A Review of Cisplatin-Associated Ototoxicity

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ABSTRACT

Cisplatin, an effective antineoplastic drug used in the treatment of many cancers, has ototoxic potential, thus placing cancer patients, receiving this treatment, at risk of hearing loss. It is therefore important for health care professionals managing these patients to be aware of cisplatin's ototoxic properties and its clinical signs to identify patients at risk of developing a hearing impairment. Eighty-five English peer-reviewed articles and two books, from January 1975 to July 2015, were identified from PubMed, ScienceDirect, and EBSCOhost. An overview of cisplatin-associated ototoxicity, namely its clinical features, incidence rates, molecular and cellular mechanisms, and risk factors, is presented in this article. This review further highlights the importance of a team-based approach to complement an audiological monitoring program in reducing any further loss in the quality of life of affected patients, as there is currently no otoprotective agent routinely recommended for the prevention of cisplatin-associated ototoxicity.

KEYWORDS: cisplatin, ototoxicity, hearing loss, ototoxicity monitoring program, cancer, otoprotectant

Cancer has been identified as the leading cause of death in both more and less economically developed countries.[1] Projections based on the GLOBOCAN 2012 estimates predict a substantive increase to 19.3 million new cancer cases per year by 2025, due to growth and aging of the global population.[2] This is likely to result in an increase in the use of cancer chemotherapy agents, such as cisplatin, which assist in preventing the proliferation, invasion, and metastases of the cancer cells.[3] While considered to be one of the most potent cancer chemotherapeutics in children and adults, due to its effectiveness against many cancers,[4] namely, osteogenic sarcoma, medulloblastoma, and testicular, cervical, and ovarian cancers,[5] cisplatin has an expansive toxicity profile, involving the gastrointestinal, hematologic, renal, and auditory systems.[5]

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Ototoxicity refers to the hearing disorder that results from the temporary or permanent inner ear dysfunction after treatment with an ototoxic drug[6] such as aminoglycosides, loop diuretics, quinine, nonsteroidal anti-inflammatory drugs,[7] and antiretroviral therapy (ART).[8] Therefore, it is possible that some individuals may be receiving treatments which consist of the simultaneous use of more than one ototoxic drug, increasing the likelihood of ototoxicity.

All healthcare professionals managing patients with cancer should be knowledgeable about the ototoxic properties of cisplatin. Hence, this review aims to serve as a resource for health professionals to enhance their understanding of ototoxicity as well as their roles within an ototoxicity-monitoring program by providing an overview and description of this condition in patients diagnosed with cancer and receiving cisplatin chemotherapy.

METHOD

The review identified peer-reviewed articles published between January 1975 and July 2015 in the area of cisplatin-associated ototoxicity and ototoxicity monitoring, and included English articles only. Studies were identified using keyword, and MeSH term searches of electronic databases depicted in Table 1, followed by a manual search of relevant authors and journals. Additional potential publications were identified by reviewing the references cited by each publication, review or book chapter. A criterion for selection was that the article had to present data on either cisplatin ototoxicity and/or ototoxicity monitoring in human participants, and no research designs were excluded.

A total of 2,106 records were initially identified, of which 1,581 were excluded based on the title and/or abstract as well as duplication. Eighty-five relevant articles, comprising of six national (South Africa) and 79 international articles, as well as four internationally published books were selected to provide an overview in the following eight areas: the mechanisms of cisplatin ototoxicity, clinical presentation, risk factors, incidence rates in adults and children, the effect on quality of life, ototoxicity monitoring, otoprotective strategies, and the management of an ototoxic hearing loss.

The Mechanisms of Cisplatin Ototoxicity

Cisplatin ototoxicity is produced by several distinct mechanisms[9] as depicted in Fig. 1. One such mechanism, the antioxidant model, involves the formation of reactive oxygen species (ROS) within the cochlea and consequent reduction in antioxidant enzymes following exposure to cisplatin chemotherapy.[9–13] Another mechanism of cisplatin ototoxicity involves the significant contribution of nicotinamide adenine dinucleotide phosphate oxidase 3 isoform (NOX3) to the generation of ROS within the cochlea, when activated by cisplatin,[10,14] while a third mechanism relates to the activation of transient receptor potential vanilloid 1 (TRPV1) channel.[15–17]

The molecular mechanisms of cisplatin ototoxicity therefore include "creation of ROS, depletion of antioxidant glutathione and its regenerating enzymes, increased rate of lipid

Table 1 Search and MeSH Terms Used in the Literature Search

Electronic database	Search term	MeSH term
PubMed (Medline)	Ototoxicity [All Fields] AND monitoring [All Fields]	(("cisplatin"[MeSH Terms] OR "cisplatin"[All Fields]) AND ototoxicity [All Fields]) OR (("cisplatin"[MeSH Terms] OR "cisplatin"[All Fields]) AND ("hearing loss"[MeSH Terms] OR ("hearing"[All Fields] AND "loss"[All Fields]) OR "hearing loss"[All Fields]))
ScienceDirect		"cisplatin ototoxicity" or "cisplatin hearing loss" "ototoxicity monitoring"
EBSCOhost	Cisplatin ototoxicity or cisplatin hearing loss Ototoxicity monitoring	

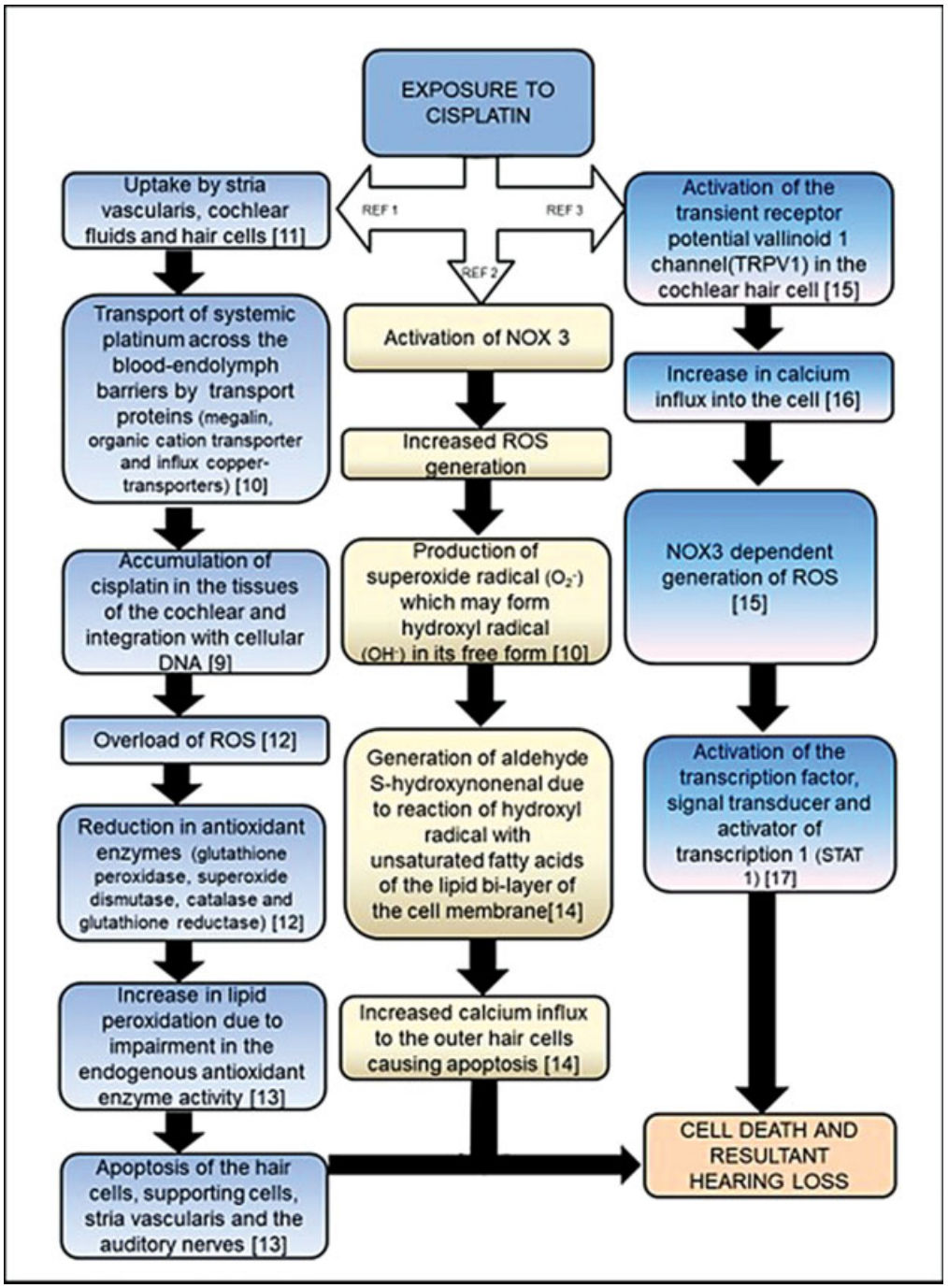

Figure 1 Mechanisms of cisplatin ototoxicity.[1–17]

peroxidation, oxidative modifications of proteins, nucleic acids damage by caspase system activation, and S-Nitrosylation of cochlear proteins."[18] With the cellular mechanisms of cisplatin-associated ototoxicity including damage to the outer hair cells, supporting cells, marginal cells of the stria vascularis, spiral ligament, and the spiral ganglion cells,[18] it is evident that the structures of the inner ear are most susceptible to damage by cisplatin chemotherapy; with apoptotic degeneration of the hair cell in the Organ of Corti being most prominent.[19] The outer hair cells in the basal turn

of the cochlea are most affected. This leads to an initial elevation of high-frequency audiometric thresholds, followed by a progressive loss into the lower frequencies with continued therapy.[20,21] Knowledge of the different mechanisms of cisplatin ototoxicity is important for health care professionals as it will create an awareness of its complexity and the resulting clinical presentation.

Clinical Presentation and Risk Factors

Cisplatin-associated ototoxicity usually manifests as irreversible, progressive,[5] bilateral, high-frequency sensorineural hearing loss[22] with tinnitus.[23] Tinnitus may occur with or without a hearing loss,[22] and may be permanent or transient. While most of the hearing loss is permanent, there is sometimes sporadic and partial recovery.[24] Furthermore, rare cases of unilateral hearing loss have been reported, and these are usually explained by tumor location and surgical or therapeutic intervention on the affected side.[25]

The degree of hearing loss varies and is often dose dependent, that is, the higher the cumulative dose, the greater the ototoxic effect.[26,27] The duration, number of cycles administered,[28] and method of administration[29] also influence cisplatin-associated ototoxicity. Additional factors that may increase the risk for ototoxicity include exposure to concomitant noise,[26,30] chemicals and other ototoxic medications,[26] as well as having a higher melanin content,[31] and/or presenting with renal insufficiency, that is, high levels of serum creatinine,[26] and preexposure hearing loss.[29,32] Genetic risk factors, such as megalin and glutathione S-transferases gene polymorphism, also influence cisplatin ototoxicity,[33] as do physiological factors such as age, with younger children[34] and older adults (older than 46 years)[35] presenting with a greater severity of hearing damage. Awareness of these risk factors may assist health care professionals with informational counselling of the patient receiving cisplatin chemotherapy.

Cisplatin-Associated Hearing Loss in Adults and Children

The incidence of cisplatin ototoxicity is variable in adults (Table 2)[5,26,27,36–44] and children (Table 3).[34,38,45–47] The variations may be due to several factors, such as differences in the dose, both within a cycle and the total amount administered over multiple cycles; time interval between courses; method of administration; treatment duration; as well as differences in patient population. Further exploration in this regard is therefore necessary.

QUALITY OF LIFE

Ototoxicity poses a major problem to the cancer patient, as the quality of life after receiving cisplatin chemotherapy may be negatively affected. Tasks that normal hearing persons take for granted may become challenging and frustrating,[48] with the hearing loss possibly resulting in psychosocial and physical health problems, as well as depression and social isolation.[49] Hence, hearing loss, often referred to as the invisible condition, has serious visible ramifications on the quality of life of an individual with hearing loss.[48]

The impact of an ototoxic hearing loss may be more profound for infants and young children who are at a critical stage of their speech and language development.[50] Furthermore, the high-frequency nature of an ototoxic hearing loss may result in speech recognition and comprehension being compromised,[51] resulting in possible neurocognitive and psychosocial delays.[52] There is also an elevated risk for academic learning problems and psychosocial difficulties in school-aged children and adolescents.[53] Hence, cisplatin-associated ototoxicity further complicates the morbidity of patients with cancer,[5] as it may isolate them from family members and significant others at a time when they require the greatest support.

OTOTOXICITY MONITORING

An audiological monitoring program can avert, to a large extent, the reduced quality of life as a result of hearing loss, as patients on cisplatin chemotherapy can be identified early, counselled, monitored, and managed appropriately through medical and hearing interventions in a logical, systematic, and coherent manner.[54] Prospective audiological evaluations remain the only reliable method for detecting ototoxicity before it becomes symptomatic[55] and a communication problem evident. An ototoxicity

Table 2 Studies Reflecting Cisplatin-Associated Hearing Loss in Adults

Study	Country	Type of study	Audiological tests conducted	Patient population	No. of patients who developed ototoxicity
Malgonde et al[36]	India	Prospective	Pure tone audiometry (frequencies not specified) and short increment sensitivity index test	34 patients with head and neck cancers receiving cisplatin-containing chemotherapy and concomitant radiation therapy	34 (100%)
Whitehorn et al[37]	South Africa	Retrospective cross sectional	Air (0.25–8 kHz) and bone conduction pure tone audiometry	107 patients receiving cisplatin-containing chemotherapy, irrespective of the type of the cancer	59 (55.1%)
Nitz et al[38]	Germany	Prospective longitudinal trinational population based	Air (0.125–8 kHz) and bone conduction pure tone audiometry	1 patient with soft-tissue sarcoma and 16 with osteosarcoma, receiving cisplatin- and/or carboplatin-containing chemotherapy	6 (35.3%)
Arora et al[5]	India	Prospective, randomized, and observational	Pure tone air (0.25–16 kHz) and bone conduction audiometry Results are reflective of frequencies 4–16 kHz	57 patients receiving cisplatin-containing chemotherapy: 10 patients (low-dose group—carcinoma of the larynx) 35 patients (middle-dose group—head and neck cancers, carcinoma of the cervix) 12 patients (high-dose group—carcinoma of the lung and carcinoma of the testis	- 6 (60%) 35 (100%) 12 (100%)
Dell'Aringa et al[39]	Brazil	Case series	Tympanometry, acoustic reflex threshold testing, DPOAEs, air (0.25–8 kHz) and bone conduction pure tone audiometry, speech audiometry	17 patients with extracranial head and neck cancers receiving cisplatin-containing chemotherapy and concomitant radiation therapy	12 left ears (70.5%), 11 right ears (64.7%)

Table 2 (*Continued*)

Study	Country	Type of study	Audiological tests conducted	Patient population	No. of patients who developed ototoxicity
Schultz et al[40]	Brazil	Prospective	Full audiometric evaluations, with only air (0.25–8 kHz) and bone conduction pure tone audiometry thresholds computed	31 patients receiving cisplatin-containing chemotherapy, irrespective of the type of cancer	NCI 12 criteria—12 (38%), Brock et al's criterion—19 (65%), ASHA criteria—17 (54%), David and Silverman's criteria—9 (29%)
Zuur et al[41]	The Netherlands	Prospective	Air (0.125–16 kHz) and bone conduction pure tone audiometry	60 patients with locally advanced head and neck cancer, receiving cisplatin-containing chemotherapy and concomitant radiation therapy	Up to 8 kHz—19 (31%) Up to 16 kHz—28 (47%)
Dutta et al[27]	India	Prospective	Pure tone audiometry (frequencies not specified)	60 patients receiving cisplatin-containing chemotherapy—type of cancer not indicated	9 (15%)
				51—low-dose group	6 (12%)
				9—high-dose group	3 (33%)
Strumberg et al[42]	Germany	Retrospective	Pure tone air (0.125–12 kHz) and bone conduction audiometry, TEOAE test	32 patients with testicular cancer receiving cisplatin-containing chemotherapy	21 (70%)
Nagy et al[43]	USA	Retrospective	Tympanometry, air (0.25–8 kHz) conduction pure tone audiometry	53 patients with oesophageal, lung, or head and neck cancer receiving cisplatin-containing chemotherapy and concomitant radiation therapy (only for head and neck cancer)	19 (36%)
Bokemeyer et al[26]	Germany	Retrospective	Pure tone air (0.5–8 kHz) and bone audiometry	86 patients with testicular cancer receiving cisplatin-containing chemotherapy	57 (66%)

(*Continued*)

Table 2 (*Continued*)

Study	Country	Type of study	Audiological tests conducted	Patient population	No. of patients who developed ototoxicity
Waters et al[44]	Canada	Retrospective	Pure tone air (0.25–8 kHz) and bone conduction audiometry, immittance audiometry, and speech audiometry	60 patients with advanced ovarian carcinomas receiving cisplatin-containing chemotherapy	
				39—low-dose, short treatment (25 from LDE group and 14 new cases after treatment modification)	6 (15%)
				8—low-dose, blocks	0 (0%)
				25—low-dose, extended treatment	9 (36%)
				13—high-dose, short treatment	12 (92%)

Abbreviations: ASHA, American Speech Language Hearing Association; DPOAEs, distortion product otoacoustic emissions; LDE, low dose extended treatment; TEOAE, transient evoked otoacoustic emission.

monitoring program should involve a health care team comprising of an oncology nurse, oncologists, audiologist, and pharmacist to ensure effective sustainability of such a program, if implemented, with the patient being the central focus, as depicted in Fig. 2.[56,57] The principles of early identification and early intervention are a part of ototoxicity monitoring, and the audiologist can manage such a program.[46]

In countries without ototoxicity management guidelines, the "Guidelines for the audiological management of individuals receiving cochleotoxic drug therapy" developed by ASHA[55] may, consequently, guide the audiologist in the implementation of an ototoxicity monitoring program. For widespread acceptance and use, ototoxicity monitoring programs need to incorporate efficient and cost-effective ototoxicity identification techniques,[58] while considering the health care system and demographics of the patient population being managed. For any population receiving ototoxic medication, the following should be considered: (1) the patient's level of alertness or ability to respond reliably; (2) the most appropriate times during the treatment protocol for test administration; and (3) the test should comprise the baseline, monitoring, and post-treatment evaluations.[59] Appropriate time intervals for audiological assessments may differ depending on the type of cancer as well as the frequency and dose of cisplatin (Fig. 3).[55]

The audiological assessments should incorporate a detailed case history, otoscopic examination, immittance audiometry, speech audiometry, distortion product otoacoustic emissions (DPOAEs) testing, and conventional and extended high-frequency audiometry (HFA; i.e., up to 20,000 Hz).[55,59] These procedures are all conducted for the baseline assessment and the 6-month follow-up evaluation.[55,59] While auditory brainstem response test may be used, it is not considered a standard procedure for monitoring ototoxicity.[59]

Monitoring audiological evaluations during treatment and the 1 and 3-month follow-up evaluations include case interview, otoscopy and immittance audiometry, as well as air conduction pure tone and objective testing.[59] However, full-frequency threshold testing is impractical for many patients on cisplatin chemotherapy, as

Table 3 Studies Reflecting Cisplatin-Associated Hearing Loss in Children

Study	Country	Type of study	Audiological tests conducted	Patient population	No. of patients who developed ototoxicity
Nitz et al[38]	Germany	Prospective longitudinal trinational population based	Air (0.125–8 kHz) conduction pure tone audiometry	93 patients with osteosarcoma and 19 with soft-tissue sarcoma receiving cisplatin and/or carboplatin-containing chemotherapy	55 (49.1%)
Knight et al[45]	USA	Prospective	Otoscopy, tympanometry, pure tone audiometry (0.5–8 kHz), DPOAEs, and ABR	32 children with different types of cancers treated with cisplatin- and/or carboplatin-containing chemotherapy	20 (62.5%)
			Otoscopy, tympanometry, extended pure tone audiometry (0.5–16 kHz), and DPOAEs	17 children with different types of cancers treated with cisplatin- and/or carboplatin-containing chemotherapy	16 (94.1%)
Coradini et al[34]	Brazil	Retrospective	Tympanometry, pure tone audiometry (0.25–8 kHz), TEOAEs, and DPOAEs	23 children with malignant hepatic tumor, osteosarcoma, and germ cell tumors receiving cisplatin-containing chemotherapy	Pure tone—12 (52%), TEOAEs—5 (22%), DPOAEs—16 (71%)
Bertolini et al[46]	France	Prospective	Otoscopy, immittance audiometry, speech audiometry, play audiometry or free-field audiometry, conventional pure tone audiometry or ABR (depending on the age of the participant)	102 children with either neuroblastoma, hepatoblastoma, germ cell tumor, or osteosarcoma,	-
				96 received cisplatin- and/or carboplatin-containing chemotherapy,	39 (41%)
				52 received cisplatin only	19 (37%)
Stavroulaki et al[47]	Greece	Prospective	Otoscopy, immittance audiometry, pure tone audiometry (0.25–8 kHz), TEOAEs, and DPOAEs	12 children with neuroblastoma, osteosarcoma, medulloblastoma, rhabdomyosarcoma, or primitive neuroectodermal tumor receiving cisplatin-containing chemotherapy	6 (50%)

Abbreviations: ABR, auditory brainstem response; DPOAEs, distortion product otoacoustic emissions; TEOAE, transient evoked otoacoustic emission.

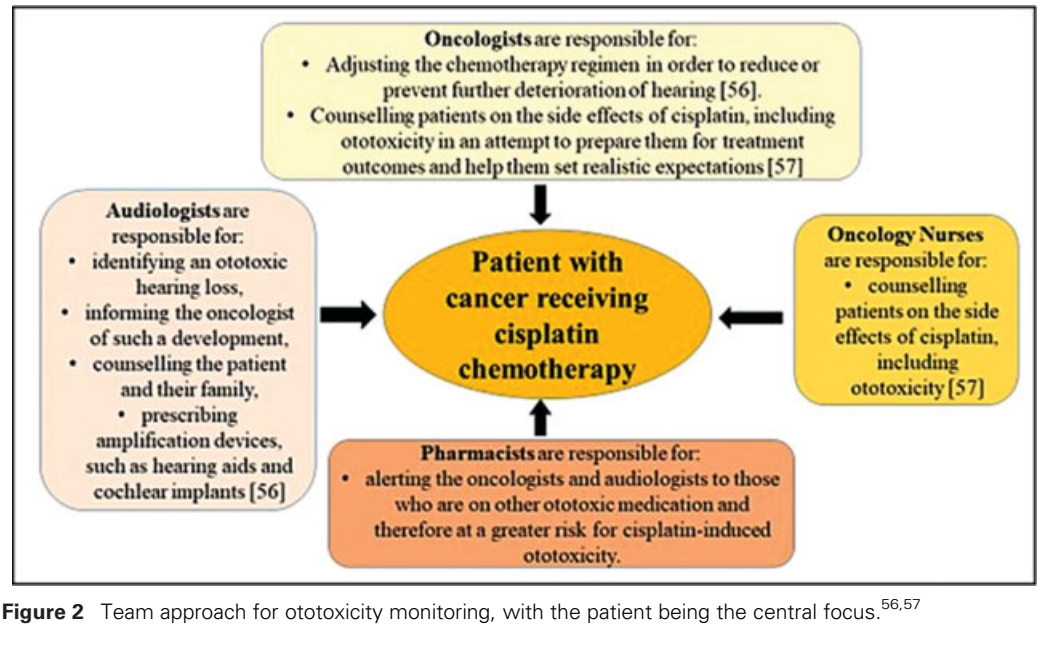

Figure 2 Team approach for ototoxicity monitoring, with the patient being the central focus.[56,57]

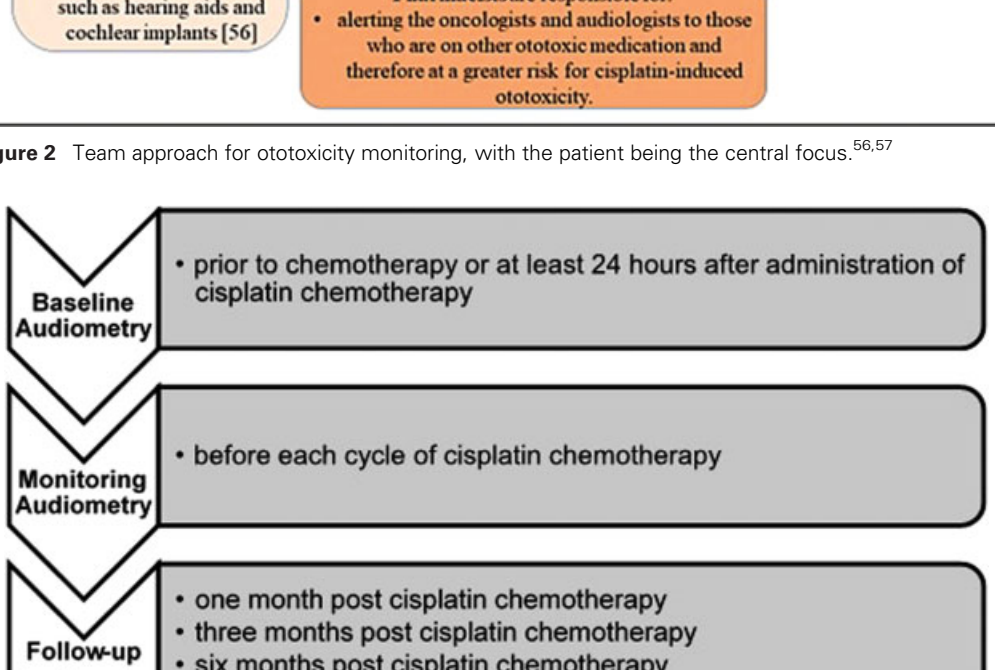

Figure 3 Timelines for audiological assessments.[55]

these individuals are often extremely ill and easily fatigued. The use of abbreviated threshold monitoring procedures that are clinically practical for these patients, such as the sensitive range for ototoxicity (SRO), are therefore recommended. This is the highest frequency with a threshold at or below 100 dB SPL followed by the next six lower adjacent frequencies in 1/6-octave steps or the one octave range near the highest audible frequency.[59] SRO is usually determined during the baseline evaluation and is dependent on each patient's hearing threshold configuration. During monitoring evaluations, air conduction thresholds should be determined within the patient's defined SRO, with full frequency testing conducted within the same session if an ASHA significant hearing change is noted within the SRO.[55]

The protocol presented earlier would be suitable for a patient who is alert; however, a patient who has limited responsiveness may be required to undergo the same audiological evaluations, excluding speech audiometry. Only objective testing, such as otoscopy, tympanometry, acoustic reflexes, and DPOAEs or ABRs,[59] is considered suitable for the assessment of those patients who are too ill or too young to respond.

While pure tone audiometry in the conventional frequency range is suitable for evaluating hearing in the range responsible for speech understanding, as well as for differential diagnosis, it is less sensitive to detecting early ototoxic change.[7,56] The two tests identified as being the most important for the early detection of cisplatin ototoxicity are HFAs and otoacoustic emissions, each also having limitations (see Table 4).[5,7,28,34,45,56,58,60–63] Therefore, using each test in isolation may not be as effective as utilizing a test battery approach, as it increases the chances of obtaining reliable audiologic monitoring data over time. Furthermore, utilizing these two tests to complement one another in every cycle of chemotherapy would possibly ensure the earliest detection of ototoxicity.[64]

In developing countries such as South Africa and India, no programs have been formally implemented to identify and monitor ototoxicity in patients on cancer chemotherapy.[65] As a result, there is no contextually relevant research to steer the implementation of an accountable and effective ototoxicity monitoring program in the country. This is probably one of the main reasons for ototoxicity monitoring programs not being commonplace in local hospitals and clinics. However, the creation of an audiological monitoring program allows for better control of cancer-related comorbidities, while research focuses on identifying the most suitable otoprotective strategy against cisplatin ototoxicity.

OTOPROTECTIVE STRATEGIES

Over the years, several studies have investigated the use of otoprotectants with cisplatin, their purpose being to protect the inner ear from any injury while not interfering with the antitumor

Table 4 Clinical Significance and Limitations of HFA and OAEs

HFA (>8 kHz)	OAEs
Clinical significance for ototoxicity	
• HFA is considered to be the most sensitive test to identify ototoxic hearing loss[5,45,60]	• OAES is considered a noninvasive objective measure of cochlear outer hair cell function[63]
• HFA is not as affected by middle ear pathologies as OAEs[7]	• DPOAEs can be regarded as a more sensitive measure for the early detection of hearing loss than conventional pure tone audiometry[34]
• The criteria of change for ototoxicity is established[7]	• OAEs is time efficient[7]
	• DPOAEs provide frequency-specific information[58]
Limitations	
• HFA is not standardized.[7]	• OAEs is significantly affected by middle ear pathology[28]
• HFA is not commonly used, due to the need for additional equipment such as circum-aural headphones[61]	• There is no universal value for the criteria of change indicating ototoxicity[63]
• HFA may not always be applicable, as patients with hearing loss in the conventional frequency range may not have measurable hearing in the extended high-frequency range[62]	• OAEs is absent in patients with moderate degrees of hearing loss[58]
	• OAEs has a limited frequency range (generally up to 8,000 Hz)[58]
• Test efficiency may be affected due to HFA being time consuming[56]	

Abbreviations: DPOAEs, distortion product otoacoustic emissions; HFA, high-frequency audiometry; OAEs, otoacoustic emissions.

effects of cisplatin.[51] Otoprotective strategies include reducing the formation of free radicals by maintaining glutathione levels and antioxidant activity.[20] Three mechanisms may provide protection against cisplatin, namely, endogenous molecules, exogenous agents, or a combination of exogenous agents that trigger endogenous protective mechanisms. However, endogenous agents are not effective against cisplatin when the dose exceeds a certain threshold.[10,66]

Nearly all of the otoprotective agents are sulfur- or sulfhydryl-containing compounds (thio compounds), known as antioxidants, and potent heavy metal chelators.[67] The numerous otoprotective agents utilized in clinical and animal studies include Amifostine, D-or L-methionine, methylthiobenzoic acid, lipoic acid, tiopronin, glutathione ester, sodium thiosulfate,[68] melatonin,[69] vitamin E,[70] N-acetylcysteine,[71] dexamethasone,[72] and resveratrol.[73] However, none of these agents have been found to be unequivocally beneficial in preventing cisplatin ototoxicity and no agent is currently recommended for routine use.[74] Further research is needed to find new methods and optimize old ones to prevent and/or treat hearing loss during cisplatin therapy. In addition, administering medication intratympanically together with gene therapy needs to be further explored.[18] Intratympanic administration involves the diffusion of the otoprotective agent across the round window into the inner ear, where its therapeutic effect is exerted. Alternatively, gene therapy may prove to be beneficial in protecting an individual against cisplatin-induced hearing loss as several genes, namely megalin, glutathione-S-transferases, Thiopurine *S*-methyltransferase, and catechol-*O*-methyl transferase, may be responsible for susceptibility to hearing loss.[75]

MANAGEMENT OF AN OTOTOXIC HEARING LOSS

If a cisplatin-associated hearing loss results in communication difficulties, it is the audiologist's ethical responsibility to begin or recommend aural rehabilitation.[55] However, this intervention should not only occur once hearing loss has been detected but before the patient begins the cisplatin chemotherapy. Aural rehabilitation techniques such as speech reading and counselling on compensatory communication strategies should be conducted. The counselling should include spouses and significant others, as hearing loss may not only impact the person with cancer but also frequent communication partners.[76] Patients with sensorineural hearing loss due to the use of cisplatin may benefit from the use of assistive listening devices such as hearing aids or cochlear implants.[6] Children with ototoxic hearing loss also may require the use of remote microphone technology to improve the signal-to-noise ratio in the classroom.

Furthermore, with the recent developments in hearing aid technology, a patient with an ototoxic hearing loss is more likely to receive the desired amplification benefit. These developments in technology include extended bandwidth hearing aids[77] and hearing aids with frequency lowering technology achieved by linear frequency transposition, nonlinear frequency compression, or spectral envelope warping.[78]

CONCLUSION

This review has highlighted that cisplatin ototoxicity is a common side effect of cisplatin chemotherapy that may negatively affect the quality of life of patients with cancer. The different molecular and cellular mechanisms involved in cisplatin-associated ototoxicity highlight the complexity of this condition and the consequent difficulty in identifying an effective otoprotective agent. The varying incidence rates reported in both adults and pediatrics may be due to the different audiological tests employed in the monitoring of the patient's hearing status and therefore highlight the importance of the use of extended HFA and DPOAEs in ototoxicity monitoring. An audiological monitoring program comprising of a team of health care professionals, knowledgeable about cisplatin ototoxicity, may serve to improve evidence-based service delivery to these patients.

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CONFLICT OF INTEREST

None.

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