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High incidence of cisplatin-induced ototoxicity in paediatric patients in the Western Cape, South Africa

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Background: Fourteen million new cancer cases are reported annually, and up to 10% of those involve children below 15 years. Cisplatin, a commonly used anti-cancer drug for its high success rate, is associated with ototoxicity. Cisplatin-induced [illegible]y is characterised by permanent bilateral severe-to-profound hearing loss. Hearing loss, when occurring during childhood, can impact negatively communication development, scholastic performance and quality of life.

Aim: To determine the incidence of cisplatin-induced ototoxicity in paediatric oncology.

Setting: A retrospective records review of paediatric oncology patients who underwent cisplatin-based chemotherapy and had ototoxicity monitoring from January 2015 to December 2017 at a children's hospital.

Method: Data collected included demographic, cisplatin treatment and audiometric information. The data were analysed using descriptive and inferential statistics.

Results: A total of 49 records meeting the inclusion criteria were reviewed. Ototoxic hearing loss was found in 39 (80%) of the patients whose records were reviewed and the majority (56%) presented with bilateral moderate-to-severe sensorineural hearing loss. Distortion product otoacoustic emissions were absent in 32 (67%) patients. Cumulative dose (> 200 mg/m^2) was associated with higher incidences of ototoxicity (odds ratio [OR]: 1.81; 95% confidence interval [CI]: 1.07–17.34; $p = 0.044$). Younger patients (< 10 years) had higher odds of developing ototoxicity, but was not statistically significant (OR: 4.00; 95% CI: 0.82–19.46; $p = 0.085$).

Conclusion: This study found a high incidence of cisplatin-induced ototoxicity in paediatric oncology patients. This is concerning because hearing loss during this age can have long-term negative impact on a child's development and overall quality of life. Early identification of ototoxicity-induced hearing loss and appropriate intervention are highly recommended in this patient group.

Introduction

Cancer is the second most commonly diagnosed non-communicable disease and one of the leading causes of death globally. It accounted for an estimated 8 million deaths globally in 2015.[1] Approximately 14 million new cancer cases are reported annually and up to 10% affects children below the age of 15 years.[1] In South Africa, over 100 000 individuals are diagnosed with cancer every year.[2] Specific to paediatrics, between 33.4 and 47.2 per million children were diagnosed with cancer between 2003 and 2007, while an estimated 62.6 and 87.8 per million children were diagnosed with cancer in the Western Cape and Free State provinces, respectively.[2] With regard to the survival rate, South African children were reported to have a 51% survival rate for childhood cancer in 2014.[2]

Cisplatin-based chemotherapy is the common anti-cancer treatment for both children and adults because of its high success rate, lower cost and availability.[3] Cisplatin, a platinum-based chemotherapeutic, has been used effectively in the treatment of various soft tissue cancers for over 30 years.[3] Unfortunately, it is also associated with high incidences of ototoxicity. Ototoxicity refers to drug or chemical-induced damage to the structures of the inner ear.[4,5] The incidence of cisplatin-induced ototoxicity in paediatric patients varies considerably, ranging from 13% to 96%.[4,5] This variability could be attributed to the use of different diagnostic criteria for ototoxicity and/or use of different ototoxicity grading scales and use of different audiometric tests to diagnose ototoxicity-induced ototoxicity.

Cisplatin-induced ototoxicity is characterised by symmetrical sensorineural hearing loss accompanied by tinnitus, otalgia, poor speech discrimination and aural fullness.[4,6] Furthermore, the hearing loss is permanent and usually starts in the higher frequencies on the audiogram before progressing to the lower frequency range.[5,6,7] Hearing loss during childhood can leave debilitating effects on speech–language acquisition, socio-emotional development, and reading and writing abilities. Furthermore, childhood hearing loss can lead to poor scholastic performance, academic achievement and overall quality of life, for both the child and his or her family.[8] It is, therefore, imperative that cisplatin-induced hearing loss should be prevented, especially in this patient group.

One of the ways to prevent or minimise the occurrence of treatment-induced hearing loss in children during cisplatin-based chemotherapy is to closely monitor their hearing status during treatment (i.e. ototoxicity monitoring). Ototoxicity monitoring involves prospective collection of serial audiometric data at regular intervals to ensure early detection of changes in hearing thresholds presumably attributed to treatment regimen.[9] If a deterioration in patient's hearing thresholds is detected in time, the oncologist has an option to explore alteration to the treatment to avoid more serious hearing loss, for instance discontinuing the use of cisplatin and replacing it with a less ototoxic alternative (e.g. carboplatin).[9]

Cisplatin-induced ototoxic damage typically starts at the basal end of the cochlear, the region of the inner ear that is responsible for high-frequency encoding.[10] The continued use of cisplatin may lead to the damage extending to the apical end of the cochlea, where the low-frequency information is encoded.[10] Therefore, ototoxicity monitoring protocols must include audiological tests that are sensitive to changes in high-frequency thresholds (i.e. test frequencies > 8 kHz) or otoacoustic emissions to ensure early detection of changes in patients' hearing thresholds.[9] Studies that investigated the incidence of cisplatin-induced ototoxicity in paediatric oncology patients are scarce in the African continent. This study therefore aims to address this information gap and will determine the incidence of cisplatin-induced ototoxicity as well as document factors associated with the risk for developing cisplatin-induced ototoxicity in a paediatric population in South Africa.

Methods

This was a retrospective records review of consecutive paediatric patients (< 15 years old) who underwent cisplatin-based chemotherapy and ototoxicity monitoring at Red Cross War Memorial Children's Hospital from 01 January 2016 to 31 December 2017. Patients' records were selected and included in this study if they had a baseline audiogram showing normal hearing thresholds, at least one monitoring audiogram, and the patient was aged between 5 and 18 years old. Records of patients who received prior radiation therapy in the head and neck region and those who were previously treated with ototoxic medications were excluded from the study. Primary endpoints were hearing loss, distortion product otoacoustic emission (DPOAE) findings expressed as a 'pass' or 'refer' (where a pass indicates normal cochlear functioning and, a refer indicates cochlear pathology), presence of tinnitus, vestibular dysfunction and reports of otalgia. Secondary outcomes were to identify treatment and patient factors associated with ototoxicity following cisplatin chemotherapy.

Data abstracted from patient records were captured using an online password protected form designed with Google Forms and subsequently transferred onto an Excel spreadsheet. Limiting access and using proxy patient identifiers maintained patient confidentiality. The following variables were captured: age, sex, ethnicity, type of cancer, cumulative cisplatin dose received, treatment duration, pure tone audiometric and extended high-frequency audiometry results, DPOAE results, otoscopic examination results and tinnitus reports. The American Speech–Language–Hearing Association (ASHA)[11] significant threshold shift (STS) criteria were used to determine the presence or absence of ototoxicity-induced hearing loss. The grading of the ototoxicity was done according to the International Society of Paediatric Oncology Boston (SIOP) Scale.[12]

Statistical analysis was performed using the IBM SPSS Statistics version 24 for Macintosh software. Categorical variables were expressed as frequencies and percentages. Logistic regression was used to determine associations between patient and treatment variables and the likelihood of developing ototoxicity during chemotherapy treatment.

Ethical considerations

Ethical approval for the study was sought and obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 465/2017).

Results

A total of 122 records of paediatric patients who underwent cisplatin-based chemotherapy at Red Cross War Memorial Children's Hospital during the study period were accessed for review. Fifty-eight records met the inclusion criteria and thus were selected for inclusion in this study. However, nine of the records had missing information and therefore were also excluded. In the end, 49 records were included in the final review (see Table 1 for a description of patients' characteristics).

Bilateral sensorineural hearing loss was observed in 80% (n = 39) of the patients when utilising extended high-frequency audiometry (9 kHz – 12 kHz) in comparison to 49% (n = 24) when conventional audiometry (0.25 kHz – 8 kHz) was used. Consistent with pure tone audiometry, DPOAEs were absent in 32 (67%) (n = 32) participants. There was also a strong positive correlation (Pearson's r = 0.899) between DPOAE and extended high-frequency pure tone audiometry. The majority of the participants (56%) presented with the SIOP grades 2–4 ototoxic hearing loss (see Figure 1).

TABLE 1: Participant demographic and treatment characteristics (n = 58).

Demographic characteristics	Number of participants n (%)
Age	
5–10 years	44 (76.0)
11–15 years	14 (24.0)
Gender	
Male	33 (56.8)
Female	25 (43.2)
Type of cancer diagnosed	
Neuroblastoma	20 (34.0)
Lymphoma	13 (22.0)
CNS tumours	14 (25.0)
Osteosarcoma	6 (10.0)
Hepatoblastoma	4 (7.0)
Pleuropulmonary blastoma	1 (2.0)
Treatment information	
Cumulative cisplatin dose	
< 200 mg/m²	35 (52.0)
> 200 mg/m²	23 (48.0)
Duration of treatment	
0–3 months	11 (19.0)
4–6 months	47 (81.0)

Note: Nine of the records did not have the required hearing loss information and were therefore excluded from the final review.
CNS, central nervous system.

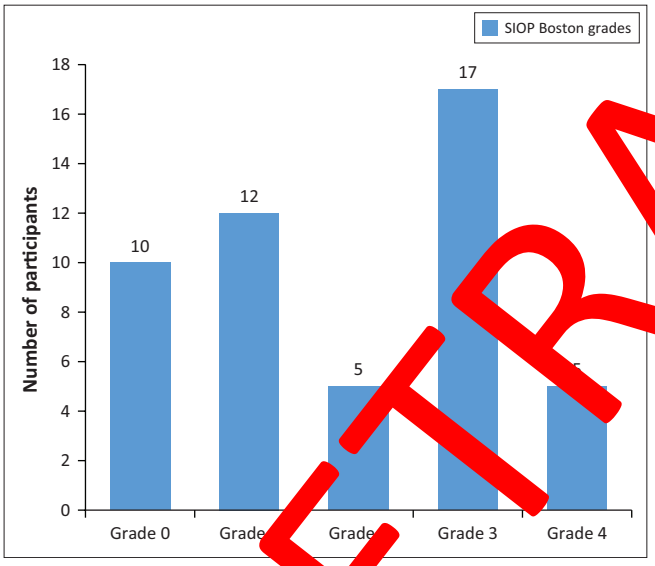

FIGURE 1: Hearing loss grading us[illegible] International Society of Paediatric Oncology (SIOP) Boston ototoxicity scale.

Six (10%) partic[illegible]pants re[illegible]orted high-[illegible]itched tinnitus. Other observed audi[illegible]y pa[illegible] in the sample included cerumen impactio[illegible]which was observed in 29 (60%) participants at the end [illegible]hemotherapy.

Further analysis of the results using logistic regression analysis showed that a higher cumulative dose (> 200 mg/m²) was associated with a higher incidence of hearing loss during cisplatin-based chemotherapy (odds ratio [OR]: 1.81; 95% confidence interval [CI]: 0.67–17.34; p = 0.044). With respect to age, in comparison to patients older than 10 years, those below the age of 10 years were four times more likely to develop hearing loss; however, this was not statistically significant (OR: 4.00, 95% CI: 0.82–19.46; p = 0.085). Sex and treatment duration also showed higher odds of developing hearing loss, but these ass[illegible] were not statistically significant (see Table 2).

TABLE 2: Inferential statistics.

Variables	Ototoxicity (n = 39)	Odds ratio	p-value
Age, < 10 years	27	4.00 (95% CI: 0.82–19.46)	0.09
Gender (male)	15	1.34 (95% CI: 0.39–4.57)	0.47
Cumulative dose	34	1.81 (95% CI: 0.67–17.34)	0.04†
Treatment duration (5–6 months)	39	2.27 (95% CI: 0.58–8.83)	0.23

Note: Ototoxicity group consists of participants who developed hearing loss following cisplatin chemotherapy.
†, Logistic regression; CI, confidence interval.

Discussion

This was one of [illegible] first studies [illegible]do[illegible]ment the incidence of cisplatin-in[illegible]ced oto[illegible]xicity in [illegible]aediatric oncology in South Africa. The[illegible]di[illegible]s of this study indicated that a high proportio[illegible](80%) o[illegible]aediatri[illegible] patients who underwent cisplati[illegible]hemotherapy a[illegible]d Ross War Memorial Children's Hosp[illegible]d[illegible]ng January 2016 – December 2017 developed hearing loss f[illegible]wing cisplatin-based chemotherapy. The i[illegible]dence of heari[illegible]loss following cisplatin chemotherapy in the paediatric population reported in previous studies is known to vary considerably (42%[13] to 94%[14,15]). However, despite this v[illegible]iability, these studies consistently reported a high in[illegible]ence of cisplatin-induced hearing loss, espec[illegible]ly if more sensitive tests of detecting changes in patient's hearing thresholds are used as was the case in the [illegible] study.

About 55% of the patients in this study developed moderate-to-severe hearing loss, which is classified as disabling[16] because of its known negative impact on function and quality of life. Disabling hearing loss[16] can have a debilitating impact, particularly in this study's age group, in terms of difficulty in understanding speech, psychosocial development, reading and writing abilities, scholastic performance and academic achievement and quality of life, for both the patients and their families.[16,17,18]

Cisplatin-induced ototoxicity is believed to be related to the formation of reactive-oxygen-species (ROS) and depletion of anti-oxidant scavenger molecules, subsequently inducing calcium influx and cell apoptosis.[19] Yancey et al.[13] further illustrated that one target of ROS-induced cochlear damage is the outer hair cells (OHCs), which may lead to sensory hearing loss. Therefore, an abnormality of DPAOE, a test that is known to be sensitive to changes in OHCs function, seems to confirm this as a possible site of lesion.

A strong positive correlation was found between DPOAEs and extended high-frequency audiometry results with respect to early detection in patients' auditory status. These findings therefore suggest that in cases where it is not possible to perform behavioural audiometric assessments, such as extended high-frequency audiometry, DPOAEs can be used as an alternative test.[20,21] This is especially important in paediatric oncology where obtaining reliable extended

high-frequency audiometry results can be challenging.[15] Behavioural audiometric tests, such as extended high-frequency audiometry, require a patient to be fully awake and concentrating for the full duration of the test. This may be difficult in children who are undergoing cancer treatment because they can get tired quickly and lose their concentration, thus resulting in unreliable results.[21]

With respect to diagnostic protocols, 80% of the patients were diagnosed with ototoxicity when utilising extended high-frequency audiometry (9 kHz – 16 kHz), when compared to only 49% when using conventional audiometry (0.25 kHz – 80 kHz). This shows that extended high-frequency audiometry was more sensitive in terms of early identification of changes in hearing threshold than conventional audiometry. Several studies have also reported on the effectiveness of extended high-frequency audiometry and its superiority to conventional audiometry when it comes to early detection of ototoxicity-induced hearing loss.[10,14] Owing to the demographic characteristics of this study's sample, particularly age, early identification of hearing loss would, therefore, be of paramount importance to overcome the negative impact of hearing loss.

Treatment factors such as duration of cisplatin chemotherapy treatment and dose have been reported to be associated with higher likelihood of developing cisplatin-induced hearing loss during cisplatin chemotherapy.[6,13,14] In this study, a higher cumulative dose (> 200 mg/m^2) was found to be associated with a high likelihood of developing hearing loss during cisplatin-based chemotherapy, which was consistent with the findings of previous studies. However, in regard to cumulative cisplatin dose, the present study found a relatively lower cumulative cisplatin dose (mg/ associated with hearing loss, when compared to mg/m^2, which is reported by other scholars in the field.[13,23]

Patient factors such as age and sex have also been identified as risk factors for developing hearing loss.[12] Association between younger age and a higher likelihood of developing hearing loss was reported in previous studies.[15,23] In the present study, children below the age of were more likely to develop hearing loss when compared to those above 10 years. However, this was found to be statistically significant, possibly because of the small sample size of the current study.

Existing literature on sex as a risk factor for developing cisplatin-induced ototoxicity is variable; Yancey et al.[13] reported that males were four times more likely to develop ototoxicity, while Li et al.[24] indicated that female sex is associated with higher incidences of ototoxicity. The current study found that males were 34% (OR: 1.34) more likely to develop hearing loss following cisplatin chemotherapy when compared to females. However, this was not statistically significant (p = 0.47), possibly because of the small sample size of this study.

An unexpected finding in this study was the fact that a high proportion of patients developed impacted cerumen following cisplatin chemotherapy. All the participants had clear external auditory meatus with insignificant amounts of cerumen pre-cisplatin chemotherapy, whereas at the end of treatment almost half of the participants (49%) had cerumen impaction. This finding may seem to suggest that cisplatin may alter the cerumen production mechanism within the external auditory meatus. While literature linking cisplatin chemotherapy to increased cerumen production is limited, this finding of a high incidence of cerumen impaction in the study cohort is worth noting because cerumen impaction can contribute to an increase in the prevalence of hearing loss.[25] This finding, therefore, highlights the need for routine otoscopic examinations in paediatric patients undergoing cisplatin chemotherapy to identify patients who might have cerumen impaction and need this to be removed.

Study limitations

The findings of this study must be interpreted with caution owing to its methodological limitations – a retrospective record review with a relatively small sample size. However, despite these limitations, this was one of the first studies to determine the incidence of cisplatin-induced ototoxicity in a paediatric oncology population in South Africa. We believe that these findings will prompt action from clinicians managing these patients to try to put appropriate interventions in place to prevent hearing loss in children who undergo cisplatin chemotherapy.

Conclusion

This study showed that a high proportion (80%) of patients who underwent cisplatin-based chemotherapy at Red Cross War Memorial Children's Hospital during the study duration ended up developing ototoxic hearing loss. A higher cumulative dose (> 200 mg/m^2) and younger age (< 10 years old) were associated with an increased likelihood of developing hearing loss following cisplatin-based chemotherapy. Given the high proportion of patients in this study who developed hearing loss following cisplatin-based chemotherapy, it is important that such patients are closely monitored (ototoxicity monitoring) to enable early detection of cisplatin-induced ototoxicity. Extended high-frequency audiometry and DPOAE compared to conventional audiometry were found to be more successful in detecting changes in patients' hearing thresholds following treatment. It is also important that routine otoscopic examinations should be part of the ototoxicity monitoring protocol.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

M.P. was the lead investigator and L.R. was the advisor and supervisor for this study.

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