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Incidence of cisplatin-induced ototoxicity in adult cancer patients based on audiometric confirmation of patient self-report

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Introduction: Robust clinically relevant epidemiological and audiological data are needed to prepare for future clinical trials aiming at preventing cisplatin-induced ototoxicity in this suffering cancer population. We assessed the incidence, severity, and potential risk factors of symptomatic cisplatin-induced hearing loss in a large cohort of adults.

Methods: Retrospective cohort study at a tertiary care university hospital. The study group included consecutive patients over 18 years old treated with cisplatin-based chemotherapy without concomitant inner ear radiotherapy or other ototoxic medication. Every participant underwent baseline pretreatment audiometry and was asked for audiological symptoms (tinnitus or subjective hearing loss) during the treatment. If symptomatic, comparative standard audiometry (0.125 to 8 kHz) was performed. Hearing loss was defined by a threshold shift $\geq$15 dB HL in at least one of the tested frequencies.

Results: A total of 401 cancer patients (59% males) with a mean age of 56 years (range 18-80) were included. Eighty-one patients (20%) developed symptomatic hearing loss, predominantly affecting the high frequencies from 4 to 8 kHz. Among them, 49 (60%) experienced simultaneous new-onset tinnitus. None of the analyzed potential risk factors (age, sex, smoking, hypertension, diabetes, dyslipidemia, chemotherapeutic regimen, and cumulative cisplatin dose) was statistically correlated with hearing loss.

Discussion: At least 1 out of 5 patients treated with cisplatin developed audiological symptoms associated with audiometric hearing loss within the 0.125 to 8 kHz range, for which new-onset tinnitus is a sensitive symptom. Not all audiological symptoms are accompanied by audiometric change. No predisposing factor could be identified. Standardized audiological monitoring before and during cisplatin-based chemotherapy allows quantitative assessment of early audiometric signs of ototoxicity, offering to optimize anticancer therapy while minimizing morbidity in a multidisciplinary setting.

KEYWORDS

cisplatin, platinum, ototoxicity, hearing loss, tinnitus, cancer, sensorineural hearing loss, chemotherapy

1. Introduction

According to the World Health Organization (WHO), cancer is the leading cause of death worldwide, with 10 million human lives lost in 2020 (WHO, 2022). Nevertheless, ever-improving anticancer therapies and a longer life expectancy lead to more cancer survivors (Miller et al., 2016; Arnold et al., 2019). Therefore, chemotherapy-induced acute adverse effects such as nausea, anorexia, diarrhea, and loss of hair, as well as long-term sequelae such as neurotoxicity, nephrotoxicity, and hearing loss (Di Maio et al., 2015), among others, are becoming more prevalent and essential to palliate to. The inner ear is sensitive to various insults, including iatrogenic insults such as surgery (Simon, 2011), ionizing radiations (Mujica-Mota et al., 2013), and certain drugs (Roland and Rutka, 2004). When side effects of medicines impair hearing (cochlear damage) and balance (vestibular damage), the phenomenon is referred to as *ototoxicity*. Several drugs (summarized in Table 1) are ototoxic; among them, cisplatin stands out in potency and prevalence. However, vestibulotoxicity is poorly investigated, and the correlation between symptoms and examination should be interpreted cautiously (Prayuenyong, 2018; Prayuenyong et al., 2020). Additionally, measurements of vestibular impairment are expensive and time-consuming and, therefore, not routinely performed in our clinic in the absence of symptoms. For these reasons, this article will focus only on cochleotoxicity.

Cisplatin (Cis-diamminedichloroplatinum(II), $[Pt(NH_3)_2Cl_2]$) is an active platinum-based complex authorized for human use since 1978 (Kelland, 2007). Today, it is one of the most efficient anticancer agents against solid tumors (Dasari and Tchounwou, 2014) in adults and children and has been included in the WHO's list of "essential medicines" (WHO, 2021). Synergistic effects with different molecules have been described (Dasari and Tchounwou, 2014) together with a radio-sensitization effect potentializing radiotherapy (Yanfang Dong et al., 2017). Cisplatin-containing regimens are given with curative intent in various clinical settings, such as cervical, head and neck, lung, bladder, and testicular cancers. Among many chemical analogs with different toxicity and efficacy profiles, only carboplatin and oxaliplatin have brought an advantage over cisplatin regarding the adverse event profile, particularly ototoxicity (Kelland, 2007; Dasari and Tchounwou, 2014), and are also considered by the WHO as essential medicines (WHO, 2021). Because of the intrinsic and unspecific cytotoxic mechanisms (DNA alkylation, DNA repair, and replication inhibition), cisplatin is widely associated with toxic adverse effects, such as nausea, nephrotoxicity, neurotoxicity, cardiotoxicity, hepatotoxicity, gastrotoxicity, myelosuppression, allergic reactions and prevalent ototoxicity (Dasari and Tchounwou, 2014).

Some adverse events such as nephrotoxicity can be partly palliated (Bajorin et al., 1986), but no preventive drug or measure has been validated against ototoxicity (Chattaraj et al., 2023). Cisplatin-induced ototoxicity typically induces bilateral, symmetrical, irreversible sensorineural hearing loss, affecting primarily high frequencies, commonly in combination with tinnitus (Mujica-Mota et al., 2013), which can occur transiently or permanently and even without hearing loss. The cumulative dose, number of cycles, method of administration (bolus, continuous), and impaired renal function influence the occurrence and severity of cisplatin ototoxicity (Paken et al., 2016; van As et al., 2016). In addition, noise exposure, concomitant chemicals, and other ototoxic drugs can potentiate hearing loss (Paken et al., 2016). Genetic susceptibility may be an essential factor (Tserga et al., 2019). In the oncological context, it is important to note that cranial radiotherapy—another free-radical inducing therapy—is, *per se*, a significant risk factor, with a sensorineural hearing loss occurrence of up to 33% (Jereczek-Fossa et al., 2003). At the cellular level, the most reported cisplatin-related ototoxic mechanism involves reactive oxygen species (ROS) upregulation, leading to cochlear inflammation, stria vascularis degeneration, and apoptosis of outer hair cells, inner hair cells, and spiral ganglion neurons (Sheth et al., 2017).

Ototoxicity (including hearing loss, tinnitus and vestibular disorders) durably impact the quality of life of patients (Phillips et al., 2023; Sanchez et al., 2023a). The occurrence of cisplatin ototoxicity reported in clinical studies ranges from 26 to 100%, although the clinical relevance of these numbers is questionable (a selection of the literature including pretreatment audiogram is listed in Table 2). The wide variation of occurrence and severity across different studies mainly results from differences in methodologies, outcome measurements (especially hearing loss criteria), patient characteristics, and grading scales used, the latter having limitations (Waissbluth et al., 2017). Furthermore, the baseline pretreatment audiometry is often missing, limiting adequate interpretation of later exams during or after chemotherapy; this limitation is especially relevant in elderly cancer patients often suffering from concomitant age-related hearing loss (Nagy et al., 1999). Finally, despite the methodological differences, a significantly higher occurrence and severity of ototoxic hearing loss has been observed in young children (Landier, 2016).

At the dawn of a new age of otology, where promising treatment strategies aiming at otoprotection and regeneration are being tested in preclinical trials and await translation into clinical trials (Rousset et al., 2015; Isherwood et al., 2022), there is an increasing need for high-quality pragmatic data regarding cisplatin ototoxicity. The present study aims to establish solid clinically relevant epidemiological and audiological bases for the oncologists and otolaryngologists, besides helping institutions interested in preparing for future clinical trials aiming at preventing cisplatin-induced ototoxicity and offering to this suffering patient population adequate and timely translation of innovative treatment modalities to minimize morbidity. This study retrospectively assessed the incidence, severity, and potential risk factors of symptomatic cisplatin-induced ototoxicity in a large cohort of adults with various cancer types who were treated with cisplatin without concurrent other ototoxic drugs or head radiotherapy.

2. Materials and methods

2.1. Design

Single-center (tertiary care) retrospective study in a cohort of consecutive patients, after obtaining authorization from the Geneva's Cantonal Ethics Commission for Research on

TABLE 1 Ototoxic drugs are classified according to their potency, with a summary of the main ototoxic characteristics of each compound.

Drug	Ototoxicity	Characteristics
T-cell receptors gene therapy; Johnson et al. (2009) and Seaman et al. (2012)	+ + +	Up to 50%, mostly reversible
Aminoglycosides; Brummett and Fox (1989) and Ariano et al. (2008)	+ + +	Up to 41%, permanent
Platinum derivatives	+ + +	At least 20%, permanent
Deferoxamine; Roland and Rutka (2004)	+ + +	Around 20%, partial reversibility
Salicylates; Cazals (2000)	++	Dose-related and reversible, but rare nowadays (Cuffel and Guyot, 2013)
NSAIDs; Roland and Rutka (2004) and Curhan (2010)	+	
Macrolides; Ikeda (2018)	+	Dose-related, mostly reversible
Loop diuretics; Rybak (1993)	+	Reversible or permanent. Potentiate aminoglycosides' ototoxicity
Antimalarials; Roland and Rutka (2004), Shine and Coates (2005), and Jourde-Chiche et al. (2012)	+	Mostly reversible
Cyclophosphamide; Tuknayat (2018)	+	
Nitrogen mustard; Cummings (1968)	+	
Bleomycin; Cummings (1968)	+	
Immune checkpoint inhibitors; Rosner (2020) and Tampio et al. (2021)	+	Not clear
Estrogens; Hultcrantz et al. (2006)	(+)	
Interferon-α; Formann et al. (2004)	(+)	
Cocaine; Stenner et al. (2009)	(+)	
Phosphodiesterase-5 inhibitors; Khan et al. (2011)	(+)	
Polymyxin; Roland and Rutka (2004)	(+)	
Chloramphenicol; Roland and Rutka (2004)	(+)	
Vancomycin; Moellering (1984) and Bruniera et al. (2015)	(+)	
Vinca alkaloids; Roland and Rutka (2004)	(+)	

+ + + often, ++ sometimes, + rare, (+) very rare.

Human Beings (protocol no. 2018-02065). All the analyses were performed anonymously in accordance with the Declaration of Helsinki, thus no consent was needed in agreement with the Ethics Committee. The comprehensive literature review on cisplatin-induced ototoxicity (Table 1) was conducted in MEDLINE, with the keywords *ototoxicity*, *cisplatin*, *platinum*, and *hearing loss*, until May 2023. We selected representative prospective and retrospective studies in adults treated with cisplatin-based regimens that incorporated baseline audiometry before the treatment, in English language.

2.2. Subjects

Patients above 18 years of age, with baseline audiometric examination and treated with at least one dose of cisplatin-based chemotherapy between January 2015 and January 2019 at the Geneva University Hospitals, were included. Exclusion criteria included pre-existing bilateral cophosis, bilateral ear pathology not compatible with accurate hearing measurement, disease of the central auditory pathways, concomitant ototoxic drug therapy (such as aminoglycosides, deferoxamine, carboplatin, cyclophosphamide), concomitant inner ear radiotherapy, and chronic renal insufficiency. The medical files were analyzed for disease and treatment-specific data, pre-existing and concurrent risk factors including age, sex, smoking, hypertension, diabetes, dyslipidemia, and cumulative cisplatin dose. Cisplatin was either administrated alone or in combination with etoposide phosphate, gemcitabine, bleomycin, pemetrexed, docetaxel, cetuximab, fluorouracil, vinorelbine, ifosfamide, paclitaxel, cytarabine, mitomycin, rituximab, bevacizumab, methotrexate, vinblastine, doxorubicin, dacarbazine, and interferon-α (the most prevalent regimens are presented in Table 3). Cisplatin chemotherapy was flanked in every case with intravenous administration of dexamethasone (mostly 12 mg) for anti-emetic purposes.

2.3. Hearing assessment

An examination by an otolaryngologist followed by a tonal audiometry with a frequency range from 0.125 to 8 kHz (*Equinox 2.0*, *Interacoustics*, in a soundproof booth) by a trained audiometrist were performed in every case before the onset of the chemotherapy. Speech audiometry was not routinely performed. The oncologist routinely asked patients about any audiological symptoms during the chemotherapy, meaning tinnitus and new-onset hearing loss. If the patient reported one of these two symptoms during or after the treatment, a new consultation with tonal audiometry was performed. The otolaryngologist compared the baseline and follow-up audiometric curves. For this study, the most recent audiogram was analyzed for each symptomatic patient. Significant *hearing loss* was defined as a threshold shift of $\geq$15 dB HL in any of the tested frequencies, keeping in mind that there is an experimental error of $\pm$5 dB HL across audiograms (Flamme et al., 2014) and, as a consequence, a 10 dB HL threshold shift in any isolated tested frequencies would still be considered non-significant. We did not use previously used ototoxic hearing loss criteria because of their limitations, such as lack of objectivity and precision (Waissbluth et al., 2017).

TABLE 2 Representative literature from the beginning of cisplatin FDA approval, reporting ototoxicity in adults with baseline pretreatment audiometry, is listed.

References	Methodology	Population	Chemotherapy	Outcome
Okada and Kitagawa (2023) Japan	Prospective	100 adults (41–83 years, 75% male) with different cancers. Baseline audiometry (0.5–8 kHz) Follow-up 1 month after last cisplatin administration.	Cisplatin-based (mean dose 240 mg/m^2), 81% received radiotherapy	28% hearing loss (>25 dB HL averaged at two contiguous frequencies). 33% tinnitus.
Fernandez et al. (2021) USA	Combined prospective and retrospective	277 adults (54–66 years, 85% male) with head and neck squamous cell carcinomas. Baseline audiometry (0.250–12.5 kHz). Follow up max 90 days.	Cisplatin-based (median dose 200 mg/m^2)	49% hearing loss among non-statin users and 38% in statin users (CTCAE criteria).
Monfared et al. (2017) Iran	Prospective	124 adults (18–78 years, 65% male). Baseline audiometry (1–8 kHz).	Cisplatin (mean dose 454 mg/m^2) + cyclophosphamide and adramycin in 6% + methylprednisolone in 6%	26% hearing impairment (>10 dB HL in at least one frequency). 3% tinnitus.
Niemensivu et al. (2016) Finland	Prospective	22 adults (40–74 years, 77% male). Baseline audiometry (0.125–8 kHz).	Cisplatin (mean dose 205 mg/m^2) + radiotherapy in pharyngo-laryngeal region	50 % hearing loss (≥10 dB at 4 or 8 kHz). 40% tinnitus.
Malgonde et al. (2015) India	Prospective	34 patients (age not specified) with head and neck malignancies. Baseline audiometry (frequencies not specified).	Cisplatin (cumulative dose not specified) + radiotherapy	100% hearing loss at 1 year
Greene et al. (2015) USA	Retrospective	30 adults (17–81 years, 47% male) with head and neck, brain, lung, bladder, uterus, pelvic, ovarian cancers, unknown primary cancers. Baseline audiometry (0.25–10 kHz).	Cisplatin (mean dose 148 mg/m^2), 20% received cranial radiation	63% hearing loss (≥40 dB HL at ≥1 kHz or >20 and <40 dB HL at <4 kHz or >20 and >40 dB at 4 kHz)
Whitehorn et al. (2014) South Africa	Retrospective	107 mostly adults (14–75 years, 74% male) with head and neck cancers, lymphoma, osteosarcoma and others. Baseline audiometry (0.5-8 kHz).	Cisplatin (cumulative dose median 180 mg/m^2 in group without ototoxicity and 236 mg/m^2 in group with ototoxicity)	55% ototoxicity (≥20 dB HL at any frequency or 10 dB HL at any two adjacent frequencies)
Arora et al. (2009) India	Prospective	57 adults (19–76 years, 64% male) with cancer types not specified. Baseline audiometry (0.5–16 kHz). Follow-up 3 months.	Cisplatin groups low-dose ≤60 mg/m^2, middle-dose 61-80 mg/m^2, high dose ≥81 mg/m^2	100% hearing loss in middle- and high-dose groups (>10 dB HL of mean value of hearing thresholds at 0.5, 1 and 2 kHz or >20 dB HL at individual frequency)
Dell'Aringa et al. (2009) Brazil	Prospective	17 adults (40–75 years, 88% male) with head and neck cancers. Baseline audiometry (0.25–8 kHz).	Cisplatin (mean dose 299 mg/m^2) + concomitant radiotherapy including skull base	70% of hearing loss (≥20 dB HL in an isolated frequency or of ≥10 dB HL in two or more successive frequencies)
Schultz et al. (2009) Brazil	Prospective	31 mostly adults (7–66 years, 51% male) with cancer types not specified. Baseline audiometry (frequencies not specified).	Cisplatin (mean dose 299 mg/m^2)	29%-61% of hearing loss depending of criteria (CTCAE, Brock, ASHA, David and Silverman)
Zuur et al. (2008) Netherlands	Prospective	60 adults (mean age 62 years, 68% male) with sinus, oral, oropharynx, hypopharynx, larynx, neck, lung and esophagus cancers. Baseline audiometry (0.125–16 kHz).	Cisplatin (median cumulative dose 220 mg/m^2) + radiotherapy reaching the inner ear field in 96% of patients	31% in low-dose group (CTCAE criteria up to 8 kHz). 47% hearing loss (CTCAE criteria up to 16 kHz)
Low et al. (2006) Singapore	Prospective	58 mostly adults (15–74 years, 88% male) with nasopharyngeal carcinoma. Baseline audiometry (0.5–4 kHz). Control group of 57 adult (30–70 years, median 43, 77% male) with same disease. Follow up 2 years.	Radiotherapy followed by cisplatin (median dose 160 mg) and fluorouracil, control group treated with radiotherapy only	Hearing threshold worse at all frequencies comparing to the control group.

(Continued)

TABLE 2 (Continued)

References	Methodology	Population	Chemotherapy	Outcome
Dutta et al. (2005) India	Prospective	60 adults (83% male) with cancer types not specified. Baseline audiometry (frequencies not specified).	Cisplatin low dose in 51 patients (100 mg/m^2 in three doses) and high dose in 9 patients (120 mg/m^2 in two doses)	33% hearing loss in high dose group
Nagy et al. (1999) USA	Retrospective	53 adults (40–75 years, 77% male) with esophagus, lung, or head and neck cancers. Baseline audiometry (0.25–8 kHz).	Cisplatin at doses either 160 (87%) or 240 mg/m^2 (13%). Possibly until 38% received concurrent radiation therapy to the head and neck	36% hearing loss (>10 dB HL for any pure tone average or >20 dB HL for any frequency)
Waters et al. (1991) Canada	Retrospective	60 adults (18–71 years) with ovarian carcinoma. Baseline audiometry (0.25–8 kHz).	Cisplatin at different doses (50−100 mg/m^2) + adramycin	92% hearing loss in high dose treatment (>15 dB HL at any frequency)
Reddel et al. (1982) Australia	Prospective	32 adults (16–64 years) with germ cells tumors, ovary carcinoma and others. Baseline audiometry (0.25-8 kHz).	Cisplatin (mean cumulative dose 203 mg/m^2)	47% hearing loss (≥15 dB HL in one or more frequencies)
Aguilar-Markulis et al. (1981) USA	Prospective	50 adults (100% male) with genitourinary cancers. Baseline audiometry (0.5–8 kHz).	Cisplatin 1 mg/kg 1/week 6x and every 3 weeks thereafter for at least 12 months	64% ototoxicity (≥15 dB HL at any frequency)
Helson et al. (1978) USA	Prospective	104 children and adults (8–78 years) with cancer types not specified. Baseline audiometry (0.5–8 kHz).	Cisplatin median dose 430 mg/m^2 for age 8–20, 255 mg for age 21–45, 220 mg for age >46	91% hearing loss (>20 dB HL at 2 any frequency)
Piel et al. (1974) USA	Retrospective	30 adults (11–62 years, 60% male) with cancers types not specified. Baseline audiometry (0.25–8 kHz).	Cisplatin (dose not specified)	60 % hearing loss (≥15 dB HL at 8 kHz in one ear or ≥10 dB HL in both ears). 6% tinnitus.

Different ototoxic hearing loss criteria were used in the studies, detailed hereafter, highlighting their limitations.
CTCAE criteria (Institute NC, 2017): minimum ≥15 dB HL threshold shift averaged at two contiguous frequencies at least in one ear relative to baseline audiogram or subjective change in hearing. Ordinal 4-scale depending on the severity. Limitations: Highly subjective. Does not specify affected frequencies.
ASHA criteria (ASHA, 1994): minimum ≥20 dB HL threshold shift in one frequency or ≥10 dB HL in two adjacent frequencies. Limitations: A 10 dB HL loss can be due to inter-test experimental error. Does not provide quantification nor affected frequencies.
Brock criteria (Brock et al., 1991): minimum ≥40 dB HL threshold shift at 8 kHz. Ordinal 4-scale depending on the lower frequencies. Limitations: Lacks of sensitivity.
Davis and Silverman criteria (Davis and Silverman, 1978): minimum >20 dB HL threshold shift of mean value at 0.5,1 and 2 kHz. Ordinal 4-scale from mild to profound. Limitations: does not include the high frequencies typically affected in cisplatin-induced ototoxicity.

2.4. Statistical analysis

The incidence of hearing loss and tinnitus were described as percentages. The severity of hearing loss (i.e. hearing threshold shift) was described in mean. The association between the occurrence of ototoxicity and other variables (age, mean cumulative cisplatin dose, sex, smoking habits, diabetes, hypertension, dyslipidemia, cisplatin-based chemotherapeutics regimen) was assessed with multivariate logistic regression and the association between the severity of the hearing loss and age and mean cumulative cisplatin dose was evaluated with multivariate linear regression. All employed statistical tests included two-sided analysis, and the significance level was set as $\alpha = 0.05$. The data analysis for this study was generated using Stata Statistical Software: Release 17, StataCorp. 2021. College Station, TX: StataCorp LLC.

3. Results

A total of 401 patients were included in the study. The cisplatin dose was available in 355 patients, and every other variable analyzed was available in 401 patients. Table 3 summarizes the pertinent patient-related data. Cisplatin was administered for 30 different types of cancers in the patient collective.

3.1. Hearing loss and tinnitus

138 patients (34%) reported audiological symptoms, among them, audiometric hearing loss was found in 81 patients (20%). No difference was found regarding hearing loss occurrence and severity between the right and left ears (overlapping of 95% confidence interval). Therefore, the average of both ears for each patient was used in this analysis. In patients exhibiting hearing loss, the average threshold shift over the entire frequency spectrum was 9.5 dB HL ± 6.5, with greater involvement of the 4, 6, and 8 kHz frequencies (threshold shift 18 dB HL ± 12), as shown in Figures 1, 2. Of the 81 patients with hearing loss, their most recent audiometry available was performed after a mean of 102 days ± 183 after the first dose of cisplatin, and 17 patients (21%) had preexisting hearing impairment detected at baseline audiometry according to the WHO's definition (average

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TABLE 3 Demographic and clinical characteristics of the patients.

Total number of patients	401
Mean age—years (range)	56 (18–80)
Sex—no. of patients (%)	
Male	236 (59)
Female	165 (41)
Risk factor—no. of patients (%)	
Smoking	141 (35)
Hypertension	88 (22)
Diabetes	37 (9)
Dyslipidemia	49 (12)
Chemotherapy regimen—no. of patients (%)	
Cisplatin only	127 (31)
Cisplatin + docetaxel	75 (19)
Cisplatin + etoposide phosphate	65 (16)
Cisplatin + pemetrexed	38 (10)
Cisplatin + gemcitabine	32 (8)
Cisplatin + bleomycin + etoposide phosphate	20 (5)
Cisplatin + others	44 (11)
Mean cisplatin dose (n=355)—mg/m^2 ± SD	418 ± 223
Audiological symptoms—no. of patients (%)	138 (34)
Hearing loss—no. of patients (%)	81 (20)
Mean time since first dose of cisplatin—days ± SD	102 ± 183
Pre-existing hearing loss—no. of patients (%)	17 (21)

hearing threshold >25 dB HL at the frequencies of 0.5, 1, 2, and 4 kHz in the better ear) (WHO, 1991). When the information was available (n = 37), hearing loss was reported to occur after the first cycle of chemotherapy in 54% of the cases and in 29% after the second cycle. Of the 81 patients with symptomatic hearing loss, 49 (60%) reported the occurrence of simultaneous tinnitus.

3.2. Risk factors

None of the potential risk factors was associated with a significant change in the occurrence of hearing loss. Including or removing the mean cisplatin cumulative dose variable from the multivariate logistic regression did not significantly change the odds ratios of developing hearing loss. Although there is a trend of developing more hearing loss in males than females, it did not reach statistical significance. There was no significant difference in ototoxicity occurrence in the most prevalent cisplatin-based chemotherapeutic regimens compared to cisplatin only. Details are provided in Table 4. The average hearing threshold shift in 81 patients with hearing loss was not correlated with the cumulative dose of cisplatin (adjusted $r^2 = 0$, $p = 0.18$) nor the age (adjusted $r^2 = 0$, $p = 0.9$).

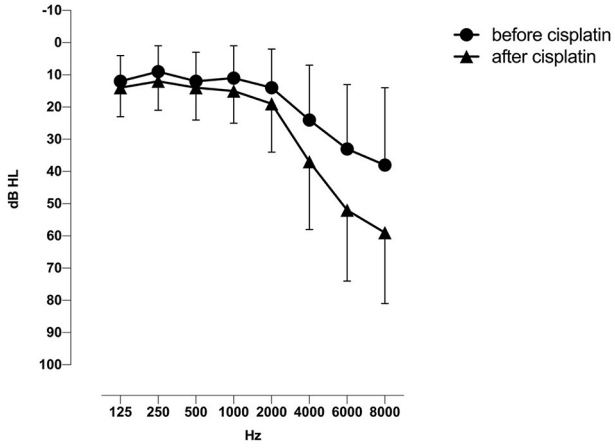

FIGURE 1
Mean sensorineural hearing thresholds (±1 SD) averaged for both ears, before and after cisplatin in 81 patients with symptomatic hearing loss.

4. Discussion

4.1. Cisplatin-induced hearing loss

In this cohort of 401 consecutive adult patients treated with cisplatin-based therapy flanked by intravenous application of dexamethasone, a total of 20% developed a symptomatic and audiometric hearing loss in at least one of the tested frequencies between the pretreatment baseline and the follow-up audiometry during or after the chemotherapy. A recent prospective study of 100 adults treated with cisplatin found a similar rate of symptomatic patients (20%), with a slightly higher hearing loss occurrence (28%), possibly due to the prospective nature of the analysis compared to ours (Flamme et al., 2014). Similar to the global literature, hearing loss was sensorineural, affecting both ears symmetrically and predominantly the high frequencies beyond 4 kHz (shown in Figures 1, 2) with an average threshold shift of 18 dB HL ± 12. None of the patients developed cophosis. Other large studies including baseline audiometry and no other concomitant ototoxic insults reported an occurrence of ototoxicity around 50% (Whitehorn et al., 2014; Fernandez et al., 2021). Still, their use of ototoxicity criteria with acknowledged limitations (Waissbluth et al., 2017) makes comparative analysis difficult. This is because the assessment is conducted by various means and there is no standardized criterion or accepted definition of cisplatin-induced ototoxicity in adults (Waissbluth et al., 2017). We therefore used conservative criteria of any audiometrical threshold shift ≥15 dB HL in any of the tested frequencies comparing to baseline testing. In our experience, clinical cisplatin-induced hearing loss occurrence is far from some extreme numbers reported in the literature, close to 100% (see Table 2). These numbers can be falsely alarming for the patient and the oncologist during their informative pretreatment consultation, and quantitative occurrence should be communicated with caution. We feel that the patient and the oncologist will benefit much more from clinically relevant

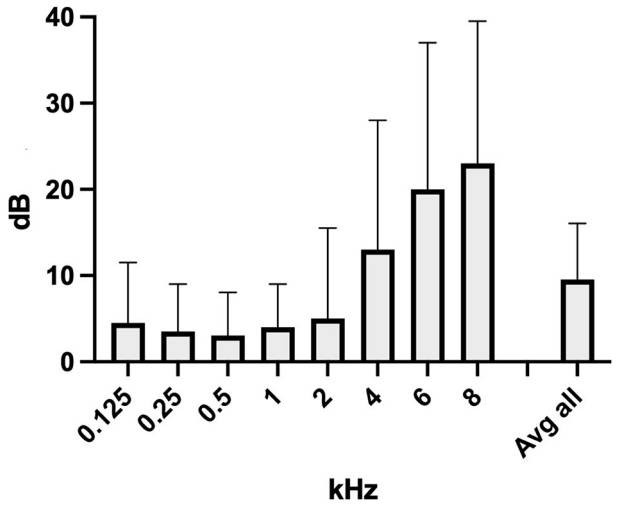

FIGURE 2
Mean threshold shifts (+1 SD) across frequencies, averaged for both ears, in the same 81 patients with symptomatic ototoxic hearing loss.

information on symptomatic ototoxicity, rather than descriptive numbers without a clinical correlate.

Following our analysis, hearing loss primarily occurred after the first cisplatin cycle and to a lesser extent after the second, suggesting as a hypothesis a cisplatin exponential ototoxicity with a fast saturation of the ototoxic effect following the first dose. Interestingly, platinum has been found in plasma even 20 years after treatment (Gietema et al., 2000) and is indefinitely retained in cochleae of humans and mice, suggesting that cisplatin accumulation, rather than hypersensitivity, can drive the progressive hearing loss observed in a high percentage of patients (Breglio et al., 2017).

The reported hearing loss occurrence and severity were not associated with the cumulative dose. However, several articles reported a correlation between hearing loss and the cumulative cisplatin dose, commonly accepted in daily practice (Dutta et al., 2005; Arora et al., 2009; Frisina et al., 2016; Monfared et al., 2017; Okada and Kitagawa, 2023). We can hypothesize that by adapting the dose or changing the molecule (e.g., carboplatin instead of cisplatin) at the first occurrence of hearing loss, one's may diminish the occurrence and severity of ototoxicity in our cohort, compared to others in alternative care centers. At least, in our tertiary hospital, the multidisciplinary approach foresees discussing the treatment regimen at first sight of ototoxic hearing loss for every patient.

The different cisplatin-based regimens did not influence the occurrence of ototoxicity, suggesting that cisplatin is the principal accountant of toxicity, without potentiation. Each treatment was accompanied by the adjuvant administration of dexamethasone, which, besides its anti-emetic properties against chemotherapy-induced nausea and vomiting (Hesketh et al., 2020), possesses an anti-inflammatory effect, with no ototoxicity. None of the analyzed medical cofactors was associated with the occurrence of hearing loss. Cardiovascular comorbidities

TABLE 4 Association of different possible risk factors and different cisplatin-based chemotherapeutic regimens with the occurrence of hearing loss.

Risk factor	Adjusted odds ratio (95% CI)	*P* value
Multivariate logistic regression in 355 patients (not including cisplatin dose)		
Male sex	1.7 (1.0–3.0)	0.06
Age (per year)	1.0 (1.0–1.0)	0.24
Dose of cisplatin (per mg/m^2)	1.0 (1.0–1.0)	0.13
Smoking	1.2 (0.7–2.1)	0.43
Diabetes	0.7 (0.3–1.9)	0.46
Hypertension	0.5 (0.2–1.1)	0.08
Dyslipidemia	1.6 (0.7–3.6)	0.19
Multivariate logistic regression in 401 patients (including cisplatin dose)		
Male sex	1.6 (1.0–2.8)	0.06
Age (per year)	1.0 (1.0–1.0)	0.36
Smoking	1.3 (0.8–2.1)	0.35
Diabetes	0.8 (0.3–2.0)	0.58
Hypertension	0.5 (0.2–1.0)	0.06
Dyslipidemia	1.7 (0.8–3.7)	0.15
Multivariate logistic regression in 401 patients		
Cisplatin only	1.6 (0.8–3.6)	0.2
Cisplatin + docetaxel	1.2 (0.5–2.9)	0.65
Cisplatin + etoposide phosphate	1.1 (0.4–3.0)	0.8
Cisplatin + pemetrexed	1.7 (0.6–4.5)	0.32
Cisplatin + gemcitabine	1.8 (0.6–4.9)	0.28
Cisplatin + bleomycin + etoposide phosphate	0.5 (0.1–2.7)	0.44

did not seem to precipitate cochlear damage, as could have been expected (Madhan et al., 2023; Saba et al., 2023; Sanchez et al., 2023b), considering that the inner ear is a sensitive organ with terminal vascularity and, therefore, vulnerable to ischemia (Tabuchi et al., 2002; Mom et al., 2005; Gyo, 2013). This may be due to a too small side-effect. Albeit there is a tendency for increased hearing loss occurrence in males, it did not reach statistical significance. The literature about comorbidities predisposing to ototoxicity remains non-conclusive today.

4.2. Tinnitus

Another essential finding was the high prevalence of tinnitus (60%) in patients with symptomatic audiometric hearing loss. Tinnitus may be an indicator of hidden hearing loss (Song et al., 2021), and other studies reported an association with cisplatin ototoxicity at various rates (Piel et al., 1974; Frisina et al., 2016; Niemensivu et al., 2016; Monfared et al., 2017; Okada and Kitagawa, 2023; Sanchez et al., 2023a). Therefore, when new-onset tinnitus

develops during the course of the chemotherapy, it may be an early sign of hearing damage and a complete audiometric evaluation should follow. If mild and oligosymptomatic hearing loss, the treatment should be thoroughly discussed between the patient, the otolaryngologist, and the oncologist. Either the therapy is continued with an equivalent or lower dose, or modified with a lesser ototoxic compound (e.g., carboplatin). If severe hearing loss is acknowledged, this discussion needs to be held similarly, but strongly highlighting the eventual modification or even cessation of the chemotherapy, if the oncological evolution and overall medical context allow it.

4.3. Rehabilitation

Hearing rehabilitation must be discussed with the patient if symptomatic hearing loss persists beyond the oncological phase. In Switzerland, hearing aids are proposed if the total hearing loss is calculated ≥20% using the classification of Council on Physical Therapy, American Medical Association (CPT-AMA) (Council on Physical Therapy, 1972). Should hearing aids be insufficient—especially for speech recognition—cochlear implants can be proposed, particularly in the cases of partial deafness with preserved hearing in the low frequencies and complete deafness in the frequencies >2 kHz (Roland et al., 2018). In our cohort, none of the patients developed severe or profound hearing loss (e.g., previous moderate hearing loss precipitated by ototoxicity), and none required cochlear implantation. This is reassuring regarding the maximal severity expected in cisplatin-induced hearing loss.

Ototoxic inner ear damage may occur simultaneously or sequentially with other progressive hearing loss etiologies such as presbycusis or genetic preconditions (Joo et al., 2019). In our cohort, 21% of the patients with ototoxic hearing loss had preexisting hearing impairment to some degree, according to the WHO's definition (WHO, 1991). This highlights the need for a thorough audiological baseline examination in every patient before the onset of cisplatin or any other ototoxic chemotherapy, a practice that is still not ubiquitously adopted today (Weiss et al., 2018; Chattaraj et al., 2023).

4.4. Limitations and strengths

This study has limitations. First, although baseline audiological examination is performed in our institution, the present analysis will likely underestimate the true incidence and severity of cisplatin-induced hearing loss. Partly because of its retrospective nature, but also because auditory follow-up examinations were conducted only in patients reporting tinnitus or hearing loss spontaneously or after being asked explicitly by their oncologist. For this reason, patients without auto-reported hearing-related symptoms—often not a priority on health agenda compared to other cancer-related morbidities—may not have been included in the analysis, and their hearing loss remained undetected. In a similar fashion, a deterioration of hearing in the high-frequency range could probably not be self-recognized by many patients. Other studies with a prospective enrollment of cancer patients following strict audiological workup protocols corroborate this hypothesis. Those studies reported a much higher ototoxicity occurrence, reaching up to 64%, depending on the hearing loss criteria (Helson et al., 1978; Aguilar-Markulis et al., 1981; Reddel et al., 1982; Schultz et al., 2009). Furthermore, centers performing additional extended high-frequency audiometry (up to 20 kHz) reported a higher occurrence of cisplatin ototoxicity than centers with the standard audiometric testing (up to 8 kHz), as used in the present study (Zuur et al., 2008; Arora et al., 2009). Additionally, once ototoxicity or some other side effects developed, some patients benefited from a change of regimen for carboplatin instead of the ongoing cisplatin. This study did not include audiometric analyses starting from this point to avoid bias. Therefore, the severity of the cisplatin-induced hearing loss may have been underestimated.

On the other hand, the patients may benefit from being informed about the risk of potential symptoms, rather than purely descriptive subclinical damages, like neuropathy and renal insufficiency. The present study has the advantage of providing pragmatic risk quantification of developing hearing loss based on a rather large cohort of patients. Moreover, the chosen hearing loss criteria were conservative and objective (compared to baseline), applied to symptomatic patients only, making the occurrence and severity reported clinically relevant. Additionally, one out of ten patients developed audiological symptoms (such as tinnitus or subjective hearing loss) during the treatment without audiometric change. This information can help reassure the patient and the oncologist during the treatment phase if no threshold change is found in the audiogram. However, a patient complaining of hearing difficulties in noisy environments, although with a normal audiogram, may have developed hidden hearing loss. The latter is a subtle sign of early damage to the hearing, especially in high frequencies (Song et al., 2021), reflecting cochlear synaptopathy or neuropathy, for which diagnostic tools are yet to be validated (Kohrman et al., 2020; Valderrama et al., 2022). Nevertheless, speech audiometry (in silence and in noise) and extended high-frequency tonal audiometry (up to 20 kHz) may reveal hearing damage in symptomatic patients with normal standard audiometry (Frisina and Frisina, 1997; Song et al., 2021). Similarly to the early loss of ribbon synapses (the highly specialized inner hair cells' tonic synapses) in age-, noise-, and aminoglycoside-induced hearing loss in animal models (Liu et al., 2013; Kujawa and Liberman, 2015; Xiong et al., 2020), cisplatin-induced synaptopathy may occur in humans as well. Indeed, the auditory synapse has been found to be the most vulnerable part of the cochlea regarding cisplatin ototoxicity in mice (Nacher-Soler et al., 2022).

4.5. Otoprotection

This extensive retrospective analysis of consecutive cancer patients treated with cisplatin-based chemotherapy showed symptomatic hearing loss in 20% of the cases, adding morbidity to this already suffering population (Phillips et al., 2023). Therefore, preventing ototoxic hearing loss through molecular or pharmacological intervention would interest thousands of patients worldwide. To this end, our and many other institutions currently undertake translational research projects aiming at otoprotection

by different methods (Rousset et al., 2015; Waissbluth et al., 2017; Nacher-Soler et al., 2022). We believe that a strong collaboration between clinicians and basic scientists will significantly increase the chances of developing an effective preventive therapy against cisplatin ototoxicity in the future, tailored to the patient's need and with a meaningful mode of application for otologists.

5. Conclusion

At least 1 out of 5 patients treated with cisplatin developed audiological symptoms correlated with audiometric hearing loss within the 0.125–8 kHz range, for which new-onset tinnitus is a sensitive symptom. Not all audiological symptoms are accompanied by audiometric change. No predisposing factor could be identified. To improve early detection, the systematic application of a thorough audiological examination before, during, and after the completion of cisplatin chemotherapy is mandatory. Early detection of ototoxic hearing loss is a prerequisite for a multidisciplinary discussion and a potential modification of the treatment regimen to maximize anticancer action while minimizing morbidity for each patient. In addition, pragmatic clinical data lays a sound base for imminent clinical trials aiming to prevent cisplatin-induced ototoxicity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving humans was approved by Geneva's Cantonal Ethics Commission for Research on Human Beings. The study was conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because all the analyses were performed anonymously in a retrospective manner, in accordance with the Declaration of Helsinki, thus no consent was needed in agreement with the Ethics Committee.

Author contributions

FV contributed to conception and design of the study, collection of data, statistical analyses, and original draft preparation. AV, DM, GN-S, FR, and TD contributed to writing sections of the manuscript. PS contributed to conception and design of the study and writing and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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