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Cisplatin Ototoxicity Affecting Cochlear Implant Benefit

Michael S. Harris, M.D.[1,4], **Jaimie L. Gilbert, Ph.D.**[1,2], **Kelly A. Lormore, M.S.**[3,4], **Swapna A. Musunuru, B.S.**[4], and **Michael H. Fritsch, M.D.**[1,4]

[1]DeVault Otologic Research Laboratory, Department of Otolaryngology – Head & Neck Surgery

[2]Speech Research Laboratory, Indiana University, Department of Psychological & Brain Sciences

[3]Department of Audiology

[4]Indiana University School of Medicine

Abstract

Objective—Report a case of loss of cochlear implant benefit following cisplatin therapy to treat osteosarcoma. Examine the implications for the loci of cisplatin-associated cochleotoxicity.

Study Design—Retrospective Case Review

Setting—Tertiary Referral Center

Patients—Single Case Study

Intervention(s)—None

Main Outcome Measure(s)—Cochlear implant programming levels

Results—Increase in cochlear implant programming T- and C-levels following cisplatin therapy.

Conclusions—Cisplatin therapy likely affects spiral ganglion cells. It appears that auditory cells other than outer hair cells in the organ of Corti are affected by cisplatin since the hearing sensitivity of this patient with non-functioning outer hair cells declined after receiving chemotherapy. Implications of these findings are discussed.

Keywords

cisplatin; ototoxicity; cochlear implant; spiral ganglion cells

Introduction

Cisplatin is a critical component of many chemotherapy regimens currently used to treat malignancies of childhood and has a host of toxicities associated with its use. Chemotherapeutic properties of cisplatin are based on the formation of platinum-DNA adducts causing helical distortion and cross-linkages, which ultimately lead to cellular apoptosis (1,2,3). One of cisplatin's toxicities is the well-recognized problem of ototoxicity: an irreversible, bilateral, sensorineural hearing loss (SNHL) occurs in 40% to 70% of children treated with this medication (4-7). Hearing loss associated with cisplatin initially presents at higher frequencies (e.g., 4,000 Hz to 8,000 Hz) and typically progresses to lower frequencies (e.g., 500 Hz to 2000 Hz) when cumulative dose exceeds 400 mg/m^2 in children

Address correspondence and reprint requests to: Michael S. Harris, M.D., DeVault Otologic Research Laboratory, Indiana University School of Medicine, Department of Otolaryngology – Head & Neck Surgery, 702 Barnhill Drive, Suite 0860, Indianapolis, IN 46202; Telephone: 317-274-1985; Fax: 317-274-4949, michharr@iupui.edu.

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(7). The hearing loss directly relates to the cumulative dose of cisplatin administered (8-10); other contributing factors include age, gender, concurrent ototoxic drug exposure, administration schedule, renal function, and cranial irradiation (1,4,10). Cisplatin ototoxicity traditionally has been considered to be permanent and stable following the initial insult. However, some evidence suggests that hearing loss related to cisplatin may progress beyond the therapeutic timeframe (6). The long-term significant negative consequences of cisplatin-induced ototoxicity include poor speech and language development and poor academic and social outcomes later in life (11).

The objective of the current study is to report a unique case of hearing loss in an individual treated for osteosarcoma who had a cochlear implant (CI) placed approximately 12 years prior and subsequently lost benefit from his device following cisplatin chemotherapy. To our knowledge, this is the first reported case of cisplatin-associated hearing loss occurring after cochlear implantation and has important implications with respect to the site and nature of cisplatin's cochleotoxicity. Internal Review Board (IRB) approval was granted.

Case Report

The patient was a 14-year old male with a history of SNHL of an unknown etiology initially detected in the second year of life. Audiologic findings (auditory brainstem response, oto-acoustic emissions, and behavioral testing) at age 2 years were indicative of a severe-to-profound bilateral hearing loss. The patient was fit with traditional amplification and received appropriate auditory training and speech and language therapy. Despite appropriately fit hearing aids and services, auditory skills did not progress and the patient was unable to detect conversational speech. The patient was evaluated for cochlear implantation. A pre-operative computed tomographic (CT) scan showed patent cochleae and normal inner ear anatomy suitable for cochlear implantation bilaterally. At 35 months of age, his right ear received a fully-inserted Nucleus 22 CI (Cochlear Corp., Lane Cove, New South Wales, Australia) with a Spectra speech processor and SPEAK coding strategy. The 22 electrode array was set at bipolar (BP) + 1 mode and a pulse width of 100 Hz.

Post-implantation, the patient demonstrated substantial improvement. Three months prior to implantation, speech awareness thresholds (SAT) under headphones were obtained at 105 dB HL for the right ear and at 100 dB HL for the left ear. At his one-year follow-up appointment post- CI activation, the patient demonstrated a sound field SAT of 26 dB HL. Figure 1 shows pre-CI unaided, pre-CI aided, and 1 year post-CI auditory thresholds. As the patient grew older, over a period of four years serial speech reception threshold (SRT) levels were obtained ranging from 28 – 42 dB HL. From the time of implantation, he was educated in an auditory-oral environment and performed well in a mainstream curriculum. Subsequent surgical history was pertinent only for correcting the implant electrode, which had eroded through and perforated the tympanic membrane (TM) at age 13 years with no change in audiometric settings.

At age 14 years an evaluation of right leg pain disclosed a sclerotic and lytic lesion. Subsequent biopsy confirmed a localized fibroblastic osteosarcoma in the right distal femur with extension into the musculature of the thigh. Positron emission tomography/CT imaging and bone scan disclosed no evidence of distant metastatic disease. A chemotherapy regimen (AOST-0331 protocol) consisting of methotrexate, doxorubicin, and cisplatin was administered over the course of a 9-month period. Per protocol, cisplatin was given for a total of 4 cycles (weeks 1, 6, 12, and 17). Cumulative dosage of cisplatin according to the protocol was 480 mg/m^2, with 60 mg/m^2/day. Surgical resection of the primary lesion was performed at 11 weeks, following 5 cycles of chemotherapy. The patient has remained in disease-free remission to the present.

New hearing difficulties were first noted at 21 weeks of chemotherapy after 4 cycles of cisplatin. At that time, the patient reported increasingly relying on lip-reading cues for communication. An integrity test of the device showed that it was functioning appropriately. Psychophysical assessment of his hearing at that time showed the patient performing 20 to 50 units decreased from the previous, pre-chemotherapy assessment. The mapping changes required over time are represented in Tables 1 and 2.

With continued hearing difficulties, a mode adjustment to BP +3 was made, which improved the patient's speech discrimination ability, but was untenable due to non-auditory sensations. Settings were returned to a BP + 1 stimulation mode. At this point, the patient was able to detect but not discriminate the Ling Six Sounds without the addition of visual cues. Two months after reprogramming, the patient reported discontinued use of the CI due to lack of benefit and reliance on lip reading for communication. The presence of tinnitus was also newly noted. The stimulation mode was changed to BP + 4, and T- and C-levels were overall reduced from previous mapped levels (Tables 1 & 2). Wider stimulation modes allow electrical stimulation across a greater population of neurons, increasing the likelihood that functioning nerve fibers would be activated. However, this also resulted in poorer spectral resolution. With this change in programming, detection of tones and speech was still within expected ranges for CI patients. In spite of this, successful benefit from the implant was severely reduced. Although the patient was able to detect that speech was present at 10 dB HL (SAT), speech was not recognizable at any intensity level (i.e., unable to complete an SRT). At last report, the patient had transferred to a school for the deaf, where American Sign Language (ASL) is the predominant mode of communication, for the remainder of his secondary education.

Discussion

The case presented here is unique because cisplatin-related hearing changes occurred after several years of successful CI use. The original severe-to-profound bilateral hearing loss was of an idiopathic sensory origin. Upon right cochlear implantation, any remaining functional outer hair cells (OHCs) likely incurred damage. Benefit was gained from the CI as documented by post-CI audiometry (Fig 1) and the levels at which the patient was not only aware of auditory speech but could also recognize speech. This benefit diminished following cisplatin therapy, prompting a review of the effects of cisplatin ototoxicity on the auditory system.

The mechanism of cisplatin-associated ototoxicity is traditionally believed to be related to cochleotoxic effects mediated by generation of reactive-oxygen-species (ROS) and depletion of anti-oxidant scavenger molecules such as glutathione peroxidase (12). Lipid peroxidation and generation of malondialdehyde and other toxic agents subsequently induce calcium influx and apoptosis (1,12,13).

One target of ROS-mediated auditory damage that has been demonstrated in vitro as well as in numerous studies utilizing animal models is the outer hair cells (OHCs) in the organ of Corti (12,14,16). In addition to the OHCs, ROS-induced apoptosis has been shown *in vitro* and in animal models to affect the spiral ganglion cells and the marginal cells of the stria vascularis (16-18). Whether the effects seen in both the organ of Corti and the spiral ganglion are mutually dependent or develop in parallel has been investigated using a guinea pig model (19,20). Intraperitoneal injections of cisplatin (2 mg/kg/day) were performed for 4, 6, or 8 consecutive days and the animals were monitored histologically (19) and electrophysiologically (20) for development of apoptotic changes at the two sites. This time sequence did not reveal any evidence of one ototoxic process triggering another, suggesting that the two processes run in parallel.

This case study provides *in vivo* supporting evidence that structures such as the spiral ganglion are likely affected by cisplatin ototoxicity, and that damage is not restricted to the OHCs. Given the history of sensorineural hearing loss and CI placement, it can be presumed that our patient did not have functional OHCs prior to cisplatin therapy. Successful use of the device also implies that the OHCs were bypassed, as electric hearing occurs via the implanted electrodes transmitting electrical impulses to the auditory nerve. Thus, the changes demonstrated in this patient's hearing are highly unlikely to be related to any further damage to the OHCs resulting from cisplatin. Rather, the changes in hearing are most likely representative of an injury to the spiral ganglion cells directly.

It is important to note that mapping adjustments (Tables 1 & 2) continued to reflect diminution of CI benefit following cisplatin exposure even after chemotherapy was completed. Bertolini and collegues demonstrated a progression of hearing loss following the end of cisplatin therapy in a large cohort of children treated for a number of malignancies of childhood (6). Using Brock's Hearing Loss Grades (21) – a 0 to 4 measure designed to detect cisplain-associated high frequency hearing loss with each grade representing progressively greater loss of critical speech tones – Bertolini and collegues found that while only 11% of audiograms showed a Grade 2 or poorer hearing loss upon early post-therapy evaluation, 44% demonstrated a Grade 2 or poorer after 2 or more years of follow-up. It may be possible that the continued deterioration of our patient's CI benefit represents a similar progression or late-stage effects of cisplatin therapy on spiral ganglion cells.

It should be acknowledged that there is the possibility of late electrode migration contributing to the loss of CI benefit coincident with cisplatin therapy in this patient. We regard this as hightly unlikely, however, given that the electrode was in place for several years and likely scarred into position at the time of cancer treatment.

While metastasis of osteosarcoma of the femur to the temporal bone is exceedingly rare, there are reports of such (22). Initial PET/CT imaging and bone scan disclosed no evidence of distant metastatic disease, however, shortly before onset of hearing deterioration.

Knowing that cisplatin-associated injury to the spiral ganglion cells exists raises the possibility of preventative measures. Not using the cisplatin chemotherapy is at present unrealistic as it can be a life-saving intervention. One approach to preventing ototoxicity may be to follow the lead of previous studies examining a number of exogenous otoprotective molecules in animal models and in limited human clinical trials. These molecules protect targets of either oxidative stress and resulting cell death pathways or free radicals (14). Sodium thiosulfate, the most widely studied in human subjects, appears thus far to confer otoprotection without compromising the tumor-killing cytotoxicity of cisplatin (23). The degree to which these agents may protect against ototoxicity to CI hearing is unstudied, however.

The National Institute on Deafness and Other Communication Disorders (NIDCD) estimates approximately 41,500 adults and 25,500 children in the United States currently use CIs (24). As this case demonstrates, individuals in this population are susceptible to changes in hearing ability from at least one ototoxic medication. Cochlear implant recipients are often successful with their devices; however, individuals may also become reliant upon them for successful speech communication. Ototoxic effects may take away or significantly alter these individuals' primary method of communication. In instances of a primary severe ototoxic hearing loss, this case study suggests that the benefits of cochlear implantation may be eliminated by cisplatin chemotherapy acting on the spiral ganglion cells. Therefore, further research into the possible effects of ototoxicity and the elucidation of which individuals are susceptible to these effects is imperative. Prevention and awareness of sensitivity to ototoxins in both pediatric and adult CI recipients is important in the event that CI users may require ototoxic medications at some point during their lifespan.

Acknowledgments

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References

1. Rybak LP, Whitworth CA, Mukherjea D, Ramkuma V. Mechanisms of cisplatin induced ototoxicity and prevention. Hear Res. 2007; 226:157–67. [PubMed: 17113254]
2. Ryback LP, Mukherjea D, Jajoo S, Ramkumar V. Cisplatin Ototoxicity and Protection: Clinical and Experimental Studies. Tohoku J Exp Med. 2009 November; 219(3):177–186. [PubMed: 19851045]
3. Garcia-Berroca JR, et al. The anticancer drug cisplatin induces an intrinsic apoptotic pathway inside the inner ear. Br J Pharmacol. 2007; 152:1012–20. [PubMed: 17906689]
4. Coradini PP, Cigana L, Selistre SGA, Rosito LS, Brunetto AL. Ototoxicity from cisplatin therapy in childhood cancer. J Pediatr Hematol Oncol. 2007; 29(6):355–60. [PubMed: 17551394]
5. Berg A, Spitzer JB, Garvin JH. Ototoxic impact of cisplatin in pediatric oncology patients. Laryngoscope. 1999; 109:1806–14. [PubMed: 10569412]
6. Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: long term follow up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004; 26(10):649–55. [PubMed: 15454836]
7. Grewal S, Merchant T, Reymond R, et al. Auditory late effects of childhood cancer therapy: a report from the children's oncology group. Pediatrics. 2010; 125:e938–50. [PubMed: 20194279]
8. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 2004; 40(16):2445–51. [PubMed: 15519518]
9. Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer. 2006; 107(2):417–22. [PubMed: 16779793]
10. Yancey, A.; Harris, MS.; Egbelakin, A.; Gilbert, J.; Pisoni, DB.; Renbarger, J. Gender is a predictor of cisplatin ototoxicity. Presented at the 23rd Annual Meeting of the American Society of Pediatric Hematology/Oncology (ASPHO); Montreal, Quebec, Canada. April 7-10, 2010;
11. Knight K, Kraemer DF, Neuwelt AE. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005; 23(34):8588–96. [PubMed: 16314621]
12. Clerici WJ, DiMartino DL, Prasad MR. Direct effects of reactive oxygen species on cochlear outer hair cells. Hear Res. 1995; 84:30–40. [PubMed: 7642453]
13. Lee JE, Nakagawa T, Kita T, et al. Role of reactive radicals in degeneration of the auditory system of mice following cisplatin treatment. Acta Otolaryngol. 2004; 124:1131–35. [PubMed: 15768804]
14. Rybak L. Mechanisms of cisplatin ototoxicity and progress in otoprotection. Curr Opin Otol Head & Neck Surg. 2007; 15:364–69.
15. Cardinaal RM, De Groot JC, Huizing EH, Smoorenburg GF, Veldman JE. Ultrastructural changes in the albino guinea pig cochlea at different survival times following cessation of 8-day cisplatin administration. Acta Otolaryngol. 2004; 124(2):144–54. [PubMed: 15072416]
16. Kim HJ, Lee JH, Kim SJ, et al. Roles of NADPH oxidases in cisplatin-induced reactive oxygen species generation and ototoxicity. J Neurosci Res. 2010; 30(11):3933–46.
17. Lee JE, Nakagawa T, Kim TS, et al. Role of reactive radicals in degeneration of the auditory system of mice following cisplatin treatment. Acta Otolaryngol. 2004; 124:1131–35. [PubMed: 15768804]
18. Lee JE, Nakagawa T, Kita TS, et al. Mechanisms of apoptosis induced by cisplatin in marginal cells in the mouse stria vascularis. ORL J Otorhinilaryngol Relat Spec. 2004; 66:111–18.
19. van Ruijven MW, de Groot JC, Klis SF, Smoorenburg GF. The cochlear targets of cisplatin: an electrophysiological and morphological time-sequence study. Hearing Res. 2005; 205(1-2):241–8.

20. van Ruijven MW, de Groot JC, Smoorenburg GF. Time sequence of degeneration pattern in the guinea pig cochlea during cisplatin administration. A quantitative histological study. Hearing Res. 2004; 197(1-2):44–54.

21. Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: a practical grading system. Med Pediatr Oncol. 1991; 19:295–300. [PubMed: 2056973]

22. Pfleiderer AG, Molyneux AJ, Tee MK. Metastatic spread of osteosarcoma to the temporal bone in a patient with Paget's disease: a case report. J Otolaryngol. 1992; 21(2):112–4. [PubMed: 1583704]

23. Harned TM, Kalous O, Neuwelt A, et al. Sodium thiosulfate administered six hours after cisplatin does not compromise antineuroblastoma activity. Clin Cancer Res. 2008; 14(2):533–40. [PubMed: 18223229]

24. National Institutes on Deafness and Other Communication Disorders. [accessed 8/17/10] Cochlear implants. http://www.nidcd.nih.gov/health/hearing/coch.asp

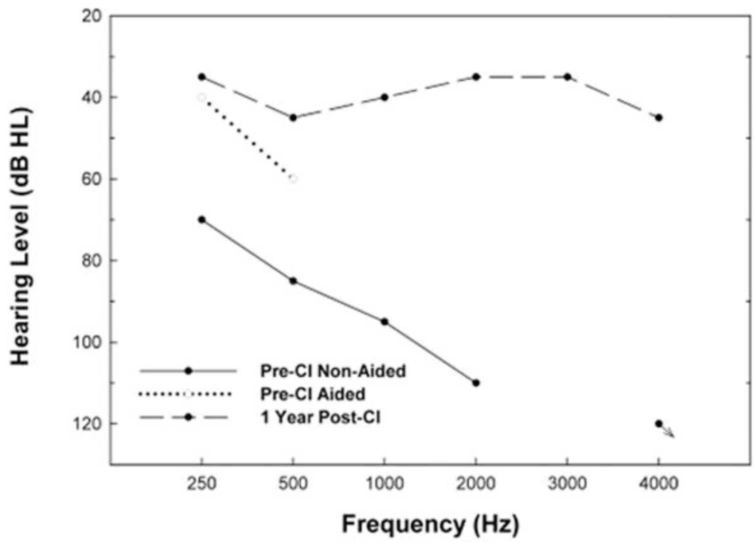

FIG. 1.
Pre-CI unaided (solid line), pre-CI aided (dashed line), and 1-year post-CI hearing levels (dB) for tested frequencies (Hz). Pre-CI unaided, pre-CI-aided, and post-CI thresholds were obtained using warble tone stimuli. The downward pointing arrow indicates no response to the limit of the audiometer at 4000 Hz for the pre-CI aided condition. Pre-CI aided thresholds were obtained using binaural acoustic amplification.

Table 1

Electrical Audiogram T-Levels

	T-levels (c-units)		
Electrode	**Pre-Cisplatin BP + 1**	**Post-Cisplatin BP + 1**	**2 Year Post-Cisplatin BP + 4**
19	153	174	Inactive
18	153	195	Inactive
16	148	>243	183
15	150	209	178
14	153	208	168
10	153	198	178
9	150	183	168
6	130	169	183
5	133	164	173
4	130	172	178

T-levels represent the lowest programming level, similar to a detection threshold. T-levels are programmed in current-units (c-units). Pre- and Post-Cisplatin T-levels were mapped using a BP + 1 stimulation mode. Two Year Post-Cisplatin T-levels were mapped using a BP + 4 stimulation mode.

Table 2

Electrical Audiogram C-Levels

	C-levels (c-units)		
Electrode	Pre-Cisplatin BP + 1	Post-Cisplatin BP + 1	2 Year Post-Cisplatin BP + 4
19	232	>255	Inactive
18	234	>255	Inactive
16	239	>255	230
15	244	>255	230
14	250	>255	230
10	255	>255	205
9	255	>255	205
6	224	252	220
5	225	226	205
4	214	223	215

C-levels represent the most comfortable listening level. C-levels are programmed in current-units (c-units). Pre- and Post-Cisplatin C-levels were mapped using a BP + 1 stimulation mode. Two Year Post-Cisplatin C-levels were mapped using a BP + 4 stimulation mode.