Original Article

Auditory function and quality of life in patients receiving cisplatin chemotherapy in head and neck cancer: A case series follow-up study

ABSTRACT

Background: Cisplatin is one of the anticancer drugs used for head and neck cancers. Although some studies have shown that cisplatin can cause ototoxicity, periodic audiometric assessments have not been extensively studied in the Indian rural population. Hence, this study has been undertaken to evaluate the effects of cisplatin on hearing.

Materials and Methods: Fifty-nine patients with squamous cell carcinomas of head and neck, who received cisplatin chemotherapy, were recruited. Serum creatinine, blood urea, serum proteins, and audiometry were assessed before and after the first, second, and third chemotherapy cycle. The cochleotoxic effect of cisplatin was assessed by pure tone audiometry. Hearing loss was graded accordingly. All patients were administered a quality of life questionnaire at baseline and at the end of the third cycle.

Results: Hearing loss was observed in 12 patients at speech frequencies and those at higher frequencies were 12 (4000 Hz), 18 (6000 Hz), and 28 (8000 Hz). The hearing loss was symmetrical, sensorineural, and showed a strong correlation with the low serum albumin levels at the end of the third cycle. Dizziness was seen in eight patients, at the end of the study. The commonly observed adverse effects were nausea, vomiting, hair loss, fatigue, and tinnitus.

Conclusion: The studies have shown hearing loss in higher frequencies, but in our study, we have observed hearing loss at speech frequency in 22.2% of patients receiving cisplatin, who also had low serum albumin levels. Periodic audiometric monitoring and serum albumin level may be helpful to provide timely intervention to prevent further hearing loss and deterioration in the quality of life.

KEY WORDS: Audiometry, cisplatin, hearing loss, serum albumin

Balamurali Kalyanam, N. Sarala, S. M. Azeem Mohiyuddin[1], Ravi Diwakar[2]

Departments of Pharmacology, [1]Otolaryngology and Head and Neck Surgery and [2]Medical Oncology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India

For correspondence:
Dr. N. Sarala, Department of Pharmacology, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka, India.
E-mail: n_sarala@rediffmail.com

INTRODUCTION

Over one-third of all cancers in India occur in the head and neck region, and the vast majority of head and neck cancers are squamous cell carcinomas.[1,2] The commonly employed strategies for improving outcome in squamous cell carcinomas of head and neck (SCCHN) is chemo-radiotherapy, although chemotherapy, not considered curative by itself, can be used to enhance the effect of radiotherapy, and can also be a palliative measure.[3]

Cisplatin, one of the earliest developed platinum-containing anticancer drug,[2] inhibits tumor growth by interfering with DNA synthesis. Although some studies have shown that cisplatin can cause ototoxicity,[4] the exact degree, time of onset and relation to the dosage schedule, duration of chemotherapy, and periodic audiometric assessments have not been extensively studied in the Indian rural population. The etiology for this is not clearly known, differences in pharmacokinetics, genetic factors and metabolic status of the individual could be a possibility. As there is a paucity of data on audiometric monitoring during cisplatin chemotherapy, its relation to dosage schedule, protein level, the present study was undertaken.

MATERIALS AND METHODS

This study was conducted by the Departments of Pharmacology, Otolaryngology Head and Neck

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Surgery and Medical Oncology. The study protocol was approved by the Institutional Ethics Committee, and informed consent was obtained from the patients. Patients with SCCHN, receiving cisplatin therapy after surgery, were recruited for the study. The duration of the study was for 1½ years.

The primary objectives were to study the auditory functions in patients receiving cisplatin for head and neck cancer, establish a relationship between serum albumin levels and ototoxicity and assess the quality of life in these patients. Inclusion criteria were patients of either gender, above 40 years with SCCHN receiving cisplatin, cisplatin with 5-flurouracil, and the combination of radiotherapy and cisplatin. We excluded patients with a history of acoustic/noise induced trauma, those receiving ototoxic drugs (such as aminoglycosides, cyclosporine), kidney disorders, hypersensitive to cisplatin, and pregnant and lactating women.[5]

The patients' demographic details, history, clinical examination, hearing (tuning fork tests) and vestibular functions were assessed and recorded. Their serum creatinine, blood urea, serum albumin, and audiometry tests were done at baseline, i.e., after surgery and radiotherapy but before administration of chemotherapy and repeated after each chemotherapy cycle. The dose of cisplatin and 5-flurouracil was calculated based on the body surface area and administered, patients were followed up after the first, second, third cycle of chemotherapy during which they were asked for symptoms such as hearing loss, tinnitus, and vertigo.[6]

The ototoxic (cochleotoxic) effects of cisplatin were assessed by pure tone audiometry (PTA) at conventional audiometric frequencies (125, 250, 500, 1000, 2000, 4000, and 8000 Hz), 4 times per patient; the first at baseline before starting cisplatin and repeated 2 weeks after the completion of each cycle. Increase by 10 dB in the speech frequencies (Fisher scale– 500, 1000 and 2000 Hz) and an increase of 20 dB at higher frequencies from the baseline were considered statistically significant. The patients who complained of vertigo or dizziness were administered a Dizziness Handicap Index (DHI) questionnaire. This assessed the incapacities in physical, functional, and emotional areas of a patient's life. DHI has an allotment of 28 points (7 items) for the physical aspect, 36 points (9 items) for each of the functional and emotional aspect. The answers were scored as "0" for "no" (absence of symptoms), 2 for "sometimes" (occasional symptoms), and 4 for "yes" (severe symptoms). Thus, the minimum punctuation would be 0 points, and the maximum would be 100. These scores were later classified as 16–34 points (mild handicap), 36–52 points (moderate), and 54+ points (severe).

All patients were administered a modified European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30 before chemotherapy, and at the end of the third cycle. This consisted of 10 questions which evaluated physical functioning (pain in the mouth, lacked appetite, and diarrhea), emotional functioning (feeling of depression), social functioning (contact with family), and financial functioning (family support).[7] This was rated on a scale of 1 (not at all) to 4 (very much). The minimum and maximum score on this scale were 10 and 40, respectively.

Statistical analysis

The sample size was calculated by considering the incidence of hearing loss to be 6% in the general population and a sample proportion of 15% with power of the study fixed at 80% and an α error of 5%. With a dropout rate of 10%, the required sample was found to be 59 patients. Continuous variables were presented as mean ± standard deviation and categorical as percentage (%). Variables within the group and between the groups were analyzed by paired *t*-test and unpaired *t*-test. Pearson's correlation was used for establishing correlation between serum albumin and hearing loss. The quality of life scale was assessed using Wilcoxon Signed-rank test. $P \leq 0.05$ was considered statistically significant. The statistical tests were done with SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 59 patients clinically diagnosed with SCCHN by the oncologists were recruited. Patients received three cycles of radiotherapy with 15 Gy, with a minimum gap of 1 week, before starting chemotherapy, and then the baseline parameters were taken. Fifty-six patients received only cisplatin and three cisplatin with 5-fluorouracil. 54/59 completed three cycles of chemotherapy, rest five were lost to follow-up, hence were included only for demographic analysis. There were 26 males with and 33 female patients with the mean age of the patients being 54.94 ± 8.11 years. Patients having cancer of the buccal mucosa were 21 (35.6%) and maximum in number, among them majority were females (18), whereas the cancers of the supraglottis (10) and oropharynx (3) were seen only in males. The different doses of cisplatin that were administered per cycle were 40 mg, 50 mg, 60 mg and 70 mg and the numbers of patients who received the following doses were 2, 55, 1, 1. Fifty-four patients who received a dose of 50 mg per cycle only completed the study.

However, the serum creatinine value at baseline was 0.91 ± 0.23 mg/dl which changed to 0.96 ± 0.21 mg/dl at the end of the third cycle of chemotherapy; this change was not statistically significant.

The hemoglobin level in patients who had a significant hearing loss at Fisher's scale was 9.91 ± 1.37 g% and in those who had no significant hearing loss at Fishers scale was 11.71 ± 1.56 g%. This difference was statistically significant ($P = 0.001$).

There was a significant worsening of the quality of life as shown by the increased scores after the third cycle of chemotherapy. The mean baseline score was 22.00 ± 4.44 and

after the third cycle of chemotherapy it was 24.37 ± 4.44, this was statistically significant ($P = 0.001$). The minimum and maximum score on this scale were 10 and 40, respectively. The vestibulotoxicity was assessed using the DHI score, only in those patients who complained about dizziness during follow-up. The scores of 8/54 who complained of dizziness are as follows; two patients had a mild handicap (score 16–34), four moderate handicap (score 36–52), and two severe handicap (score 54+).

The most commonly seen adverse effects to cisplatin therapy were nausea and vomiting, seen in 43 patients followed by fatigue (39), hair loss (38), tinnitus (36), diarrhea (13), numbness in fingers (7), rashes (5), melena (5), generalized itching (3), and jaundice (1).

DISCUSSION

In the present study, 59 patients with SCCHN region were recruited. Cancer of buccal mucosa was found to be more in females, probably due to increased incidence of chewing tobacco. All the patients were given three cycles of chemotherapy succeeding radiotherapy with 15 Gy. Although radiation can induce sensorineural hearing loss, it develops by 6–12 months, and it is a dose-related phenomenon which affects hearing only in doses >50–60 Gy.[8] Patients who underwent radiation had their ipsilateral temporal bone and ear protected by beam modification devices (shielding block made up of lead) to avoid the effect of radiation on hearing.

Our study involved patients only above the age of 40 years. As there was only one adult in this study with moderate hearing loss in both ears at baseline, the effect of preexisting hearing loss is not being addressed here as literature offers no clear consensus. However, Kopelman *et al*. described the "plateau" effect.[9] According to this effect in the presence of preexisting hearing loss, administration of cisplatin chemotherapy will not worsen hearing at frequencies between 3000 Hz and 8000 Hz and hearing impairment of 40–60 dB. This is explained by the fact that once all outer hair cells (OHCs) of cochlea have been destroyed there can be no further hearing loss expected by subsequent administration of cisplatin. In our study, three patients who had received a cumulative dose of 150 mg/m^2 showed this effect.

Cisplatin binds to serum albumin and only unbound form is active. It may be reasonable to assume that low protein binding of the drug may be responsible for greater toxicity which occurs at low serum albumin levels[10] [Table 1]. All patients had undergone routine urine analysis to rule out albuminuria. The reasons for the decreasing albumin levels could possibly be attributed to intolerance to chemotherapy.

Fisher's scale refers to the average of the decibel levels at 500 Hz, 1000 Hz, and 2000 Hz, which is important for perceiving speech. In PTA as per [Table 2 and Figures 1, 2] it was observed that in the Fisher's scale, there was a shift in the mean decibel level in both ears from the baseline to a higher value. Although many of our patients had insignificant changes in the decibel levels from baseline, 12 (22.2%) patients had significant hearing loss in the Fisher's scale and at 4000 Hz, 6000 Hz, and 8000 Hz [Table 3]. Among the 28 patients who had hearing loss at 8000 Hz, three of them had maximum hearing loss, their hearing threshold after the third cycle was between

Table 1: Albumin levels at baseline and follow-up visits

Albumin	Range	Mean±SD	*P*
Baseline	2.90-5.90	3.85±0.54	-
Cycle 1	2.70-5.00	3.75±0.51	0.086
Cycle 2	2.50-5.10	3.63±0.49	0.005†
Cycle 3	2.10-4.90	3.53±0.50	0.005‡

†Second and ‡Third cycle values compared with baseline. SD=Standard deviation

Table 2: Pure tone audiometric findings in the right ear and left ear

	Range	Mean±SD	*P*
Right ear			
Baseline	13.33-50.00	22.48±8.53	-
Cycle 1	15.00-50.00	23.51±8.53	0.002*
Cycle 2	15.00-60.00	26.22±9.70	<0.001†
Cycle 3	15.00-63.33	29.53±11.70	<0.001‡
Left ear			
Baseline	11.60-45.00	23.23±9.02	-
Cycle 1	13.33-45.00	24.13±8.86	0.002*
Cycle 2	13.33-65.00	27.00±10.36	<0.001†
Cycle 3	13.33-75.00	30.95±13.30	<0.001‡

*First, †Second, and ‡Third cycle values compared with baseline. The hearing loss was expressed in decibels as shown in Table 2. There was progressive and significant worsening of hearing in the right and left ears after every cycle of chemotherapy. SD=Standard deviation

Table 3: Hearing loss at different frequencies

Frequency	Significant (%)	Nonsignificant (%)
Fisher's scale	12 (22.2)	42 (77.8)
4000 Hz	12 (22.2)	42 (77.8)
6000 Hz	18 (33.3)	36 (66.7)
8000 Hz	28 (51.8)	26 (48.2)

Increase in the number of patients showing high frequency (6000 and 8000 Hz) hearing loss

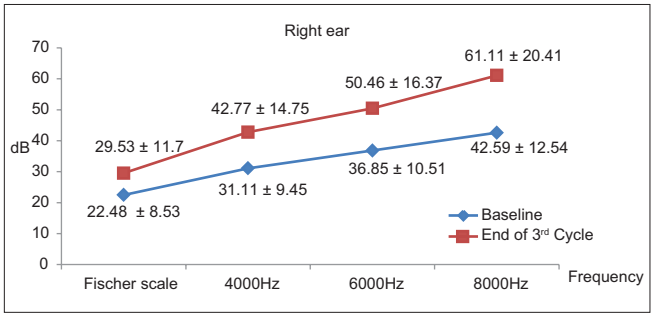

Figure 1: Mean decibel level of the right ear at the corresponding frequencies at baseline and the end of the third cycle of chemotherapy. There is an increase in the mean decibel level from baseline to postchemotherapy assessment at all the frequencies, maximum being at 8000 Hz (18.52 dB)

81 and 100 dB in both ears. These observations [Tables 3 and 4] were comparable to the studies by Laurall *et al.*, who reported hearing loss in 22% patients at 4000–6000 Hz and Fausti *et al.*, who found significant high-frequency (>8000 Hz) hearing loss in 71% patients.[11]

In our study, we found that cisplatin-induced ototoxicity begins at high frequencies and then involves the lower frequencies; the hearing loss was bilateral, symmetrical and sensorineural. It typically affects the ultra-high frequency (9000 Hz–16,000 Hz) first, but we have restricted the assessment in this study to <8000 Hz. Cisplatin ototoxicity appears rather quickly after drug administration and is fairly stable after 3 days.[12] However, the recovery of strial function and cochlear electrophysiology takes a considerably longer time.[13] The specific action of cisplatin on the inner ear may be related to the small size of the molecule enabling it to cross the blood-labyrinth barrier or the fact that cisplatin is not cell-cycle specific and thus can affect even the nondividing cells of the inner ear such as the OHCs. Furthermore, mitochondria which are common in the OHCs and the metabolically active stria vascularis are known to be important cellular targets for cisplatin.

The association of serum albumin level with hearing loss was established by applying Pearson's correlation coefficient. The serum albumin and hearing loss were found to have an inverse correlation in both ears [Table 5]. This fact is congruent with the study by Blakely *et al.* which assessed the association between albumin and cisplatin.[13] This correlation was found to be stronger and significant after the third cycle of cisplatin chemotherapy [Table 5]. By applying logistic regression, we have found that the level of albumin is the salient factor affecting hearing in patients receiving cisplatin ($P = 0.01$). However, it can be hypothesized that low serum albumin level means that fewer binding sites are available so that more cisplatin is in the free form. A coincidental finding in our study was the significant difference in the hemoglobin level between the patients who had a significant hearing loss at Fisher's scale ($n = 12$) and those who did not have a significant hearing loss at Fisher's scale ($n = 42$). This decrease in hemoglobin value could also contribute to increased ototoxicity. The synthesis of hemoglobin requires globular proteins, low levels of albumin may alter protein synthesis, and may adversely affect the hemoglobin production further studies may be required to establish this. It may be hypothesized that the ability of the blood to carry oxygen is decreased, rendering the inner ear more susceptible to damage as show by Blakely *et al.*[14] The involvement of the vestibular organ in cisplatin-induced ototoxicity in humans has been controversial.[14] In our study, 8 out of 54 patients had dizziness which could indicate vestibulotoxicity and needs further monitoring and testing.

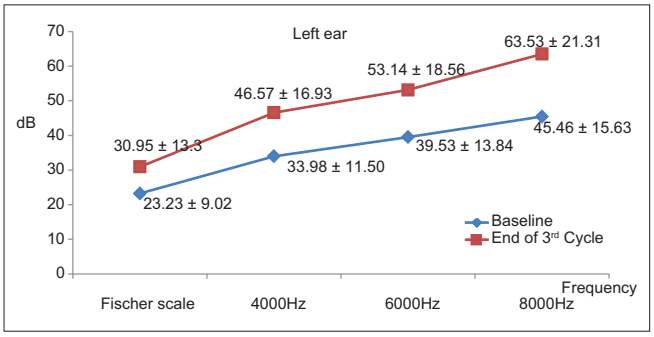

Figure 2: Mean decibel level of left ear at the corresponding frequencies at baseline and the end of the third cycle of chemotherapy. There is an increase in mean decibel level from baseline to post chemotherapy assessment at all frequencies, maximum being at 8000 Hz (18.05 dB)

Finally, for patients undergoing cisplatin chemotherapy the predicted hearing loss was calculated using baseline albumin levels [Table 6]. This can help patients in the future as we have found that if the baseline albumin levels are low; then, there is a higher possibility of hearing loss in speech frequencies. There are studies which show hearing loss in higher frequency, but in our study, we have observed hearing loss at speech frequencies in 22.2% of patients undergoing cisplatin chemotherapy. This is an important aspect which has to be considered seriously because this will affect their day-to-day activities and also may deteriorate the quality of life. This finding was observed at the end of the third cycle of chemotherapy, so intervention at this juncture is essential [Figure 3a and b]. It can be in the form of increasing the interval between the cycles, allowing the albumin level to

Table 4: Data with respect to total number of ears (*n*=108) tested (total number of patients=54)

Frequency (Hz)	Follow-up	0-20 (dB)	21-40 (dB)	41-60 (dB)	61-80 (dB)	81-100 (dB)
4000	Baseline	14	80	12	2	-
	End of third cycle	10	42	44	9	3
6000	Baseline	9	68	26	5	-
	End of third cycle	7	31	40	27	3
8000	Baseline	7	47	39	14	1
	End of third cycle	5	20	29	35	19
Fisher scale	**Follow-up**	**0-25 (dB)**	**26-40 (dB)**	**41-55 (dB)**	**56-70 (dB)**	**71-90 (dB)**
	Baseline	78	24	6	-	-
	End of third cycle	43	48	12	4	1

Mean baseline hearing threshold tested at all frequencies was 34.5 dB which increased to 46.5 dB after the third cycle of chemotherapy. Toward the end of the third cycle of chemotherapy an increase in the number of ears with mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), and severe (71-90 dB) hearing loss were observed. None had profound hearing loss in either ear (i.e., >91 dB)

return to normal or infusing proteins and reducing cisplatin dose without compromising the efficacy.

Cisplatin is known to cause nephrotoxicity, and it has been the major reason for renal dysfunction in patients receiving it. In our study, the practices of hydration and administration of mannitol were used along with resumption of chemotherapy only on return of the renal parameters (serum creatinine, blood urea) to normal values, which helped in reducing the incidence of renal dysfunction [Table 7]. Although there have been, the studies testing the efficacy of the reducing agent Ethiofos (WR2721) to decrease the incidence of renal toxic reactions it failed when it came to reducing ototoxicity.[15]

Persistent nausea, vomiting, fatigue, hair loss, and tinnitus were the frequently seen adverse effects. As cisplatin is a highly emetogenic drug, nausea and vomiting induced by it was treated using ondansetron in a dose of 8 mg intravenous (i.v.) (0.15 mg/kg) or granisetron 1 mg i.v. (0.01 mg/kg). These antiemetics were given along with 20 mg of dexamethasone as dexamethasone has a major role in the prevention of acute and delayed chemotherapy-induced nausea and vomiting.[16]

Hair loss as seen in our study was a consequence of direct toxic insult on the rapidly dividing cells of the hair follicle.[16] Cisplatin-induced ototoxicity was present with transient or permanent tinnitus and showed high inter-individual variability. Exact etiopathogenesis of even the high inter-individual variability is unknown, but the differences in genetic factors and metabolic status of the individuals are implicated.[17]

Fatigue was seen in 39 patients. This could be due to many reasons such as fall in hemoglobin levels, diarrhea or stress, and by a lesser-known mechanism contributing to cancer-related fatigue involving abnormalities in adenosine triphosphate synthesis caused by carnitine deficiency as a result of cisplatin chemotherapy.[17]

Table 5: Correlation of serum albumin with hearing loss (*n*=12)

Parameters	Right ear	*r*	Left ear	*r*
Baseline albumin	0.16	−0.452	0.42	−0.271
Third cycle albumin	0.03*	−0.649	0.01*	−0.701

**P*=0.03 and 0.01 implies significance. Twelve patients, who suffered hearing loss in Fisher's scale at the end of the third cycle of chemotherapy, correlation between low albumin levels and hearing loss in these patients was weak at baseline but became stronger and significant at end of the third cycle of chemotherapy

Table 6: Equation to predict the hearing loss based on baseline albumin levels

	Prediction equation	*r*	*P*
Baseline	Hearing loss=48.15-6.72 × baseline albumin	−0.379	0.005**
Chemotherapy			
Cycle 1	Hearing loss=54.42-7.91 × baseline albumin	−0.492	0.001**
Cycle 2	Hearing loss=58.27-7.54 × baseline albumin	−0.532	0.001**
Cycle 3	Hearing loss=60.14-8.80 × baseline albumin	−0.539	0.001**

***P*=0.005 and 0.001 implies significance. The linear equation with different constants as per the number of chemotherapy cycles and albumin level. If baseline albumin is known, then the expected hearing loss can be predicted using the above equation

Table 7: Levels of blood urea at baseline and follow-up visits

Blood urea	Range (mg/dl)	Mean±SD (mg/dl)	*P*
Baseline	11.00-43.00	23.83±6.28	-
Cycle 1	14.00-50.00	26.14±7.36	0.029*
Cycle 2	15.00-71.00	27.66±7.94	0.001†
Cycle 3	16.00-51.00	28.05±6.66	0.001‡

*First, †Second, and ‡Third cycles values compared with baseline. The blood urea levels showed a progressive increase after every cycle of chemotherapy, which is statistically significant when compared to baseline

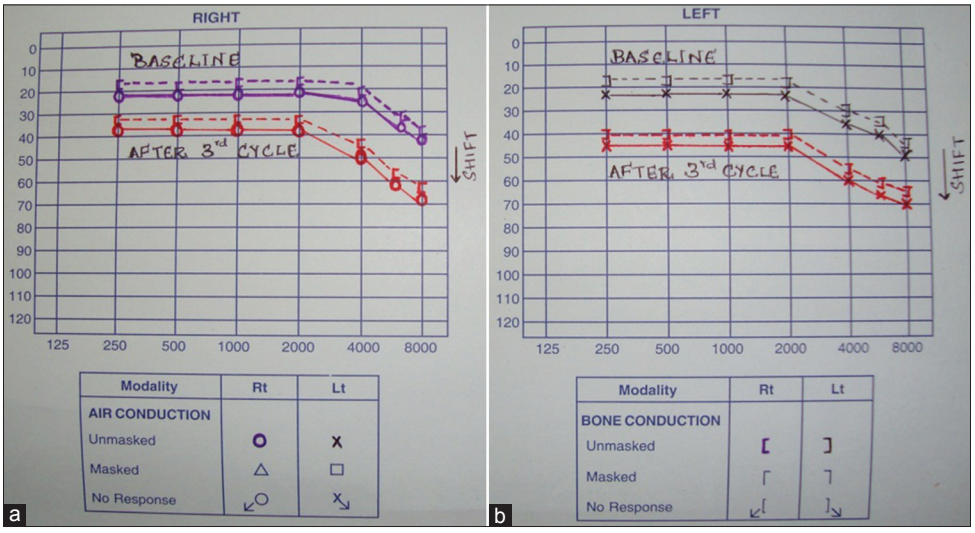

Figure 3: (a and b) Audiogram of a 50-year-old patient. Audiogram shows increase in decibel levels at all frequencies after the third cycle of chemotherapy. Pure tone audiometry value has increased from 20 dB to 40 dB and 25 dB to 45 dB in the right and left ear, respectively

Patients also experienced physical symptoms such as persistent soreness in the mouth, difficulty in swallowing food, and financial problems such as funding their treatment. Lack of prolonged family support added to the worsening of quality of life score. The adverse effects of cisplatin as mentioned above also led to the worsening of quality of life.

CONCLUSION

Cisplatin though discovered in 1970, still continues to be one of the common drugs effective in treatment of malignancies. Most of the treating physicians are well aware of the nephrotoxicity associated with it and also take precautions to check the renal status before drug administration. Other measures to minimize nephrotoxicity by administering fluids and diuretics are also followed. Similarly, the oncologists should anticipate, evaluate, and intervene to minimize the ototoxicity produced by cisplatin. Monitoring the auditory functions can be helpful in detecting hearing loss at an early stage and also adopting other preventive measures such as reducing the dose or substituting cisplatin with carboplatin/oxaliplatin can be done. Therefore, pretreatment and periodic audiograms should be done in patients receiving cisplatin. As patients with malignancy have to face a lot of mental agony and stress related to the disease, simple measures such as audiometric testing at high and speech frequencies can assure them a better life to lead in their battle against malignancy.

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Conflicts of interest

There are no conflicts of interest.

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