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Early detection of platinum-induced ototoxicity in adults

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Abstract. *Early detection of platinum-induced ototoxicity in adults. Problems/objectives:* Multiple toxicities, including ototoxicity, have been reported for patients treated with the widely used, anti-solid tumour agent, cisplatin. We now present a concise review of the literature, and the results of a study into incidence rates for ototoxicity in adult patients receiving cisplatin.
Methodology: Eighty patients receiving cisplatin-based chemotherapy or chemo-radiotherapy were prospectively enrolled in our monitoring program; head and neck cancer patients also received radiotherapy on the cochlea. Histories, clinical examinations, and audiometric studies were performed before treatment, and then after three cycles of chemotherapy. Hearing was evaluated using different criteria for the diagnosis and grading of ototoxicity.
Results: Using the well-known ASHA (American Speech-Language-Hearing Association) criteria, ototoxicity, with and without high frequency audiometry, was identified in 28 (35%), and 40 patients (50%), respectively. Common Terminology Criteria for Adverse Events identified ototoxicity in 19 patients (24%), with 5 (6%), 4 (5%), and 10 (13%), manifesting severe, moderate, or mild hearing impairments, respectively. Fourteen patients (18%) reported being symptomatic, with only 14 demonstrating baseline, bilateral DPOAE.
Conclusions: Depending on the diagnostic criteria/grading system used, ototoxicity during cisplatin-based chemotherapy/chemo-radiotherapy occurred in up to half of our patients, supporting the need for more pro-active patient monitoring. High sensitivity, high frequency audiometry enables diagnoses to be reached before hearing loss becomes clinically relevant. Unfortunately, DPOAE measurements are mostly absent at baseline in older patients, rendering these of limited use in assessing this patient group.

Introduction

Since the 1970's, cisplatin therapy has been widely used for solid tumours, including lung, bladder, cervical, and head and neck cancers. However, severe side effects to cisplatin limit its use. Notably, ototoxicity follows neurotoxicity as the second most common side effect. The mechanisms of ototoxicity are not fully understood, but destruction of the cochlear outer hair cells appears to be crucial.[1] Ototoxicity generally manifests as bilateral, symmetric, and irreversible sensorineural hearing loss, that commences at high frequencies, accompanied by tinnitus.[2]

In this study, we present a concise review of ototoxicity in cisplatin patients, with a discussion of incidence, risk factors, pathophysiology, prevention, and diagnosis. Then we present the results of a study into the incidence of ototoxicity in patients receiving cisplatin (primarily for head and neck, and lung cancers). We compared incidence rates using different criteria of ototoxicity, examined the role of high frequency audiometry and otoacoustic emission screening, and sought predictive factors for ototoxicity.

Incidence

The reported incidence rates for ototoxicity vary because of differences in cisplatin treatment schedules, grading scales, and the monitoring programs being used. An added complication is underreporting, given that high-frequency hearing loss might go unnoticed by the patient.[3,4] While

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an incidence of 42% has been reported in adult patients receiving high-dose cisplatin (cumulative dose of 420mg/m^2)[5] , rates ranging from 9 to 90% have also been published.[6]

Risk factors

While ototoxic side effects are largely determined by cumulative cisplatin dose, several risk factors have been identified. Further, ototoxicity can occur after a relatively small cumulative dose. Risk factors include pre-existing renal impairment, anaemia or hypoalbuminaemia, concomitant radiation therapy, coincident administration of other ototoxic drugs such as aminoglycosides, or concomitant chemotherapy with vincristine.[3] Whether pre-existing hearing loss should be considered a risk factor is debatable. Genetic factors that alter drug uptake and detoxification can also modulate ototoxicity.[3] Children are more susceptible than adults, and up to 60% of cisplatin-treated paediatric patients develop irreversible hearing loss.[7]Some authors have used these criteria to predict at-risk patients.[4]

Pathophysiology

After the discovery of its cytotoxic/antineoplastic effect (i.e. genotoxic injury that triggers apoptosis), and consequent clinical testing, cisplatin received FDA approval in the 1970s. Cisplatin ototoxicity has been shown to have at least three major targets in the cochlea: the organ of Corti, spiral ganglion cells, and the lateral wall (stria vascularis and spiral ligament).[8] While the biochemical basis for ototoxicity remain unknown, there are histopathologic data showing destruction of the outer hair cells in the organ of Corti.[6]

Cisplatin's route of entry into hair cells is primarily apical, after being trafficked into the endolymph via the stria vascularis. Alternatively, basolateral uptake is possible after entering the perilymph following transit of the blood labyrinth barrier, aided by several transporters.[2,8] Injury of the blood brain barrier (by noise exposure or diuretics) significantly increases damage.[9] The generation of reactive oxygen species (ROS) also plays a significant pro-apoptotic role for outer hair cells.[1] These species arise through activation of the nicotinamide adenine dinucleotide phosphate oxidase 3 isoform, which then disrupts the synthesis of antioxidant enzymes. ROS generation leads to plasma membrane lipid peroxidation and the alteration of proteins and DNA. When these lesions reach a critical threshold, apoptosis is triggered.[10] This destructive pattern of outer hair cell loss progresses from the lateral to medial direction, starting at the cochlear base (high frequencies) and progressing to the cochlear apex (low frequencies). Despite recent advances in understanding cisplatin-induced ototoxicity, much of its mechanism remains illusive, which hampers our ability to develop novel clinical strategies for its prevention.[1]

Treatment and the prevention of ototoxicity

Currently, there is no treatment for cisplatin induced ototoxicity.[10,11] Interventions to attenuate ototoxic side effects and prevent hearing loss take one of two approaches: the augmentation of cytoprotective pathways or the inhibition of cell death pathways, without interfering with antitumor effects.[3] Both experimental and clinical studies have been published. Experimental studies have supported the efficacy of hyperbaric oxygen therapy, epigallocatechin therapy, and intratympanic lactate. In addition, promising results have been reported for oral sertraline, sodium butyrate, the intratympanic administration of short interfering RNAs, minocycline, and rosmarinic acid. However, experimental studies have also revealed a poor efficacy for intratympanic N-acetylcysteine and intratympanic and systemic dexamethasone therapy.[11] One study using caffeic acid phenethyl ester was promising in mice.[12]

Clinical studies have demonstrated minor otoprotective effects with intratympanic dexamethasone, but no effects with systemic amifostine and intratympanic L-N-acetylcysteine.[11]

Finally, sound preconditioning is now being attempted in mice, which involves sound stimuli designed to induce the cochlear expression of cytoprotective heat shock proteins (HSPs). These HSPs can then protect against subsequent cisplatin induced ototoxicity.[13]

Detection of ototoxicity

The role of routine audiometry for monitoring is ill-defined with recommendations that vary widely.[6,14,15] Some investigators have suggested that screening be limited to those patients receiving

high cumulative cisplatin doses, or with other risk factors.[14,15]

Although early (subclinical) detection fails to prevent ototoxic damage, it can alert the clinician to attempt alternative treatment strategies so as to prevent further clinical hearing loss at speech frequencies.

As ototoxicity is defined by shifts in hearing threshold, baseline audiograms are mandatory. This is especially true for elderly patients in which a similar pattern of high-frequency hearing loss due to presbyacusis may already be apparent (in baseline measurements).[6]

Many monitoring schemes have been proposed. Pure tone audiometry remains the standard. Since ototoxicity manifests initially at high frequencies, high-frequency audiometry is considered to be the more sensitive tool.[16] As the paediatric oncology population is frequently difficult to test behaviourally, distortion product otoacoustic emissions (DPOAE) and auditory brainstem response audiometry (ABR) are sometimes used in this population. There is also a need for rapid and easy-to-perform audiological diagnostics in adults, as these patients are often too ill to perform pure tone audiometry. While DPOAE is objective, non-invasive, and sensitive in determining outer hair cell damage, studies using this method to monitor adults for cisplatin ototoxicity are sparse.[17]

The various criteria used to detect hearing loss in patients with head and neck cancers have been reviewed by Theunissen *et al*.[4] A more recent review from Waissbluth *et al.*[18] also highlights the variability in classification systems, the differences between children and adults, and states that high frequency testing should be considered as the gold standard.

The American Speech Language Hearing Association (ASHA) criteria[19], which describe ototoxicity as a shift of $\geq$ 20dB at any BC frequency, or $\geq$ 10dB at 2 or more consecutive BC frequencies, is a widely used screening tool. The advantages of these criteria are their sensitivity, especially when the higher frequencies are taken into account. Alternatively, the National Cancer Institute (NCI) criteria (also called the Common Terminology for Criteria for Adverse Events (CTCAE)) can be used.[20] The main advantage of CTCAE is its definition of 4 categories of hearing impairment, which makes grading feasible. Currently, the fifth version is under review. The World Health Organization (WHO) also has a grading system based on the average threshold shift at 0.5, 1, 2, and 4 kHz, in the superior functioning ear. However, this scheme suffers shortcomings that includes its failure to use high frequencies, and a failure to detect unilateral hearing loss, which reduces sensitivity.[18]

Alternatively, one could consider using a Speech-In-Noise (SPIN)-test to detect early hearing loss. The Digit-Triplet SPIN-test, which is an automated and rapid self-test, has been shown to have a high sensitivity and specificity for the detection of hearing loss in noise exposed listeners. While this test demonstrates a good correlation with pure tone average at 2, 3, 4, and 6 kHz,[21]reliable and valid thresholds can only be obtained in a sound-proof room, using a high-quality, well-calibrated audiometer, and by a well-trained administrator. Thresholds also need to be determined for several audiometric frequencies. This makes the test time-consuming and expensive, which is not ideal for the screening of large populations. A Speech-In-Noise test (SPIN this test has yet to be used in screening for cisplatin ototoxicity. To conclude, at present, there is no generally accepted protocol with which to screen for ototoxicity.

Methods

*Patient and treatment characteristic*s

Between February 2013 and September 2015, 149 patients receiving cisplatin-based chemotherapy or chemo-radiotherapy for lung, cervical, or head and neck cancers, were prospectively enrolled in our monitoring program. Of the 149 enrolled patients, 80 subsequently attended follow-up appointments. The principal reasons for the high dropout rate were the cessation of chemotherapy because of rapid tumour progression, patients forgetting to attend their appointments, or fatigue. Only data from the 80 followed patients were taken into account in our analysis (n = 80). The majority of patients were treated for lung cancer (n = 71), followed by head and neck cancer (n = 8), and then cervical cancer (n = 1). The mean patient age was 64 years, most patients were male (64%), and most were receiving treatment in a curative setting (57%).

History taking, clinical examinations, and audiometric studies were completed prior to treatment and then, generally, after three or four cycles of chemotherapy, or when symptoms developed. At

this point, we reasoned that sufficient chemotherapy had been delivered to detect hearing-loss, with the option remaining to prevent further damage. All patients received chemotherapy intravenously. The mean cumulative dose was 338mg or 190mg/m^2, which is a relatively low dose due to our early follow-up. Head and neck cancer patients received concomitant radiotherapy schedules of 70 gray (Gy), in daily fractions of 2 Gy. The mean cochlear radiotherapy dose was 15.9 Gy. Patient demographic data are shown in Table 1.

Table 1
Demographic data

Demographics	
Number of patients (n)	80
Median age: years (range)	64.5 (34-81)
Gender	
Male	51 (64%)
Female	29 (36%)
Time between baseline and follow-up days (range)	68 (30-207)
Setting	
Curative	46 (57%)
Palliative	34 (43%)
Primary tumour site	
Head and neck	8 (10%)
Lung	71 (89%)
Cervical	1 (1%)
Total cisplatin dose (mg)	
Mean	337.84
Median	359.25
Range	92-578
Number of administrations	
Mean	4.16
Median	3
Range	2-7
Cochlear radiotherapy	
Number of patients	8 (10%)
Mean dose on cochlea (Gray)	15.9 Gy
Baseline hearing (dB)	
High PTA1-2-4 right side	23.65
High PTA1-2-4 left side	23.75
Ultrahigh PTA8-10-12 right side	62.40
Ultrahigh PTA 8-10-12 left side	63.38
Baseline symptoms	
Baseline hearing loss	20 (25%)
Baseline tinnitus	4 (5%)
Baseline otoacoustic emissions	
Absent right	58 (73%)
Absent left	57 (71%)
Present bilaterally	14 (18%)

Audiometric evaluation

At each visit, classic pure tone audiometry, and high frequency pure tone audiometry (according to the 5dB up, 10dB down method (Hughson-Westlake)) were performed. In addition, DPOAE measurements were collected, and 226 Hz-tympanometry conducted. All tests took place in sound-proof audiometric rooms with the InteracousticsÒ Equinox 2.0 device (InteracousticsÒ, Denmark). Headphones were SennheiserÒ HDA 200. Audiometry at follow-up was performed prior to the next administration, giving any temporary threshold time to recover. For frequencies of 250 Hz to 4 kHz, bone conduction (BC) thresholds were used. For frequencies at 0.125, 8, 10, 12.5, and 14 kHz, air conduction (AC) thresholds were applied. Maximal hearing threshold intensities were 100dB, 90dB, and 90dB, for the 10, 12.5, and 14 kHz frequencies, respectively (extended range). When maximum thresholds were reached, no response was noted on examination, and audiometric data were recorded as being 5dB above the level to differentiate between responses at the maximum threshold, versus no responses.

We calculated mean thresholds at two pure tone averages (PTAs): 1, 2, and 4 kHz, called "high PTA", and 8, 10, and 12.5 kHz, termed "ultrahigh PTA". These averages represent speech perception in noise, and the perception of high-pitched sounds such as natural sounds or music, respectively

DPOAE measurements were obtained with the Neurosoft Neuro Audio Screen (DIFRA®, Belgium). Responses at 8 frequency bands were measured. To record a "pass", an SNR ³6 for at least 5 bands was required. 226 Hz-tympanometry was accomplished using the Interacoustics Titan (Interacoustics®, Denmark).

Classification schemes

We compared three tools to diagnose ototoxicity. First, diagnoses were made using the ASHA criteria (with or without the use of high frequency audiometry), which defines ototoxicity as a shift of

≥ 20dB at any BC frequency, or ≥ 10dB at 2 or more consecutive BC frequencies. Secondly, we defined ototoxicity as a hearing loss of ≥ 15dB with high PTA (1, 2, 4 kHz) and ultrahigh PTA (8, 10, 12.5 Hz). We used this average of higher frequencies instead of the classic PTA scheme (0.5, 1, and 2kHz) given the vulnerability of higher frequencies to ototoxicity and their role in speech perception in noise. Finally, we used the CTCAEv3 to diagnose ototoxicity. Figure 1 shows the different grades of ototoxicity for CTCAEv3. Use of the newer CTCAEv4 required tone audiometry at 3 kHz and 6 kHz, which we could not test. However, CTCAEv4 and its predecessor, CTCAEv3, are similar, with one of the main differences being that symptoms without audiometric changes are not considered as ototoxic. Using CTCAEv4 (without 3 kHz and 6 kHz) in our analysis led to the same results as with CTCAEv3, although sensitivity might have been improved with the 3 and 6 kHz tests. Diagnoses using the PTA and ASHA criteria were made per ear, with CTCAEv3 evaluations per patient.

Statistics

Statistical analyses were performed with SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Patient characteristics were compared with unpaired t-tests for continuous variables, and Fisher's exact test, or the Mantel-Haenszel chi-square test, for categorical variables. A multivariate logistic regression model was designed to predict ototoxicity (Yes/No) from the following covariates: gender, age, cumulative dose, number of administrations, baseline audiometry, tumour size, etc. Analyses were per patient (n = 80), and per ear (n = 160).

Results

Overall hearing loss and grading

Figures 1 and 2 summarize incidence rates for ototoxicity when using the CTCAE and ASHA-criteria, respectively. Use of the commonly accepted ASHA criteria, and high frequency audiometry, resulted in up to 50% of patients being diagnosed with ototoxicity. Figure 2 shows the rates of ototoxicity for the right ear, left ear, and left or right ears, with either a classic or high frequency audiogram. Fresh symptoms occurred in

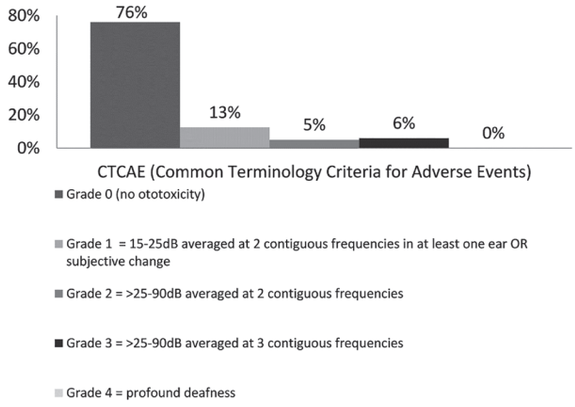

Figure 1
Grading ototoxicity with the Common Terminology Criteria for Adverse Events (CTCAEv3).[23]

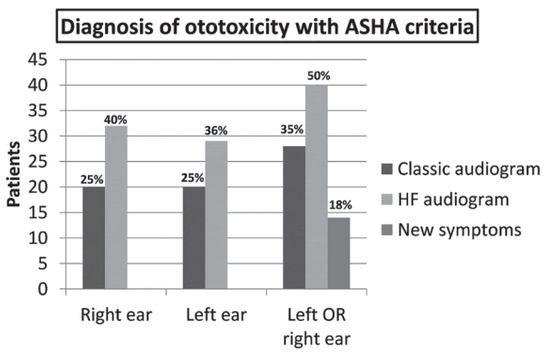

Figure 2
Diagnosis of ototoxicity using the American Speech Language Hearing Association (ASHA) criteria that describes ototoxicity as a shift of ≥ 20dB at any BC frequency, or ≥ 10dB at 2 or more consecutive BC frequencies.[21] HF denotes high frequency.

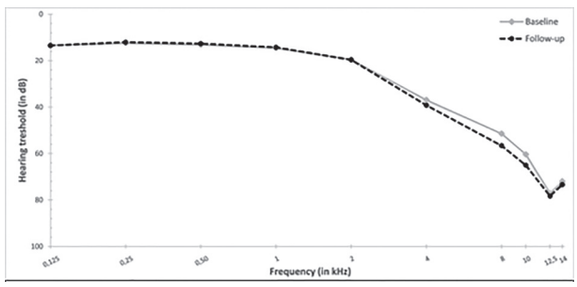

Figure 3
Mean difference in dB between baseline and follow-up. We detected a mild but statistically significant mean change in dB at 4, 8, and 10kz (4kHz: -2.2dB ($p < 0.01$); 8kHz: -5.3dB ($p < 0.0001$); 10kHz: -4.7dB ($p < 0.0001$).

18% of patients (14% reporting hearing loss, and 8%, tinnitus). Figure 3 shows the mean hearing thresholds before and after chemotherapy, with

statistically significant, although mild reductions of 2.3dB ($p = 0.0063$), 5.2dB ($p < 0.0001$), and 4.7dB ($p < 0.0001$) at 4, 8, and 10 kHz, respectively. Baseline thresholds were already poor at the higher frequencies. The mean time between baseline and follow-up was only 68 days, which eliminates any effect from presbyacusis.

PTAs at high (PTA 1, 2, 4 kHz) and ultrahigh frequencies (PTA 8, 10, 12.5 Hz) were less sensitive in diagnosing ototoxicity (when using a ≥15dB loss as the cut-off): high frequency PTA data revealed right-side toxicity in 6 patients (8%), and left-side toxicity in 4 patients (5%). Ultrahigh PTA data demonstrated right- and left-side toxicity in 8 patients (10%), and 10 patients (13%), respectively.

Data analyses

When comparing diagnoses of ototoxicity (by the previously discussed criteria) with patient characteristics (age, gender, baseline high frequency hearing loss, other chemotherapeutic drug, cochlear radiotherapy, cumulative cisplatin dose, number of administrations, dose per administration), no associations were found when using unpaired t-tests for the continuous variables, and Fisher's exact test or the Mantel-Haenszel chi-square test for categorical variables. Logistic regression analysis subsequently identified cisplatin dose per administration as a small positive predictive factor for ototoxicity when completing our analysis per ear (n = 160). This only held for cases diagnosed on the basis of a hearing loss of ≥15dB at high PTA or ultrahigh PTA frequencies. The respective odds ratio data (OR) were 1.27 (95% confidence interval: 1.07-1.51) and 1.06 (95% confidence interval: 1.01-1.11). For diagnoses with the ASHA criteria, with or without the use of high frequencies, and when analysing per patient (n=80), no covariates reached statistical significance.

Discussion

Although cisplatin toxicity has been extensively studied in the paediatric population, its relevance to older patients has been of secondary interest given the largely palliative nature of most chemotherapy regimens. However, contemporary use of this (radio)-chemotherapy has increasingly switched to a curative setting. Less ototoxic alternatives such as carboplatin are available, but these drugs are also less potent antineoplastic agents. Consequently there is renewed interest in addressing cisplatin induced hearing loss in the adult population.[6]

Although time to follow-up was short in our study, the incidence of ototoxicity was already as much as 50% when using high frequency audiometry, which increases the sensitivity of diagnosis significantly. Although some selection bias could be envisaged given that symptomatic patients would be expected to attend their follow-up visits, this incidence seems sufficiently high to warrant baseline audiometry (inclusive of high frequencies) in all patients. We found that the ASHA-criteria were more sensitive in establishing functional decline that the PTA or CTCAE-criteria. This may reflect early small changes in hearing threshold that are difficult to detect with PTA, for which a diagnosis of hearing loss necessitates a mean decline of 15dB at three frequencies. We could expect that the reported incidence of ototoxicity might be higher in longer follow-up studies that report on higher cumulative cisplatin doses. However, the present study design, with a follow-up after three cycles, seemed more reasonable than testing before each administration given that patients are often tired and ill. Further, after three cycles the possibility remained to prevent further damage, although the cumulative dose would be sufficient to detect ototoxicity. Our data agrees with Waissbluth *et al.,* in showing that incidence rates differ widely when using varied ototoxicity criteria,[18] which leads us to suggest that centres choose one testing system, depending on availability. The high dropout rate of this study emphasizes our need for less time-consuming screening tools for ill and fatigued patients. One possibility is automated and rapid self-testing that could be assessed in the future,[21]reliable and valid thresholds can only be obtained in a sound-proof room, using a high-quality, well-calibrated audiometer, and by a well-trained administrator. Thresholds also need to be determined for several audiometric frequencies. This makes the test time-consuming and expensive, which is not ideal for the screening of large populations. A Speech-In-Noise test (SPIN possibly using tablets issued to the oncology department to self-test test before each administration.

Although useful in a younger population with normal baseline hearing, DPOAE testing was of limited use in older patients given the loss of baseline DPOAEs for this patient group.

While cochlear radiotherapy is a well-known

risk factor for ototoxicity, this was not reflected by our data.[4] Plausible explanations include our small cohort size, the short follow-up period leading to low cochlear radiotherapy doses, and because radiation effects ordinarily manifest several months after therapy. In a recent review of radiation of the temporal bone in head and neck cancer patients, cochlear irradiation of 50 Gy (vs. our mean dose of 15.9 Gy) was associated with sensorineural hearing loss that developed from 6 weeks, and continued for many years post therapy (vs. our mean follow-up time of 68 days).[22]

We found no difference in the average cumulative cisplatin dose in subjects with and without hearing loss. This may reflect our early follow-up, low cumulative cisplatin doses (mean 337mg), and the fact that we frequently switched therapy when ototoxicity arose. This finding is comparable to another study with a short follow-up.[23] In contrast, in our statistical analyses with logistic regression on 160 ears, cisplatin dose per administration was a predictor for ototoxicity, and demonstrated a small, but consistent effect. This could indicate that higher peak cisplatin blood levels enhance ototoxicity, in addition to well-known cumulative effects. Previously, it has been shown that patients in receipt of small but frequent doses of cisplatin were less likely to experience the ototoxic effects of cisplatin,[24] with this peak dose effect described in the context of neurotoxicity and nephrotoxicity.[25] However, our small patient number warrants careful interpretation of these data.

The most vexing aspect of this topic is whether to switch or cease chemotherapy. This decision has to be taken by a multidisciplinary team, and involves the patient, the ENT surgeon, and the medical oncologist. We should note that a shortcoming of the ASHA criteria is that a change in hearing does not necessarily indicate a hearing loss that affects communication, especially when only very high frequencies are affected. When asymptomatic hearing loss occurs in patients for whom continuation of cisplatin treatment in a curative setting is crucial, then intensive monitoring would appear to be the best approach. In those patients, there might be a role for future preventative therapies such as intratympanic injections.

Conclusions

In summary, depending on the diagnostic criteria/grading system being used, ototoxicity during cisplatin-based chemotherapy or chemo-radiotherapy occurs in up to 50% of patients, even after low cumulative cisplatin doses, and at early follow-up. This supports the need for active monitoring of all patients receiving this treatment. High frequency audiometry makes screening more sensitive, enabling us to reach diagnoses before hearing loss becomes clinically important. Use of high frequency audiometry and early follow-up makes it possible to engage in multidisciplinary decision making as to whether to stop or switch chemotherapy before further damage develops. As DPOAEs are mostly absent at baseline in older patients, they are of limited use in assessing this patient group, while they remain of considerable use in the paediatric population. Further research is necessary to reach a consensus as to the optimum screening protocol and diagnostic criteria to use. Until then, centres should choose one monitoring system depending on availability for auditory testing. Use of the ASHA criteria, including high frequencies at baseline, and a short follow-up, is a feasible approach with which to monitor ototoxicity in our adult patients receiving cisplatin. Unfortunately, ill chemotherapy patients find classic auditory testing too time-consuming, which, combined with fatigue, can lose patients to follow-up. Therefore, automated bedside self-testing such as digit in noise tests could be evaluated in the future.

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