Teaching Case

Cisplatin-Induced Ototoxicity and the Role of Pharmacogenetic Testing

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INDEX TERMS cisplatin, ototoxicity, pharmacogenetics, thiopurine *S*-methyltransferase (TPMT)

J Pediatr Pharmacol Ther 2012;17(4):395–399

CASE

A 10-year-old white male presented with a chief complaint of swelling and pain in the left distal femur that worsened when he participated in sports at school. After several weeks of continued pain and swelling an x-ray was performed and revealed the presence of a large mass. Magnetic resonance imaging confirmed a large primary bone tumor located on the left femur, and open biopsy subsequently confirmed the diagnosis of osteosarcoma. The tumor was 9 cm long in the axis and 7 cm in diameter. Further tests revealed that the disease was localized to that area. The patient weighed 36 kg and was 145 cm tall at the time of diagnosis, placing him in the 75th percentile for age and sex.

The patient was started on chemotherapy based on a standard Children's Oncology Group (COG) treatment protocol of high-dose methotrexate, doxorubicin, and cisplatin. He received cisplatin at a dose of 120 mg/m^2 approximately every 5 weeks for a total of 4 treatments. For each treatment, cisplatin 60 mg/m^2/day was administered via intravenous infusion on 2 consecutive days. Based on the patient's body surface area of 1.2 m^2, he received a cumulative dose of 576 mg of cisplatin (480 mg/m^2). He was also placed on an appropriate antiemetic regimen per COG protocol. He was not on any other medications known to cause ototoxicity or nephrotoxicity. His renal function was normal at baseline and all subsequent lab tests thereafter. Genotyping for thiopurine *S*-methyltransferase (TPMT) mutations was not performed prior to initiation of cisplatin therapy.

Standard audiometric monitoring was performed prior to administration of the first cisplatin dose, and the results were all within the normal range (Brock Grade 0 [Table]).[1] The patient completed the full cisplatin treatment course, and audiometric monitoring was performed prior to administration of the second and third cisplatin treatments with no significant hearing impairment noted. On follow-up 2 months after completing the third treatment course, the patient reported having trouble hearing. The loss manifested initially as bilateral tinnitus and ultimately progressed to bilateral hearing loss. Audiometric monitoring performed at this visit revealed moderate to severe hearing loss, defined as a Brock score ≥2 (Table). This translates to educationally significant hearing loss presumed to be caused by the ototoxic effects of cisplatin. Hearing tests performed 6 months and 1 year later revealed that the patient's hearing had declined slightly but remained in Brock Grade 2, suggesting that the initially observed hearing deficit was likely progressive and irreversible.

RESPONSE

Osteosarcoma is the most common malignant bone tumor in the pediatric population, affecting an estimated 400 children and adolescents younger than 20 years in the United States each year.[2,3] The incidence of this malignancy peaks during the second decade of life, when adolescents typically experience a marked growth spurt.[3] The most active chemotherapy agents used in the treatment of pediatric osteosarcoma

Table. Brock Scoring System for Cisplatin-Induced Bilateral Hearing Loss[1]

Grade	Bilateral Hearing Loss
0	<40 dB at all frequencies
1	≥40 dB at 8000 Hz only
2	≥40 dB at 4000 Hz and above
3	≥40 dB at 2000 Hz and above
4	≥40 dB at 1000 Hz and above

are cisplatin, methotrexate, ifosfamide, and doxorubicin.[2,4] As single agents in the treatment of osteosarcoma, these cytotoxins have roughly the same activity in terms of tumor eradication (about 30%).[2] However, it is common to see these agents used together in various combinations.

Cisplatin, an antineoplastic platinum compound, is often selected as a first-line therapy because it is the most widely studied platinum compound in the pediatric population and is associated with cure rates of 85% in children diagnosed with solid tumors of any kind.[5,6] Cisplatin is also widely used in clinical trials and appears in a number of COG protocols, including those for osteosarcoma, neuroblastoma, and germ cell tumors. Despite its efficacy, cisplatin treatment is often limited by severe bilateral ototoxicity, a side effect that occurs in up to 61% of treated children. This hearing loss is often irreversible, as is the case in the current patient.[7]

The specific mechanisms by which cisplatin induces its ototoxic effects remain unknown. However, several potential mechanisms of injury have been proposed. Studies have indicated that cisplatin can activate apoptosis in hair cells lining the organ of Corti in the inner ear, resulting in direct cellular toxicity.[8,9] Similar effects on the spiral ganglion and stria vascularis, leading to myelin sheath detachment (spiral ganglion) and edema, bulging, and rupture (stria vascularis), have also been noted. Additionally, cisplatin is known to increase the generation of reactive oxygen species in all 3 subregions of the cochlea, leading to depletion of the cochlear antioxidant system that normally scavenges and neutralizes reactive oxygen species. This, in turn, leads to increased formation of proinflammatory cytokines and further activation of proapoptotic pathways.

The degree of hearing impairment following cisplatin treatment is highly variable and may range from reversible tinnitus to irreversible hearing impairment in the speech frequencies. Although hearing loss is more common and severe in the higher-frequency ranges, it can progress to involve lower frequencies.[9,10] Typically, hearing loss is bilateral; however, unilateral and asymmetric loss have been reported.[11,12] Hearing impairment is frequently permanent, accompanied by transient or permanent tinnitus, and has the capacity to worsen over time as demonstrated in the current patient.[13]

The onset of ototoxicity may also vary greatly from patient to patient. Toxicity can appear within hours to days after cisplatin administration, or it may be delayed significantly, especially in the pediatric population. In one study conducted by Bertolini et al,[14] only 5% of patients had marked hearing impairment during their treatment course with cisplatin, but 44% of those patients had significant hearing loss at 2-year follow-up. Another study found the median time to reach first significant hearing decrease in children was 135 days. Follow-up in this study lasted from 6 to 44 months and confirmed the progression of hearing loss even after drug administration was discontinued.[15]

Cisplatin-induced hearing loss can significantly impact language and speech development and can have lasting consequences on social and cognitive development, particularly in young children.[16] Given that they may not be able to hear verbal cues from their peers, young children may also respond inappropriately and experience altered socioemotional development. In school-aged children, cognitive development may be negatively impacted, given that hearing is vital to learning vocabulary and developing literacy. Altered cognitive development can, in turn, lead to difficulties in school and academics. Regardless of age, children with cisplatin-induced hearing impairment have difficulty interpreting speech in environments with a background noise similar to that they will experience in school and later work environments.[17] These communication difficulties may, in turn, lead to lowered self-esteem and/or social isolation. Preventing (or at least minimizing) hearing impairment in cisplatin-treated children is therefore an extremely important goal of any pharmacotherapeutic plan in this patient population.

Audiometric monitoring is currently the gold standard for identifying and monitoring progression of hearing loss in cisplatin-treated patients.[18] According to the Platinol (Cisplatin, Corden

Pharma Latina SpA, Sermoneta-Latina, Italy) product label, all patients in whom cisplatin is being considered should have audiometric monitoring performed prior to initiation of therapy.[19] Additional monitoring should also be performed prior to each dose of medication and for several years after completion of the treatment course.[18,19] COG suggests that all childhood cancer survivors be screened yearly for potential complications from their chemotherapy or radiation.[18] For children previously treated with cisplatin, recommended yearly screenings include assessments for hearing difficulties (with and without background noise), tinnitus, and vertigo.

Although it is difficult to predict with certainty which children will develop hearing impairment and/or loss during cisplatin treatment, there are certain patient-, disease-, and treatment-specific factors that can be used to assess an individual child's risk. Two of the most important predictors of ototoxicity are age at treatment and the cumulative dose of cisplatin received.[20] Studies have shown that patients younger than 5 years have a significantly greater risk of developing ototoxicity.

Hearing loss also appears to be dose related and occurs more frequently in patients receiving higher cumulative doses (≥360 mg/m^2 in most studies).[2] The size of each individual cisplatin dose may also have an impact on the development of ototoxicity, as evidenced by the fact that administration of 60 mg/m^2 for 2 consecutive days appears to be less ototoxic than a single 120 mg/m^2 dose, regardless of the cumulative dose received.[4] Other important risk factors include central nervous system tumors, concurrent central nervous system radiation, and the presence of coexisting ear pathologies (e.g., chronic otitis media, middle-ear effusions, cerumen impaction). Concurrent administration of other ototoxic drugs (e.g., aminoglycosides) and impaired renal function may also increase the risk of ototoxicity. It is important to note, however, that children without any of these known risk factors may develop ototoxicity.[18] This is illustrated by the current patient, who was outside of the age range typically considered at increased risk for hearing loss, was dosed during 2 consecutive days for each treatment, and did not receive any concomitant ototoxic medications.

There is increasing evidence to suggest that genetics may play an important role in determining individual susceptibility to cisplatin-induced ototoxicity. Recently, 2 loss-of- function variants in the gene encoding TPMT, a phase II drug metabolizing enzyme responsible for catalyzing the methylation of thiopurine compounds, were found to be highly associated with cisplatin-induced hearing loss in children.[7] In a retrospective study of 162 cisplatin-treated children (median cumulative dose of 400 mg/m^2) enrolled into independent discovery (n=54) and replicative (n=112) cohorts, the *TPMT*3B* and *TPMT*3C* variants were associated with a significantly increased risk of hearing loss (odds ratio, 17.0; 95% confidence interval, 2.3–125.9). Both the **3B* (460G>A) and **3C* (719A>G) variant alleles result in missense mutations that lead to significant decreases in the amount of functional TPMT protein and enzyme activity. Individuals with 2 variant alleles have low or no TPMT activity (0.3% of whites), whereas those with 1 variant allele have intermediate TPMT activity (6%–11% of Caucasians).[21] It is hypothesized that reduced TPMT activity conferred by the presence of one (or both) of these variants leads to an enhancement of cisplatin's normal cytotoxic effects via reduced TPMT-mediated inactivation of cisplatin-purine compounds that form DNA cross-links, and causes cell death.[7] Increased concentrations of *S*-adenosylmethionine may also contribute to the increased risk of ototoxicity in patients with one or more loss-of-function variants.

Data from this initial pediatric cohort demonstrate great potential for TPMT genotyping as a clinical screening tool to identify children at risk for cisplatin-induced ototoxicity. Although only 16% of cisplatin-treated children were found to carry one or more of the TPMT gene variants, presence of the variant(s) was highly specific for hearing loss (98%), and the positive predictive value for the genetic test was 96%.[7] It is important to note, however, that children who do not carry a TPMT variant are still at risk for ototoxicity (negative predictive value, 40%). This may in part be due to the fact that there are several other functionally significant polymorphisms in relevant candidate genes (e.g., catechol-*O*-methyltransferase, megalin) that have been associated with hearing loss in cisplatin-treated patients.[6] The predictive value and clinical utility of these gene-response associations have yet to be determined.

These promising data led to a change in the Cis-

platin product label in December 2011 to include new safety information related to the association of TPMT gene variants and risk of cisplatin-induced ototoxicity in children.[19] To date, however, specific recommendations regarding how TPMT genotyping should be applied in cisplatin-treated children have not been developed. This creates a unique opportunity for pediatric pharmacists to not only educate their patients and colleagues regarding the use of TPMT genotyping, but to also help develop and create guidelines for the optimal use of this tool in cisplatin-treated children. It may be possible to identify children at higher risk for cisplatin-induced ototoxicity based on their individual genotype so that alternate yet equally effective treatment options (e.g., carboplatin) can be considered. Given that cell injury is likely irreversible, however, genotyping is likely to be of greatest benefit when performed prior to the initiation of cisplatin therapy. Genotyping also cannot be used to definitively rule out the risk of ototoxicity because more than half of children who do not carry a *TPMT*3B* or *TPMT*3C* allele will still develop serious hearing deficits.[7] In patients without a TMPT mutation, otoprotective agents such as sodium thiosulfate may be useful in reducing toxicity risk.[22] However, these agents are currently still under evaluation in clinical trials.

At present, data are insufficient to support routine use of TPMT genotyping in all children who are candidates for cisplatin treatment, and cost-benefit analyses are needed prior to implementation of such a strategy. A preliminary economic analysis conducted in British Columbia and Canada suggests that genotyping all children with cancer for whom cisplatin is a first-line therapy could potentially avoid $71,168 in societal net costs per tested patient, $4504 of which is health care related in Canadian dollars.[23] This translates to more than $2.4 million annually in British Columbia and $19.6 million in Canada. Other important factors to consider include test availability, turnaround time for results, sampling requirements (particularly in pediatric patients), and reimbursement/payment issues. Several commercial laboratories across the United States perform TPMT genotyping at a cost of $150 to $250 per test.[23] Most assays performed by commercial laboratories require 3-5 mL of whole blood and provide results within 3 to 5 days after sample receipt.

TPMT genotyping provides pediatric clinical pharmacists with a promising new tool that can be used in conjunction with patient-, drug-, and disease-specific information to guide therapeutic decision making in children receiving cisplatin treatment. Although this test cannot be used to definitively rule out the risk of ototoxicity, it does significantly improve our ability to identify at-risk children and improve treatment outcomes in this patient population. Genotyping is likely to be of greatest benefit when performed prior to the initiation of cisplatin therapy. The precise role of TPMT genotyping, however, has yet to be determined. Pediatric pharmacists therefore have a unique opportunity to assist in the creation, development, and implementation of guidelines for the optimal use of this tool in cisplatin-treated children.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS COG, Children's Oncology Group; TMPT, thiopurine *S*-methyltransferase

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REFERENCES

1. Brock PR, Bellman SC, Yeomans EC, et al. Cisplatin ototoxicity in children: a practical grading system. *Med Pediatr Oncol.* 1991;19(4):295-300.
2. Chou A, Geller D, Gorlick R. Therapy for osteosarcoma: where do we go from here. *Pediatr Drugs.* 2008;10(5):315-327.
3. St. Jude Children's Research Hospital. Disease information: solid tumor: osteosarcoma. http://www.stjude.org/stjude/v/index.jsp?vgnextoid=e6ab061585f70110VgnVCM1000001e0215acRCRD. Retrieved April 25, 2012.
4. Lewis M, DuBois S, Fligor B, et al. Ototoxicity in children treated for osteosarcoma. *Pediatr Blood Cancer.* 2009;52(3):387-391.

5. Helt-Cameron J, Allen P. Cisplatin ototoxicity in children: implications for primary care providers. *Pediatr Nurs.* 2009;35(2):121-127.
6. Mukherjea D, Rybak L. Pharmacogenomics of cisplatin-induced ototoxicity. *Pharmacogenomics.* 2011;12(7):1039-1050.
7. Ross C, Katzov-Eckert H, Dube M, et al. Genetic variants in TPMT and COMT associated with hearing loss in children receiving cisplatin chemotherapy. *Nat Genet.* 2009;41(12):1345-1350.
8. Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevetion. *Hear Res.* 2007;226(1-2):157-167.
9. Rybak LP, Mukherjea D, Jajoo D, Ramkumar V. Cisplatin ototoxicity and protection: clinical and experimental studies. *Tohoku J Exp Med.* 2009;219(3):177-186.
10. Stohr W, Langer T, Kremers A, et al. Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system. *Cancer Invest.* 2005;23(3):201-207.
11. Waters GS, Ahmad M, Katsarkas A, et al. Ototoxicity due to cis-diamminedichloroplatinum in the treatment of ovarian cancer: influence of dosage and schedule of administration. *Ear Hear.* 1991;12(2):91-102.
12. Schmidt CM, Knief A, Lagosch AK, et al. Left-right asymmetry in hearing loss following cisplatin therapy in children – the left ear is slightly but significantly more affected. *Ear Hear.* 2008;29(6):830-837.
13. Einarsson E, Petersen H, Wiebe T, et al. Long term hearing degeneration after platinum-based chemotherapy in childhood. *Int J Audiol.* 2010;49(10):765-771.
14. 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):649-655.
15. Knight K, Kraemer D, Neuwelt E. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. *J Clin Oncol.* 2005;23(34):8588-8596.
16. Goffi-Gomez M, Liberman P, Goncalves I, Schultz C. Audiologic consequences of ototoxicity: case report with deterioration of the intelligibility of speech. *Appl Cancer Res.* 2009;29(2):95-99.
17. Einarsson E, Petersen H, Wiebe T, et al. Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aid. *Int J Audiol.* 2011(10);50:642-651.
18. 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(4):938-950.
19. Platinol [package insert]. Sermoneta-Latina, Italy: Corden Pharma Latina SpA.; 2011.
20. Li Y, Womer R, Silber J. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. *Eur J Cancer.* 2004;40(16):2445-2451.
21. McLeod HL, Siva C. The thiopurine S-methyltransferase gene locus – implications for clinical pharmacogenomics. *Pharmacogenomics.* 2002;3(1):89-98.
22. Brock PR, Knight KR, Freyer DR, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. *J Clin Oncol.* 2012;20:2408-2417.
23. Dionne F, Mitton C, Rassekh R, et al. Economic impact of a genetic test for cisplatin-induced ototoxicity. *Pharmacogenomics J.* 2012;12(3):205-213.