



# Ototoxicity and Its Early Diagnosis in Patients Receiving Cancer Chemotherapy – A Prospective Clinical Study

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## ABSTRACT

### Introduction

Antineoplastic drugs play an important role in the treatment of cancer at different levels & are the most cited ototoxic agents. The main aim of this study is early detection of ototoxicity in individuals receiving chemotherapy as an attempt to reduce the challenge in diagnosis and management of ototoxicity.

### Materials and Methods

A prospective study was conducted at a tertiary care center in the Departments of Otorhinolaryngology & Oncology from October 2019 to September 2021 among 140 cancer patients. Baseline audiological evaluation was done using DPOAE and Pure Tone Audiometry at baseline, followed by within 24 hours, at the end of third & the sixth month.

### Results

81.4% study subjects received combination chemotherapy, among that 21% received a combination of a Taxane and a Platinum derivative & the rest received single drug regimen. Ototoxic effects were assessed in terms of tinnitus, vertigo & hearing loss. There was a significant hearing loss of 15 dB from baseline in high frequencies were observed in patients receiving taxanes, platinum compounds or both.

### Conclusion

The study findings has led to the conclusion that ototoxic effects were more pronounced among the study subjects who had received Taxanes, Platinum compounds or both (Taxanes & Platinum). Hence it is recommended that audiological assessment at base line and at all stages of the therapy should be established as a protocol to be followed in patients receiving cancer chemotherapy.

### Keywords

Ototoxicity; Pure Tone Audiometry; DPOAE

Cancer is considered to be a global burden, leading cause of death & a hurdle to extend the life expectancy. According to the estimates of the GLOBOCAN database 2020 in concurrence with the WHO there is a surge in the incidence around 19.3 million and 10 million cancer deaths world-wide. This global surge in cancer leads to the likely use of antineoplastic drugs,

which assist in the prevention of proliferation, invasion and metastasis of cancer cells.<sup>1</sup>

The term “Chemotherapy” was first coined by a German chemist Paul Ehrlich in 1900 & defined it as use of chemicals to treat a disease. The field of cancer therapy was dominated by surgery and radiotherapy until the accidental discovery of the first chemotherapeutic agent nitrogen mustard gas during World War II. The National Cancer Act was passed in 1971 that reiterated the benefits of cancer chemotherapy.<sup>2</sup>

Drug ototoxicity is defined as a transient or permanent, acquired hearing disorder of auditory or vestibular function

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which is usually bilateral & progressive, induced by therapeutic agents. The most common symptoms reported till date are tinnitus, hearing loss and vertigo.<sup>3</sup>

The American Position statement on provision of ototoxic monitoring by audiologist states that audiological monitoring for ototoxicity is done mainly for two main reasons. First and foremost is to express the principle of early identification & also to embrace the principle of early intervention. Audiological monitoring for ototoxicity still remains to be a part of active research topic even in the recent era.<sup>4</sup>

Audiological methods that are potentially in value for monitoring drug toxicity includes basic audiological assessment, High Frequency Audiometry (HFA) and Otoacoustic Emissions (OAE).<sup>4</sup>

The current study is aimed to determine the ototoxic effects of the most commonly used chemotherapeutic drugs, to establish a standard feasible ototoxicity monitoring protocol for its early diagnosis & to efficiently manage ototoxicity following cancer chemotherapy.<sup>4</sup>

## Materials and Methods

A prospective clinical study was conducted in the Departments of Otorhinolaryngology & in the Department of Oncology at a tertiary care center in Bangalore from October 2019 to September 2021. All the diagnosed cancer patients above the age of 18 years attending the Oncology department for cancer chemotherapy were included in the study. Individuals with prior history of ear disease, ear surgery, noise exposure or trauma, patients with severe to profound hearing loss & patients below 18 years of age were excluded from the study. All the patients enrolled in the study underwent PTA & DPOAE tested at frequencies 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz were assessed at baseline, within 24 hours of receiving the 1st cycle, within 24 hours of receiving the 2nd cycle, within 24 hours of receiving the 3rd cycle, 03 months from start of chemotherapy & 06 months from start of chemotherapy. During all the cycles after chemotherapy, PTA and DPOAE were done only after stabilization of the patient. Those patients who

reported tinnitus & vertigo after receiving chemotherapeutic drugs during any one of the cycle after commencement of treatment were also followed up.

**Pure Tone Audiometry (PTA):** The Pure Tone Audiometer used for our study is Arphi Diagnostic Audiometer 2001 SN 657 model & was calibrated by the audiologist daily. The hearing loss were measured by the Ototoxicity grading scales given by the National Cancer Institute & Common Terminology Criteria For Adverse Events (CTCAE) Ototoxicity Grades for children.

The NCI CTCAE ototoxicity grades for children (**with adult guidelines in parentheses**) are as follows

**Grade 1:** Threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear (same for adults);

**Grade 2:** Threshold shift or loss of >25-90 dB, averaged at two contiguous test frequencies in at least one ear (same for adults);

**Grade 3:** Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., >20 dB bilateral HL in the speech frequencies; >30 dB unilateral HL; and requiring additional speech language related services) (Adults: >25-90 dB, averaged at three contiguous test frequencies in at least one ear);

**Grade 4:** Indication for cochlear implant and requiring additional speech language related services (Adults: profound bilateral hearing loss >90 dB HL).

*Note: For children without baseline evaluation, baseline thresholds are assumed to be <5 dB HL.*<sup>4</sup>

**Distortion Product Oto Acoustic Emissions (DPOAEs):** The DPOAE model used in our institution for all patients were Neurosoft 5 vorouin str Ivanovo model SN 05150W. The results were interpreted either as pass or refer.

## Data Management & Statistical Analysis:

Data collected from the patients were analyzed using SPSS software version 16.0. Quantitative variables were summarized as mean, standard deviation & median. Qualitative data were expressed in terms of frequency and proportion. For the purpose of bivariate analysis, the whole data set had been reclassified into five groups based

on the chemotherapeutic agent received. Of which 1-Taxane, 2-Platinum derivatives, 3-Taxane & Platinum derivative, 4-Multiple drug regimen & 5-Single drug regimen.

The tests of significance done were Spearman correlation, Chi-square and Independent sample Kruskal Wallis H test. For all the above tests, the level of significance was fixed at 5% (0.05) and p-values of less than 0.05 were considered statistically significant. Following the Kruskal Wallis test, a pair-wise comparison was performed in order to find out the differences in the outcome between different pairs of the above-mentioned five groups.

Bonferroni Corrected or adjusted p-values were calculated for each of the ten different pairs of categories. The p-value after Bonferroni adjustment is 0.049; which implied that the pair-wise comparisons with a p-value less than 0.049 will be considered statistically significant. The sample size calculated was 140, by using Medcalc online sample calculator, with type 1 error of 0.015 & a power of 90% with reference to the study "Incidence of Cisplatin induced Ototoxicity in adults in Head & Neck cancer" by Joshua B Greene et al, published in 2015.

#### Ethical Considerations:

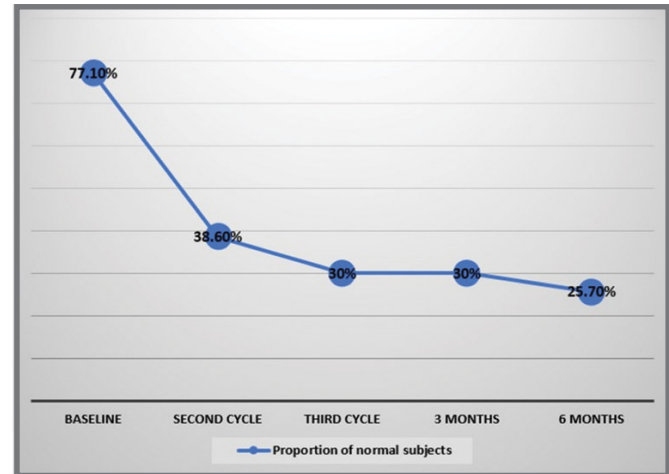
Institute Ethics Committee clearance was obtained prior to the commencement of the study. A written informed consent was taken from all study participants and there was no financial burden on the study subjects.

#### Results

The study participants enrolled were 140, among which 91 were male & 49 were female. The mean age of the study population was 49.38 years with a SD of 14.45 years. The minimum age was 18 years & maximum age was 77 years. Around 60% of the study population were aged 51 years & above. The most common organ system involved among the study population was the gastrointestinal system. Only a quarter of the study population were found to have comorbidities. The other sociodemographic variables were not significant.

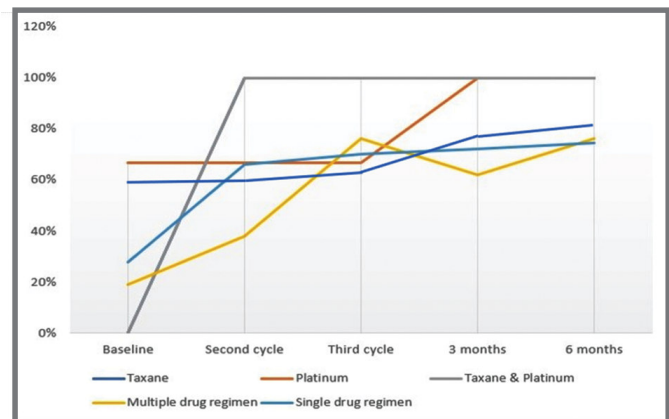
The analysis of hearing loss was done by PTA &

DPOAE during the study. At baseline 77.1% of the study population had normal DPOAE & by the end of the study only 25.7% of the study population had normal DPOAE (Fig.1).



**Fig. 1. Graph showing the normal proportion of the subjects after each cycle among the study population.**

It was also observed that there was a gradual worsening pattern of hearing loss among the patients who received Taxanes, Platinum derivatives & patients who had received a combination of Platinum & Taxane derivatives (Fig. 2).



**Fig. 2. Graph showing correlation of different antineoplastic drugs received & the hearing loss developed among the study population.**

The analysis of hearing loss by PTA were done at baseline & speech frequencies, the overall median hearing loss at baseline & hearing loss with respect to

antineoplastic drugs received at high frequencies 4000Hz & 8000 Hz were calculated. The hearing loss calculated was graded with the NCI CTCAE ototoxicity grading scale for adults and children.

Among the study population who received platinum derivatives, the median hearing loss (Rt =20 dB, Lt=16.67dB) & had grade I ototoxicity. Taxanes & Platinum derivatives (Rt=16.67dB, Lt=10dB) & had grade I ototoxicity only on the right ear. The study subjects who had received carboplatin was found to have a median hearing loss (Rt = 18.33 dB, Lt = 15.83 dB) especially between audiometric assessment prior to the second & the third cycle. Also a median hearing loss (Rt=15.83, Lt = 15 dB) between the third cycle & the cycle at 03 months from the start of chemotherapy.

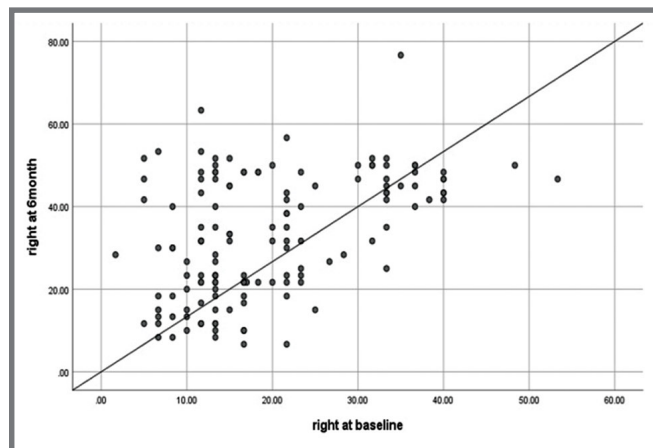
There was a significant hearing loss among the study subjects who received Platinum derivatives(15 to 35 dB), Taxanes(10 to 20 dB), Taxane & Platinum derivative combination (30 dB to 35dB) and for the patients who received multiple drug regimen(17.5dB).The hearing loss analysed were more pronounced at the higher frequencies at 4000Hz & 8000Hz.

The median hearing loss at 4000Hz among the study population who received Paclitaxel (Rt =15dB, Lt = 12.5dB),Cisplatin (Rt =15dB, Lt = 15dB) ,Platinum derivative & Taxane (Rt=10dB, Lt= 15dB) & Carboplatin (Rt =25dB, Lt = 27.5dB) was observed at the second cycle.

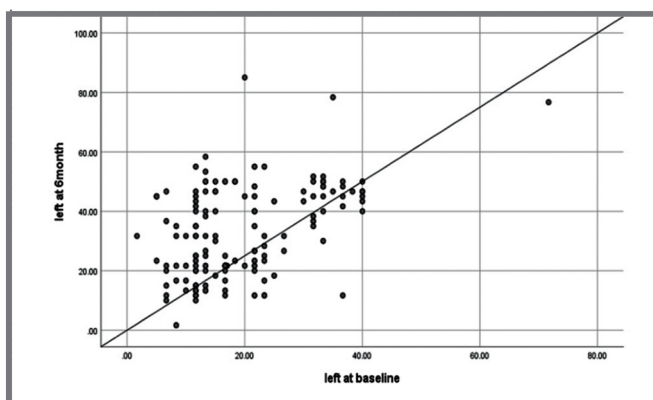
The median hearing loss at 8000Hz among the study population who received Paclitaxel (Rt =10dB, Lt = 15 dB), Platinum derivative & Taxane ( Lt = 20 dB) & Carboplatin (Rt =25dB, Lt = 27.5dB) was observed at the third cycle. And the study subjects receiving Cisplatin had median hearing loss (Rt =20dB, Lt =20dB) at the end of 03 months. The median hearing loss assessed at higher frequencies 4000 Hz & 8000 Hz were statistically significant. Among the study population 19.3% reported tinnitus , 10% reported vertigo & 9.3% reported both tinnitus & vertigo.

Hearing at the baseline and hearing at the end of 6 months were tested for correlation using Spearman

correlation and was found to be positively correlated with a correlation co-efficient of 0.412 (p-value <0.01) in the right ear and 0.393 (p-value <0.01) in the left ear (Fig. 3 & 4)



**Fig. 3. Scatter plot to show correlation between hearing in the right ear at baseline and hearing at the end of 6 months.**



**Fig. 4. Scatter plot to show correlation between hearing in the left ear at baseline and hearing at the end of 6 months.**

Among the study population, Kruskal wallis H test & Bivariate analysis (Table I & Table II ) were carried out & was found that the differences in median hearing loss between the groups of the pairs who received Platinum derivatives & single drug regimen , Taxane & Platinum derivative with any other single drug regimen, Any drug combination with any single drug regimen were statistically significant for the right ear (Fig. 5 & Fig. 6).

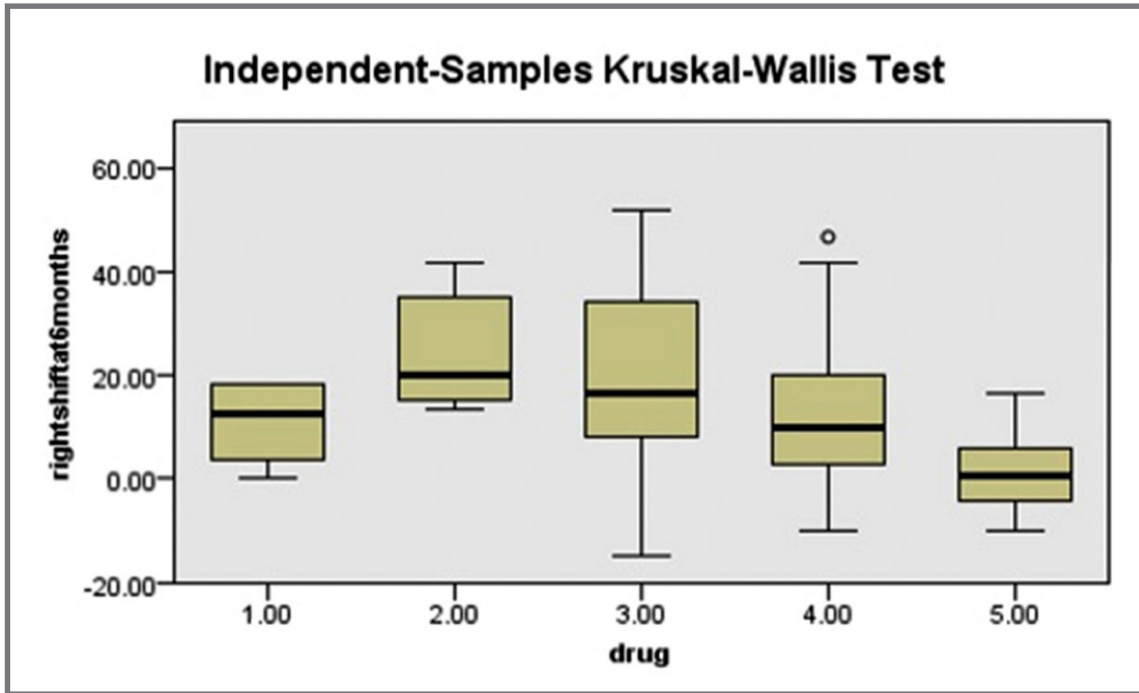


Fig. 5. Independent sample Kruskal-wallis Test on Right ear

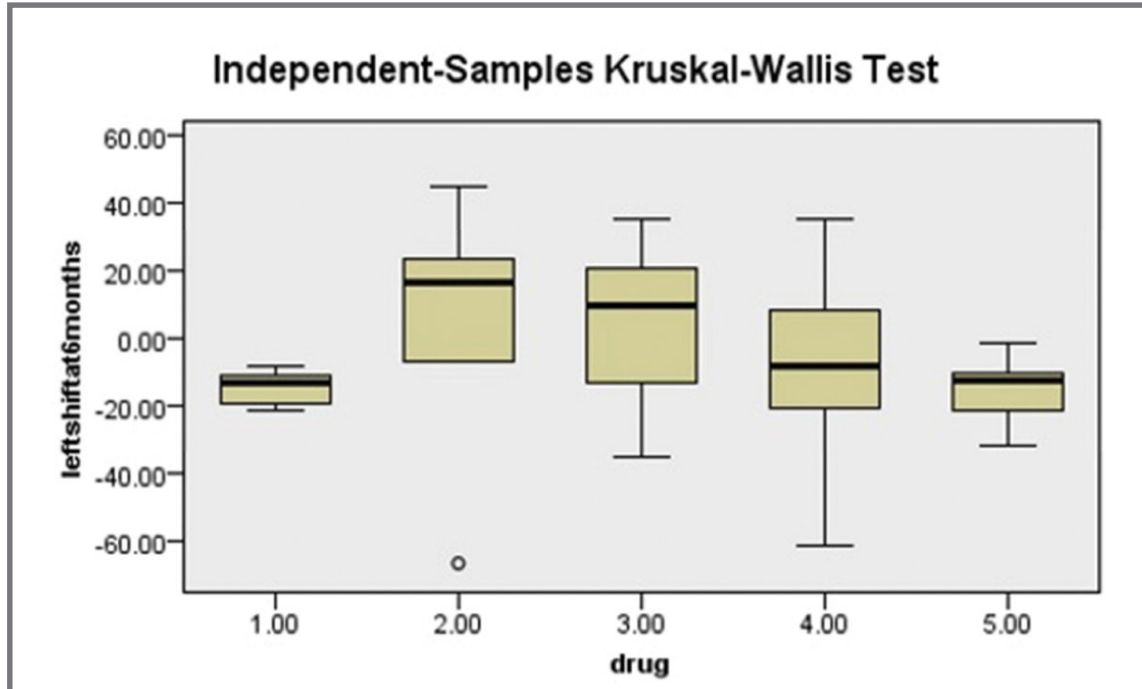


Fig. 6. Independent sample Kruskal-Wallis Test on Left ear

The median hearing loss relative to baseline between the groups in the left ear was not statistically significant although the median hearing loss when each group considered individually was found to be significant.

**Table I: Results of an Independent Samples Kruskal Wallis H test in the Right ear – (Each row in the table tests the null hypothesis)**

PAIRS (GROUP 1 - GROUP 2)	TEST STATISTIC	SIGNIFICANCE (P-VALUE)	
		OBTAINED	ADJUSTED
Group 1 and Group 5	36.917	0.068	0.684
Group 4 and Group 5	37.238	0.003	0.027
Group 3 and Group 5	57.77	0.000	0.001
Group 2 and Group 5	76.65	0.000	0.001
Group 1 and Group 4	-0.321	0.985	1.000
Group 1 and Group 3	-20.857	0.266	1.000
Group 1 and Group 2	-39.738	0.078	0.779
Group 3 and Group 4	20.536	0.036	0.357
Group 2 and Group 4	39.417	0.013	0.130
Group 2 and Group 3	18.881	0.286	1.000

**Table II: Results of an Independent Samples Kruskal Wallis H test in the Left ear – (Each row in the table tests the null hypothesis)**

PAIRS (GROUP 1 - GROUP 2)	TEST STATISTIC	SIGNIFICANCE (P-VALUE)	
		OBTAINED	ADJUSTED*
Group 1 and Group 5	0.042	0.998	1.000
Group 4 and Group 5	16.80	0.176	1.000
Group 3 and Group 5	39.79	0.007	0.067
Group 2 and Group 5	47.48	0.014	0.138
Group 1 and Group 4	-16.76	0.326	1.000
Group 1 and Group 3	-39.75	0.034	0.341
Group 1 and Group 2	-47.44	0.035	0.354
Group 3 and Group 4	22.99	0.019	0.188
Group 2 and Group 4	30.68	0.053	0.534
Group 2 and Group 3	7.69	0.664	1.000

\* Bonferroni adjusted level of significance = 0.049.

## Discussion

The chemotherapeutic agents commonly used and their mechanism of action is briefly discussed as below (Table : III)

At the assessment after 6 months, a total of 54 patients had significant hearing loss in the right ear and 25 had significant hearing loss in the left ear. The left ear was not affected alone, while 29 patients were affected in the right ear alone. Both the sides were affected in 29 patients, more frequently among the patients who received Platinum derivatives either singly or in combination with a Taxane.

The median hearing loss (140 patients tested = 280 ears tested) at frequencies 250 Hz, 500 Hz, 1000 Hz and 2000 Hz was 15dB, and at the end of 6 months at the same frequencies was 40 dB. At high frequencies 4000 Hz and 8000 Hz, the median hearing loss was 20 dB at the start of the cycle and at 6 months, it had worsened to 50 dB. This finding is comparable with the study done by Arora et al titled "Cisplatin based chemotherapy : Add

high frequency audiometry in the regimen" where the threshold during the start of therapy was 54.4dB at all tested frequencies and 73.1dB after 3 months.<sup>7</sup>

Patients who had received Taxane alone had a median hearing loss of 12.5dB in the right ear. The median hearing loss was 20dB in the right ear and 16.67dB in the left ear for patients who received Platinum derivatives alone. For the patients who had received a combination of any Taxane and a Platinum derivative, was 16.67dB in the right ear and 10dB in the left ear. The hearing loss was found to be significant in patients who had received Platinum derivatives either singly or in combination.

At higher frequencies, patients receiving Taxanes or Platinum derivatives either singly or in combination were observed to have hearing loss too early when compared to the other drug groups. This finding is comparable with the finding in the study done by Arora et al, where the cohort which received Cisplatin, had moderate hearing loss relative to base line at higher frequencies.<sup>7</sup>

**Table III: List of Chemotherapeutic drugs causing Ototoxicity – Adapted from Goodman & Gillman of Pharmacology -13 th edition**

Other Antineoplastic Drugs	EGFR inhibitor	Cetuximab
	Platinum Derivatives	Carboplatin, Cisplatin, Oxaliplatin.
	Protein Kinase Inhibitors	Dasatinib, Imatinib, Sorafenib, Sunitinib
	HER 2 receptor inhibitor	Trastuzumab
Drugs Altering The Immune System Response	Mefenamic Acid, Azathioprine, Tacrolimus	
Immunomodulator	Natalizumab	
Sex Hormones	Medroxy Progesterone Acetate, Norethisterone	
Hormone Antagonist	Letrozole, Toremifene	
Prostate Cancer And Gonadotropin Releasing Antagonist	Buserelin, Flutamide, Goserelin	
Cytotoxic Drugs	Vinca Alkaloids & Etoposide Vinblastine ,Vincristine, Vinde	
Tyrosine Kinase Inhibitors	Imatinib	

Bivariable analysis was applied to find out association between age and gender with tinnitus & vertigo. But it did not yield statistically significant results implying that tinnitus and vertigo are independent of age or gender. Both tinnitus and vertigo showed an association with the category of drug received which was statistically significant (p-value <0.001).

Hearing at baseline was positively correlated with hearing at the end of the study & it was statistically significant. This is in contrast with the study done by Arora et al that there was no correlation between the baseline hearing level and cisplatin induced hearing loss. Hearing loss was significant numerically as well as statistically in both the ears between different categories of drugs. But the hearing loss was independent of age.

Among the patients who received Taxanes alone, 33.33% developed either tinnitus or vertigo or both following treatment. In the study done by Sarfaraz et al, 3.88% patients developed either Tinnitus or Vertigo following Taxane therapy.<sup>6</sup>

The Kruskal wallis H test & Bivariate analysis for the study population were carried out & was found that the differences in median hearing loss between the groups of the following pairs were statistically significant only for the right ear & the left ear was not statistically significant. Although median hearing loss relative to baseline between the groups in the left ear was not statistically significant, the median hearing loss when each group considered separately was found to be significant. These results are in comparison with the study done by F.S Palatt et al which stated that “A recent publication where 200 study subjects were treated for childhood cancer with Cisplatin chemotherapy, caused hearing loss in 41.9% in the right ear & 47.3% in the left ears, with 11.6 times greater risk of hearing loss in the right ear and 17.6 times greater in the left ear, compared to the patients not treated with Cisplatin”.<sup>4</sup> The limitation of the study is that the sample size for each drug category was not adequate enough to generalise all the findings obtained from the study, hence studies with greater number of participants are warranted.

## Conclusion

Overall, this study adds to literature on the ototoxic adverse effects of chemotherapeutic agents. This study has however observed the ototoxicity with Taxanes alone or in combination with a Platinum derivative, which is in slight contrast to what is already known about Taxanes. Hence, high frequency audiometry along with DPOAE, could be established as a monitoring protocol for all patients receiving cancer chemotherapy.

Hence, it is recommended that patients on chemotherapy should be monitored for ototoxicity for early identification & early intervention or maybe even change in treatment protocols by replacing with less ototoxic drugs. It is recommended that there should be a clear ototoxicity monitoring protocol in all the centres where cancer chemotherapy is provided. This aids in identification of hearing loss at the earliest & could assist the patient & the patient’s family to maintain effective communication, especially when the hearing deterioration had migrated into the speech frequencies. In those patients with severe hearing loss in young age the use of assistive learning devices could be recommended. The results of this study is consistent and generalised with other studies. There is no set ototoxicity monitoring protocol or ototoxicity grading scales till date. Hence further research is recommended in establishing a feasible ototoxicity monitoring protocol Nation-wide.

## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338
2. DeVita VT, Chu E. A History of Cancer Chemotherapy. *Cancer Res.* 2008 Nov 1;68(21):8643–53
3. Fernanda Soares Aurélio Patatt, Laura Faustino Gonçalves, Karina Mary de Paiva, Patrícia Haas, Ototoxic effects of antineoplastic drugs: a systematic review, *Brazilian Journal of Otorhinolaryngology*, 2021
4. American Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA* 1994; 36 (Suppl 12):11-9

5. Devina Maru & Ghada-Al Malky (2018) Current practice of ototoxicity management across the United Kingdom (UK), *International Journal of Audiology*, 57:sup4, S29-S41, DOI: 10.1080/14992027.2018.1460495
6. Sarafraz M, Ahmadi K. Paraclinical evaluation of side-effects of Taxanes on auditory system. *Acta Otorhinolaryngol Ital*. 2008 Oct;28(5):239-42. PMID: 19186452; PMCID: PMC2689535
7. Arora R, Thakur JS, Azad RK, Mohindroo NK, Sharma DR, Seam RK. Cisplatin based chemotherapy. *Bioline International*. 2016; 19:509
8. Purushothaman Ganesan, Jason Schmiedge, Vinaya Manchaiah, Simham Swapna, Subhashini Dhandayutham and Purushothaman Pavanjur Kothandaraman, Ototoxicity: A Challenge in Diagnosis and Treatment, *Journal of Audiology and Otology*, 10.7874/jao.2017.00360, 22, 2, (59-68), (2018)
9. Joshua B. Greene, Robert Standring, Farzan Siddiqui and Syed F. Ahsan Incidence of Cisplatin Induced Ototoxicity in Adults with Head and Neck Cancer *Advances in Otolaryngology Volume 2015*, Article ID 245613, 4 pages <http://dx.doi.org/10.1155/2015/245613>.