this study, the records spanned a time period of 10 years and some records were incomplete. In addition, not all patients were enrolled on institutional studies and dose adjustments or cessation may have been missed, which could lead to underestimation of at-risk patients in our analysis. However, treatment regimens and protocol specifications in general were extremely stable over time. Patients undergoing chemotherapy often have co-morbid conditions arise which entail the use of other potentially ototoxic drugs such as vancomycin, gentamicin, amphotericin B, and furose-mide. Additionally, carboplatin is used in preparative chemotherapy regimens for neuroblastoma patients undergoing stem cell transplant and use of this platinum agent can lead to augmentation of cisplatin-associated hearing damage [3,14,15]. While we documented exposure to these medications, we did not have sufficient records to evaluate specifics such as dosages and duration.

The evaluation of associated hearing loss has been problematic due to the variability in assessment strategies. The Brock criteria were used in this study due to the relatively high frequency with which it is seen in previous literature at the time of this study. The Brock criteria focus on high frequency hearing loss, where cisplatin-associated ototoxicity first manifests. The risk of underestimating the level and impact of hearing loss is high with conventional grading systems. In this current study, only 7 of the 29 patients (24%) with moderate to severe hearing loss had a cisplatin dose modification on record. There is a need for standardization of the evaluation, monitoring, and plan of care across pediatric studies [16]. There has been a recent shift in the characteristics of ototoxicity criteria, with more emphasis being placed on functional outcome correlation. Recently, Chang and Chinosornvatana [8] have proposed a model that modifies the Brock criteria to provide a more clinically consistent and applicable grading system. A multidisciplinary and international consensus will be a crucial step in more successful evaluation and management of cisplatin ototoxicity so that research efforts and monitoring protocols are comparable and streamlined. Agreement on a carefully characterized phenotype of cisplatin-related hearing loss will allow for a more effective pursuit of biomarkers and predictors of ototoxicity.

The variability observed in the degree of ototoxicity in children who have received cisplatin is not fully accounted for by clinical variables such as age and cumulative dose. In this cohort, a difference was seen between tumor types, with only a single germ cell tumor patient exhibiting hearing loss. While this finding overall may be related to dosing regimen, it was interesting to discover that this patient was one of the older patients in the germ cell group. Such differences in hearing outcome among patients may be due, in part, to genetic variability in exposure or response to the drug. In 2000, Peters et al. [13] reported a protective effect on ototoxicity of the GSTM3*B allele. Subsequently in 2007, Oldenburg et al. [17] found an association between cisplatin ototoxicity and the GSTP1 genotype in

testicular cancer survivors. In a study of osteosarcoma patients, the XPC genotype was associated with cisplatin ototoxicity [18]. Ross et al. [9] reported a significantly increased risk for ototoxicity with variant alleles of TPMT and COMT in children. While these genes are able to effectively identify children at high risk for hearing loss if patients express specific genetic variants, there are still a significant number of children receiving cisplatin who experience hearing loss and cannot be preemptively identified using these genomic biomarkers. Future investigation of genetic variants in combination with other types of biomarkers may provide valuable insight into cisplatin disposition, metabolism, and sensitivity as they relate to ototoxicity. This ultimately may allow for more optimal drug dosing and potential improvement in quality of life of these pediatric cancer patients.

As advances in pediatric cancer therapies accelerate and survivorship increases, it is important to place additional focus on toxicities and long-term side effects. Cisplatin has proven to be a highly effective agent in treating pediatric solid tumors, but it is accompanied by a variable yet significant degree of ototoxicity. The findings of this retrospective cohort study validate earlier studies demonstrating that cumulative dose and gender are associated with the presence of hearing loss and that younger age correlates with the severity of hearing loss. Additionally, while the previously mentioned pharmacogenetic literature helps explain a portion of cisplatin ototoxicity, the etiology and risk factors in a significant proportion of patients remain unknown. The results reported here represent early efforts toward cisplatin pharmacotherapy aimed at optimizing efficacy while minimizing toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Severity of ototoxicity is inversely related to age ($P = 0.02$). Mean age (and cumulative dose) of patients with Brock grades 1, 2, and 3 were 11.5 ± 5.3 years (437.7 mg/m^2), 7.2 ± 4.7 years (404.1 mg/m^2), and 4.5 ± 4.9 years (454.3 mg/m^2), respectively.

TABLE I

Characteristics of Pediatric Cancer Patients Treated With Cisplatin (n = 102)

	Neuroblastoma	Osteosarcoma	Hepatoblastoma	Germ Cell Tumor	Overall	P-Value
No. (%)	29 (28%)	46 (45%)	7 (6.7%)	20 (19.6%)	102 (100%)	
Sex, no. (%)						
M	17 (59%)	29 (63%)	6 (86%)	6 (30%)	58	0.013 ^a
F	12 (41%)	17 (37%)	1 (14%)	14 (70%)	44	
Mean age at diagnosis (year)	2.7	12.2	5	11.1	8.7	<0.0001 ^b
SD	1.7	3.9	3.7	5.6	5.67	
Range	1.2–10.0	2.0–17.0	2.0–10.0	1.7–17.0	1.2–18.0	
Mean cumulative cisplatin dose (mg/m ²)	377.9	437	478	400	417.7	0.005 ^c
SD	85.4	83.1	93	61.2	86	
Range	200–510	240–480	360–600	300–600	200–600	
Race, no. (%)						
Caucasian	26 (90%)	40 (87%)	7 (100%)	13 (65%)	86 (84%)	0.110 ^d
African-American	2 (7%)	6 (13%)	0 (0%)	5 (25%)	13 (13%)	
Other	1 (3%)	0 (0%)	0 (0%)	2 (10%)	3 (3%)	
Brock grade 1 (%)	14 (48%)	23 (50%)	5 (71%)	1 (5%)	43 (42%)	0.002 ^e
Brock grade 2 (%)	12 (41%)	12 (26%)	5 (71%)	0 (0%)	29 (28%)	0.007
Brock grade 3 (%)	7 (24%)	3 (6%)	2 (28%)	0 (0%)	12 (11.7%)	0.018

^a χ^2 (3, N = 99) = 10.81, P = 0.013;

^b F (25, 71) = 8.69, P < 0.0001;

^c F (3, 92) = 4.51, P < 0.005;

^d χ^2 (6, N = 99) = 10.37, P = 0.110;

^e χ^2 (3, N = 102) = 15.39, P = 0.002.

TABLE II

Profile of Children With Hearing Loss (Brock 1) Versus Without Hearing Loss (Brock 0) Following Cisplatin Treatment

	Hearing loss (Brock 1)	No hearing loss (Brock 0)	P-Value
# Patients	43	59	
Median Age (years)	7.8	8.6	0.48
Males: Females	33: 10	24: 35	0.0003
Cumulative Dose (mg/m ²)	429 ± 78	391 ± 102	0.03
Vancomycin Exposure	25	18	0.37
Gentamicin Exposure	34	9	0.07
Amphotericin B Exposure	1	3	0.63
Furosemide Exposure	4	39	0.72
Carboplatin Exposure	13	7	0.02
Renal Dysfunction ^a	4	6	0.99

^aDefined in this cohort as changes in creatinine, electrolytes, or glomerular filtration rate (GFR) that persisted at completion of therapy.