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Clinical Practice Recommendations for the Management and Prevention of Cisplatin-Induced Hearing Loss Using Pharmacogenetic Markers

Jong W. Lee
The University of British Columbia

Kusala Pussegoda
BC Children's Hospital Research Institute

Shahrad R. Rassekh
BC Children's Hospital

Jose G. Monzon
University of Calgary

Geoffrey Liu
University of Toronto

See next page for additional authors

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Authors

Jong W. Lee, Kusala Pussegoda, Shahrar R. Rassekh, Jose G. Monzon, Geoffrey Liu, Soomi Hwang, Amit P. Bhavsar, Sheila Pritchard, Colin J. Ross, Ursula Amstutz, Bruce C. Carleton, Michael R. Hayden, Stuart MacLeod, Anne Smith, Liam Brunham, Folefac Aminkeng, Neil H. Shear, Gideon Koren, Shinya Ito, Parvaz Madadi, Michael J. Rieder, Richard Kim, Maurica Maher, and David Flockhart

CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT AND PREVENTION OF CISPLATIN-INDUCED HEARING LOSS USING PHARMACOGENETIC MARKERS

Jong W. Lee^{1,2,3,10}, Kusala Pussegoda^{3,10}, Rod S. Rassekh^{2,3,4}, Jose G. Monzon⁵, Geoffrey Liu⁶, Soomi Hwang⁷, Amit P. Bhavsar^{3,8}, Sheila Pritchard^{3,4}, Colin J. Ross^{1,2,3,8}, Ursula Amstutz^{2,3,9,11}, Bruce C. Carleton^{2,3,8,11}, and the CPNDS clinical recommendations group¹²

¹Center for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; ²Pharmaceutical Outcomes Programme, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; ³Child and Family Research Institute, Vancouver, British Columbia, Canada; ⁴Department of Pediatrics, Division of Pediatric Hematology/Oncology/Bone Marrow Transplant, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; ⁵Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, Alberta, Canada; ⁶Department of Medical Oncology, Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada; ⁷Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; ⁸Division of Translational Therapeutics, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia; ⁹Institute of Clinical Chemistry, Inselspital Bern University Hospital, University of Bern, Switzerland.

¹⁰These authors contributed equally to this review

¹¹These authors are co-senior authors to this work

¹²The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) clinical recommendation group: *Vancouver, BC, Canada*: University of British Columbia, British Columbia Children's Hospital, Child and Family Research Institute: Bruce Carleton, Michael R. Hayden, Ursula Amstutz, Soomi Hwang, Colin J. Ross, Stuart MacLeod, Rod Rassekh, Anne Smith (deceased), Liam Brunham, Sheila Pritchard, Folefac Aminkeng. *University of Calgary, Alberta, Canada*: Jose Monzon. *Toronto, ON, Canada*: Sunnybrook Health Sciences Centre: Neil H. Shear; Hospital for Sick Children: Gideon Koren, Shinya Ito, Parvaz Madadi; Ontario Cancer Institute: Geoffrey Liu. *London, ON, Canada*: University of Western Ontario and London Health Sciences Centre: Michael J. Rieder, Richard Kim. *Ottawa, ON, Canada*: Department of National Defence: Maurica Maher. *Indianapolis, IN, U.S.A.*: Indiana University: David Flockhart (deceased).

Corresponding Author: Correspondence and requests for materials should be addressed to **Professor Bruce C. Carleton.**

Canadian Pharmacogenomics Network for Drug Safety, Child and Family Research Institute, University of British Columbia, 950 West 28th Avenue, Vancouver, BC V5Z 4H4, Tel.:+1 604-875-3609, Fax: +1 604-875-2494, E-mail: bcarleton@popi.ubc.ca

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Abstract:

Currently no pharmacogenomics-based criteria exist to guide clinicians in identifying individuals who are at risk of hearing loss from cisplatin-based chemotherapy. This review summarizes findings from pharmacogenomic studies that report genetic polymorphisms associated with cisplatin-induced hearing loss and aims to (1) provide up-to-date information on new developments in the field; (2) provide recommendations for the use of pharmacogenetic testing in the prevention, assessment and management of cisplatin-induced hearing loss in children and adults; and (3) identify knowledge gaps to direct and prioritize future research. These practice recommendations for pharmacogenetic testing in the context of cisplatin-induced hearing loss reflect a review and evaluation of recent literature and are designed to assist clinicians in providing optimal clinical care for patients receiving cisplatin based chemotherapy.

Keywords: Cisplatin, ototoxicity, hearing loss, pharmacogenetic testing, clinical practice recommendations

1. INTRODUCTION

1.1 Cisplatin

Cisplatin (PLATINOL[®]) is a widely used chemotherapeutic agent as a standard treatment for a variety of solid tumours. It is one of the most effective chemotherapeutic agents for children and has contributed to the dramatic increase in survival from many solid tumors including neuroblastoma, hepatoblastoma, brain tumors, osteosarcoma, and germ cell tumors. In fact, cisplatin has shown efficacy in standard risk hepatoblastoma, such that it can be used as monotherapy with an over 80% 3-year event-free survival¹. Cisplatin is also used to treat a variety of adult cancers including ovarian, gastrointestinal, testicular, lung, and head and neck tumours^{2,3}. A major complication that limits the clinical use of cisplatin is the risk of drug-induced ototoxicity that can result in life-long disability⁴. Cisplatin ototoxicity manifests as permanent, bilateral hearing loss which affects 10-25% of adults and 26 -90% of children⁵⁻⁸. In particular, even mild hearing loss in children can significantly influence speech and language development, social-emotional development and increase the risk of learning difficulties⁹.

1.2 Clinical presentation and assessment of cisplatin-induced hearing loss

In patients receiving the same dose of cisplatin, the inter-individual variability of ototoxicity is profound, ranging from no hearing loss to high frequency hearing loss and progresses to severe hearing impairment in the speech frequencies¹⁰. Pure-tone audiometry measurements are used to determine the degree of hearing loss in patients, which is reported as a numeric grade. Several different grading criteria for ototoxicity have been developed over the years. The most commonly used methods are the Common Terminology Criteria for Adverse Events 4.0 (CTCAE) [ENREF 15](#),¹¹ and the Brock scale⁶ (Table 1). However, various other grading schemes exist such as the Muenster

classification for early detection of hearing loss¹², Chang scale¹³ and the recently developed International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Grading Scale¹⁴. In standard treatment protocols, the occurrence of moderate to severe cisplatin ototoxicity leads to dose reduction or the termination of cisplatin treatment, which may affect survival rates¹⁵.

1.3 Mechanisms influencing outcomes

There is a significant amount of evidence suggesting that the major mechanism of action of cisplatin is the formation of intra-strand and inter-strand crosslinks with DNA. This activates multiple signal transduction pathways associated with cellular processes including cell-cycle arrest, DNA repair, and programmed cell death¹⁶. Platinum cochlear toxicity is thought to occur due to interference with signal transduction in the cochlea. Evidence indicates that cisplatin damage by apoptosis occurs at three sites in the cochlea: the outer hair cells in the organ of Corti, the spiral ganglion and the stria vascularis¹⁷.

Cisplatin-induced hearing loss is difficult to treat, primarily as the mechanisms involved in this process are not well understood. Several lines of evidence suggest that the generation of reactive oxygen species (ROS) are involved in the toxicity associated with cisplatin therapy¹⁸. ROS-mediated damage occurs as a consequence of antioxidant depletion and increased lipid peroxidation in the cochlea. The increase in ROS has been reported to lead to morphological and functional changes in the organ of Corti¹⁹. The production of ROS changes acoustic transduction by modulating the outer hair cell motility in the organ of Corti resulting in cell death²⁰.

1.4 Risk factors for cisplatin-induced ototoxicity

Clinical risk factors are known to influence the susceptibility of cisplatin-induced ototoxicity. These include cumulative cisplatin dose and dosing schedule, patient age at treatment, pre-existing hearing impairment, concomitant use of aminoglycosides and cranial irradiation (Box 1)²¹. It is now recognized that there is significant variability in hearing loss between individual patients receiving similar cumulative doses and application schedules of cisplatin suggesting that clinical risk factors alone are insufficient predictors of safety¹⁵.

Genetic variation in the genes involved in the biotransformation, transport, and targets of drugs have been recognized to influence patient drug response and susceptibility to adverse drug events, including ototoxicity²². Specific variations in the DNA sequence (single nucleotide polymorphisms (SNPs), insertions, deletions) that alter gene expression or protein function may thus influence the susceptibility to drug-induced toxicity and could facilitate the stratification of patients based on toxicity risk. To date, studies have implicated multiple genes in the susceptibility to cisplatin-induced hearing loss. Specifically, genetic variants in methyltransferases (*TPMT*, *COMT*), transporters (*ABCC3*, *CTR1*), glutathione-S-transferases (*GSTs*), megalin (*LRP2*) and DNA repair genes (*XPC*) have been associated with cisplatin-induced ototoxicity. [ENREF 11 ENREF 30](#)Evidence regarding associations of variation in these genes was reviewed and is summarized below (Section 2), with a more detailed summary provided in the Supplemental Material (<http://links.lww.com/TDM/A140>).

1.5 Scope and purpose

Currently no pharmacogenomics-based criteria exist to guide clinicians in identifying individuals who are at risk of cisplatin-induced hearing loss. This review is intended to (1) summarize and evaluate recent literature from pharmacogenomic studies that report associations of genetic polymorphisms with cisplatin-induced hearing loss to provide up to date information on new

developments in the field; (2) provide recommendations for the use of pharmacogenetic testing in the prevention, assessment and management of cisplatin-induced hearing loss in children and adults; and (3) identify gaps in knowledge to direct and prioritize future research. These practice recommendations for pharmacogenetic testing in the context of cisplatin-induced hearing loss are designed to assist clinicians in providing optimal clinical care for patients receiving cisplatin based chemotherapy.

Specifically, recommendations are provided to address the following questions:

1. Should genetic testing be performed in patients with an indication for cisplatin therapy, in order to reduce the occurrence of cisplatin-induced hearing loss? What genes and gene variants should be tested?
2. Which patients should be tested and when?
3. How should patients undergoing cisplatin therapy be managed based on their genetic test results?

2. SUMMARY OF SUPPORTING EVIDENCE

2.1 Methytransferase genes (*TPMT* and *COMT*)

Genetic polymorphisms in *TPMT* are implicated in the susceptibility to cisplatin-induced hearing loss in children (see detailed evidence summary in the supplementary materials and Supplementary Table S1, <http://links.lww.com/TDM/A140>). Specifically, *TPMT* variants rs12201199, rs1800460 and rs1142345 have been associated with ototoxicity in three independent pediatric cohorts^{15,23}. These risk variants include the *TPMT****3B**, ***3C** and ***3A** (***3B** + ***3C**) loss of function alleles, which lead to rapid degradation of the *TPMT* proteins²⁴. In a cohort of 317 children, 43 (91.5%) carriers of the *TPMT* risk variant developed hearing loss compared to only four carriers (8.5%) patients without hearing loss (Table S10), conferring a specificity of 96.8% and sensitivity of 22.3%²³. Three studies differing from the previous reports in patient cohorts and the treatment regimens used, reported non-significant associations between the *TPMT* variants and cisplatin-induced ototoxicity, however similar trends were observed in sub-cohorts of similarly treated patients²⁵⁻²⁷. Thus, evidence suggests an association of *TPMT* variants with cisplatin-induced hearing loss but with limitations in generalizability and the number of studies available (+++ **evidence**; **Table 2**).

Variants in *COMT* (rs9332377 and rs4646316) have shown similar trends of associations in four independent pediatric cohorts (Table S1)^{15,23,26}. These associations reached statistical significance only in two of the four cohorts while two additional studies have also reported effect sizes in the opposite direction^{25,27}. Taken together, the evidence supporting the role of *COMT* is encouraging but requires further replication with specific attention to using comparable patient cohorts (++ **evidence**). *COMT* and *TPMT* enzymes utilize the same substrate, *S*-adenosylmethionine, and variants of these genes are hypothesized to alter cisplatin cytotoxicity by modulating cross-linking with purines in DNA¹⁵. Furthermore, *S*-adenosylmethionine has been demonstrated to increase cisplatin nephrotoxicity in rats²⁸.

2.2 Cisplatin transporters (*ABCC3*, *CTR1*)

To date, two studies reported associations of a synonymous variant in *ABCC3* (rs1051640) with cisplatin-induced hearing loss in pediatric patients (Table S2)^{15,23}. [ENREF 31](#) *ABCC3* is a transporter that mediates the efflux of organic anions, xenobiotics and glutathione *S*-conjugates, including glutathione *S*-conjugated cisplatin^{29,30}. Reduced activity of *ABCC3* may thus affect cisplatin detoxification through reduced transport of toxic compounds out of the cell. Evidence supporting a role of *ABCC3* in cisplatin-induced ototoxicity is promising (**++ evidence**), but this association requires further replication to strengthen the current evidence. Furthermore, the functional consequences of the synonymous rs1051640 variant has yet to be identified and should be determined.

Copper transporter proteins (*CTRs*) are major plasma membrane transporters that mediate both cisplatin uptake and export at the plasma membrane³¹. A study in non-small cell lung cancer patients treated with cisplatin reported a variant in *CTR1* (rs1098169) associated with increased ototoxicity in adults³². Independent replication and investigations in pediatric cohorts are necessary to extend this promising finding (**++ evidence**).

2.3 Glutathione S-Transferases (*GSTs*)

One of the mechanisms of cisplatin detoxification is the conjugation of the active platinum metabolite with glutathione by glutathione *s*-transferases (*GSTs*)^{33,34}. [ENREF 42](#) Several studies have therefore examined polymorphisms in *GST* genes (*GSTM*, *GSTP*, *GSTT*) in the context of cisplatin-induced hearing loss (Tables S3-S6)^{15,35-41}.

One study reported a higher frequency of the *GSTM3*B* allele in pediatric patients with normal hearing compared to patients with ototoxicity (Table S3)³⁵. [ENREF 50](#) However, a second study investigating *GST* polymorphisms in ovarian cancer patients could not replicate this association³⁸ (**+ evidence**). In a study by Oldenburg *et al.*, *GSTP1* rs1965 was significantly associated with cisplatin-induced ototoxicity in adult testicular cancer survivors (Table S4)³⁶. However, this association did not achieve statistical significance in an extended patient cohort³⁷. Rednam *et al.* reported an opposite effect of *GSTP1* rs1965 on cisplatin-induced hearing loss in a pediatric medulloblastoma cohort⁴². Furthermore, five studies (4 pediatric, 1 adult) reported no significant association of *GSTP1* with hearing loss^{15,23,35,37,38}. Overall, evidence regarding an effect of *GSTP1* rs1965 on ototoxicity is thus inconsistent (Table S4) (**+ evidence**). Finally, associations with cisplatin-induced ototoxicity have also been reported for *GSTM1* (Table S5)^{36,37} and *GSTT1* (Table S6)³⁹. However, numerous other studies have not replicated these associations^{15,35-38,41,42} (**+ evidence**).

[ENREF 47](#)

2.4 Megalin (*LRP2*)

Two non-synonymous variants (rs2075252, rs2228171) in *LRP2* have been examined in four different studies of children treated with cisplatin (Table S7)^{15,23,39,43}. Riedemann *et al.* reported a significant association between rs2075252 and cisplatin-induced ototoxicity⁴³. A nonsignificant trend for an association for rs2228171 was also identified. Conversely, Choeprasert *et al.* found that rs2228171 was negatively associated with cisplatin-induced hearing loss with no association for rs2075252³⁹. In two additional large studies, both variants were not associated with cisplatin-induced hearing loss in children^{15,23}. Overall, given these inconsistent findings, further evidence is required to determine the relevance of rs2075252 and rs2228171 for cisplatin-induced ototoxicity (**+ evidence**).

2.5 DNA repair genes

To date, the association of genetic variants in the DNA repair pathway with cisplatin-induced ototoxicity has been investigated in three studies (Table S8). A small study of pediatric and adult patients reported a significant association of a non-synonymous SNP in *XPC* rs2228001 with hearing loss⁴⁴. However, this finding has yet to be replicated, with a lack of association reported in a larger pediatric cohort of 317 patients²³. Another independent study also did not observe any association of variants in *ERCC1*, *XPD* and *XRCC1* with cisplatin ototoxicity (Table S8)³⁸. Given the lack of replication, it is difficult to draw any conclusions about an effect of rs2228001 on cisplatin ototoxicity (+ *evidence*).

2.6 Genes associated with hereditary or age-related deafness

Variants in *GJB2*, *SLC26A4* and mitochondrial (mtDNA) polymorphisms in *MTRNR1*, *MTTL1* and *MTTS1* have been associated with aminoglycoside-mediated ototoxicity and progressive nonsyndromic high frequency hearing loss. Two studies investigating the role of mtDNA polymorphisms for cisplatin-induced hearing loss in children showed no evidence for a contribution of these variants to the susceptibility to cisplatin-induced hearing loss (Table S9)^{45,46}. Therefore, there is currently no evidence to suggest an association of genes involved in hereditary deafness with cisplatin-induced ototoxicity (+ *evidence*). One study examining variants in otospiralin (*Otos*), an inner ear protein implicated with age-related hearing deterioration, reported a significant association between a protective haplotype and cisplatin-induced ototoxicity (Table S9)⁴⁷. Although the evidence is limited at this time, these findings provide the basis for larger replication studies to validate this genetic association (++ *evidence*).

3. CLINICAL PRACTICE RECOMMENDATIONS

Recommendations and considerations

3.1 Should genetic testing be performed in patients prior to initiation of cisplatin, in order to reduce the occurrence of cisplatin-induced hearing loss? What genes and gene variants should be tested?

There are genetic variants that should be tested in patients prior to initiation of cisplatin therapy to alert physicians and patients/families about the increased risk of cisplatin-induced hearing loss in susceptible patients.

TPMT functional variants (A):

Recommendation: We recommend **pharmacogenetic testing for the associated functional *TPMT* variants (*3A, *3B, *3C)** and the known, relatively common, and functionally inactive *TPMT* *2 variant **in pediatric patients to receive cisplatin** (level A – strong recommendation; Table 3).

Considerations: In over 95% of Caucasian and Asian patients, low *TPMT* activity is explained by three alleles (*TPMT* *2, *3B, and *3C)⁴⁸. In African populations, *3C and *2 are also common. All of these variants demonstrate reduced *in vitro* enzyme activity⁴⁹. Around 10% of the population

carry one of these *TPMT* risk variants, which account for approximately 25% of patients with ototoxicity (accounting for 27.9%, 21.9%, and 24% of ototoxicity in 3 independent patient cohorts)^{15,23}. Thus, the *TPMT* risk variants do not account for all cases of cisplatin ototoxicity. However, the high positive predictive value (92%) of the *TPMT* variants indicates that a vast majority of patients who carry these variants develop hearing loss. The importance of identifying risk of hearing loss in children and the potential management strategies warrant a strong recommendation that children should be genotyped for risk variants in the *TPMT* gene. If genotyping is unavailable or impractical, *TPMT* phenotyping may be an alternative method to identify patients with low enzyme activity, even though this has not been investigated in any studies yet.

Variants in *COMT*, *ABCC3*, *CTRI*, *GSTs*, *LRP2*, DNA repair and deafness genes (C):

Testing for variants in *COMT*, *ABCC3*, *CTRI*, *GSTs*, *LRP2*, DNA repair genes and genes associated with deafness is currently not recommended for clinical use (level C – optional recommendation). Further research is needed to determine the optimal strategy for the utilization of genotype information for these genes in therapeutic decision-making and strengthen the evidence supporting the genetic associations (see section 4).

3.2 Which patients should be tested and when?

3.2.1. Pediatric patients

Recommendation: Studies of pediatric oncology patients suggest that **all children undergoing cisplatin therapy should be tested for genetic variants in *TPMT*** (A). Ideally, children should be tested prior to the initiation of therapy to enable optimal consideration of therapeutic options in the context of genetic test results. However, the genetic test may also provide valuable information for patients who are already undergoing treatment, e.g. to guide decision-making on post-treatment follow-up.

Considerations: The current standard of care in pediatric oncology for treatment with cisplatin is to monitor hearing with audiograms before further doses of cisplatin are given. Patients who develop clinically significant hearing loss generally have a 50% reduction of subsequent doses of cisplatin⁵⁰. Further hearing loss often results in complete elimination of cisplatin from the treatment plan. The use of pharmacogenetic information to define a patient at high risk of hearing loss can thus be used to consider potential dose reductions earlier in treatment. This approach is not much different than a dose reduction after toxicity onset, but allows the clinician to consider making this change sooner in the treatment plan. There are exceptions to this rule, such as cisplatin used in the treatment of hepatoblastoma, where no dose reduction is suggested at any point, given the critical role of cisplatin with regards to cure^{51,52}. An important area of future investigation is how much sooner than actual toxicity (i.e., hearing loss) potential dose changes can be made without compromising cure rates.

3.2.2. Adult patients

Recommendation: Currently, the impact of the genetic variants recommended for testing in children is unknown in adult patients. At this point, genetic testing to identify patients at risk for cisplatin-induced hearing loss is NOT recommended in adult patients (C). This guideline will be updated to incorporate recommendations regarding genetic testing in adults as more studies become available. In the meantime, it is recommended that **all adult patients to be treated with cisplatin receive audiometric testing before treatment initiation and at least one post-treatment follow-up** to monitor the occurrence of cisplatin-induced hearing loss.

3.3 How should patients undergoing cisplatin therapy be managed based on their genetic test results?

The current endpoint for clinical intervention in cisplatin therapy is moderate to severe, irreversible hearing loss. By knowing in whom cisplatin hearing loss is likely to occur, clinicians have the possibility to consider altering therapy or monitoring before hearing loss occurs. Importantly, information gained from genetic testing should be used in the context of the unique circumstances of each individual patient to evaluate optimal treatment strategies, taking into consideration the balance between risk of toxicity and potential impact of management strategies on anti-tumour efficacy of therapy and cancer survival. Post-test treatment options will vary based on cancer type and should fall within the current guidelines and standards for cancer care. In the future, additional studies should be conducted to investigate the potential of individualized interventions based upon a patient's cisplatin pharmacogenetic risk factors.

In Table 4, a breakdown of the risk genotypes for cisplatin ototoxicity and their interpretations is provided. Based on the genetic variants currently recommended for pharmacogenetic testing, patients who carry **ANY nonfunctional TPMT variant** (*3A, *3B, *3C, *2) should be considered **at high risk** of cisplatin-induced hearing loss. In these patients, the following management options are recommended:

(1) Physicians are encouraged to consider the use of otoprotectants (i.e. amifostine, sodium thiosulfate) if the patient's tumour type is one for which otoprotectants may be effective to prevent cisplatin-induced ototoxicity without adversely affecting antitumour activity (C; see section 2.9 in the supplementary materials, <http://links.lww.com/TDM/A140>, for a discussion of evidence on the effectiveness of otoprotectants). Current standard of care guidelines for the respective tumour types should be consulted to determine if otoprotectants are an option.

(2) Alternative treatments may be prescribed when they have demonstrated equal efficacy, manageable and acceptable toxicity, less ototoxicity, and are considered options within the current standards of care (C). For example, studies have reported similar outcomes in pediatric germ cell tumour patients treated using carboplatin, etoposide and bleomycin compared to treatment with cisplatin, etoposide and bleomycin but with less ototoxicity^{53,54} and treatment with carboplatin, etoposide and bleomycin has been suggested as an alternative treatment in young children⁵⁵. A possible role for carboplatin has also been suggested in the treatment of neuroblastoma, where one study reported similar survival between patients receiving cisplatin therapy and patients receiving partial substitution of cisplatin therapy with carboplatin⁵⁶.

In adult patients, the substitution to carboplatin is not recommended as it is found to be inferior to cisplatin in therapeutic effectiveness for several tumours, such as testicular, bladder, head and neck cancers⁵⁷. Oxaliplatin however, has been investigated as an alternative to cisplatin in some tumour types. For example, oxaliplatin-based regimens have been recommended as an alternative to cisplatin-based therapy for the treatment of advanced gastric cancer⁵⁸. Studies have also reported comparable outcomes to cisplatin-based therapy with reduced toxicity for advanced non-small-cell lung cancer⁵⁹.

Considerations: Several factors must be considered when considering alternative treatments in patients at high risk of cisplatin-induced ototoxicity. These include goals of treatment, patient and physician preference, and socioeconomic considerations. For instance, the margin for acceptable toxicity risk may be much lower for treatments that are merely palliative in nature versus those with curative intent. In addition, patient preference may play an important role in the decision to use an alternative treatment. For example, a professional musician may not wish to risk any level of ototoxicity. This lowered margin for acceptable risk also holds true in the situation where alternative, equally effective treatments are available, albeit at an increased financial or clinical cost.

(3) Where appropriate, physicians are encouraged to increase monitoring in high-risk patients (C). In these cases, increased monitoring may lead to earlier detection of hearing loss and allow physicians to implement alternative methods of treatment earlier to prevent further damage, such as the above recommendations. Similarly, management of hearing loss (speech therapy, hearing aids) may be initiated earlier to facilitate language development in children and minimize learning and social difficulties associated with hearing loss.

(4) High risk patients should be encouraged to receive more frequent follow-up audiometric hearing tests after treatment has ended (C). These are usually offered as standard care by medical service plans.

Considerations: Current Children's Oncology Group (COG) recommendations for audiological screening for children treated with cisplatin suggest that all subjects have full hearing testing at the conclusion of their treatment or at the transition to a survivorship clinic. No further hearing testing at a later time point is recommended by the COG except in situations where there are specific clinical concerns. Similarly, there are currently no guidelines as to when audiogram hearing tests should be conducted post therapy. However, there is evidence that cisplatin can be isolated in the inner ear 20 years post therapy⁶⁰. Moreover, there are recent reports of late onset hearing loss occurring after treatment with cisplatin⁶¹. Therefore, additional and long-term follow-up investigating hearing outcomes should be considered in high-risk patients. In particular, follow-up tests may be missed by patients living in remote areas, until severe hearing loss occurs, at which time there are no preventative options to consider. The optimal frequency and duration of audiometric hearing tests post therapy remains unknown and requires further study.

4. FUTURE DIRECTIONS

4.1 Standardized clinical classification of cisplatin-induced hearing loss

Currently, a major challenge in assessing cisplatin-induced ototoxicity is the lack of a standardized grading scheme of patient hearing in all studies. Several different grading criteria are available, which are inconsistently used to phenotype patients. This can lead to discrepancies in research findings and difficulties comparing results between studies as differences in the classification of patients can significantly alter the results of an association study. For clinical application, it is essential to validate genetic findings in independent patient cohorts for assessment of reproducibility and generalizability. A standardized phenotyping method would significantly facilitate accurate replication studies, and enable cross-study comparison of research findings.

4.2 Analyses of associated variants in additional patient populations

It is important to recognize that children and adults metabolize, distribute and eliminate certain drugs differently, which could result in different genetic variants being responsible for cisplatin-induced toxicity. The importance of genetic risk variants may also differ between treatments for different malignancies due to differences in treatment protocols. However, due to limited sample sizes it has been difficult to carry out subgroup analyses to determine whether genetic associations are specific to certain treatment protocols. For example, based on a recent study²⁵, a possible impact of concomitant amifostine or craniospinal irradiation on the association of *TPMT* and *COMT* variants with cisplatin-induced hearing loss in children requires further investigation to ascertain the impact of these confounding factors on genetic associations. In addition, a majority of studies have been carried out in populations of European ancestry. Whether these same genetic variants are also associated in different patient populations with other ancestries still needs to be investigated. Due to these potential differences between patient populations, the genetic testing recommendations provided here currently apply only for cisplatin therapy in children. Studies in adult patients are underway and are expected to become available in the near future to provide information on the relevance of these gene variants in the adult population.

[ENREF 52](#)

4.3 Predictive modeling to combine genetic and clinical risk factors

Multi-marker predictive models combine the effects of several genes and/or clinical factors into one predicted outcome. Pussegoda *et al.* developed a predictive model that includes the *COMT* and *ABCC3* variants, along with *TPMT* variants²³. In this model, based on currently available evidence, the *COMT* and *ABCC3* variants do not contribute to the prediction of patients at high risk of cisplatin-induced ototoxicity (supplementary materials, <http://links.lww.com/TDM/A140>). Instead, the model suggests that the *COMT* and *ABCC3* genotypes may enable the stratification of patients between intermediate and lower risk. However, additional research is needed on how to optimally incorporate genetic information from these genes to improve the prediction of low versus intermediate risk patients, and on how to optimally adjust therapy in these risk groups. For example, whether patients at low risk need less intensive monitoring or could be treated with higher doses to improve survival without increasing cisplatin-induced hearing loss requires further investigation. Furthermore, other genetic variants that demonstrate reproducible associations should also be incorporated into risk prediction models in order to assess their optimal use for patient stratification. In addition to genetic factors, clinical factors affecting the risk of ototoxicity should be included in such a predictive model. The evidence of clinical risk factors in cisplatin-induced deafness has not been systematically reviewed in this guideline and is therefore not included in current recommendations. However, the combined inclusion of clinical and genetic risk factors may improve the stratification of patients at high risk compared to using genetic risk factors alone.

Ultimately, by including both clinical and genetic factors into a model it may be possible to move to a simple risk score-based model to classify patients as high, intermediate and low risk.

4.5 Prospective studies, alternative treatments, cost effectiveness

All genetic association studies for cisplatin-induced ototoxicity thus far have been retrospective. The recommendations at this time are therefore based on retrospective evidence of clinical validity. It will be important to prospectively investigate the clinical utility of these tests in the future. In addition, prospective studies are needed to optimize the real-world clinical utility (effectiveness) of predictive pharmacogenetic testing by evaluating additional therapeutic options in high-risk patients in the context of therapeutic effectiveness and patient survival. In particular, further studies are needed to investigate the use of alternative medications (e.g. carboplatin, oxaliplatin), as well as alternative administration routes (e.g. continuous infusion vs. bolus) of cisplatin in high-risk patients. For example, even though evidence is ambiguous regarding the overall risk of hearing loss for continuous infusion vs. bolus administration of cisplatin⁶², it is possible that a different administration route provides an advantage specifically for patients with a genetically increased risk for ototoxicity.

Similarly, it is important to conduct prospective trials to confirm whether otoprotective agents are effective in protecting against ototoxicity in children treated with cisplatin and other platinum based chemotherapy agents. Future trials should assess large patient cohorts stratified by genetic ototoxicity risk factors for outcomes including ototoxicity, anti-tumour efficacy, adverse effects and quality of life. A few phase III trials are currently ongoing in pediatric patients to assess whether sodium thiosulfate (STS) and amifostine can prevent hearing loss in children while maintaining efficacy of chemotherapy. Additional large clinical trials with amifostine, STS and other otoprotective agents such as N-acetyl cysteine (NAC) and D-methionine should be carried out in both adults and children with a variety of different tumour types to strengthen evidence and enable conclusions about their effectiveness.

The provided recommendations only include clinical actions that fall within current standards of care, such as increased monitoring and alternative chemotherapy drugs that are within standard treatment protocols. In the future, new evidence may support the use of alternative cisplatin dosing or new otoprotective strategies. The recommendations in this guideline are thus considered iterative, and should continue to build upon new evidence as it is generated. Updates of recommendations are planned on a regular basis to incorporate new evidence. Finally, as genetic testing for cisplatin-induced hearing loss is used more frequently, an evaluation of the cost-effectiveness of genetic testing will become increasingly important and should be performed.

5. METHODS

The same literature review, evidence appraisal, and recommendation development process was followed as described previously^{63,64}. In brief, a standard guideline development process was followed, in accordance with the quality criteria suggested by the Appraisal of Guidelines Research and Evaluation Enterprise (AGREE)⁶⁵. Following a systematic literature search, critical appraisal of

evidence was performed (Table 2), with specific considerations for quality and number of studies, consistency of results and magnitude of the effect. Recommendations were developed during a meeting of guideline development group members, with each recommendation assigned a level of strength, based upon the robustness of the underlying evidence, the balance between benefits and risks of genetic testing and genotype-guided treatment, as well as the likelihood of variability in a patient's values and preferences (Table 3). Internal and external review by development group members, subject experts and members of the intended target audience was performed. A detailed description of the literature search strategy is provided in the Supplementary Materials (<http://links.lww.com/TDM/A140>) along with further details on the intended target audience and scope of this document, and the recommendation development group.

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DISCLOSURE OR CONFLICTS OF INTEREST

Bruce Carleton, Colin Ross and Michael Hayden are inventors on patents and patent applications that relate to genetic polymorphisms that are predictive of hearing loss after treatment with cisplatin.

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Box 1. Clinical risk factors for cisplatin-induced ototoxicity

- Higher cisplatin cumulative dose and bolus administration of cisplatin dose^{62,69}. Total dose also associated with severity; patients at risk of developing hearing loss in the speech frequencies when doses exceed 400 mg/m²⁷⁰.
- Younger age at time of treatment, patients less than 5 years of age have 20 times higher risk compared to similarly treated older patients⁷¹. Age reported to have inverse relationship with hearing loss severity⁷².
- Aminoglycoside antibiotics share similar toxicity profile with cisplatin, causing nephrototoxicity, neuropathy and ototoxicity⁷³.
- Cranial irradiation can cause irreversible hearing loss independently and with greater effect in combination with cisplatin^{74,75}.

Table 1: Criteria used to determine the grade of cisplatin-induced hearing loss in patients

Grading Scheme	Grade 0 Normal Hearing	Grade 1 Mild Hearing Loss	Grade 2 Moderate Hearing Loss	Grade 3 Severe Hearing Loss	Grade 4 Severe Hearing Loss
CTCAE Criteria 4.03 ¹⁵	<20 dB hearing loss at all frequencies	Hearing loss of ≥ 20 dB at 8 kHz	Hearing loss of ≥ 20 dB at 4 - 8 kHz	Hearing loss of ≥ 20 dB at 2 - 8 kHz	Hearing loss of ≥ 40 dB at 1 - 8 kHz
Brock Criteria ⁶	< 40 dB hearing loss at all frequencies	Hearing loss of ≥ 40 dB at 8 kHz	Hearing loss of ≥ 40 dB at 4 kHz and above	Hearing loss of ≥ 40 dB at 2 kHz and above	Hearing loss of ≥ 40 dB at 1 kHz and above
Muenster Criteria ¹⁶	<10 dB at all frequencies	>10 to <20 dB at all frequencies	Hearing loss ≥ 4 kHz, >20 dB 2a: >20 to ≤ 40 dB 2b: >40 to ≤ 60 dB 2c: >60 dB	Hearing loss <4 kHz; >20 dB 3a: >20 to ≤ 40 dB 3b: >40 to ≤ 60 dB 3c: >60 dB	Mean hearing loss <4 kHz; ≥ 80 Db
Chang Criteria ⁷⁵	< 20 dB at 1, 2, and 4kHz	Hearing loss of 1a: ≥ 40 dB at 6-12 kHz 1b: >20 to < 40 dB at 4kHz	Hearing loss of 2a: ≥ 40 dB at 4 kHz and above 2b: >20 to < 40 dB below 4kHz	Hearing loss of ≥ 40 dB at 2 or 3 kHz	Hearing loss of ≥ 40 dB at 1 kHz
SIOP Boston Criteria ¹⁸	<20 dB hearing loss at all frequencies	Hearing loss of >20 dB above 4 kHz	Hearing loss of >20 dB at 4 - 8 kHz	Hearing loss of >20 dB at 2 - 8 kHz	Hearing loss of > 40 dB at 2 - 8 kHz

Table 2: Grading scheme used for critical appraisal of evidence

Grade	Results	Description
++++	Consistent, generalizable	Strong general conclusions can be drawn that are unlikely to change based on further research
+++	Consistent, but limited quantity, quality or generalizability	Evidence allows general conclusions , but with reduced confidence ; further research is likely to have an important impact on confidence in conclusions
++	Inconsistent or insufficient quantity/quality, encouraging	No general conclusions can be drawn or conclusions are likely to change based on further research, but current evidence is encouraging
+	Inconsistent or insufficient quantity/quality, discouraging	No conclusions can be drawn or conclusions are likely to change based on future studies, and current evidence is discouraging

Table 3: Grading scheme used for clinical practice guidelines

Level	Strength	Evidence basis
A	Strong	Based on strong scientific evidence; benefits clearly outweigh risks
B	Moderate	Based on reduced confidence scientific evidence and expert opinion; benefits likely to outweigh risks
C	Optional	Based mainly on expert opinion , for use with evidence development in a research context

ACCEPTED

Table 4: Summary of genotype-based risk stratification

Tested Variant	Genotype	Frequency*	Interpretation
TPMT*3C (rs1142345)	G/G	Rare (<1%)	Increased risk of Cisplatin-induced Ototoxicity
	A/G	Infrequent (0-14%)	Increased risk of Cisplatin-induced Ototoxicity
	A/A	Common (88-100%)	Standard risk for Cisplatin-induced Ototoxicity
TPMT*3B (rs1800460)	A/A	Rare (<1%)	Increased risk of Cisplatin-induced Ototoxicity
	A/G	Infrequent (0-10%)	Increased risk of Cisplatin-induced Ototoxicity
	G/G	Common (89-100%)	Standard risk for Cisplatin-induced Ototoxicity
TPMT*3A haplotype (rs1142345 + rs1800460)	G/G + A/A	Rare (<1%)	Increased risk of Cisplatin-induced Ototoxicity
	A/G + A/G	Infrequent (0-10%)	Increased risk of Cisplatin-induced Ototoxicity
	A/A + G/G	Common (89-100%)	Standard risk for Cisplatin-induced Ototoxicity

* Range of allele and haplotype frequencies for worldwide ancestries ^{76,77}