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Original Article

Clinical Evidence of Hearing Loss in Patients Treated with Cisplatin for Head-and-Neck Squamous Cell Carcinomas

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Abstract

Background: Cisplatin is a chemotherapeutic agent that is widely used to treat a variety of malignant tumors. Serious dose-limiting side effects such as ototoxicity, nephrotoxicity, and neurotoxicity are likely to occur with its use.

Aim of the study: The aim of the study was to do audiological evaluation of patients on cisplatin before and after chemotherapy for squamous cell carcinomas of head and neck and analyze for hearing loss (HL).

Materials and Methods: A total of 46 patients undergoing cisplatin administration were included in the study. History taking, preliminary ENT examination, and audiological evaluation with pure-tone audiometry were done. A pure-tone average (PTA) was calculated using the speech frequencies (500, 1000, and 1500 kHz). High-frequency pure-tone audiometry was also done in all patients to know the basal auditory threshold before starting cisplatin therapy. Baseline audiometry was done Prior to Chemotherapy or at least 24 h after administration of Cisplatin. Monitoring audiometry was done before each cycle of Cisplatin therapy. Follow-up audiometry was done 1, 3, and 6 months after chemotherapy. Dosage of cisplatin ranged from 50 mg to 115 mg with cumulative dose ranging from 250 mg to 850 mg in all the patients. All the data were analyzed using standard statistical methods.

Observations and Results: Among 46 patients, there were 33 males and 13 females (28.26%) with a male-to-female ratio of 2.53:1. Patients were aged between 45 years and 70 years and the mean age was 55.35 ± 2.70 years. 22/46 (47.82%) patients were in the range of 55–65 years age group followed by 15/46 (32.60%) patients who were in the 45–55 years age group. 9/46 (19.56%) patients were in the 65–75 years age group. Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz.

Conclusions: In this study, all the patients showed significant evidence of severe mixed type of HL. The HL was significant in all the age groups and in both the genders. Six months follow-up showed no recovery of HL presumable resulting in permanent HL. Very few patients showed vestibular involvement. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity.

Key words: Cisplatin, Cochlea, Ototoxicity, Sensorineural Loss and Pure-tone Audiometry

INTRODUCTION

Hearing loss (HL) observed after the usage of cisplatin chemotherapy appears to be varying with different patients. It appears to be dose related and also depends on age, noise exposure, nutritional status, anemia, low serum albumin, and concurrent radiation to head-and-neck region.[1-3] HL is usually permanent and bilaterally symmetrical.[1] Apart from HL patients also complain of pain in the ear and tinnitus.[4] The prevalence of tinnitus among cisplatin used patients was 2–36% in the study by Reddel *et al.*[4] High-frequency thresholds are usually affected first followed by middle frequencies when doses in excess of 100 mg/m^2 are used.[2] Reports of dose-related HL in 20% of men in whom cisplatin was used for testicular carcinomas are available in literature.[1] Very high doses of cisplatin >400 mg/m^2 were found to be associated with permanent HL.[1] Patients with

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nasopharyngeal carcinoma appear to be very susceptible to the interaction of cisplatin chemotherapy with cochlear irradiation. Radiation doses greater than 48 Gy increased the HL in these patients.[5] However, radiation therapy to the head-and-neck region with intensity-modulated radiation therapy as for brain tumors, such as medulloblastoma, can be modified using to reduce the doses of radiation to the cochlea.[6] A recent study showed that patients receiving <40 Gy radiations for head-and-neck malignancies did not suffer from HL, but when these patients received additional cisplatin as chemotherapy high-frequency HL was noted. At the end of the therapy, only 5% of patients showed HL on audiograms, but follow-up of these patients for more than 2 years revealed HL in more than 44% of the patients.[7] Additional follow-up for 6–44 months showed mild further progression of HL of 10–15 dB after completion of therapy.[8] The American Speech–Language–Hearing Association[9] recommends cost-effective ototoxicity identification for any population receiving ototoxic medication. The following should be considered: "(1) The patient's level of alertness or ability to respond reliably; (2) the most appropriate times during the treatment protocol for test administration; and (3) the test should comprise the baseline, monitoring, and post-treatment evaluations."[10] In this context, a clinical study was undertaken by conducting audiological evaluation of patients undergoing combined or adjuvant chemotherapy using cisplatin for the treatment of head-and-neck squamous cell carcinomas.

MATERIALS AND METHODS

A cross-sectional prospective and analytical study was conducted by including 46 patients who were undergoing cisplatin administration used as concurrent to radiotherapy or adjuvant chemotherapy in a tertiary teaching hospital of Telangana. An institutional ethical committee clearance was obtained before the commencement of the study. An ethical committee cleared consent letter was used for the study.

Inclusion Criteria

(1) Patients who were diagnosed as squamous cell carcinoma of head-and-neck region were included. (2) Patients receiving cisplatin as one of the drugs in chemotherapy were only included. (3) Patients undergoing concurrent radiotherapy were included. (4) Patients undergoing adjuvant chemotherapy were included.

Exclusion Criteria

(1) Patients who are debilitated with malignancy were excluded. (2) Patients with earlier ear pathology were excluded. Patients with sensorineural deafness were excluded. (3) Patients with uncontrolled diabetes mellitus, hypothyroidism, and renal failure were excluded. All the patients were subjected to thorough history taking, preliminary ENT examination, and audiological evaluation with pure-tone audiometry which were done. The patients were questioned about hearing impairment; tinnitus or vertigo before and after chemotherapy, and a record was created. A pure-tone average (PTA) was calculated using the speech frequencies (500, 1000, and 1500 kHz). High-frequency pure-tone audiometry was also done in all patients to know the basal auditory threshold before starting cisplatin therapy. The pure-tone audiometry was repeated after every cycle of chemotherapy with cisplatin that is at the end of the 1st, 2nd, and 3rd cycles. An appropriate time interval for audiological assessments depending on the frequency and dose of cisplatin was undertaken. Baseline audiometry was done Prior to Chemotherapy or at least 24 h after administration of Cisplatin. Monitoring audiometry was done before each cycle of Cisplatin therapy. Follow-up audiometry was done 1, 3, and 6 months after chemotherapy. Dosage of cisplatin ranged from 50 mg to 115 mg with cumulative dose ranging from 250 mg to 850 mg in all the patients. All the data were analyzed using standard statistical methods.

OBSERVATION AND RESULTS

A total of 46 patients who were undergoing cisplatin administration used as concurrent to radiotherapy or adjuvant chemotherapy in a tertiary teaching hospital of Telangana. Among the 46 (71.73%) patients, there were 33 males and 13 females (28.26%) with a male-to-female ratio of 2.53:1. Patients were aged between 45 years and 70 years and the mean age was 55.35 ± 2.70 years. 22/46 (47.82%) patients were in the range of 55–65 years age group followed by 15/46 (32.60%) patients who were in the 45–55 years age group. 9/46 (19.56%) patients were in the 65–75 years age group [Table 1].

Patients in the age group of 65–75 years showed HL with mean PTA values of 55.65 ± 2.20 when compared to basal audiometry values of 34.50 ± 2.85 dB which was

Table 1: The age, gender incidence, and basal audiometry (PTA) findings of the study group (*n*=46)

Age group in years (%)	Male–33 (71.73%)	Female–13 (28.26%)	Basal audiometry (mean and SD of PTA)
45–55–15 (47.82)	11 (23.91)	4 (8.69)	22.45±2.15 dB
55–65–22 (32.60)	16 (34.78)	6 (13.04)	26.30±2.10 dB
65–75–9 (19.56)	6 (13.04)	3 (6.52)	33.45±2.85 dB

SD: Standard deviation, PTA: Pure-tone average

statistically significant with $P = 0.012$ ($P < 0.05$). Patients in the age group of 55–65 years showed HL with mean PTA values of 50.25 ± 4.30 when compared to basal audiometry values of 25.60 ± 2.10 dB which was statistically significant with $P = 0.035$ ($P < 0.05$). Patients in the age group of 45–55 years showed HL with mean PTA values of 45.25 ± 2.15 when compared to basal audiometry values of 24.35 ± 2.15 dB which was statistically significant with $P = 0.041$ ($P < 0.05$) [Table 2].

Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz. The actual mean air conduction values are shown in Table 3.

Among the 46 patients, three patients complained of tinnitus after the 1st cycle of cisplatin therapy. Two patients complained or vertigo after the 2nd cycle that was treated with medical management. The cumulative dose of cisplatin was ranging from 225 mg to 800 mg/m^2.

DISCUSSION

Ototoxicity due to cisplatin is well recorded in literature but neglected by both the patients and the physicians unless the severity of HL impairs the daily activities of the patient. The HL is of bilateral nature and involves both the speech frequencies and high frequencies equally. The HL is also permanent in nature.[11,12] The high-frequency loss may be due to susceptibility of basal turn of cochlea to cumulative concentration of the drug cisplatin.[1] It is postulated that initially the higher frequencies are affected first; later, progressively, the speech frequencies are affected resulting in the subject's hearing capabilities.[13] Rise in thresholds of speech frequencies results in difficulty in discriminating the consonant sounds of the speech, especially in ambient noise.[14] HL in speech frequencies would result in clinical, behavioral, and psychological disorders resulting in impairment in functional status, cognitive status, depressive symptomatology, and disability.[13] There are many studies in literature revealing the high incidence of permanent, and irreversible high-frequency bilateral symmetrical loss in patients administered cisplatin for various malignancies.[4,7-10] In the present study, patients in the age group of 65–75 years showed HL with mean PTA values of 55.65 ± 2.20 when compared to basal audiometry values of 34.50 ± 2.85 dB which was statistically significant with $P = 0.012$ ($P < 0.05$). Patients in the age group of 55–65 years showed HL with mean PTA values of 50.25 ± 4.30 when compared to basal audiometry values of 25.60 ± 2.10 dB which was statistically significant with $P = 0.035$ ($P < 0.05$). Patients in the age group of 45–55 years showed HL with mean PTA values of 45.25 ± 2.15 when compared to basal audiometry values of 24.35 ± 2.15 dB which was statistically significant with $P = 0.041$ ($P < 0.05$). Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz. Literature also shows that the vestibular end-organ degeneration following the use of cisplatin,[4,15] but in this study, there only three patients who complained of tinnitus and two patients who complained of vertigo. Tinnitus is reported to occur in a progressive and dose-dependent manner.[11,12] In the present study, it was observed that patients who were diagnosed as carcinoma nasopharynx and underwent concurrent radiotherapy were administered high doses of cisplatin >640 mg/m had severe HL when compared to other malignancies. This can be explained as the same patients were subjected to curative doses of radiotherapy also resulting in severe HL. 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

Table 2: The audiological evaluation before and after cisplatin chemotherapy (*n*=46)

Age group	Basal audiometry (mean and SD of PTA)	Audiometry after the 1st month cycle: Mean and SD PTA	Audiometry after the 3rd month cycle: Mean and SD PTA	Audiometry after the 6th month cycle: Mean and SD PTA	*P*-value
45–55 years	24.35±2.15 dB	31.55±3.25	39.42±3.30	45.25±4.10	0.041
55–65 years	25.60±2.10 dB	39.10±4.15	42.75±3.55	50.25±4.30	0.035
65–75 years	34.50±2.85 dB	46.25±4.20	51.40±4.60	55.65±2.20	0.012

PTA: Pure-tone average

Table 3: The mean air conduction thresholds of high frequencies on audiometry (*n*=46)

Age group	3000 kHz	4000 kHz	5000 kHz	6000 kHz	8000 kHz	10,000 kHz	12,000 kHz
45–55 years	35.30±2.10	38.20±2.15	42.30±2.85	48.55±3.10	50.45±2.60	52.35±2.30	55.30±1.75
55–65 years	38.10±1.30	44.55±3.65	49.45±3.90	53.30±1.85	54.20±1.35	56.35±2.25	58.95±2.30
65–75 years	40.50±1.70	45.30±2.85	51.50±2.80	55.20±2.95	56.20±3.10	57.10±1.50	59.10±3.05

the drug dosage may be modified. Despite these efforts, ototoxicity will still occur after cisplatin administration.

CONCLUSIONS

In this study, all the patients showed significant evidence of severe mixed type of HL. The HL was significant in all the age groups and in both the genders. Six months follow-up showed no recovery of HL presumable resulting in permanent HL. Very few patients showed vestibular involvement. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity.

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