Genetic variants associated with cisplatin-induced hearing loss

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Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy
Ross et al. (2009)
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Although there are many factors that contribute to a patient’s response to therapy, genetic factors account for a significant proportion of variability in drug response and are estimated to play a role in at least half of all adverse drug reactions (ADRs) (1). Genetic variability in drug metabolizing enzymes and transport systems involved in absorption, distribution, excretion and metabolism may lead to drug-induced toxicity causing, life-long disability or even death (2). This is of particular concern in the paediatric population because less than 25% of approved pharmaceuticals have been tested in children and result in inadequate guidelines for safety and efficacy (2).

Cisplatin is an effective and widely used chemotherapeutic agent for the treatment of solid
tumours. It is used as a standard of care treatment for many types of cancer in children, including neuroblastoma, osteosarcoma and hepatoblastoma in addition to cancers of the ovary, lung and bladder in adults. Cisplatin is one of the most effective chemotherapeutic agents for children with a cure rate of 85%. A serious drawback of cisplatin therapy is severe hearing loss which affects 10–25% of adults and 41–61% of children (3, 4). This toxicity is dose-related and frequently leads to dose reduction or termination of cisplatin treatment with signs of hearing loss. Ross et al. hypothesized that although there is significant interindividual variability in hearing loss with patients receiving similar doses of cisplatin, genetic factors may be responsible for toxicity.

Case-control cohorts of oncology patients treated with cisplatin were recruited through an active ADR surveillance network (Canadian Pharmacogenomics Network and Drug Safety). Children receiving cisplatin were recruited to the study and DNA samples were genotyped for approximately 2000 single nucleotide polymorphisms (SNPs) to capture the genetic variation in 220 key genes involved in drug absorption, distribution, metabolism and excretion. The degree of hearing loss was classified based on standardized CTCAE criteria (Common Terminology Criteria for Adverse Events). The authors used a multistage approach to increase the power to detect clinically relevant genetic variants (5). A discovery cohort of 54 children treated with cisplatin from a single hospital in Canada was first genotyped, yielding a homogeneous sample set which was followed with a second, independent replication cohort of 112 children recruited from multiple sites across Canada.

Two genetic variants in thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT) were found to be highly associated with cisplatin-induced deafness in both the discovery and replication cohorts. The TPMT risk allele was carried by 25 (23.6%) cases and in one (1.8%) control patient in the combined cohort (odds ratio 17.0, Fisher exact allelic test \( p = 1.81 \times 10^{-4} \)). Sequencing of COMT revealed a low activity variant in lactate dehydrogenase (LD) with the initially discovered SNP located in a 7.5 kb haplotype block that was present in 31 (42.5%) of the patients with cisplatin-induced hearing loss and 4 (7.1%) of the control patients in the combined cohort (odds ratio 5.4, Fisher exact allelic test \( p = 1.09 \times 10^{-3} \)).

The genetic variants TPMT and COMT risk alleles combined were carried by 51 (48.1%) cases and in 4 (7.1%) controls (odds ratio, 12.1, Fisher exact allelic test \( p = 3.4 \times 10^{-8} \)). The combined genetic variants have a high specificity and moderate sensitivity for detecting deafness in individuals on cisplatin therapy. The specificity of these variants indicates that 92.9% of patients identified with the risk alleles will develop hearing loss. TPMT and COMT account for only 48% of the cases of severe hearing loss induced by cisplatin. The cause of deafness is still unexplained for 52% of patients. To investigate whether these variants were found in children that developed deafness in the absence of cisplatin therapy, Ross et al. genotyped 192 children with general hearing loss. They confirmed that both TPMT and COMT were not associated with deafness in this group of children. It is probably that there are additional genetic variants that were not part of the original focused candidate gene study that may account for a significant proportion of cases.

Cisplatin binds to purines and forms intra- and interstrand cross-links with DNA leading to cell death. TPMT inactivates these purine compounds such as cisplatin, thereby regulating DNA cross-linking. Therefore, a loss-of-function mutation in TPMT would result in increased DNA cross-linking efficiency which is one potential mechanism behind increased toxicity. The authors also propose that toxicity may result from reduced TPMT and COMT activity due to increased S-adenosylmethionine (SAM) levels. TPMT and COMT are methyl transferases which require SAM, a methyl donor substrate in the methionine pathway. A study conducted in mice suggests that toxicity associated with cisplatin may be related to an accumulation of SAM substrate in the presence of cisplatin (Fig. 1). A study conducted using an enzyme with 60% similarity to that of COMT, showed that the function was essential for proper auditory function in both humans and mice. This indicates that a loss of COMT may result in hearing loss. Questions still remain as to why the cells in the cochlea are particularly sensitive to cisplatin-induced toxicity.

These findings show the identification of genetic variants that are associated with cisplatin-induced hearing loss. In the future, genetic testing for these variants could identify those patients at risk for this ADR, so that they could be placed on alternative medications, or receive a modified dose, or more aggressively monitored. By screening patients prior to therapy for predictive diagnostic markers, it may be possible to reduce the incidence of ADRs, thereby decreasing healthcare cost and improving safety and efficacy of treatment.
Fig. 1. Proposed mechanism of how methyltransferases, thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT) result in cisplatin-induced ototoxicity. The decreased activity of TPMT and COMT results in the accumulation of S-adenosylmethionine (SAM) substrate in the methionine pathway in the presence of cisplatin. Increase in SAM causes toxicity affecting cells in the cochlea, resulting in hearing loss.

References