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Original Article

Hearing Loss among Children Treated with Chemotherapy at Paediatric Oncology Department in Tanzania

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ABSTRACT

Chemotherapy-induced hearing loss bears significant impairment of skills, language development, and cognitive performance in children. Hearing loss pattern is mostly bilateral and sensorineural, affecting high frequencies above 8 kHz, which is important in speech discrimination and background noise perception. Pathophysiology is related to damage to the basal cochlea outer hair cell, which can progress to those in the apical turn. Despite challenges encountered during monitoring chemotherapy ototoxicity in children, monitoring is very advantageous since it guides in the early identification of hearing loss and provides proper intervention such as treatment interruption, dose modification, and suspension of drugs. This study aimed to determine the prevalence and pattern of hearing loss among children treated with chemotherapy at the paediatric department in a Tertiary hospital. This was a prospective longitudinal study. A total of 52 participants were enrolled, whereby hearing assessment was done before and after receiving two cycles of chemotherapy. Tympanometry was done after otoscopic examination in all participants, play and pure tone audiometry for participants aged 2 to 6 years and 7 years, respectively, and a destruction test for those below 2 years of age. Statistical Package for Social Science (SPSS) version 26 was used to obtain cross-tabulations. Fifty-two participants with a mean age of 6.6±2.3 years were enrolled in the study. There was a male preponderance with a male-to-female ratio of 3:1. Prevalence of hearing loss after chemotherapy was 15.4%. The pattern of hearing loss was predominantly bilateral, high frequency, and sensorineural type of hearing loss. Nasopharyngeal tumours were related to hearing loss as compared to other tumour sites. Hearing loss was frequently associated with the use of cisplatin as compared to vincristine and carboplatin. The commonly used chemotherapies such as cisplatin, carboplatin, and vincristine can cause hearing loss, which can affect the quality of life and therefore require audiological monitoring.

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INTRODUCTION

Chemotherapeutic agents are the cornerstone in the treatment of childhood cancers; commonly treated neoplasms are neuroblastoma, hepatoblastoma, osteosarcoma, brain tumours, and leukaemia, but despite their effectiveness in treating malignancies, they can cause hearing loss by damaging cochlea outer hair cells, which is noticeably at high frequencies that may be associated with tinnitus or vertigo[1]. Although cisplatin and carboplatin are well-known hearing loss, chemotherapeutic causative agents, other agents like vincristine can seldom cause hearing loss.

Globally, there is a lack of adequate information on the magnitude of chemotherapy-induced hearing loss due to underreporting of ototoxicity. However, literature has shown that the magnitude of chemotherapy-induced hearing loss widely varies from 4% to 90% but is significantly higher in children and has no known overall prevalence in Africa or East Africa. A study done on paediatric patients in South Africa in 2018 revealed a magnitude of 80% [2,3]. In addition, no paediatric population study has been done to reveal the magnitude and patterns of hearing loss after being treated with chemotherapeutic agents in Tanzania.

The negative impacts of hearing loss in children include developmental delay in receptive and communication skills, language deficit that causes learning problems, social isolation, and poor self-regard due to communication difficulties. The earlier the hearing loss diagnosis and intervention, the lesser the developmental consequences in children and vice versa. [1,4,10, 21]

The causes of hearing loss in children include childhood infections such as meningitis, ear infections such as otitis media, conditions at birth such as birth asphyxia and neonatal jaundice, noise exposure, and ototoxic medicines such as chemotherapy, antimalarial, and antibiotics. Types of hearing loss are conductive, sensorineural, and mixed hearing loss. [5,6]

The ear is divided into the outer, middle, and inner ear; the outer ear is made of the pinna and external auditory canal, the middle ear is an air-filled cavity that has a tympanic membrane, ossicles, and eustachian tube, and the inner ear consists of the cochlea that contains the organ of corti which has outer and inner hair cells. The mechanism of hearing involves the conduction of sounds into the outer and middle ear with transduction of sound vibrations into nervous impulses by hair cells of the organ of corti, and impulses are carried by the auditory nerve into the brainstem and auditory cortex; thus, the hearing occurs.[7]

Risk factors for hearing loss following ototoxic agent exposure are age extremes, <5 years, type of the tumour, gender; males are 4 times more likely to develop hearing loss than females, cranial irradiation, concomitant use of other ototoxic agents, dehydration, pre-existing hearing loss, dose, duration, and route of administration. [8,9]

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In addition, the burden of ototoxicity is higher in very young children, culminating in significant impairment of cognitive performance, language development, and skills.[10]

Chemotherapy-induced hearing loss has relatively expected patterns as the initial damage is to the basal cochlea outer hair cells and progresses to apical turn with a classic characteristic of bilateral symmetrical sensorineural hearing loss (SNHL) affecting high frequencies of typically above 80000 Hz, which is the key frequency for speech discrimination in background noise and music perception.[1]

Audiological monitoring protocol for ototoxic hearing loss comprises three phases, which are baseline(pre-treatment), serial (during treatment), and maintenance(post-treatment) monitoring, which is crucial for reliable outcomes, and missing one component during monitoring can cause an incapability to detect and prevent hearing loss.[11]

On the other hand, monitoring of ototoxicity in children involves the use of audiometry tests like pure tone and play audiometry; others are otoacoustic emissions (OAEs) and auditory brainstem response (ABR), which are frequently used for unresponsive children. OAEs detect cochlea outer hair cell damage even before the development of hearing loss on an audiogram, while ABR measures the function of auditory structures and transmission of nerve impulses generated by sound into central auditory systems. [12,13,14,15]

Moreover, difficulties in monitoring and reporting ototoxicity in children are due to limited audiological testing, patient-related risk factors, chemotherapeutic dosing scheduling, and various ototoxic criteria. [16]

Besides, the importance of monitoring ototoxic hearing loss includes the provision of care to the patient, early identification of hearing loss and prevention of hearing loss, influencing good drug prescription manner like giving small or less frequent doses, interruption or treatment suspension, and auditory rehabilitation. [4,17]

In contrast to hearing assessment, which ascertains the presence of hearing loss, hearing screening identifies children who may have hearing loss. The components of hearing screening are PTA, OAEs, otoscopic examinations, and immittance screening tests that include tympanometry and acoustic reflexes. While pure tone audiometry (PTA) screening test measures hearing by air conduction means, immittance screening points out middle ear problems, and otoscopy provides additional information on hearing status, though the tests have limitations of age and responsiveness.[18]

Another screening test is the destruction test, which is done from the age of 6 to 18 months for infants who can sit unsupported with good neck control; response is measured by checking the neck turn toward the introduced sound.[19]

Hearing loss is a common notable adverse effect of chemotherapy in children that can impair cognitive performance, language, skills development, and overall quality of life. According to 2011 World Health Organization (WHO) data, 360 million people had hearing loss globally, of whom 32 million were children, whereas the prevalence of hearing loss after receiving chemotherapy ranges from 60% to 90% in paediatric populations [1,2,20,21]. In Tanzania, the prevalence and pattern of chemotherapy-induced hearing loss in the paediatric population are not known; however, in adults, the prevalence is estimated to be 71% [22]

The study addressed the existing knowledge gap regarding hearing loss as an adverse effect in children who are treated with chemotherapy. The findings will help alert healthcare workers, researchers, and policymakers as it will provide them with a better understanding of the magnitude of hearing loss in paediatrics treated with chemotherapy to set the preventive and curative measures.

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MATERIALS AND METHODS

Study Area

The study was conducted at the Paediatric oncology department in a Tertiary hospital from December 2022 to May 2023 in Tanzania.

Study Design

This was a prospective longitudinal hospital-based study.

Study Population

The study included all children aged 0 to 17 years with histologically proven cancer who were treated with vincristine, cisplatin, and carboplatin. A total of 52 children were enrolled.

Data Collection and Analysis

Participants who were meeting the inclusion criteria were enrolled in the study. Explanation about the study was given to parents and participants, and then consent forms were signed. Data was collected by the principal and 2 assistant investigators using data sheets, and every participant had his or her own sheet. The collected information was recorded in the datasheet, which included age, sex, address, type of drug, dose of the drug, type of malignancy, ear examination findings, and audiological assessment results. Ear infection, foreign bodies, wax impaction, and other disorders were managed accordingly before the hearing test. Thereafter, participants were sent for audiological assessment before starting treatment (baseline assessment) and after 2 cycles of chemotherapy (serial assessment).

Determination of Hearing Loss

Hearing loss was determined by measuring different sound intensities and frequencies in decibels and Hz, respectively. Measurement included different sound frequencies from 250 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz and also sound intensity from 0 to 120 decibels. Furthermore, type B and C tympanometry results were used to determine conductive hearing loss from participants who had middle ear effusion. Normal hearing was defined when sound intensity was between 10 to 25 decibels, and severity of hearing was classified as mild hearing loss (26-40 decibels), moderate hearing loss (41-60 decibels), severe hearing loss(61-80 decibels) and profound hearing loss(81 decibels and above). All audiological measurements were performed after otoscopic examination in a soundproof booth room by using Piano Inventis clinical audiometer version 2013 for play audiometry, pure tone audiometry, and distraction hearing tests, whereby the flute viola middle ear analyser tympanometer 2013 version was used for tympanometry at MNH audiology unit during baseline and serial assessment.

Tympanometry results were classified as type A, B, and C, where type A was regarded as normal, while type B and C were classified as middle ear effusion (conductive hearing loss). Audiometric measures were done in air conduction by introducing different sound intensities of 0 to 120 decibels and frequencies of 250 to 8000 Hz. The distraction test was positive when there was a response to head turn toward the intended introduced sound intensity and frequency.

Data Analysis

Collected data was thoroughly inspected for accuracy, completeness, and internal consistency and then entered into SPSS version 26 for analysis.

In descriptive statistics, a summary of the samples and variables was presented in tables and figures. Categorical variables were analysed by using frequencies, whereas for continuous variables, mean and standard deviation were calculated. Fisher's exact test was used to obtain the p-value where a p-value < 0.05 was considered significant.

Ethical Consideration and Confidentiality

Ethical approval to carry out this study was obtained from a directorate of Research and Publications of MUHAS, and approval to conduct this study at the hospital was obtained from a directorate of research and publication at MNH. Study participants were enrolled after signing

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informed consent and assent forms in the Swahili language, and assent forms were used for minors. All data collected during the study was handled with utmost confidentiality by the principal investigator.

RESULTS

This study enrolled a total of 52 participants with a mean age of 6.6±2.3 years; age was categorised into 0-5 years, 6 -10 years, and ≥ 11 years. The majority of the participants, 33(63.5%), were in the age group of 6-10 years. Males were predominant, with a male-to-female ratio of 3:1 (*Table 1*).

Table 1: Age and sex distribution of the study participants.

Age group years	Sex n(%)		
	Male	Female	Total
0 -5	12(80)	3(20)	15(28.8)
6 -10	24(72.7)	9(27.3)	33(63.5)
≥11	3(75)	1(25)	4(7.7)
Total	39(75)	13(25)	52(100)

The overall prevalence of hearing loss was higher after treatment than before, at 15.4% (*Figure 1*).

Figure 1: Overall prevalence of hearing loss

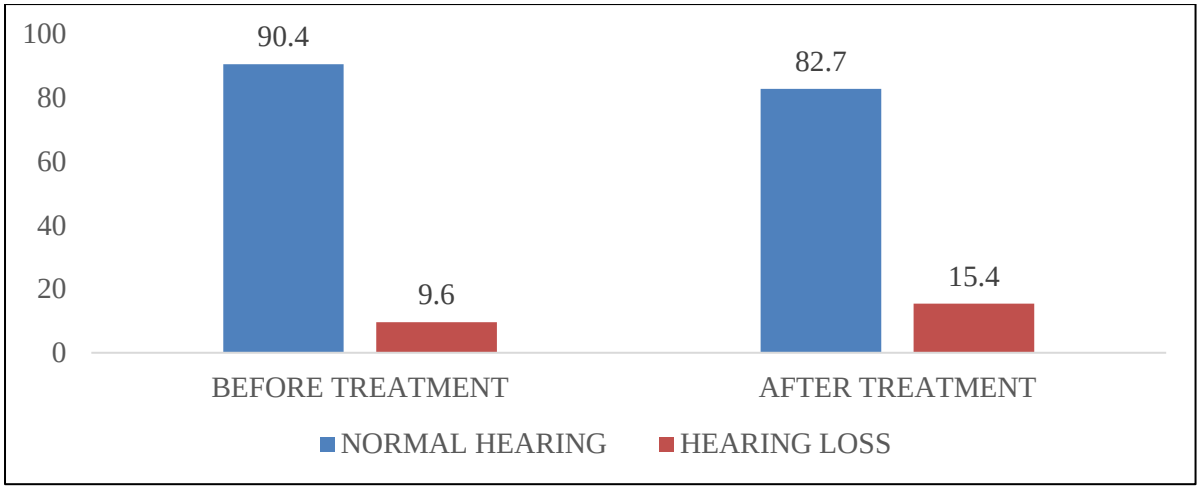
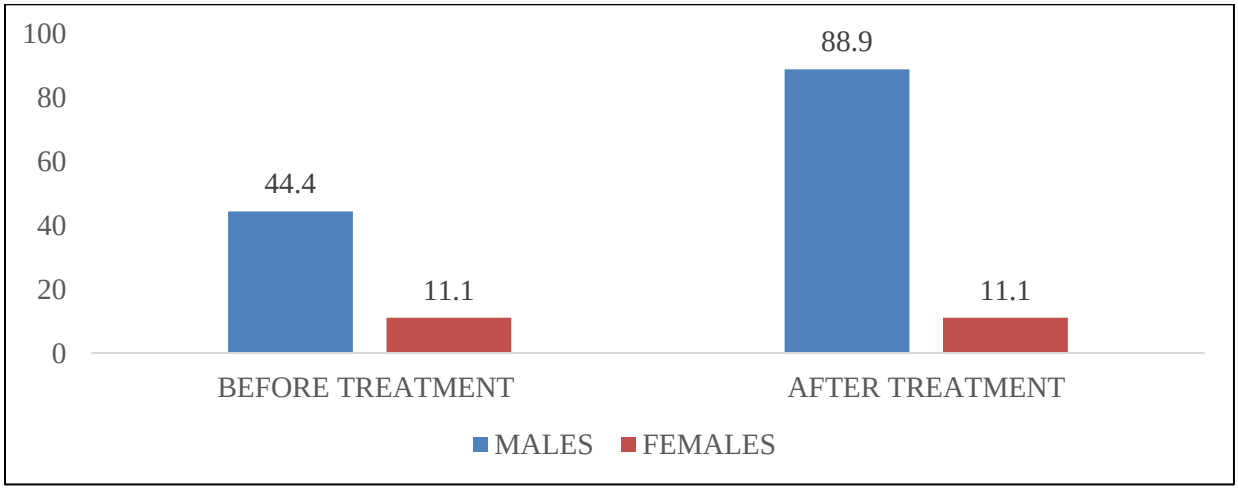


Figure 2 shows that males had a higher prevalence of hearing loss (88.9%) than females (11.1%).

Figure 2: Prevalence of hearing loss according to sex.



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The majority of the participants in the age group of ≥11 had a higher prevalence of hearing loss 4(100%) as compared to the age group of 0 -5 years 1(6.7%) (*Table 2*).

Table 2. Prevalence of hearing loss according to age.

Age group in years	Before treatment n(%)			After treatment n(%)		
	Normal hearing	Hearing loss	Total	Normal hearing	Hearing loss	Total
0 -5	15(100)	0	15(28.8)	14(93.3)	1(6.7)	15(28.8)
6 -10	32(97.0)	1(3.0)	33(63.5)	29(87.9)	4(12.1)	33(63.5)
≥11	0	4(100)	4(7.7)	0	4(100)	4(7.7)
Total	47(90.4)	5(9.6)	52(100)	43(82.7)	9(17.3)	52(100)

In this study, the Nasopharyngeal site was highly related to hearing loss 5(55.6%), which was noticeably mixed with hearing loss 3(60%) as it was compared to other tumour sites (*Table 3*).

Table 3: Types of hearing loss in relation to a tumour site.

Tumour site	Before treatment n (%)				After treatment n (%)			
	CHL	SNHL	MHL	Total	CHL	SNHL	MHL	Total
Nasopharynx	5(100)	0	0	5	1(20)	1(20)	3(60)	5(55.6)
Haematological	0	0	0	0	0	2(100)	0	2(22.2)
Renal	0	0	0	0	0	1(100)	0	1(11.1)
Ocular	0	0	0	0	0	1(100)	0	1(11.1)
Total	5	0	0	5(100)	1(11.1)	5(55.6)	3(33.3)	9(100)

In this study, lateralisation and type of hearing loss were predominantly bilateral 8(88.9%) and SNHL 5(55.6%); however, the minority had unilateral hearing loss 1(11.1%) (*Table 4*).

Table 4: Lateralisation of hearing loss according to type of hearing loss.

Laterality	Before treatment n(%)				After treatment n(%)			
	SHL	CHL	Mixed	Total	SHL	CHL	MHL	Total
Bilateral	0	3(100)	0	3(60)	5(62.5)	0	3(37.5)	8(88.9)
Right	0	1(100)	0	1(20)	0	1(100)	0	1(11.1)
Left	0	1(100)	0	1(20)	0	0	0	0
Total	0	5(100)	0	5(100)	5(55.6)	1(11.1)	3(33.3)	9(100)

In this study, lateralisation after treatment was predominantly bilateral hearing loss 8(88.9%), and hearing loss was notably seen among participants who were treated with cisplatin 4(80%); however, there was a lower percentage of unilateral hearing loss 1(11.1%) (*Table 5*).

Table 5: Lateralisation of hearing loss according to the type of chemotherapy used.

Drug	Before treatment n (%)				After treatment n(%)			
	Bilateral	Right	Left	Total	Bilateral	Right	Left	Total
Vincristine	0	0	0	0	2(100)	0	0	2(22.2)
Carboplatin	0	0	0	0	1(100)	0	0	1(11.1)
Cisplatin	3(60)	1(20)	1(20)	5(100)	4(80)	1(20)	0	5(55.6)
Carboplatin & vincristine	0	0	0	0	1(100)	0	0	1(11.1)
Total	3	1	1	5(100)	8(88.9)	1(11.1)	0	9(100)

In this study, the most common type and severity of hearing loss were sensorineural 5(9.6%) and mild hearing loss 8(15.4%); however, there were lower percentages of participants with moderate mixed hearing loss 1(33.3%) (*Table 6*).

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Table 6: Severity of hearing loss according to types of hearing loss

Hearing status	Before treatment n(%)				After treatment n(%)			
	Normal	Mild	Moderate	Total	Normal	Mild	Moderate	Total
Normal	47(100)	0	0	47(90.4)	43(100)	0	0	43(82.7)
SNHL	0	0	0	0	0	5(100)	0	5(9.6)
CHL	0	4(80)	1(20)	5(9.6)	0	1(100)	0	1(1.9)
MHL	0	0	0	0	0	2(66.7)	1(33.3)	3(5.8)
Total	47(90.4)	4(7.7)	1(1.9)	52(100)	43(82.7)	8(15.4)	1(1.9)	52(100)

In this study, the most common severity of hearing loss was mild hearing loss 8(15.4%), which was notably seen among participants who were treated with cisplatin caused 4(80%) (*Table 7*).

Table 7: Severity of hearing loss according to the type of chemotherapy used.

Drug	Before treatment n (%)				After treatment n(%)			
	Normal	Mild	Moderate	Total	Normal	Mild	Moderate	Total
Cisplatin	0	4(80)	1(20)	5(9.6)	0	4(80)	1(20)	5(9.6)
Vincristine	39(100)	0	0	39(75)	37(94.9)	2 (5.1)	0	39(75)
Carboplatin	5(100)	0	0	5(9.6)	4(80)	1(20)	0	5(9.6)
Carboplatin & vincristine	3(100)	0	0	3(5.8)	2(66.7)	1(33.3)	0	3(5.8)
Total	47(90.4)	4(7.7)	1(0 .9)	52(100)	43(82.7)	8(15.4)	1(1.9)	52(100)

The most common type of hearing loss was SNHL 5(55.6%). MHL 3(60%) was frequently seen among participants who were treated with cisplatin; however, there was exclusively pure SNHL among those who were treated with vincristine 2(100%) and carboplatin 1(100%) (*Table 8*).

Table 8: Type of hearing loss in relation to the type of chemotherapeutic agent used.

Drug	Before treatment n(%)				After treatment n(%)			
	CHL	SNHL	MHL	Total	CHL	SNHL	MHL	Total
Cisplatin	5(100)	0	0	5(100)	1(20)	1(20)	3(60)	5(55.6)
Carboplatin	0	0	0	0	1(100)	0	0	1(11.1)
Vincristine	0	0	0	0	2(100)	0	0	2(22.2)
Carboplatin & vincristine	0	0	0	0	1(100)	0	0	1(11.1)
Total	5	0	0	5(100)	5(55.6)	1(11.1)	3(33.3)	9(100)

DISCUSSION

Hearing loss is among the common adverse effects caused by chemotherapeutic agents, which can lead to detrimental consequences in children. Although chemotherapeutic agents are the mainstay in the treatment of childhood malignancies, they can induce permanent hearing disability, which is frequently seen in children. The impacts of hearing loss in children include developmental delay, which causes learning problems, social isolation, and poor self-regard. The study enrolled a total of 52 participants with different proven histological malignancies who were treated with cisplatin, carboplatin, and vincristine; mean age was 6.6±2.3 which was categorised into 0-5 years, 6-10 years, and ≥11. Participants were enrolled in the study after meeting the inclusion criteria, and a hearing assessment was done before and after two cycles of chemotherapy. Most participants had haematological malignancies 39(75%), the rest had nasopharyngeal cancer 5(9.6%), nephroblastoma 5(9.6%) and retinoblastoma 3(5.8%).

Three-quarters of the participants (39, 75%) were males with a male-to-female ratio of 3:1, and the predominant age group with hearing loss was ≥11

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years 4(100%) with lower percentages of hearing loss in the age group of 0 -5 years 1(6.7%).

These findings were not in agreement with previous studies done in England and the United States of America, which revealed a high prevalence of hearing loss in the young age group, especially in <5 years, although results had similarities with other previous studies due to a preponderance of male sex in prevalent hearing loss group of ≥11. [9,23] This could be because the majority of the participants in this age group had nasopharyngeal tumours.

Five and nine participants were found to have hearing loss during baseline and serial hearing assessment, respectively. However, one participant, who was among the five individuals with pre-existing hearing loss, was found to have the same unchanged audiological findings even after treatment. The prevalence of hearing loss in this study was 15.4% as compared to before treatment 9.6%. These results were consistent with the study done by Landier et al., which indicated a widely variable prevalence of hearing loss after chemotherapy used to be 4% to 90% depending on drug type, age, and sex[10]. Moreover, Baguley et al. revealed that pharmacokinetics and pharmacodynamics of the given drug, individual susceptibility such as genetics, and comorbidities like renal disease may explain the differences in prevalence among individuals, which was congruent with this study.[1]

In addition, the use of conventional audiological tests might explain the low rate of hearing loss observed in this study since it has a lower detection rate of 49% compared to highly sensitive extended high-frequency audiometry, which has a higher detection rate of 80%, as shown in the literature. [23]

All types of hearing loss were identified in relation to respective tumour sites. Among participants with hearing loss, SNHL was found to be a common type of hearing loss 5(55.6%), which occurred after receiving two cycles of chemotherapy. The nasopharyngeal tumour site was highly related to hearing loss 5(55.6%) as it was compared to other sites with a higher percentage of mixed hearing loss 3(60%), which might be explained by the effect of tumour and chemotherapy use. These findings were congruent with a study done in the United States of America, which explained the possible worsening of hearing loss in relation to nasopharyngeal tumour site as a result of tumour destruction of auditory structures culminating into middle ear effusion and cochlear nerve damage that can further deteriorate hearing loss after treatment [10].

The haematological tumour site had no relation with hearing loss due to the fact that SNHL occurred after serial assessment. These findings were not in agreement with a study done in China that related a rare occurrence of hearing loss in leukaemia, which occurs as a result of middle ear haemorrhage, hypoxia, and cochlear ossification ending up with SNHL. In contrast, a study done in Nigeria showed a relationship between hearing loss with renal tumour site due to renal failure, accumulation of serum creatinine and urea in the inner ear resulting in cochlear dysfunction, and hearing loss, although the relevance was incongruent with this study's findings. In addition, the ocular tumour site was again not connected to hearing loss but rather related to the use of chemotherapeutic agent.[1,24-26]

Moreover, lateralisation and type of hearing loss after treatment were markedly bilateral 8(88.9%) and SNHL 5(55.6%), respectively, which was more noticeable among participants treated with cisplatin 4(80%). Cisplatin was commonly related to bilateral hearing loss 4(55.6%) as compared to vincristine (22.2%), carboplatin 1(11.1%), and a combination of carboplatin and vincristine 1(11.1%). There were lower percentages of participants with unilateral hearing loss 1(11.1%) who had right CHL during baseline and serial hearing assessment despite being on cisplatin, which might explain the absent effect of cisplatin in this patient.

These findings were congruent with other studies, which showed a predominantly bilateral high-frequency SNHL after chemotherapy use in contrast to unilateral hearing loss, which

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frequently occurs as a result of tumour site damage on auditory structures; however, individual susceptibility to unilateral hearing loss has been observed.[27] Previous literature has revealed that hearing loss caused by chemotherapy is mostly bilateral moderate to severe SNHL, which is more prominent in children with less than 10 years, and severity depends on age, type, and dose of chemotherapy used.[21] Severity of hearing loss in this study ranged from mild to moderate hearing loss, with no severe or profound hearing loss observed, and frequent type and severity of hearing loss were high frequency sensorineural 5(9.6%) and mild hearing loss 8(15.4%) respectively. However, a few participants 1(20%) acquired moderate mixed hearing loss 1(33.3%) that resulted from moderate conductive hearing loss, demonstrating a change of hearing loss type without altering the severity due to the effect of medication. Mild hearing loss was more common among participants treated with cisplatin 4(80%) as compared to vincristine 2(5.1%) and carboplatin1(20%) and a combination of vincristine and carboplatin1(33.3%). These findings were in agreement with studies done in England, which described the presence of mild to severe hearing loss as a result of chemotherapeutic agents use.[1,23]

More than 50% of participants acquired SNHL after receiving two cycles of an appropriate chemotherapeutic agent, and the common type of hearing loss revealed was predominantly high-frequency SNHL 5(55.6%) that was mostly seen with cisplatin use as compared to vincristine2(22.2%) and carboplatin1(11.1%). Among the participants treated with cisplatin, the majority who previously had conductive hearing loss 5(100%) acquired mixed hearing loss 3(60%), 1(20%) had SNHL, and fewer remained with conductive hearing loss 1(20%) which was congruent with a study done in England which demonstrated higher percentages of hearing loss following cisplatin use which was more prominent in young children who are <5 years due to immature cochlea, although all participants treated with the drug in this study were aged 9 to 13 years. [21,23]

In this study, a pure SNHL was exclusively seen among all participants treated with Carboplatin 1(11.1%), vincristine 2(22.2%), and a combination of carboplatin and vincristine 1(11.1%). These findings were consistent with previous literature, which reports the infrequent presence of bilateral transient hearing loss with vincristine, which is more noticeable when vincristine is combined with a platinum compound such as carboplatin, as it was seen in fewer participants treated with vincristine and carboplatin 1(100%) in this study.[16,25]

CONCLUSION

The use of audiological monitoring protocol in children treated with chemotherapy for early detection, prevention, and rehabilitation of hearing loss is required, as most chemotherapeutic agents are associated with hearing loss. A multi-disciplinary approach that involves a paediatrician, oncologist, otolaryngologist, and audiologist is important in early diagnosis, treatment, and audiological follow-up among the paediatric population under treatment with chemotherapy.

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