Original Article

Audiologic Evaluation of Patients with Head and Neck Cancers Treated with Cisplatin Based Chemotherapy: A Longitudinal Study

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Abstract

Background: Recently, the incidence of head and neck cancers are on the increase globally and particularly in our environment. In addition, concurrent platinum-based chemoradiotherapy has become widely used in the treatment of head and neck malignancies. The objective of this study was to determine the effect of cisplatin-based chemotherapy on hearing in patients with head and neck cancers at our University Teaching Hospital.

Methodology: This was a hospital-based longitudinal case-control study that involved 54 participants attending the oncology treatment centre of the University Teaching Hospital Zaria. The study investigated the hearing threshold and degree of hearing loss pre and post cisplatin-based chemotherapy at intervals of 3 months and 6 months. The data obtained were analyzed using Statistical Product and Service Solutions (SPSS)version 20.

Results: Seventy-two participants were recruited into the study but 54 (75%) participants met the inclusion criteria and were enrolled and as well as same age and sex match controls. Thirty-one31(57.4%) of the participants had a nasopharyngeal tumour, 14(25.9%) had Sinonasal tumour and 9(16.7%) had Laryngeal tumour. Among the study group, there were 39 males (72.2%) and 15 females (27.8%) with an M: F ratio of 2.6:1. The age of the participants ranged from 13-68 years. (Mean =40.3years. SD=13.6). Assessment of hearing in the better ear showed 22 (40.7%) of subjects and 6 (11.1%) of controls had hearing loss before the onset of the study. The majority of these patients had mild hearing loss either mixed or SNHL. In the study group, 32(29.6%) ears showed changes in hearing threshold after 3 months of cisplatin therapy while68(62.9%) ears showed changes at 6 months of therapy. The overall incidence of ototoxicity after 6 months of therapy was 62.9%.

Conclusion: This study found a significant number of head and neck cancers patients with hearing impairment pre-chemotherapy. Cisplatin treatment based chemotherapy was associated with significant short term hearing impairment in patients with head and neck cancers.

Introduction

Cis-Platinum (CP) is a chemotherapeutic agent that has been used in the treatment of cancer for more than two decades. Among all the other platinum compounds Cisplatin has a better tumouricidal effect.[1] For head and neck cancers, it is usually used in combination with 5 Flouro uracil (5FU). Recently,

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Access this article online

Quick Response Code:

Website: www.nigerianmedjournal.org

How to cite this article: Shofoluwe NA, Shuaibu IY, Mohammed IB, Chitumu D, Usman MA, Nwaorgu OGB, Salisu AD. Audiologic Evaluation of Patients with Head and Neck Cancers Treated With Cisplatin Based Chemotherapy: A Longitudinal Study. Niger Med J 2021; 62; (2): 85-91

concurrent platinum-based chemoradiotherapy has become widely used in the treatment of head and neck malignancies.[2] Multiple studies supporting improved survival rates following concurrent platinum chemoradiotherapy have been reported.[3]-[5]

However, controversies still exist about the optimal dose and schedule of these modalities for head and neck cancer treatment. As high as 100 mg/m^2 3 weekly cisplatin may be tolerated by younger patients.[1] But most of the head and neck cancer patients present at an advanced age and may have lower performance status and comorbidities.[1] Hence, 40 mg/m^2 has been suggested as more appropriate for them.[1]Ototoxicity resulting from the use of platinum-based chemotherapy has been well described in the literature. [4]This Ototoxicity is usually an irreversible high-frequency sensorineural loss.[5][6]In addition, histological studies showed that the outer hair cells are most susceptible to the ototoxic effects of CP.[5][6]In several human studies, 20 to 90% incidence of hearing loss associated with CP-based regimens has been recorded.[5],[7]-[9]The high variability of this side effect observed in these patients were most likely because patients were treated with different doses under a range of schedules for a variable number of treatments courses. Other factors such as patient age, preexisting hearing loss, interaction with other drugs, and even nutritional status have been suggested as a comorbidity for the clinically observed ototoxicity.[6]

The incidence of head and neck cancers in Nigeria are currently on the increase and they are being managed with cisplatin-based chemotherapy. However, there is limited information on the effect of this drug in our locality on hearing. Therefore, this study aimed to determine the effect of cisplatin-based chemotherapy on hearing thresholds in patients with head and neck cancer.

Methodology

This was a prospective longitudinal case-control study of patients with a histologically confirmed diagnosis of nasopharyngeal/sinonasal/laryngeal cancers who had cisplatin-based chemotherapy at the radio-oncology centre of our tertiary hospital.

The study was conducted over 14 months between March 2015 and April 2016. Ethical approval was obtained from the institutional Ethical Review Committee.

The policy of the radio oncology Centre is that selected patients with head and neck cancers undergo a course of chemotherapy first while waiting for radiotherapy. This is due to the large volume of patients requiring radiotherapy. Currently, there are only 2 centres in the Northwestern Nigeria with facilities for radiotherapy and ours is the largest. It receives patients from all over Nigeria especially the Northern region. Patients from neighbouring countries like Cameroun, Niger and Chad also attend the hospital. The usual dose of cisplatin for head and neck cancers is 50-75mg/m^2. Other chemotherapeutic agents used include the 1st line Drugs: cisplatin and 5 FU 2nd Line drugs: Cisplatin and Paclitaxel.

Serial pure tone audiometric evaluation of these participants while on chemotherapy was done at commencement, at 3 and at 6months post-treatment to detect any changes in hearing threshold. Each ear is treated as a separate entity.

The sample size was obtained using Fisher's formula[7]and 72 patients were recruited for the study. A consecutive number of patients were included in the study.

Inclusion Criteria: All patients with a histologically confirmed diagnosis of nasopharyngeal / sinonasal/laryngeal cancer (who were booked to commence cisplatin-based chemotherapy) presenting to the Ear, Nose and Throat (ENT) and radio-oncology Clinics and patients who have not previously commenced chemotherapy.

Exclusion Criteria

Patients who refuse to consent or children without next of kin to consent as well as those with a past medical history that suggests chronic ear disease with hearing impairment were excluded.

Patients with nasopharyngeal/sinonasal cancer who have tympanometric evidence of middle ear affectation were excluded including those taking other ototoxic medication and those who commenced radiotherapy before the conclusion of the study.

The study was explained to each participant and informed consent was obtained. An interviewer based questionnaire was used to capture information on demographic characteristics such as age and sex, clinical information such as social history, drug history, other co-morbid conditions and site of disease. The questionnaire was administered to all the patients by the investigator.

The ear examination was done using bright bulls lamp with a head mirror and Heinze battery-powered otoscope with an appropriately sized ear speculum. The examination consisted of an inspection of the auricle and external auditory canal and was followed by otoscopy to visualize the external auditory canal and tympanic membrane. Any obstructing cerumen or foreign body in the canal was removed. The investigator then performed tympanometry followed by Pure Tone Audiometry testing for both air and bone conduction using a duly calibrated (last calibrated November 2013) Madsen Itera Diagnostic audiometer model number 211149, manufactured in November 2004 by GN Otometrics, Copenhagen, Denmark. The audiometry was done in a soundproof booth using the British Society of Audiologists (BSA) protocol.[10] The investigator was assisted by an audiologist in placing the headphone and explaining the procedure to the participants. Patients sat in the soundproof booth facing away from the audiometer. They were instructed on the use of a response switch to press the button when even the faintest sound is heard. A circum-aural headphone was applied to both ears with the red one to the right ear. Bothair and bone conduction for each ear at frequencies of, 500, 1000, 2000, 4000, 6000 and 8000(Hz) were tested at a 5dB increase sound level. The patient's response was charted on a standard audiogram.

The threshold of patients was determined based on the relationship between air and bone conduction. When air-conduction thresholds are elevated relative to normal bone conduction thresholds air-bone gap—the loss was classified as conductive. Sensorineural hearing loss is a hearing impairment wherein the bone and air thresholds are within 10dBA of each other, the thresholds are higher than 25dBA. When air and bone conduction thresholds show the same amount of hearing loss, it was regarded as sensorineural and when air conduction thresholds are elevated relative to abnormal bone conduction thresholds, the loss was classified as mixed. These procedures were done just before the commencement of chemotherapy and were repeated at 3 and 6months following commencement of therapy.

The degree of hearing loss based on the WHO criteria was determined from the pure tone average of 500Hz - 4000Hz and classified into mild, moderate, moderate-severe, severe and profound hearing loss.[11]
Patients who were noticed to have post-treatment hearing loss were counselled and given post treatment hearing rehabilitation including hearing aid prescription.

The collected data was entered into the computer system for analysis. Statistical Product and Service Solution version 20 software (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. Data were summarized using frequencies, percentages, measures of central tendency and dispersion. Analysis of variance (ANOVA) and t-test was used for comparing means and used to establish the relationship between the variables. The level of statistical significance was set at a p-value of <0.05, 95% confidence interval.

Results

Seventy-two participants who fulfilled the inclusion criteria were recruited into the study but only 54(75%) participants concluded the study. Eighteen (25%) of the participants for various reasons dropped out of the study. From the drop out statistics, 6 (33.3%) died from advanced disease,4(22.2%) opted for treatment abroad,3(16.6%) had a haemostatic dose of radiotherapy,1(5.6%) had severe thrombocytopenia,1 (5.6%) was pregnant and 3(16.6%) were lost to follow up. Of those that completed the study 31(57.4%) had a nasopharyngeal tumour, 14(25.9%) had Sinonasal tumour and 9(16.7%) had Laryngeal tumour.

The 54 participants that completed the study consisted of 39 males (72.2%) and 15 females (27.8%) with an M: F ratio of 2.6:1. The age of participants ranged from 13-68 years (mean=40.3yr.SD=13.6). Thirty-five (64.8%) of the participants were married, and 13(24.1%) were single. The sociodemographic data of the participant is shown in Table 1.

Social History and Medical Condition

Sixteen (29.6%) patients have used either alcohol or tobacco or both for over 1 year. Only 8(14.8%) had associated comorbid medical conditions such as hypertension and diabetes (Table 2).

Pre chemotherapy pure tone averages of study and control participants

Pretreatment PTA results (best hearing ear) of study and controls participants showed that 22(40.7%) patients and 6(11.1%) controls had hearing loss pretreatment (Table 3). The mean PTA findings of those who had hearing loss before the commencement of cisplatin chemotherapy in the better ear showed that pretreatment, NPC and sinonasal tumours were more

strongly associated with hearing impairment. (Figure 1). The differences in the mean pure tone averages of the patients and controls were significant in the NPC and sinonasal groups only when compared using a paired sample t-test (p = 0.000) (Table 4).

Post chemotherapy pure tone averages of study and control participants:

There were 32 (29.6%) ears that showed changes in PTA after 3 months of cisplatin therapy and 68 (63%) ears showed changes at 6 months of therapy (Table 5). These changes were either new-onset SNHL or changes in the severity of pre-existing SNHL. The differences in the baseline PTA and after 3 and 6 months' treatment with cisplatin were statistically significant when subjected to paired t-test(Table 5).

Table 1: Socio-demographic characteristics of study participants(n=54).

Socio-demographic variable	Frequency	Per cent (%)
Age		
< 21	4	7.4
21 – 30	10	18.5
31 -40	11	20.4
41 – 50	17	31.5
51 -60	7	13.0
>60	5	9.3
Gender		
Female	15	27.80
Male	39	72.20
Marital Status		
Single	13	24.10
Married	35	64.80
Widowed	4	7.40
Divorced	2	3.70
Occupation		
Farmer	15	27.80
Driver	5	9.30
Motorcyclist	5	9.30
Civil Servant	5	9.30
Student	3	5.60
Others	21	39.0

Table 2: Summary of the Clinical History of Participants

Social History	Frequency	Per cent (%)
Tobacco only	12	22.2
Alcohol &Tobacco	4	7.4
None	38	70.4
Drug History		
Aminoglycoside	0	0
Frusemide	0	0
None	30	55.6
Medical History		
Diabetes	2	3.70
Hypertension	6	11.1
None	46	85.1

Table 3: Degree of hearing loss in the better ear before treatment in 22 patients with pre-treatment hearing impairment.

	NPC	Sinonasal	Larynx	Control
Mild	8	4	1	5
Moderate	5	2	0	1
Moderate-Severe	2	0	0	0
Profound	0	0	0	0
Total	**15**	**6**	**1**	**6**

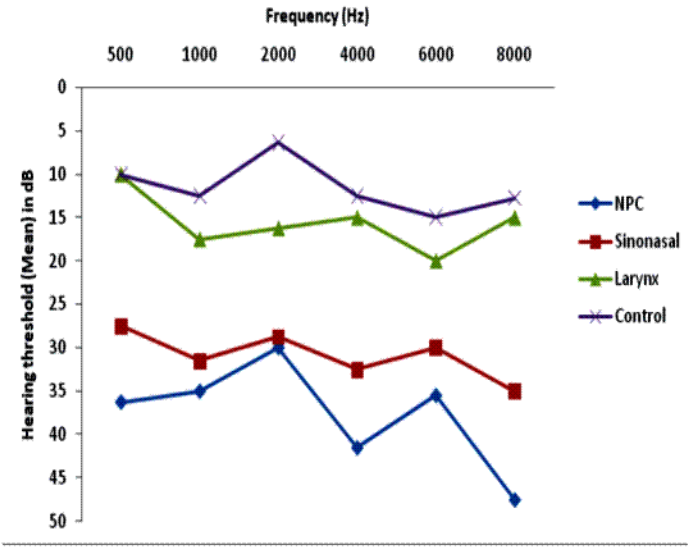

Figure 1: Hearing threshold of subjects and control pre-treatment with cisplatin.

Table 4: Comparison of mean PTAv of the patients and controls using t- test

	Mean	SD	Sig (2 tailed)
Pair 1 Laryngeal -Control	4.12	3.44	0.072
Pair 2 Sinonasal-Control	19.37	2.87	0.000
Pair 3 NPC-Control	26.12	5.15	0.000

Table 5: Number of ears with and without PTAv changes

PTA (SNHL)Changes	NPC (62)	Sinonasal (28)	Laryngeal (18)	
No Sensorineural hearing loss at 3 months	42 (67.7%)	20 (71.4%)	14(77.8%)	76 (70.4%)
Sensorineural hearing loss at 3 months	20 (32.3%)	8 (28.6%)	4 (22.2%)	32 (29.6%)
No Sensorineural hearing loss at 6 months	21(33.9%)	13 (46.4%)	6 (33.3%)	39 (36.1%)
Sensorineural hearing loss at 6 months	41(66.1%)	15 (53.6%)	12 (66.7%)	68 (63.9%)

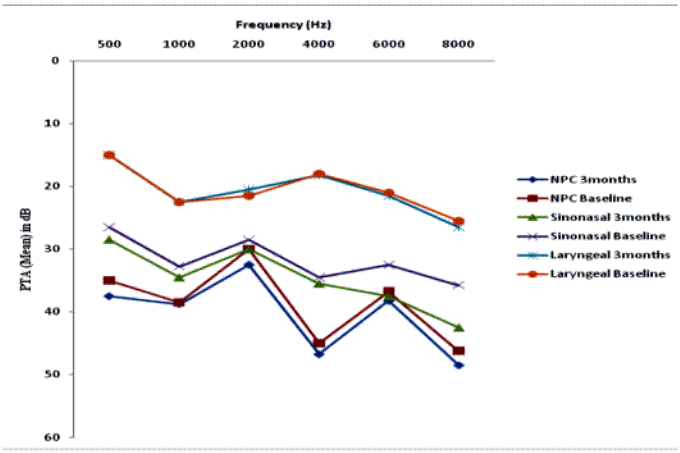

Figure 2: Mean PTAv (SHNL or Mixed) Baseline Versus 3months after commencement of Cisplatin Chemotherapy.

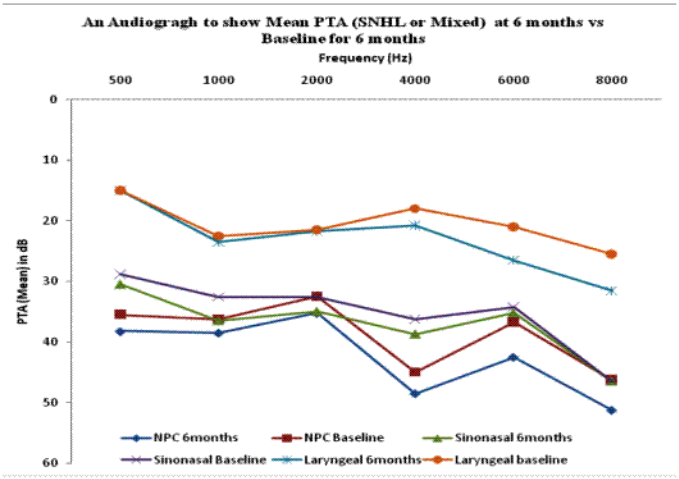

Figure 3: Audiograph showing SHNL after commencement of Cisplatin Chemotherapy at 6 months.

Discussion

Ototoxicity is a significant clinical problem that can result in vocational, educational and social consequences. Currently, there is no clinically-proven method to treat established cases of Ototoxicity.[8]A well-recognized side effect of cisplatin chemotherapy is ototoxicity, resulting in bilateral high-frequency sensorineural hearing loss (SNHL) that is typically permanent and associated with tinnitus.[8]

The mean age of the participants in this study was 40 years. This is similar to findings from other African countries [13];[14]. Blacks were observed to be two to four times more likely than Caucasians to be diagnosed before the age of 50 years ($P < 0.01$). [15]These findings thus substantiated an increased incidence and earlier age of onset of head and neck cancers in blacks compared with whites.[15]

The reason for this disparity in the age between Africans and Caucasians may be connected to issues of race, genetics, poverty and behavioural practices. Lower life expectancy in Africans compared to Caucasians and earlier exposures to risk factors have also been speculated.[15] The 41-50 year age bracket was observed in this study as the most frequently affected and this is similar to findings by Ologe et al [15], Lilly-Tariah et al[12], and Aroral et al. [16]

In this study among the three types of head and neck cancers considered; nasopharyngeal cancer was the commonest, followed by sinonasal tumour and laryngeal cancers. Reports on the overall pattern of head and neck cancers from different regions of the country similarly cited the nasopharynx as the most common site[12]. The nose and paranasal sinuses were the second most common reported sites while the larynx, was the third commonly affected site [12],[17.] In contrast, Amusa et al [18]and Otoh et al. [19]reported differently that malignancy of the oral cavity was the commonest in Ile-Ife(South-west) and Maiduguri (North East) Nigeria.

At presentation, before the commencement of cisplatin therapy, this study found 40.7% of participants had hearing loss and were mainly conductive hearing loss. In addition, the majority of the patients with pretreatment hearing loss were noted to have NPC, with the hearing loss being conductive and of moderate severity in half of the cases. Involvement of the eustachian tube by NPC invasion has been blamed for the conductive hearing loss in NPC.[20]

At 3months of cisplatin therapy, this study noted changes in PTA with one-third of the ears having new-onset sensorineural hearing loss or worsening of existing sensorineural hearing loss. These changes were mainly noticeable at the higher frequencies of 6KHz and 8KHz and consisted of a worsened hearing loss of 2-3.3dBcompared to pretreatment records. The PTA changes noted were significant in patients with NPC and sinonasal cancer. Patients with laryngeal tumours had no significant change in PTA at 3months. It was however unclear why laryngeal cancer patients on cisplatin were not showing any PTA changes after 3 months of therapy.

Studies have shown that hearing loss may be present from as early as 1 month of commencement of cisplatin.[16],[21] In this study, 32 (29.6%) ears showed changes in PTA at 3 months, whereas 76 (70.4%) did not show any changes. There is no satisfactory

explanation for this inter-patient variability and susceptibility to developing PTA changes. Whether this is as a result of differences in drug concentration within the inner ear or due to some physiological factors is yet to be established. The changes in PTA noted affected higher frequencies (>4 kHz), this is similar to findings in the study by Aroral et al. [16] and Fausti et al [22] who found similar hearing loss at higher frequencies.

At 6months into cisplatin therapy, 68 (63%) of ears showed changes in PTA either as new-onset SNHL or worsening of pre-existing SNHL. Though all frequencies were affected, the worst affected were high frequencies of 4-8KHz similar to what was observed at 3 months with worsening of hearing loss of 3-4dB observed. These changes may be worse for higher frequencies beyond 8KHz not measured in this study. The changes in the hearing threshold observed after 6 months was independent of the type of cancer. Similar studies by Malgonde et al[23] found an average hearing loss of 2.55-2.90dB after 6 months of chemotherapy. Some studies have reported elevated pure-tone thresholds in 75-100% of patients treated with cisplatin.[24] while others have reported elevated hearing thresholds in up to 100% of cisplatin-treated cancer patients. [25] Other similar studies have reported that cisplatin ototoxicity affects 23 - 50% of adults and up to 60% of children.[24] There is limited data available on the incidence of drug-induced hearing impairment in Africa. Studies [26],[27] involving follow up of patients for up to two years after cisplatin revealed that hearing loss that developed was irreversible. The incidence of ototoxicity after cisplatin treatment in this study was found to be 62.9%, this is similar to findings in a study by Joshua et al [24].

Limitations

The limitation of the study included; inability to use an Otoacoustic Emission machine which would have been the objective method for detecting the early onset of ototoxicity in this study. Effects of other chemotherapeutic agents apart from cisplatin in the combination therapy may also affect the results of this study.

Conclusion

This study found that a significant number of patients(41%) with head and neck cancer especially nasopharyngeal and sinonasal had hearing impairment pre-chemotherapy. Cisplatin treatment was associated with sensorineural hearing loss or worsening of existing hearing loss, and this was proportional to the duration of treatment and higher frequencies.

Overall, there was a high incidence of hearing loss in head and neck cancer patients managed with cisplatin. Regular audiological monitoring of patients receiving high dose cisplatin treatment is recommended to detect early changes in PTA that may suggest the onset of ototoxicity. This may help in counselling patients about hearing changes and the need for post-treatment rehabilitation.

Financial Support and Sponsorship: Nil
Conflicts of Interest: Nil

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