International Journal of Otorhinolaryngology and Head and Neck Surgery
Dwivedi G et al. Int J Otorhinolaryngol Head Neck Surg. 2019 Jul;5(4):1044-1051
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

Original Research Article

DOI: http://dx.doi.org/10.18203/issn.2454-5929.ijohns20192727

A clinical study of cisplatin induced ototoxicity in head and neck malignancies

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Received: 09 March 2019
Revised: 12 May 2019
Accepted: 14 May 2019

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ABSTRACT

Background: Head and neck malignancies are the sixth most common cancers worldwide, a vast majority of these cases is squamous cell carcinomas. Cisplatin is one of the main modalities of treatment. However it leads to dose dependent ototoxicity. The aim was to determine the cisplatin induced ototoxicity in head and neck squamous cell carcinomas. The objectives are: (1) to determine the severity and type of hearing loss; (2) to determine the effects on the vestibular system; (3) to correlate the cause effect relationship to dosage and duration of treatment; and (4) to devise a protocol for early detection and prevention of ototoxicity.
Methods: The study was conducted over 50 randomly selected head and neck cancer patients at malignat diseases treatment centre (MDTC) of a tertiary care centre in Eastern India at Command Hospital (EC), Kolkata between October 2008 and October 2010.
Results: 22% of the patients developed cochlear ototoxicity. No patient had any vestibulotoxic effects.
Conclusions: Cisplatin manifests with dose dependent ototoxicity. Pre as well as post treatment audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity.

Keywords: Ototoxicity, Head and neck cancers, Cisplatin, High frequency sensory neural hearing loss, Pure tone audiometry, Vestibulotoxicity, Tinnitus

INTRODUCTION

Cancers of head and neck are the eighth most common cancers worldwide in males and sixteenth among females with an increasing incidence in developing countries.[1] Head and Neck cancer in Indian subcontinent accounts for about 45% of all malignancies. Oral cancers are the most common site of head and neck squamous cell carcinomas (HNSCC) followed by that of oropharynx and larynx.[1] The usual sex ratio of Laryngeal carcinoma is around 10:1 (male: female). Cigarette smoking and alcohol consumption are two strongest aetiological factors for the development of HNSCC both independently and synergistically. Other aetiological factors are Human Papilloma Virus and Epstein Barr Virus, ultraviolet rays of sunlight etc.[1] Oral carcinoma is one of the ten most common malignant neoplasms and the sixth most frequent cancer worldwide. Countries of south and southeast Asia are high incidence areas for oral cavity cancers.[2] Treatment modalities are decided depending upon the stage of the head and neck cancers, which is designed to express the relative severity, or extent, of the disease to facilitate an estimation of prognosis. The treatment modalities available are surgery, radiotherapy, chemotherapy or a combination of these.[1] For squamous cell carcinoma of the head and neck, chemotherapy may be used in combination with surgery and radiotherapy as an adjuvant in radical treatment or alone as palliative treatment for advanced or recurrent disease. All chemotherapeutic agents are burdened with

severe dose dependent and dose limiting side effects. A chemotherapeutic agent is thus not characterised only by its effects but to a great extent also by its side effects.

Cisplatin is one of the most ototoxic drugs known with ototoxicity being dose-limiting side effect. It is normally manifested as a sensorineural hearing loss beginning in the high frequency ranges and successively progressing toward the speech frequency range. It is often accompanied by transient or permanent tinnitus. There is high inter individual variability in ototoxicity, where some individuals may get considerable hearing loss even after the first course. The cause of the high inter individual variability is not known, but the possible explanations are pharmacokinetic differences, genetic factors, and the metabolic status of the patient at the time of drug administration. It is not possible yet to identify susceptible individuals before treatment. Early diagnosis may be aided by monitoring of high-frequency audiograms.[3]

Fifty percent of patients receiving a cumulative cisplatin dose of >200 mg/m^2 have a significant reduction in their hearing, with a severe to profound hearing loss in both ears. Using the American Speech–Language–Hearing Association criteria, this equates to >71 dB hearing loss, which clinically translates into the patient being aware of their hearing loss in most, if not all situations and only managing without a hearing aid if they concentrate and the speaker significantly raises their voice and if there are no competing sound sources. Clearly, this degree of hearing loss is very debilitating and may not always be appreciated by the clinician, on a one-to-one basis.

Various studies have estimated that 4% to 91% of patients receiving cisplatin develop a significant hearing loss which can lead to communication difficulties and reduced physical and psychological wellbeing, isolation and depression.[4] It has been reported that a relationship exists between single and cumulative doses of cisplatin and incidence of ototoxicity.[5]

Pure tone audiometry including high frequency detection is the first choice due to sensitivity of the technique and its potential for early detection of ototoxic damage. The exact degree and time of onset of ototoxicity and the relationship to dosage and duration of chemotherapy needs evaluation. The vestibular toxicity is transient and very little is mentioned about this in available literature. Ototoxicity with cisplatin in Indian population has not been studied much. Therefore this study was conducted to study ototoxicity caused by cisplatin in SCC of head and neck undergoing chemotherapy.

Aims and objectives

The aim of this prospective study is to evaluate cisplatin induced toxicity in head and neck cancer during concurrent chemo radiotherapy (CCRT) to optimize its administration.

The objectives are to

- Determine the severity and type of hearing loss.
- Determine the effects on the vestibular system.
- Correlate the cause effect relationship to dosage and duration of treatment.
- Devise a protocol for early detection and prevention of ototoxicity.

METHODS

A prospective study was carried out and the study was analysed statistically. Patients underwent screening audiometry and thereafter audiometry after predetermined periods.

50 patients were randomly selected from malignant disease treatment centre of a tertiary care centre, Command Hospital (EC), Kolkata, India between October 2008 and 2010. The selected patients were diagnosed as squamous cell carcinoma of head and neck and were undergoing chemotherapy in form of concomitant chemo radiotherapy or neoadjuvant chemotherapy or adjuvant chemotherapy containing cisplatin.

Inclusion criteria

- Patients of head and neck squamous cell carcinoma.
- Patients receiving cisplatin as one of the drugs in chemotherapy.
- Patients undergoing concomitant radiotherapy were also included.

Exclusion criteria

- All patients with obvious ear pathology.
- Patients presenting with any past history of hearing loss.
- Patients suffering with diabetes or any other co-morbidities except head and neck SCC.
- Those that have been exposed to any ototoxic drugs earlier on.

Due clearance was obtained from the institutional ethics committee. The study was done in accordance with the principles outlined in the International Conference on Harmonisation Good Clinical Practice guidelines and in compliance with the protocol, the Data Protection Act and all other ethical and regulatory requirements, as appropriate. Written informed consent was obtained from all study participants.

After detailed history taking and complete head and neck examination, all patients underwent pure tone audiometry including high frequency audiometry prior to start of chemotherapy for use as a baseline data.

After institution of chemotherapy, the patients were followed up at the end of 1st, 2nd and 3rd cycle, and at

followed up at the end of 3 months. After each session, audiological tests were carried out. Patients were interrogated for symptoms like hearing loss, tinnitus and vertigo. Bithermal caloric tests were carried out on all patients after each cycle to determine vestibulotoxicity.

Statistical analysis of the ototoxicity caused by cisplatin in relation to age, sex, dosage, concomitant radiotherapy was carried out using SPSS 20.

To analyze the effect of the schedules administered once a week for 3 weeks and once every 3 weeks on hearing impairment, the baseline audiogram and the post-treatment audiograms of 50 eligible patients were compared and analysed. These audiograms were also used to test the difference between the schedules administered once every 3 weeks. The dependent variable was the difference between hearing threshold (in dBHL) from the baseline audiogram and the post-treatment audiogram. The parameters considered were: frequency (in hertz or kilohertz), cumulative dose of cisplatin (milligrams), and baseline hearing threshold.

Every patient was tested on both ears with three different sets of frequencies. Analysis was performed using Hortmann Neuro otometer Audiomaster PA 444 and AMPLAID 728 audiometers. Frequency was categorized into three groups: 0.5, 1, and 2 kHz (frequency I), which represent the hearing thresholds for speech in silence; 1, 2, and 4 kHz (frequency II), which represent the hearing thresholds for speech in noise; and 8, 10, 12, 16 kHz (frequency III), which represent the hearing thresholds for ultrahigh sounds. These averages are called pure-tone averages (PTAs) and are clinically relevant because they are related to the understanding of speech and perception of music.

A paired-sample t-test was performed to test the significance of the two repeated measurements on the same individual (e.g. pre- and post-treatment audiogram measurements) for the frequencies 4, 8, and 12 kHz. P values of less than 0.05 were considered significant.

RESULTS

A total of 50 patients were included in the study who were either hospitalised patients or from outpatient department at malignant disease treatment centre of a tertiary care center. The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. Treatment of these patients of head and neck squamous cell carcinomas comprised of cisplatin infusion as a radiosensitiser (concomitant chemo radiotherapy) given weekly or as a definitive treatment (neoadjuvant chemotherapy) given 3 weekly with or without radiotherapy.

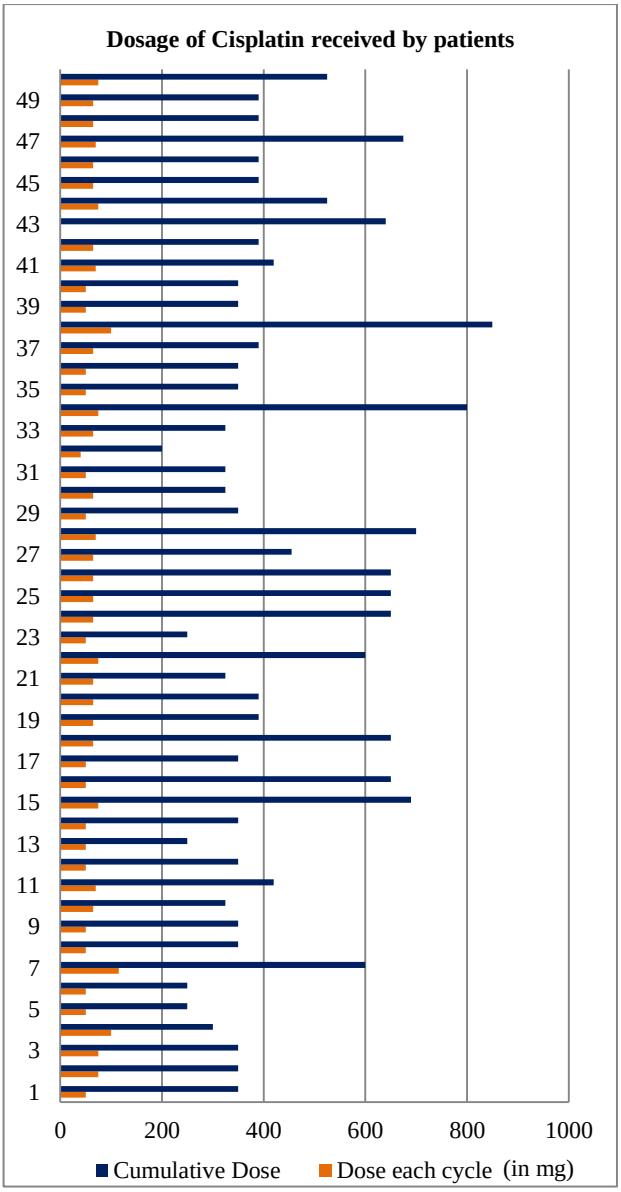

Figure 1: Dosage of cisplatin received by patients.

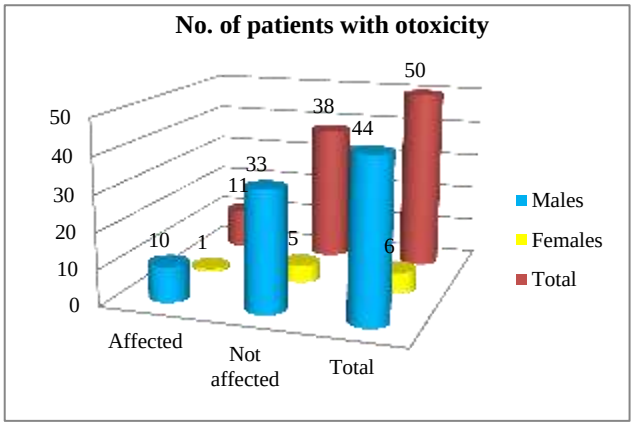

Figure 2: Number of patients displaying ototoxicity.

Dosage of cisplatin ranged from 50 mg to 115 mg with cumulative dose ranging from 250 mg to 850 mg. A baseline pure tone audiometry and bithermal caloric test were done prior to onset of treatment. These tests were repeated after every cycle of cisplatin infusion for 3 cycles and at the 3rd month of follow up after completion of therapy. In this study of 50 patients of head and neck squamous cell carcinomas, various characteristics were seen which have been illustrated as following:

- The age of our study population ranged from 23 years to 82 years with a mean age of 57.2 years. Most of the patients were in the age group 50-60 years (38%) and 60-70 years (30%). The male to female ratio was 22:3 in the present study.
- Cumulative dose of cisplatin received by patients: cisplatin was given to the patients with dose of every cycle ranging between 40 mg/m^2 to 115 mg/m^2 and the cumulative dose ranged from 250 t0 850 mg with a mean of 444.90 mg (Figure 1).

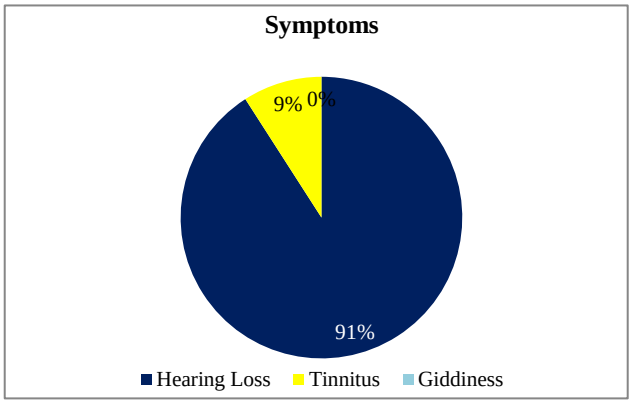

Figure 3: Symptoms displayed by patients.

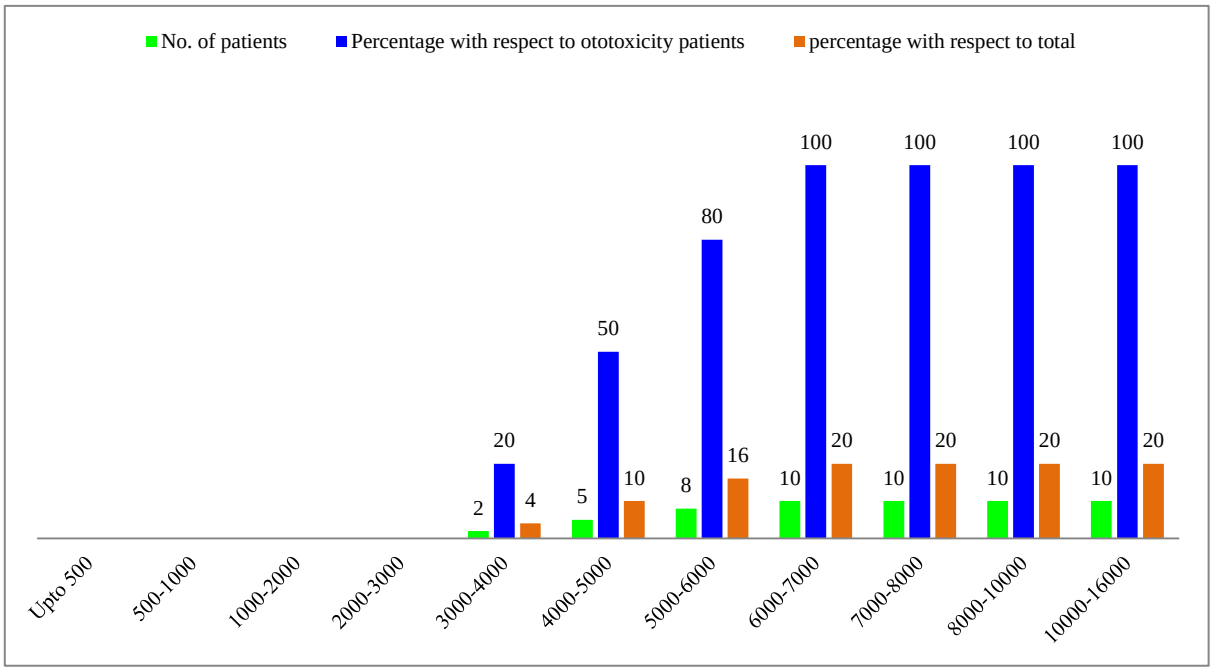

Figure 4: Frequency spectrum of hearing loss with cisplatin.

Table 1: Frequency spectrum of hearing loss with cisplatin.

Frequency range (Hz)	Up to 500	500-1000	1000-2000	2000-3000	3000-4000	4000-5000	5000-6000	6000-7000	7000-8000	10000-16000
Total no. of patients	-	-	-	-	2	5	8	10	10	10
% of total no. with ototoxicity	-	-	-	-	20	50	80	100	100	100
% of total patients	-	-	-	-	4	10	16	20	20	20

Table 2: Ototoxicity displayed with different regimens used with or without concomitant radiotherapy in relation to gender.

Regimen	No. of pts	No. of patients displaying ototoxicity		Concomitant radiotherapy (RT)		% patients with ototoxicity				
		Male	Female	Yes	No	M	F	Total	With RT	Without RT
CCRT	42	3	1	42	0	7.14	2.38	9.52	9.52	-
NACT	8	7	0	1	6	87.5	-	87.5	12.5	75

Ototoxicity

Baseline audiometry and bithermal caloric tests were performed in all the selected patients. Three frequency pure tone average in both ears ranged from 12 dB to 28.6 dB. Mean pure tone average was 22.54 dB. There was no patient with any vestibular disorder. Pure tone audiometry and bithermal caloric tests were done after each cycle and at 3rd month after completion of treatment. Most of the patients did not have any auditory or vestibular symptoms. However 11 patients (22%) were noted to have ototoxicity (Figure 2). Out of eleven only one patient complained of tinnitus and there was no patient who complained of giddiness (Figure 3). Ten patients developed high frequency hearing loss mainly in the frequency range 6, 8, and 10 KHz and beyond (Table 1, Figure 4).

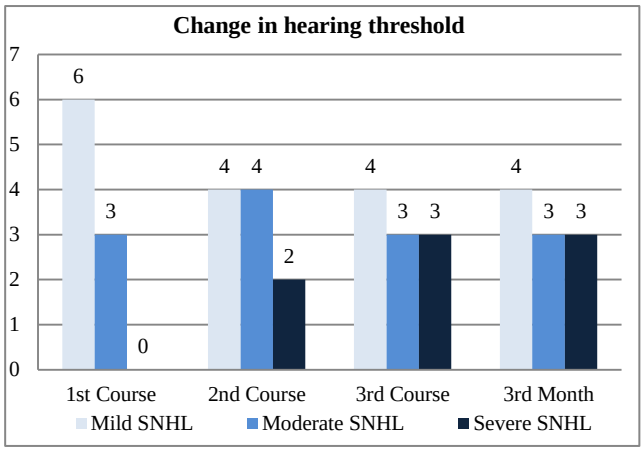

Figure 5: Change in degree of hearing threshold with duration of chemotherapy.

All patients who were noted to have hearing loss, except one, developed hearing loss just after 1st dose. One patient developed hearing loss after 2nd cycle. One patient developed tinnitus after 3rd cycle. 6 patients (12%) developed mild hearing loss after 1st cycle and 3 patients had moderate hearing loss. After 2nd cycle 4 patients (8%) developed mild, 4 (8%) developed moderate high frequency sensorineural hearing loss and 2 had severe high frequency sensorineural hearing loss. After 3rd cycle 4 patients continued to have mild hearing loss, with 3 each had moderate and severe high frequency sensorineural hearing loss. High frequency hearing loss which persisted even after 3rd month follow up after completion of therapy (Figure 5).

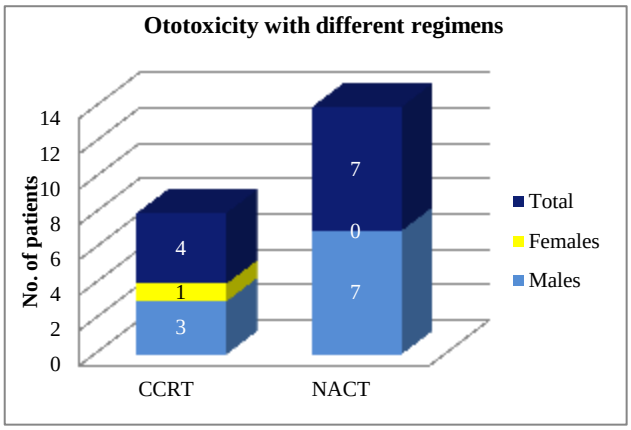

Figure 6: Ototoxicity displayed with different regimens used with or without concomitant radiotherapy in relation to gender.

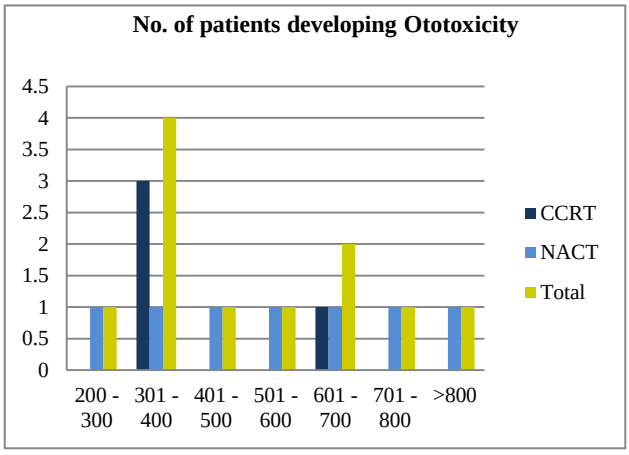

Figure 7: Number of patients developing ototoxicity with respect to cumulative dose of cisplatin.

Regimens used in the patients receiving cisplatin were either concomitant chemo radiotherapy or neoadjuvant chemotherapy with or without radiotherapy. 42 patients (84%) received concomitant chemo radiotherapy. 4 male patients and one female patient developed ototoxicity. Out of 8 male patients receiving Neoadjuvant Chemotherapy, 7 developed ototoxicity (Table 2, Figure 6 and 7).

DISCUSSION

Platinum-based ototoxicity resulting in bilateral high-frequency sensorineural hearing loss and (most commonly permanent) tinnitus occurs in a progressive and dose-dependent manner.[6,7] High frequency hearing sensitivity is usually affected initially, as high frequency regions within the cochlea appear to be more susceptible to cisplatin.[8] With continued exposure to cisplatin, the hearing loss tends to increase in severity and progressively spreads to affect hearing at the lower frequencies associated with speech.[9] Loss of pure-tone sensitivity in the 2 to 4 kHz frequency range results in difficulty discriminating consonant sounds especially when attempting to identify words in the presence of background noise and hearing loss exceeding the 20 dB hearing level (HL) in the speech frequencies impacts family and social interaction as well as work status.[10]

Platinum-based therapy may result in clinical, behavioural and psychological disorders resulting in impairment in functional status, cognitive status, depressive symptomatology and disability.[10]

Various studies have revealed high incidence of irreversible permanent bilaterally symmetric cochlear toxicity with a predilection for involvement of the higher frequencies.[8,11] In our study the patients developed irreversible sensorineural hearing loss involving higher frequencies in both the ears.

Literature has proven that the toxic effect of cisplatin may result in a degeneration of the vestibular organs as well although it is rarely diagnosed.[12,13] In our study there was no patient who had vertigo or nystagmus.

11 patients out of 50 (22%) developed ototoxicity in the form of high frequency hearing loss and tinnitus. 20% of the patients developed hearing loss which was sensorineural, bilateral and predominantly affecting frequencies above 4000Hz. This effect was dose dependent and there was no specific dose threshold below which the incidence of ototoxicity was reduced. This correlates with the literature.[14,15] Higher dosage of Cisplatin (>640 mg/m^2 cumulatie dose) as used in Ca Nasopharynx in form of neoadjuvant chemotherapy produced a higher incidence of ototoxicity than the lower doses; however, it has been noted that mild ototoxicity was reported with moderate doses of cisplatin (430 mg/m^2 cumulative dose).[14,16,17] In our study too mild ototoxicity developed in the patients receiving mean cumulative dose of 350 mg/m^2.

The reported true incidence of cisplatin ototoxicity is variable, ranging from 26% to over 90% due to many treatment and patient-related 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.

At present, the only way to prevent the cisplatin-induced ototoxicity is a limitation of the total dose per cycle, the cumulative dose, and the dose-intensity. Obviously, this might reduce the efficacy of this cytotoxic agent. Therefore, it is important to describe the ototoxicity after cisplatin infusion in different infusion schedules. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity. Moreover, for some patients, it is possible that the drug dosage may be modified. Despite these efforts, ototoxicity will still occur after cisplatin administration.

There is a need for drugs that prevent cisplatin-induced ototoxicity. Nearly all the candidate agents are sulphur- or sulfhydryl-containing compounds (thio compounds), known as antioxidants, and potent heavy metal chelators. The administration of these potential inhibitors could preserve normal glutathione levels and antioxidant enzyme activities during or after cisplatin treatment, which in turn could prevent ototoxicity. The radio- and chemoprotector, amifostine, has also been tried as a protective agent. However, from a clinical perspective it is important that preventive inhibitors do not interfere with the antitumor activity. Even though there have been studies with multiple oto-protective agents, none of these agents have been found to be unequivocally beneficial in preventing cisplatin ototoxicity.[6,9]

The molecular mechanism of ototoxicity has not yet been established fully, and relationships between the structure of cisplatin and the induction of ototoxicity have not been determined. One of the possible causes of ototoxicity could be the formation of the monohydrated complex (MHC), which is present in the circulation of cisplatin-treated patients. MHC is formed by hydrolytic biotransformation of cisplatin and is considered to be one of the important cytotoxic species mediating the reaction with DNA. It is possible that the ionic environment of the inner ear affects the hydrolysis reactions between cisplatin and MHC.[6,18] Another possible cause is the blocking of outer hair cell transduction channels by cisplatin. It is also assumed that cisplatin ototoxicity is related to depletion of glutathione and antioxidant enzymes in the cochlea, which is initiated by the production of reactive oxygen species. These enzymes would protect the cochlea against cisplatin damage and prevent hearing loss. The changes were accompanied by a marked elevation of malondialdehyde.[19,20] There is a need for drugs that prevent cisplatin-induced ototoxicity. Nearly all of the candidate agents are sulphur- or sulfhydryl containing compounds (thio compounds), known as antioxidants and potent heavy metal chelators. The administration of these potential inhibitors could preserve normal glutathione levels and antioxidant enzyme activities during or after cisplatin treatment, which in turn could prevent ototoxicity. However, from a

clinical perspective it is important that the preventive inhibitors do not interfere with the antitumor activity.[20,21]

CONCLUSION

Cisplatin ototoxicity is still considered a clinical problem after several years of use. To reduce the incidence of cisplatin-induced hearing loss efforts should be aimed at the development of methods for prediction of susceptible individuals and oto-protection. A significant number of patients in this study developed ototoxicity (22%). 10 out of 50 (20%) patients developed irreversible bilateral high frequency sensorineural hearing loss while one developed tinnitus (2%). The patients receiving higher cumulative dosages of cisplatin of more than 300 mg/m^2 had greater chances of developing ototoxicity. Regular and early audiometric evaluation and follow up of patients could detect the ototoxicity. At present, the only way to prevent cisplatin-induced ototoxicity is a limitation of the total dose per cycle, the cumulative dose, and the dose-intensity. Obviously, this might reduce the efficacy of this cytotoxic agent. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity. Moreover, for some patients, it is possible that the drug dosage may be modified or cisplatin be substituted with other oto-safe platinums like carboplatin or oxaliplatin. Despite these efforts, ototoxicity will still occur after cisplatin administration.

It is recommended that hearing assessment, including pre-treatment and post treatment audiometry, be performed in all patients undergoing combined platinum-based chemotherapy and radiation for the treatment of head and neck cancer.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dwivedi G, Kumar M, Gupta V, Sood A, Patnaik U. A clinical study of cisplatin induced ototoxicity in head and neck malignancies. Int J Otorhinolaryngol Head Neck Surg 2019;5:1044-51.