



Prospective Observational Study of Evaluating Cisplatin-Induced Ototoxicity in Patients

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Abstract

Introduction Platinum-based chemotherapeutic agents cisplatin and carboplatin are two of the most widely used drugs in cancer today. They display wide range of adverse reactions; among them, ototoxicity is an important cumulative toxicity that more commonly observed with cisplatin. At a later stage, it can affect speech of individual and lead to communication problem with decreased cognitive function and depression in cancer survivors. Periodic monitoring of hearing loss with pure-tone audiometry (PTA) provides early evidence of ototoxicity which may decrease debilitating effect of the same in a patient.

Objective The primary objective of this study was to assess cisplatin-induced ototoxicity. We also investigated its severity, reversibility, and other modifying risk factors.

Materials and Methods We conducted a prospective observational descriptive type of epidemiological study. The study was conducted over 80 randomly selected cancer patients (for estimation of sample size, the following formula was used $n = [Z\alpha^2 PQ] / d^2$), who were starting with their first cycle of cisplatin from August 2018 to July 2020. This study was conducted at tertiary cancer care center in western Gujarat which caters patients from all over India. We performed PTA in all randomized patients at baseline and periodically. We classified hearing loss according to the World Health Organization (WHO) criteria.

Results A total of 30% ($n = 24$) patients developed cisplatin-induced ototoxicity according to WHO criteria at end of 3 months after starting the first cycle of cisplatin. It was sensory neuronal, affecting both the ears equally, and was seen predominantly at high frequency. We observed hearing loss at 3 months to be significantly more common in the 301 to 400 mg/m² cumulative dose group (47%), as compared with the other two groups (0–200 mg/m² and 201–300 mg/m²; $p < 0.05$). It showed dose dependency with cisplatin. In the multivariate step-wise regression model, baseline hearing loss (odds ratio [OR] = 17.71, 95% confidence interval [CI]: 6.57–118.91, $p < 0.05$) and cumulative cisplatin dose of more than 300 mg/m² were significantly associated with hearing loss at 3 months (OR = 6.62, 95% CI: 2.33–18.74, $p < 0.05$).

Keywords

- ▶ cisplatin ototoxicity
- ▶ ototoxicity monitoring
- ▶ dose dependent toxicity
- ▶ ototoxicity
- ▶ pure-tone audiometry
- ▶ hearing loss

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Conclusion Cisplatin-induced ototoxicity manifests as a bilateral high frequency sensorineural hearing loss. Cumulative dose of cisplatin is an important predictor of development of ototoxicity. Baseline and periodic audiometric monitoring could detect ototoxicity early which leads to possible limitation on the severity of ototoxicity.

Introduction

According to the GLOBOCAN 2020 data, the total number of new cases of cancer was 19,292,789, and total mortality was 99,58,133.¹ Among them, the most common cancers diagnosed in females after breast cancer were head and neck, cervical, lung, and gastrointestinal cancers. These cancer types were observed to be common in males as well. The platinum-based chemotherapeutic agents, cisplatin and carboplatin, are two of the most widely used chemotherapeutic agents in these types of cancer.

Cisplatin has various dose limiting and cumulative toxicities. Ototoxicity is an important cumulative toxicity of cisplatin. This exclusively affects the cochlea. For cisplatin, hearing loss is bilateral, sensory neuronal, irreversible, and generally occurs at higher frequencies (>4 kHz) and is proportional to the cumulative dose of the drug.² Hearing loss is common at the higher frequencies when the cisplatin dose is greater than 60 mg/m².³ Often, it is accompanied by transient or permanent tinnitus which is commonly reversible on the completion of treatment.⁴

In literature, the rate of hearing loss is variably reported between 4 and 90%, depending on the drug dose, age of the patient, preexisting hearing loss, concurrent cranial radiation, some genetic factors, or concurrent use of other ototoxic medications.⁵ A correlation between genetic variants and hearing loss has been found for cisplatin-detoxifying enzymes (glutathione-S-transferase),⁶ nucleotide excision repair proteins, and megalin (low-density lipoprotein).⁷

Recently, sodium thiosulfate has been approved by the Food and Drug Administration (FDA) to prevent cisplatin-induced ototoxicity in children aged between 1 and 18 years.⁸ Unfortunately, it is not yet approved for adult patients. The nature of ototoxicity is such that it often goes undetected until speech intelligibility is affected⁹ and usually detected only when a communication problem becomes evident. These patients can be prescribed a hearing aid,¹⁰ cochlear implant,¹¹ or other assistive device (text messaging or audio streamers), and other special accommodations which will optimize the quality of life for cancer survivors.

Early detection of ototoxicity is an essential component of cancer care in patients receiving cisplatin. Pure-tone audiometry (PTA) remains the first-line diagnostic tool for the screening, diagnosis, and follow-up of hearing status in these patients. So, by doing baseline and periodic audiometry, we can prevent administration of such ototoxic drug in patients of preexisting hearing loss and could detect cisplatin-induced sensory neuronal hearing loss (SNHL) early.

Therefore, this study aims to serve as a resource for health professionals to enhance their understanding of ototoxicity and its regular monitoring in patients receiving cisplatin to prevent ototoxicity. The primary aim of our study is to evaluate cisplatin-induced ototoxicity in cancer patients. Our objectives were to study the dose and effect relationship of cisplatin ototoxicity, severity and reversibility of cisplatin ototoxicity, and other associated risk factors enhancing cisplatin-associated ototoxicity.

Materials and Methods

This prospective study was performed among randomly selected 80 patients with diagnosed cancer and commencing treatment with cisplatin from August 2018 to July 2020 at a tertiary cancer health care center in western Gujarat. For estimation of sample size, the following formula was used:

$$n = [Z\alpha^2 PQ] / d^2$$

Where:

- $Z\alpha$ = value of standard normal variate corresponding to α level of significance = 1.96 (corresponding to 95% confidence interval).
- P = likely value of parameter = 20%.
- $Q = 1 - P = (100 - 20)\% = 80\%$.
- d = margin of errors (measure of precision) = 0.10 (10%).

Inclusion Criteria

Inclusion criteria are listed below:

- Adults >18 years of age.
- Positive diagnosis of cancer.
- Commencing the first cycle of chemotherapy with cisplatin.
- Patients on concurrent radiation with cisplatin were also included.

Exclusion Criteria

Exclusion criteria are as follows:

- Patients presenting with profound hearing loss (more than 91 db) at baseline assessment, as it would be difficult to evaluate them according to the American Speech Language–Hearing Association criteria.¹²
- Patients who have previously received cisplatin chemotherapy.

- History of medical condition, such as tuberculosis and malaria (medications used in these conditions are ototoxic) or diabetes, heart failure, and renal failure medications, of which can affect the hearing threshold.

A total of 80 patients were randomly selected fulfilling the above inclusion criteria. Data collection was done in form of history, examination, complete blood count (CBC), biochemistry, biopsy of accessible site, imaging of relevant site, tumor markers, history regarding hearing loss, tinnitus, and pure-tone average at high frequency. PTA was performed at baseline frequency, at first, third, and sixth months (from beginning the first cycle of cisplatin) in both the ears. Patients were asked about symptoms like hearing loss, tinnitus, and vertigo with each PTA test. We have tested the hearing threshold in decibel (dB) from 250 to 1,200 Hz for both the ears during PTA at multiple time period as discussed above. But for comparison of the hearing threshold in dB, we have used only 8-kHz frequency, as cisplatin-induced hearing loss occurs only at high frequency. The difference between hearing threshold (in dBHL) from the baseline audiogram and the posttreatment audiogram of all the patients were counted.

Significant hearing loss was considered in the following scenarios: approximately 20 Db decline in hearing observed at any single test frequency, oral 0-dB decline at two adjacent frequencies, or loss of response at maximum audiometer outputs for three consecutive frequencies where there was previously measurable hearing. This was based on the American Speech Language and Hearing Association criteria.¹³ We graded severity of cisplatin-induced ototoxicity according to the World Health Organization (WHO) criteria.¹⁴

In primary outcome, we found that cisplatin ototoxicity is proportional to cumulative doses of drug. For secondary outcomes, we studied effect of age, sex, concomitant cranial radiation, chemotherapy given with cisplatin, baseline hearing loss, and cumulative dose. Among them, baseline hearing loss and cumulative doses of cisplatin, both being associated with ototoxicity, were found to be statistically significant.

Statistical Analysis

The data were entered in MS Excel spread sheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Quantitative variables were compared using paired *t*-test. Qualitative variables were analyzed using Chi-square test.

Ethics

The study was approved by the Institutional Ethics Committee clinical studies, Apollo Hospitals International Ltd., Ahmedabad, Gujarat, India. (approval no: ECR/30/INST/GJ/2013/RR; approved on July 16, 2018). The study was conducted according to the principles outlined in the International Conference on Harmonization Good Clinical Practice guidelines and in compliance with the protocol, the Data Protection Act and all other ethical and regulatory requirements, as appropriate for the study. All study participants

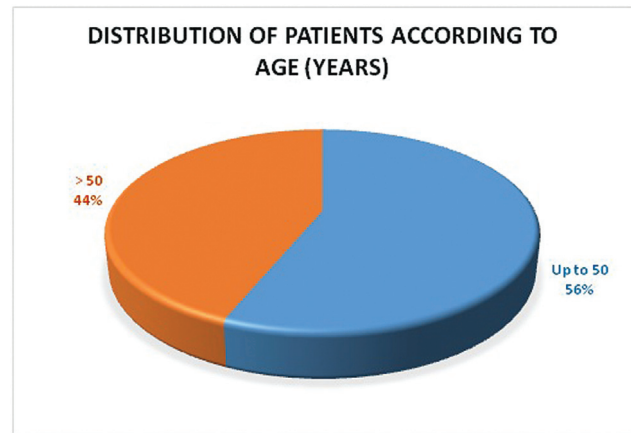


Fig. 1 Distribution of patients according to age.

were explained about study, and written informed consent was obtained from them. The Helsinki Declaration was followed which said that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

This study included 80 patients of cancer, commencing their treatment with first dose of cisplatin repeating either 1 or 3 weekly, given as concurrent with radiotherapy, as an adjuvant or as a neoadjuvant form with other chemotherapy agents or as a single agent.

We found that mean age of the patients in our study was 48.9 ± 10.11 years (range: 22–67 years; ▶ Fig. 1). Here, 70% ($n = 56$) of the patients were males and rest were women (30%, $n = 24$). The most common diagnosis for which cisplatin was prescribed was squamous cell carcinoma of head and neck (42.5%, $n = 34$). Treatment history of the patients revealed that 42.5% ($n = 34$) of the patients received cranial radiation therapy along with cisplatin. Gemcitabine, docetaxel with 5-fluorouracil, etoposide, bleomycin with etoposide, and pemetrexed were used with cisplatin, respectively, in 23.8% ($n = 19$), 10% ($n = 8$), 10% ($n = 8$), 7.5% ($n = 6$), and 6.3% ($n = 5$) of the patients.

Of our study population, 32.5% ($n = 26$) received 0 to 200 mg/m² cumulative dose of cisplatin, with median dose being 180 mg/m². A total of 43.8% ($n = 35$) patients received 201 to 300 mg/m² cumulative dose, with median dose of cisplatin being 290 mg/m². About 23.8% ($n = 19$) of patients received 301 to 400 mg/m² of cisplatin with a median dose being 320 mg/m² (▶ Fig. 2).

At baseline, the mean PTA in right ear was 22.59 ± 4.03 dB which increased significantly to 32.89 ± 16.22 dB at 3 months ($p < 0.001$), and in left ear it was 22.59 ± 3.85 dB which increased significantly to 33.01 ± 16.04 dB at 3 months ($p < 0.001$) (▶ Table 1).

Among the study population, 7.4% of the patients had mild hearing loss before starting cisplatin chemotherapy. Decibel

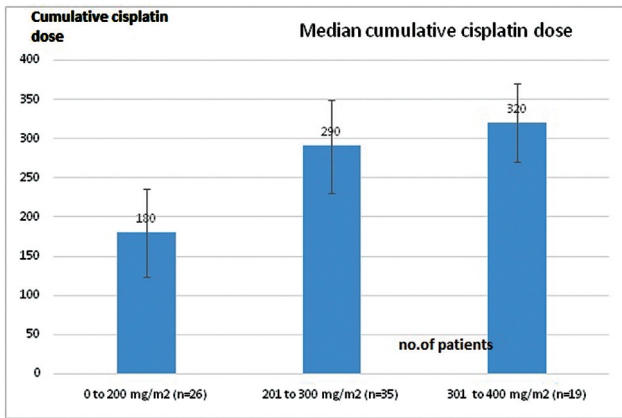


Fig. 2 Median dose of cisplatin given to the patients in the three groups.

of mild hearing loss was recorded to be 26 to 40 dB. At 1-month follow-up, we observed that 17 (21.3%) patients had hearing loss; the severity of hearing loss was not significantly associated with the dose of cisplatin, given to the patients ($p = 0.13$). At 3 months, we found that ototoxicity was associated with cumulative dose of cisplatin, as 24 patients (30%) had hearing loss, and it was significantly more common in the 301 to 400 mg/m² cumulative dose group (47%) as compared with the other two groups ($p < 0.05$; ► **Fig. 3**). Irreversible sensorineural hearing loss (SNHL) was confirmed with repeat PTA at sixth month.

We found that subjective hearing loss was significantly more common in the 301 to 400 mg/m² cumulative dose group (36.8%) as compared with patients in the other two-dose groups ($p < 0.01$). Tinnitus was not found to be significantly associated with the cumulative dose of cisplatin given to patients ($p = 0.14$), and it was reported by 8.8% (7 out of 80) of the patients.

We assessed the effects of age, gender, history of cranial radiation, chemotherapy given with cisplatin, baseline hearing loss, and cumulative cisplatin dose on ototoxicity. In multivariate step-wise regression analysis, baseline hearing loss (odds ratio [OR] = 17.71, 95% confidence interval [CI]: = 6.57–118.91, $p < 0.05$) and cumulative dose of cisplatin more than 300 mg/m² (OR = 6.62, 95% CI: 2.33–18.74, $p < 0.05$) were found to be significantly associated with hearing loss at 3 months (► **Table 2**).

Discussion

Cisplatin-induced ototoxicity manifests as bilateral high-frequency sensorineural hearing loss in a dose-dependent

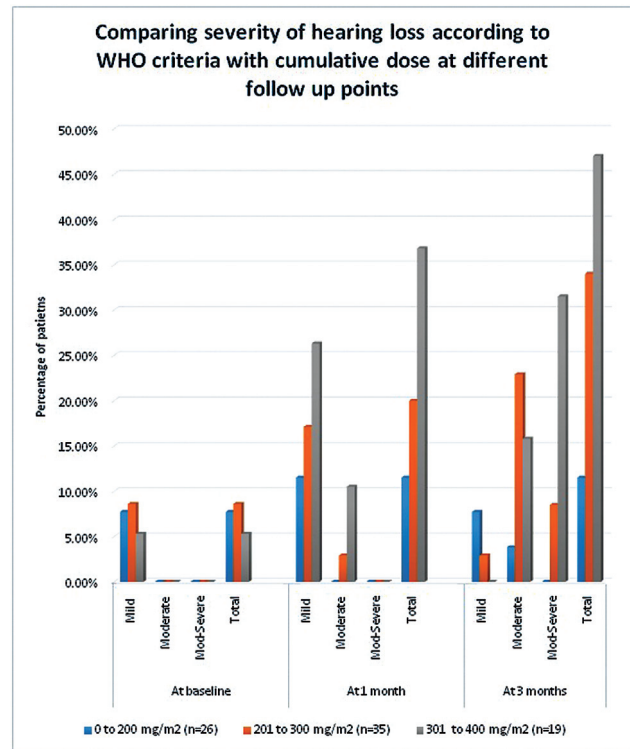


Fig. 3 Comparison of patients in different dose groups with the severity and type of hearing loss according to WHO grading. WHO, World Health Organization.

manner¹⁵ with continued exposure to cisplatin gradually, it affects low frequency associated with speech.¹⁶ This will further lead to impairment in functional status, cognitive status, and depressive symptoms in cancer survivors.¹⁷ Cisplatin ototoxicity is produced by several distinct mechanisms,¹⁸ mainly it is due to preferential damage to the basal turn of the cochlea,¹⁹ where it involves the formation of reactive oxygen species (ROS) and reduction of antioxidative enzymes within the cochlea causing intrinsic apoptosis of outer hair cells^{20,21} which are involved in neural transmission of sound.

The reported incidence of cisplatin ototoxicity is variable, ranging from 26% to over 90% due to many treatment and patient-related factors which include both genetic and non-genetic risk factors. Data from clinical trials can be difficult to compare due to differences in the dose of the drug administered, both within a cycle and the total amount administered over multiple cycles, the time interval between courses, method of administration, treatment duration, and differences in patient populations.

Table 1 Comparison of baseline and 3-month PTA for right and left ear side

	PTA (dB)	Mean	Standard deviation	p-Value
Right ear	Baseline	22.59	4.03	< 0.01
	At 3 months	32.89	16.22	
Left ear	Baseline	22.59	3.85	< 0.001
	At 3 months	33.01	16.04	

Abbreviations: dB, decibel; PTA, pure-tone audiometry.

Table 2 Factors associated with sensorineural hearing loss in our patients at 3 months

Parameter	Univariate analysis			Multivariate analysis**		
	OR*	95% CI	p-Value	OR	95% CI	p-Value
Age (in y)						
Up to 50	Reference	–	–	–	–	–
> 50	1.82	0.67–4.91	0.23	1.82	0.54 to 6.09	0.33
Female gender	1.12	0.39–3.25	0.94	–	–	–
Crania radiation Received	0.53	0.19–1.51	0.23	0.91	0.17–4.83	0.91
Concomitant chemotherapy given	4.8	1.45–16	< 0.01	2.06	0.26–16.37	0.49
Baseline HL	16.76	1.83–153.48	< 0.01	17.71	6.57–118.91	< 0.05
Cumulative cisplatin dose (mg/m ²)						
0–200	Reference	–	–	Reference	–	–
201–300	3.51	0.86–14.23	0.07	4.13	0.67–15.23	0.12
301–400	5.57	1.23–25.21	< 0.05	6.62	2.33–18.74	< 0.05

Abbreviations: CI, confidence interval; HL, hearing loss; OR, odds ratio.

Of our study population, 32.5% received 0 to 200 mg/m² cumulative dose of cisplatin, 43.8% received 201 to 300 mg/m² cumulative dose, and 23.8% received 301 to 400 mg/m² of cisplatin. The study by Dwivedi et al evaluated cisplatin ototoxicity dosage of cisplatin ranged from 50 mg to 115 mg/m² with cumulative dose ranging from 250 to 850 mg.²²

In our study, at baseline, mean PTA in right ear was 22.59 ± 4.03 dB at 8 kHz which increased significantly to 32.89 ± 16.22 dB at 3 months ($p < 0.001$) at same frequency. Similarly, at baseline, mean PTA in left ear was 22.59 ± 3.85 dB at 8 kHz which increased significantly to 33.01 ± 16.04 dB at 3 months at same frequency ($p < 0.001$). Similarly, Arora et al reported that in 57 patients, mean baseline hearing threshold at all tested frequencies was 54.4 dB which increased to 73.1 dB after 3 months.²³

In our study at 3 months, 30% of patients had bilateral sensorineural high-frequency hearing loss (at 8 kHz) according to WHO criteria, incidence and characteristics of hearing loss of our study correlate with studies done by Dwivedi et al,²² Dutta et al,²⁴ and Green et al.²⁵

We observed that 7.4% had hearing loss at baseline, increased to 21.3% at 1 month and 30% at 3 months follow-up. At 3 months, it was significantly associated with dosage of cisplatin ($p < 0.05$). We also found that moderate-to-severe hearing loss was significantly more common in patients in 301 to 400 mg/m² cumulative dose group (31.5%) as compared with patients in the other two dose groups ($p < 0.01$). This observation establishes the dose effect relationship of cisplatin-induced ototoxicity similar to study done by Bokemeyer et al²⁶ and Frisina et al.²⁷ Irreversible nature of hearing loss was confirmed by repeat PTA at 6 months which correlates with studies done by Dwivedi et al²² and Arora et al.²³

We found that tinnitus was reported (evaluated by taking history) by 8.8% of patients and was not significantly associated with the cumulative dose of cisplatin ($p = 0.14$). Incidence of same has been reported from 2 to 36% in

literature.^{28,29} Study by Skalleberg et al showed that tinnitus was not associated with cumulative dosage of cisplatin which is comparable to our study.³⁰

In literature, cumulative dose of cisplatin has been considered as an important factor enhancing cisplatin ototoxicity,²⁶ similarly we found that cumulative cisplatin dose of more than 300 mg/m² (OR = 6.62, $p < 0.05$) and baseline hearing loss (OR = 17.71, $p < 0.05$) were found to be significantly associated with hearing loss at 3 months on multivariate analysis. Apart from dose, age³¹ and sex³² are also associated with cisplatin ototoxicity but we did not find such association.

Audiological monitoring should aim to identify the hearing loss early and reduce its impact on the individual's life by means of proper medical and hearing intervention.³³ Yu et al³⁴ compared the effectiveness of monitoring cisplatin-induced ototoxicity in adult patients using extended high-frequency PTA (EHF-PTA) or distortion-product otoacoustic emission (DP-OAE). The incidence rate of cisplatin-induced ototoxicity was 40% with EHF-PTA or DP-OAE which correlates with detection rate of SNHL by PTA of our study.

There have been many studies with multiple otoprotective agents, none of these agents yet approved in preventing cisplatin ototoxicity in adults.¹⁶ Our study showed that periodic PTA could detect SNHL early. As today, the only way to prevent cisplatin ototoxicity lies on early detection followed by dose modification or substitution with other platinum compound like carboplatin. But care should be taken to prevent compromise in oncologic efficacy.

Limitations

Our study has few limitations, as we have not compared hearing loss at different high frequencies. Comparison was done only at 8 kHz at 0, first, and third months. Also after the third month, most of the patients had finished their treatment, so we were not able to change or modify the cisplatin doses. We have also not performed cost-benefit analysis.

Conclusion

We observed that at 3 months, 30% of the patients had bilateral high-frequency sensorineural hearing loss according to the WHO criteria. Patients with baseline hearing loss and cumulative dose of more than 300 mg/m² had significantly higher odds of developing cisplatin-induced hearing loss. Results of our study showed that audiometric monitoring provides early evidence of decreased hearing ability. We can modify the doses or can substitute cisplatin with other platinum compounds like carboplatin. However, it still does not completely prevent ototoxicity. We recommend audiometric testing (with main focus on high frequency), periodically for all patients at baseline, first, third, and sixth months after starting cisplatin doses.

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Pure-tone audiometry charges were taken care by primary investigator and from hospital research fund.

Conflict of Interest

None declared.

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