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REVIEW

Platinum-induced ototoxicity and hearing impairment in children and adolescents

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Abstract

Platinum compounds play a crucial role in the treatment of solid tumours in paediatric patients, significantly improving survival rates. However, these treatments can result in hearing loss as a side-effect that can significantly impact the quality of life of young cancer survivors. Whilst the therapeutic benefits of platinum compounds in paediatric oncology are indisputable, addressing the challenge of ototoxicity remains a priority. Early and regular auditory function assessments, with tools such as audiometry, otoacoustic emissions and auditory brainstem response testing, are critical during platinum-based therapy, playing key roles in the early detection of hearing loss. Interdisciplinary collaboration amongst paediatric oncologists, audiologists and otolaryngologists is essential for optimal management and to minimize the long-term consequences of hearing loss. This narrative review concludes that, whilst platinum-based chemotherapeutic agents demonstrate significant therapeutic efficacy in paediatric malignancies, platinum-induced ototoxicity remains a substantial clinical challenge. Continued research into prevention, monitoring and treatment strategies is essential for preserving hearing and improving the overall quality of life for survivors of childhood cancer.

Keywords: adolescent, children, hearing loss, platinum.

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Introduction

Platinum compounds are essential in the treatment of paediatric solid tumours, proving highly effective in managing various paediatric cancers, including germ cell tumours, neuroblastoma, osteosarcoma, hepatoblastoma, retinoblastoma, and brain tumours like low-grade gliomas, medulloblastoma or primitive neuroectodermal tumours as well as recurrent or resistant lymphomas.[1,2] However, a significant drawback of these therapies is the risk of hearing loss, which can profoundly affect the quality of life for young cancer survivors.[3]

The main platinum-based compounds include cisplatin, carboplatin and oxaliplatin, which operate by covalently binding to the purine bases of DNA. This occurs via the N7 nitrogen atom, a strong nucleophile that is not part of Watson–Crick base pairing. Such binding creates bifunctional adducts that disrupt normal DNA function.[4] Following intravenous infusion, cisplatin interacts with plasma proteins and displays a remarkable ability to infiltrate the liver, kidneys, colon, small intestine and testes. However, it typically does not access the central nervous system (CNS). Approximately 90% of the drug is excreted through the kidneys via glomerular filtration and tubular secretion, whilst the remaining 10% is eliminated through bile. Notably, around 25% of cisplatin clears from the body within 24 h of administration but platinum adducts can persist in tissues for over a decade or even indefinitely. The primary adverse effects of cisplatin treatment include nephrotoxicity, neurotoxicity and ototoxicity.[5]

Carboplatin, a derivative of cisplatin, was created to mitigate the dose-limiting toxicities associated with cisplatin. It exhibits an 8–45-fold decrease in potency compared with its predecessor, necessitating higher doses for a similar antitumour effect. Additionally, carboplatin displays a lower affinity for plasma proteins. Remarkably, around 90% of carboplatin is swiftly eliminated by the kidneys via glomerular filtration within 24 h of administration.[6,7]

Oxaliplatin, also known as trans-L-diaminocyclohexane platinum oxalate II, represents a third-generation

chemotherapy agent with pharmacokinetic characteristics akin to both cisplatin and carboplatin. Upon intravenous delivery, roughly 70% of oxaliplatin initially binds to plasma proteins, particularly albumin, with up to 95% eventually becoming protein bound. However, this binding reduces the drug's antitumour efficacy. The primary elimination pathway for oxaliplatin is through renal glomerular filtration, with only 2% excreted in faeces. Notably, oxaliplatin is generally better tolerated than other platinum-based therapies, resulting in hearing impairment in less than 1% of patients and renal toxicity under 3%. Whilst oxaliplatin can induce neurotoxicity affecting peripheral nerves, this side effect is quickly reversible because the drug does not accumulate within cells.[5,8]

This narrative review aims to present the latest data on ototoxicity induced by platinum-based chemotherapy. Ongoing research into prevention, monitoring and treatment strategies remains crucial to safeguarding hearing and enhancing the overall quality of life for paediatric cancer survivors.

Methods

This article presents a narrative review that summarizes the current understanding of the pathogenesis of hearing damage caused by platinum compounds in children and adolescents. To achieve this objective, we conducted a thorough search for relevant literature using PubMed, employing the search terms "ototoxicity" and "platinum" in conjunction with "children" and "adolescent". Following the initial search, we applied filters to select only English-language articles that had full texts available. The final search was last executed on 30/01/2025; this process yielded 223 articles, which were then evaluated by two researchers based on the relevance of their titles and abstracts to our topic. Ultimately, 68 papers were selected and included in our review.

Review

Pathogenesis of hearing damage induced by platinum compounds

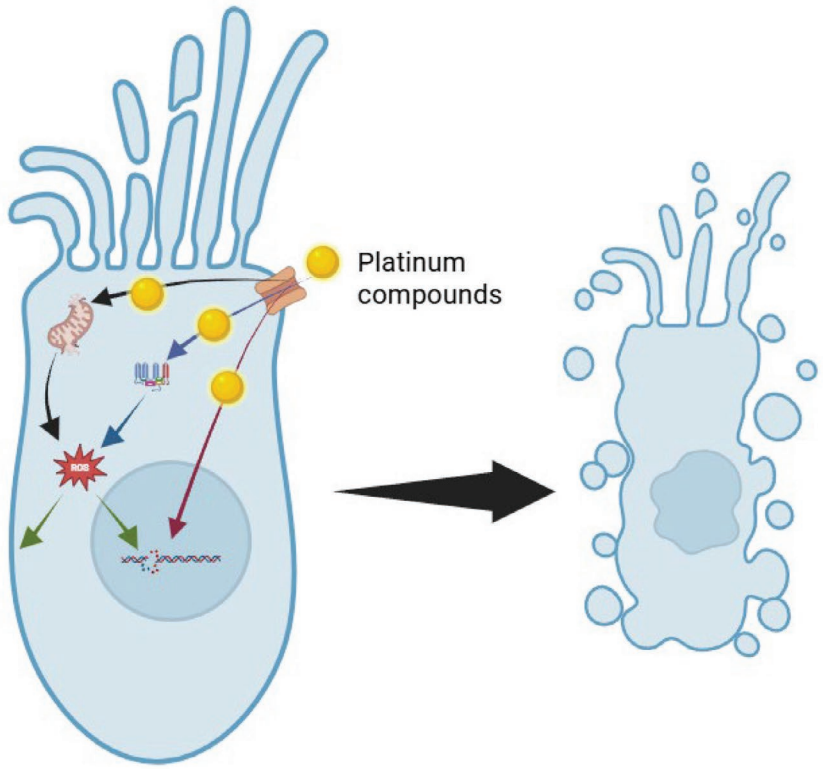
Hearing impairment results from the deterioration of sensory hair cells in the organ of Corti, the spiral ganglion, and the cells of the lateral wall of the cochlear duct (stria vascularis and spiral ligament).[9,10]

Multiple mechanisms cooperate in determining hair cell death, including oxidative stress related to the excessive production of reactive oxygen species (ROS), the activation of pro-inflammatory factors, the induction of the p53-dependent signalling pathway and, ultimately, apoptotic cell death.[11]

The organ of Corti houses approximately 3,500 inner hair cells and 12,000 outer hair cells. Outer hair cells play a pivotal role in amplifying the movement of the basilar membrane, thereby increasing sensitivity to low-intensity sounds and enhancing frequency selectivity. In contrast, inner hair cells are responsible for transforming sound-induced mechanical movements into receptor potentials, resulting in the release of glutamic acid at synapses and the activation of action potentials in cochlear afferent fibres. Bipolar sensory neurons, known as spiral ganglion neurons, are essential for the effective transmission of auditory information to the brain. The lateral wall of the cochlear duct comprises the stria vascularis and the spiral ligament. The stria vascularis is a vascular structure that plays a crucial role in forming endolymph and generating endocochlear potential, both vital for the process of mechanoelectrical transduction.

The mechanisms underlying the observed damage are likely similar to those by which platinum compounds affect neoplastic cells. These compounds interact with cellular DNA, creating monoadducts at nucleophilic sites, which can further result in intra-strand and inter-strand cross-links within DNA.[12] This interference inhibits DNA synthesis and RNA transcription leading to cell cycle arrest and ultimately apoptosis. Additionally, a secondary cell death mechanism is linked to platinum mitochondrial damage. Once inside the cell, the drug forms adducts with mitochondrial DNA, disrupting electron transport chain (ETC) function and compromising mitochondrial integrity.[13] Cisplatin forms adducts with mitochondrial DNA inhibiting transcription and reducing synthesis of essential ETC proteins. This compromised ETC function generates elevated ROS, which damage cellular constituents, including proteins, lipids and further mitochondrial DNA. This establishes a destructive cycle: mitochondrial impairment produces ROS, which exacerbates mitochondrial dysfunction, generating additional ROS. The oxidative stress overwhelms antioxidant defences, as evidenced by depleted antioxidant enzymes and increased lipid peroxidation in target tissues.[14–18] The resulting apoptosis proceeds through dual pathways: intrinsically, ROS disrupt mitochondrial membrane potential and promote cytochrome c release via Bak/Bax activation; extrinsically, ROS activate death receptors (TRAILR1/2, FasR, TNFR1) on the plasma membrane. This self-perpetuating cycle of mitochondrial damage and oxidative stress ultimately culminates in cellular demise (Figure 1).[19,20] Additionally, molecular mechanisms leading to oxidative stress after the exposure of inner ear tissues to cisplatin include the activation of nicotinamide adenine dinucleotide phosphate oxidase 3 and xanthine oxidase, inhibition of glu-

Figure 1. Pathogenesis of hearing damage induced by platinum compounds.



Platinum compounds (yellow ball) enter hair cells through membrane transport proteins. Inside the cell, they act directly on DNA (red arrow) blocking transcription into RNA and protein synthesis, with consequent activation of cell death. In addition, platinum compounds act on mitochondria (black arrows) promoting the production of oxygen radicals. Platinum compounds also activate the nicotinamide adenine dinucleotide phosphate oxidase 3 and xanthine oxidase and inhibit the glutathione peroxidases, increasing reactive oxygen species (ROS) formation (blue arrow). ROS damage cell membranes and proteins with consequent activation of apoptosis (green arrows).

tathione peroxidases, and abatement of the endogenous antioxidant system.[21]

The events earlier take place only when platinum compounds successfully traverse the blood–labyrinth barrier (BLB), which houses the sensory cells of the inner ear. Such passage can occur if cellular integrity is compromised or if paracellular permeability between adjacent endothelial cells is heightened.[22] Particularly, the BLB maintains cochlear homeostasis and generates the endocochlear potential necessary for hair cell depolarization, both critical for auditory function. This specialized barrier establishes the electrochemical environment essential for sound transduction. Cisplatin administration compromises BLB integrity, increasing vascular permeability through several mechanisms, including alterations in pericyte populations and morphology, disruption of perivascular-resident macrophage-like melanocytes and upregulation of hypoxia-inducible factor-1α with subsequent vascular endothelial growth factor expression. The resulting microvascular dysfunction allows excessive cisplatin accumulation in the strial perivascular space. This pathological leakage disrupts ionic gradients and metabolic regulation within the cochlear microenvironment compromising the positive endocochlear potential required for sensory transduction. The BLB deterioration represents a significant pathway through which cisplatin exerts its ototoxic effects beyond direct cellular damage to auditory structures.[23]

Additionally, transport systems such as megalin (LRP2), organic cation transporter 2 (OCT2; also known as SLC22A2), and high-affinity copper uptake protein 1 (CTR1; also known as SLC31A1), facilitate this process.[11,24,25] Cellular uptake and efflux of cisplatin depend on multiple transporter proteins. Influx transporters include OCT2,

CTR1, OAT1, OAT3 and MCT6. Efflux of platinum compounds occurs via several transporters, including MATE1, MATE2K, CTR2, ATP7A, ATP7B and ABCC2, whilst ABCC3 exhibits polymorphisms affecting platinum transport. These transporters play critical roles in platinum pharmacokinetics and potentially influence both therapeutic efficacy and toxicity profiles.[26]

Beyond the direct harm inflicted on hair cells by platinum compounds, an indirect damage mechanism linked to magnesium deficiency also exists. Magnesium is essential for maintaining hair cell permeability and ensuring adequate cochlear blood flow.[27,28] During treatment, platinum compounds can inflict damage on renal tubular cells, reducing their ability to reabsorb magnesium. This can lead to decreased plasma magnesium levels and a subsequent drop in its concentration in both endolymph and perilymph.[29] Such an imbalance in the ionic makeup of these labyrinthine fluids results in heightened hair cell permeability to platinum compounds.[25,30] Experimental studies in magnesium-deficient rodent models demonstrate a significant correlation between reduced serum and perilymphatic magnesium concentration and increased susceptibility to noise-induced hearing loss. Similar associations have been observed in humans exposed to acoustic trauma, where diminished serum magnesium levels correspond with greater hearing threshold shifts.[31]

During cochlear mechanotransduction, hair cells experience transient increases in potassium and calcium membrane permeability. Magnesium deficiency exacerbates this ionic flux, potentially intensifying the energy-dependent ion homeostasis requirements of auditory sensory cells. This metabolic strain may compromise cellular integrity during acoustic stimulation.[31]

Multiple pathophysiological mechanisms link magnesium deficiency to cochlear injury. Hypomagnesaemia induces elevated catecholamine release, which may directly affect hair cells by increasing intracellular calcium concentrations. Additionally, catecholamines can indirectly compromise cochlear function by reducing microcirculatory blood flow. Thromboxane A2, which demonstrates increased production in magnesium-deficient states, further contributes to cochlear microvascular constriction. In vivo microcirculatory investigations reveal pronounced vascular alterations in magnesium-deficient states. Direct examination of mesenteric microcirculation demonstrates a progressive reduction in microvascular luminal diameters affecting terminal arterioles, precapillary sphincters and venules. The severity of these microvascular constrictions correlates directly with the magnitude of magnesium depletion and results in significantly diminished blood flow throughout the microcirculatory network, affecting capillary, postcapillary and venular segments. These findings suggest that a similar microcirculatory compromise may occur in cochlear vasculature during magnesium deficiency.[31]

These converging pathways — altered ion homeostasis, elevated intracellular calcium and widespread microvascular constriction — culminate in metabolic exhaustion and potentially irreversible damage to auditory sensory cells, establishing magnesium deficiency as a significant risk factor for hearing impairment.

Characteristics of hearing damage induced by platinum compounds

Platinum-based compounds, especially cisplatin, are widely recognized for their ototoxic effects, causing harm to the delicate structures of the inner ear, including the cochlea.[32] Simultaneously, platinum compound can also injure the vestibular labyrinth, which is essential for balance. Consequently, damage to this inner ear component can result in significant postural instability, elevating the risk of falls and related injuries.[33,34] The outer hair cells, particularly those situated in the basal region of the cochlea, are the most vulnerable to such damage.

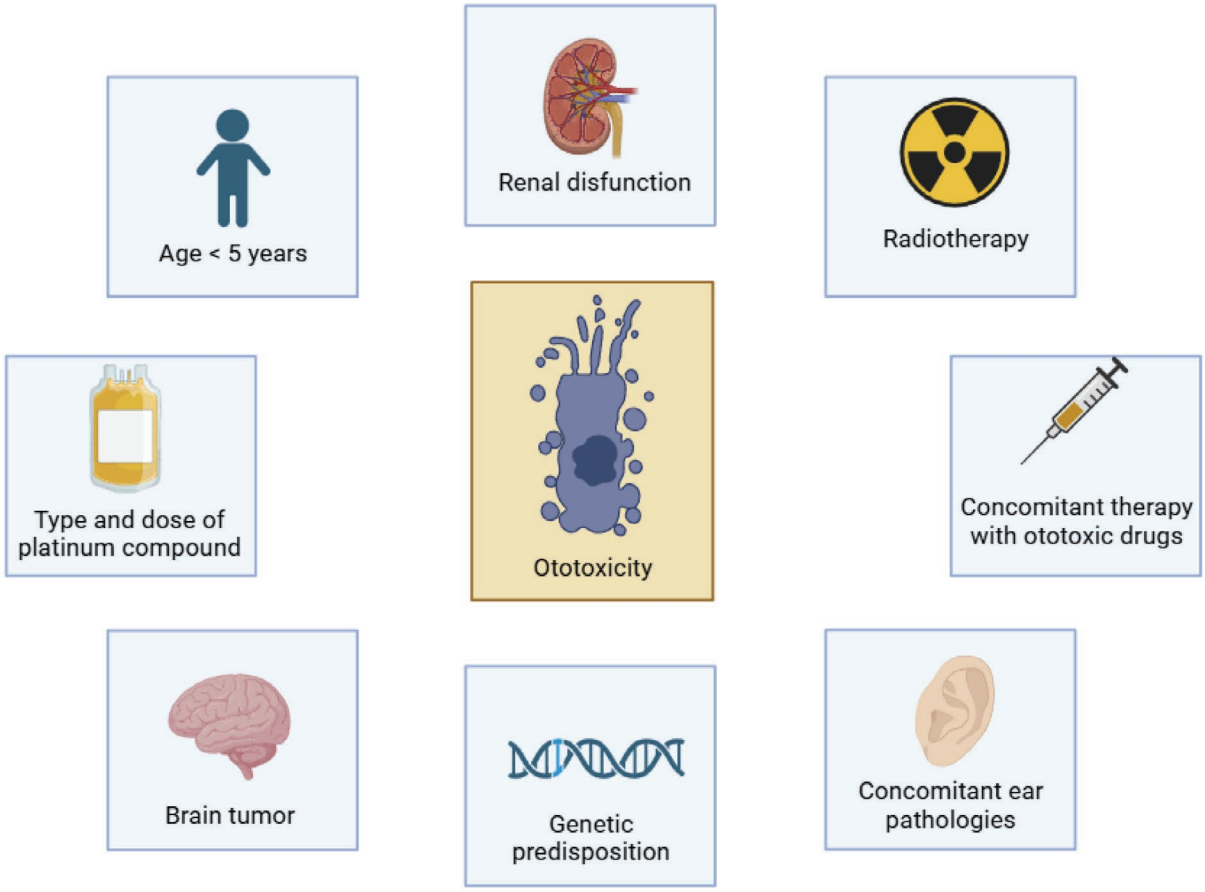
Exposure to platinum compounds initially results in deterioration of high-frequency hearing perception (typically above 6–8 kHz), followed by progressive involvement of lower frequencies as treatment continues.[35,36] Hearing loss associated with platinum compounds is typically irreversible, bilateral and symmetrical, manifesting as sensorineural hearing loss that primarily impacts high frequencies (6,000 Hz and above) and is frequently accompanied by tinnitus.[3] Notably, this hearing impairment may emerge not only during platinum-based therapy but also several years after treatment has concluded. This phenomenon can be attributed to the ability of certain compounds, notably cisplatin, to accumulate in body cells, remaining detectable in plasma for up to two decades post-treatment.[37,38]

Risk factors involved in the development of hearing damage

Ototoxicity associated with platinum compounds is influenced by various risk factors including cumulative dose, type of compound, tumour location, concurrent cranial radiation, young age, genetic factors and specific host conditions such as renal function at the time of treatment or the use of other ototoxic medications like aminoglycosides or furosemide.[39,40]

The extent of hearing loss linked to platinum-based therapies is dependent on the administered dose and the specific compound utilized. Amongst these agents,

Figure 2. Risk factors involved in the development of ototoxicity from platinum compounds.



cisplatin is the most ototoxic, whilst oxaliplatin is deemed the least hazardous. In paediatric patients, a cumulative cisplatin dose exceeding 400 mg/m² marks the threshold for significant ototoxicity, whereas in adults, this threshold rises to 600 mg/m². Carboplatin has been associated with ototoxic effects at cumulative doses greater than 400 mg/m². Notably, patients treated with both cisplatin and carboplatin exhibit the highest rates of hearing loss.[30,40] Furthermore, the method of administration plays a significant role in determining the level of ototoxicity; bolus infusions are found to be more harmful than short or continuous infusions, though there is no conclusive evidence to suggest that continuous infusions are any less toxic than short infusions.[41]

Several risk factors contribute to hearing loss induced by platinum compounds, particularly the tumour site and concurrent CNS radiation (Figure 2). CNS tumours exhibit the highest incidence of hearing loss owing to the elevated doses of platinum compounds administered during treatment and the direct damage that these tumours inflict on surrounding areas. Additionally, CNS tumours often undergo combined radiotherapy, further complicating the potential damage.[42,43] These factors obscure the accurate estimation of ototoxicity prevalence in children with brain tumours, though it may reach as high as 74% amongst those receiving combined cisplatin and radiotherapy.[44]

Radiation therapy can induce ototoxicity by impairing auditory structures at various levels. Damage to the Eustachian tube or the ossicular chain can cause conductive hearing loss whereas injuries in the cochlear or retrocochlear regions can result in sensorineural hearing loss.[44]

Children younger than 5 years are particularly vulnerable to hearing loss following platinum compound treatment.[45–48] Research indicates that this age group experiences not only a quicker progression of cisplatin-induced hearing loss within the first year of treatment but also a higher incidence of such loss over the 3 years following treatment initiation compared with their older counterparts.[49] Although the exact reasons for this heightened risk remain unclear, it is understood that the central auditory system develops extensively during the

early years of life, rendering these structures more susceptible to the toxic effects of cisplatin.[50]

Platinum compounds are primarily eliminated through the renal system, and impaired kidney function can hinder the excretion of platinum-based medications, subsequently increasing the risk of hearing loss.[30]

Drugs like aminoglycoside antibiotics and loop diuretics further contribute to ototoxicity. Aminoglycosides harm the inner hair cells by reducing the elimination of ROS and disrupting the stria vascularis, which facilitates the infiltration of platinum through the BLB. Conversely, loop diuretics reversibly inhibit the Na-K-Cl cotransporter in the inner ear, altering the ionic composition of endolymph and diminishing blood flow.

Loop diuretics, through their inhibitory action on the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) in the inner ear, disrupt the delicate ionic homeostasis that maintains normal vascular tone in cochlear microcirculation. This pharmacological inhibition triggers vasoconstriction of the spiral modiolar artery and its branches. Multiple pathways contribute to this effect including alterations in endolymphatic potential, disruption of endothelium-dependent vasodilatory mechanisms, enhanced production of vasoconstrictive prostaglandins, direct effects on vascular smooth muscle ion channels and induction of local inflammatory mediators. These mechanisms collectively result in reduced cochlear blood flow, potentially compromising oxygen and nutrient delivery to the metabolically demanding hair cells and contributing to the ototoxic profile of loop diuretics, particularly when administered concurrently with other ototoxic agents.[51] This disruption damages the endothelial barrier function, allowing other ototoxic agents, such as cisplatin and aminoglycosides, to penetrate the inner ear and exacerbate hearing loss.[51,52] Indeed, the combination of vincristine with cisplatin was found to influence the progression of cisplatin-induced hearing loss over time.[50] Previously, this relationship was noted in individual cases involving adult patients with multiple myeloma, an individual with non-Hodgkin lymphoma, and a teenager with peripheral T cell lymphoma [50]. However, more recent reports have also identified this association in children[50]. Whilst the precise mechanism remains unclear, it is theorized that vincristine's neurotoxic effects may impact the auditory nerves, potentially leading to bilateral nerve paralysis and subsequent hearing loss.[53–56] Additionally, the presence of concurrent ear conditions, such as chronic otitis media, middle ear effusions or earwax buildup, can further exacerbate hearing impairment.[30]

The hypothesis that an individual's genetic predisposition may play a role in the development of ototoxicity stems from the observation that there is considerable inter-individual variability in the onset and severity of hearing damage even amongst patients with similar demographic characteristics who receive the same platinum-based chemotherapy regimen. In recent years, many research groups have focused on genes involved in platinum-induced ototoxicity, identifying genes involved in platinum compound transport, metabolism and DNA repair as potentially responsible.[11] A recent meta-analysis highlighted six relevant single nucleotide polymorphisms within key genes for predicting platinum-based chemotherapy-induced ototoxicity[57] including *ACYP2* (rs1872328), *COMT* (rs4646316, rs9332377), *ERCC2* (rs1799793), *XPC* (rs2228001) and *GSTP1* (rs1965). Notably, genes such as *ERCC1*, *ERCC2*, *ERCC4*, *ERCC5* and *XPC* are crucial for the detoxification of platinum adducts through the nucleotide excision repair DNA pathway. Hong et al.[57] reported that the missense variant *ERCC2* rs1799793 (C>T) demonstrated protective effects on auditory function, whilst the missense variant XPC rs2228001 (G>T) was significant in predicting ototoxicity, specifically in populations who had not received radiotherapy.

The *ACYP2* gene encodes an enzyme that hydrolyses the carboxyl-phosphate bond of acylphosphates; mutations in this gene may disrupt ATP-dependent Ca^{2+} signalling, thereby affecting Ca^{2+} homeostasis in the cochlea and influencing hair cell development. Our meta-analysis revealed that the A allele of the *ACYP2* intronic variant rs1872328 is linked to cisplatin-induced ototoxicity.[57]

The catechol-O-methyltransferase (COMT) enzyme, which is pivotal in degrading catechol-containing compounds, regulates signals from the efferent fibres of the lateral olivo-cochlear complex and afferent fibres to inner hair cells. The analysis of patients treated solely with cisplatin-based chemotherapy showed that the intronic *COMT* variant rs4646316 (T) is associated with auditory function protection, whereas the intronic variant rs9332377 (T) indicates a heightened risk for ototoxicity.[57]

Glutathione S-transferases (GST), encoded by *GSTM1*, *GSTT1* and *GSTP1*, play a critical role in the cellular elimination of cisplatin.[57] Notably, the G allele of the *GSTP1* rs1695 variant is linked to a protective effect against ototoxic damage in patients who did not undergo concurrent radiotherapy.[57] Whilst genes associated with hereditary deafness have been explored as possible factors, their polymorphisms appear not to contribute to hearing loss induced by platinum compounds.[58]

Prevention strategies

The prevention of hearing damage is undoubtedly a challenge for all those involved in paediatric oncology. The integrity of auditory function is a fundamental prerequisite

for language development and, in general, for the psychological and social maturation of the individual. The primary goal is to adopt effective measures that can safeguard auditory function from platinum-induced ototoxicity without affecting or reducing the antitumour activity of these compounds. Several preclinical studies have shown that the administration of antioxidant agents, such as tiopronin, vitamin E, curcumin and others, both trans-tympanically and systemically, can facilitate the removal of ROS and improve hearing.[59–61] However, only a few clinical studies have been completed, with controversial results.[11]

Amifostine has been one of the most studied molecules in clinical trials. It is a prodrug that becomes activated through dephosphorylation by alkaline phosphatase at the tissue level, resulting in the formation of a pharmacologically active metabolite called WR-1065, which can act as a ROS scavenger. This activity primarily occurs in healthy tissues due to higher expression of alkaline phosphatase, greater vascularization and a more alkaline pH. Currently, this compound is used with cisplatin as a nephroprotectant. Only limited and non-randomized studies have confirmed its effectiveness in protecting the ear in children with average-risk medulloblastoma from severe ototoxicity, and thus its clinical use has not been established.[21,62-64]

Another substance that works similarly to amifostine, acting as a ROS scavenger, is sodium thiosulfate.[65] It has been tested in paediatric and adult patients with various types of tumours and has shown significant benefits compared with non-use.[66–69] A 2021 meta-analysis of the studies analysed showed a consistent and statistically significant reduction in hearing damage in patients treated with sodium thiosulfate compared with those who did not receive it. Sodium thiosulfate was associated with a significant reduction in the risk of ototoxicity in patients treated with platinum-based chemotherapy, especially in children. Its use was not associated with a significant increase in severe side-effects. However, some studies have reported a potential reduction in antitumour efficacy, especially when administered near cisplatin, raising concerns about a possible compromise of oncological treatment effectiveness.[70]

Sodium thiosulfate has recently been approved by the FDA (Pedmark) and European agencies (EMA and the Medicines and Healthcare products Regulatory Agency as Pedmarqsi) for use in children with tumours requiring cisplatin treatment such as neuroblastoma, hepatoblastoma, nasopharyngeal carcinoma, osteosarcoma, medulloblastoma and germ cell tumours. However, pre-approval guidelines advocate the use of sodium thiosulfate exclusively for children with standard-risk hepatoblastoma, highlighting the necessity for updates following its approval. To thoroughly evaluate the compound's ability to protect hearing and its therapeutic effectiveness in metastatic diseases, randomized clinical trials or single-arm studies, combined with biological and imaging research, are essential. Furthermore, additional pharmacokinetic studies must be conducted to explore the interaction between sodium thiosulfate and cisplatin kinetics, with a focus on measuring free cisplatin levels, which are critical for assessing clinical responses and potential toxicity.

To achieve hearing protection with sodium thiosulfate, the infusion duration of cisplatin should be reduced to a maximum of 6 h. Previous studies did not show differences in efficacy between longer and shorter infusions.[39] Studies are ongoing to assess whether sodium thiosulfate can prevent further hearing loss in patients already affected. If administered 6 h after cisplatin, sodium thiosulfate does not reduce the nephrotoxic effect of platinum compounds, which occurs before ototoxicity. The administration of sodium thiosulfate with carboplatin needs to be evaluated through additional studies, as carboplatin is chemically more stable and may be inactivated by sodium thiosulfate, potentially compromising its antitumour effectiveness.[71]

Recent research has highlighted the promising otoprotective effects of the antioxidant N-acetylcysteine (NAC) in a phase I clinical trial involving children and adolescents with localized, non-metastatic tumours undergoing cisplatin treatment. Notably, no severe adverse events were reported following NAC administration, positioning it as a potential solution for mitigating cisplatin-induced hearing loss.[72]

Whilst sodium thiosulfate has gained approval and clinical trials have shown the benefits of NAC in safeguarding paediatric patients with localized solid tumours from cisplatin ototoxicity, there is still a pressing need for the development of new therapeutic options. This is especially crucial for adults and children who are not eligible for Pedmark treatment such as those with metastatic disease. A murine model trial revealed that dabrafenib, a BRAF kinase inhibitor, can effectively prevent hearing loss without compromising the efficacy of cisplatin.[73] The mechanism of protection was through inhibition of the MAPK pathway, which is upregulated in the inner ear following cisplatin administration, but cotreatment with dabrafenib decreased MAPK activity and protected hair cells from cisplatin-induced death. Should these results translate to human applications, dabrafenib could significantly enhance the quality of life for chemotherapy patients whilst maintaining effective cancer treatment.

Since the severity of hearing damage can depend on the dose and infusion rate of cisplatin, a longer infusion

duration may reduce the risk of ototoxicity. Theoretically, a slower administration could distribute the dose more safely, reducing peaks in drug concentration in the blood and tissues. However, there is no consensus on the efficacy of this strategy. Some studies indicate that prolonged infusions (24–96 h) may reduce side-effects without compromising treatment efficacy,[39] whilst others show no significant benefits over shorter (6-h) infusions.[39] Reducing the infusion duration (e.g. to 6 h) does not seem to compromise survival rates in children treated with cisplatin. For instance, the SIOPEL 6 study, which reduced cisplatin infusion duration from 48 to 6 h, showed no significant differences in survival outcomes compared with previous studies with longer infusions, suggesting that shorter infusions can be used without compromising antitumour efficacy but with potential benefits in preventing hearing loss.[74]

Magnesium supplementation during cisplatin chemotherapy seems to offer protective benefits for renal function in paediatric patients.[75] This may help maintain its constant concentration in the endolymph and perilymph, preventing ionic imbalance of the two labyrinth fluids, which could otherwise increase the permeability of the cochlear cells to platinum.[21,24,30]

Assessment of auditory function during treatment with platinum compounds

Before starting treatment with platinum compounds, a comprehensive assessment of auditory function is necessary to obtain a baseline evaluation that can be compared with subsequent assessments during and after treatment. The baseline evaluation can be conducted using various audiological tests depending on the patient's age. Audiometry is one of the most straightforward tests available, effectively identifying a patient's minimal hearing threshold. A comprehensive audiometric evaluation encompasses both pure-tone audiometry and speech audiometry.[53] For younger children, alternative testing methods are necessary.[10] Children aged 24 months to 6 years often struggle with traditional audiometric testing; thus, they typically undergo conditioned audiometric testing, where they are instructed to perform a simple task (like placing an object in a container) upon hearing a sound. Visual reinforcement audiometry is utilized for children between 7 months and 24–30 months.[10] For infants under 7–8 months, conventional audiometry is ineffective. Instead, otoacoustic emission (OAE) measurements offer valuable insights into normal ear function, specifically assessing the performance of the cochlea's outer hair cells. While OAE measurements provide information about cochlear function, they do not quantify the severity of hearing loss. If OAE measurements are found to be abnormal, a secondary test like the auditory brainstem response can be employed.

Throughout treatment with platinum compounds and upon its completion, all patients should undergo regular auditory function assessments. This monitoring is crucial and should involve paediatric oncologists as well as audiologists or otorhinolaryngologists to facilitate early detection of hearing loss and to implement measures that can mitigate the risk of further cochlear toxicity.[74–77]

Conclusions

Platinum-based chemotherapy remains a fundamental approach in treating paediatric solid tumours, significantly enhancing survival rates. However, the risk of ototoxicity, especially hearing loss, presents a considerable challenge to the quality of life for young survivors. Ototoxicity caused by cisplatin, carboplatin and oxaliplatin is a complex process involving direct damage to cochlear structures, oxidative stress and genetic predispositions, all contributing to hearing impairment progression. Amongst these agents, cisplatin is the most ototoxic, with a clear dose-dependent relationship between cumulative exposure and the degree of hearing loss experienced.

While research into genetic predisposition has provided valuable insights into identifying patients at higher risk, effective preventive strategies are still in development. Sodium thiosulfate has shown promise in reducing cisplatin-induced ototoxicity, though its potential to interfere with the drug's antitumour effects requires careful consideration. Other antioxidants like NAC and magnesium supplementation also offer potential for otoprotection but more robust clinical evidence is needed to confirm their efficacy.

The significance of conducting early and consistent auditory function assessments during platinum-based therapy cannot be emphasized enough. Integrating monitoring tools like audiometry, otoacoustic emissions and auditory brainstem response testing into standard clinical practice is crucial for the timely identification of hearing loss. To achieve optimal management and reduce the long-term effects of hearing loss in paediatric patients with cancer, a collaborative approach involving paediatric oncologists, audiologists and otolaryngologists is essential.

Thus, whilst the therapeutic benefits of platinum compounds in paediatric oncology are indisputable, addressing the challenge of ototoxicity remains a priority. Continued research into prevention, monitoring and treatment strategies is essential for safeguarding the hearing and overall quality of life of paediatric cancer survivors.

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