Main Article

STUDY OF THE EFFECTS OF CHEMOTHERAPY ON AUDITORY FUNCTION

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Chemotherapeutic agents are known to cause multiple toxicities such as myelotoxicity, nephrotoxicity and ototoxicity. A prospective study was carried out on 60 patients receiving Cisplatin based chemotherapy in a tertiary care centre. The effects of Cisplatin on auditory function were studied using metabolic, biochemical and audiological parameters. The auditory effects were correlated with the dose and duration of chemotherapy. The study concluded that a significant percentage (15%) of patients who were subjected to chemotherapy based on Cisplatin developed high frequency sensorineural hearing loss which was permanent and irreversible in nature.

Key words: *Chemotherapy, Cisplatin, Ototoxicity*

INTRODUCTION

Chemotherapy is used in the treatment of malignancies in adjunctive, induction, concurrent and palliative roles.[1] Cisplatin is a newer chemotherapeutic agent that has been known to cause ototoxicity especially cochleotoxicity in various studies.[2] The exact degree and time of onset of ototoxicity and the relationship to dosage and duration of chemotherapy needs evaluation. The study was designed to evaluate the auditory effects of Cisplatin and correlate the auditory effects with the dose and duration of chemotherapy and to also determine the type, degree and frequency spectrum of hearing loss and correlate the ototoxic risk to metabolic parameters.

MATERIALS AND METHODS

The present study was prospective, done on 60 patients who underwent chemotherapy in the malignant diseases treatment centre of a tertiary care hospital. The patients included in this study were devoid of obvious ear pathology, past history of acoustic/noise trauma, diabetes and were not on any ototoxic drugs.

To study the auditory effects of Cisplatin the chemotherapeutic regimen followed up was Cisplatin with 5 Fluorouracil as there are no reports of any ototoxicity with 5 Fluorouracil.[1]

On the basis of dosage the patients were divided into 2 groups - The low dosage group consisting of 51 patients was given Cisplatin 100mg/sq.m in 3 divided doses over 3 days and 5 Fluorouracil 1000mg/sq.m over 96 hrs.This was repeated at 3 weekly intervals and a maximum of 6 courses were administered. The high dosage group consisting of 9 patients was given Cisplatin in a dose of 120mg/sq.m in 2 divided doses on day1&2 along with 5 Fluorouracil 1000mg/sq.m over 96 hrs. In both groups prior to Cisplatin administration every patient was prehydrated with 2 litres of normal saline and Cisplatin administration was followed by Mannitol infusion 300ml 20% solution over 20 min.

Prior to the start of chemotherapy liver and renal functions were assessed and a pure tone audiogram was carried out for use as baseline data. After the institution of chemotherapy the patients were followed up at the end of the 1st and 3rd cycle, on completion of chemotherapy and at 3 and 6 months of followup. At each session renal and liver function tests were carried out. Patients were interrogated for symptoms like hearing loss, tinnitus and vertigo and a pure tone audiogram was done.The type and degree of hearing loss was assessed, analysed and correlated with other variables. Hearing loss was graded as mild 25-40 dB, moderate 41-55dB, moderately severe 56-70 dB, severe 71-90 dB and profound > 91 dB.

RESULTS

The study group included 60 patients undergoing chemotherapy. 50 were male and 10 were female. 41 patients were over 50 years of age.

Patients receiving a higher dosage of Cisplatin showed an increased incidence of hearing loss (33%) compared to the low dosage group (12%)

11% patients had moderate SNHL and 22% had severe SNHL in the high dosage group in comparison to 6% and 6% in the

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low dosage group [Table 1].

In the low dosage group at the end of the first cycle one patient was seen to have mild SNHL,at the end of the third cycle 3 patients were seen to have moderate SNHL and at the end of 6th cycle 3 patients had moderate SNHL and 3 had severe SNHL [Table 2]. During follow up 3 patients had moderate SNHL and 3 patients had severe SNHL. Progression of SNHL from mild to moderate was seen in one patient from the 1st to the 3rd cycle. Progression from moderate to severe SNHL was seen in 2 patients from the 3rd to 6th cycle. During follow up phase there was no further change in hearing threshold observed in these patients [Table 2].

In the high dosage Cisplatin group (120mg/sq.m) out of 9 patients 2 patients developed moderate SNHL at the end of 1 course which increased to severe SNHL at the end of 3 courses.1 patient developed mild SNHL at the end of 3 courses which increased to moderate SNHL at the end of 6 courses [Table 2]. During the follow up phase there was no further change in hearing threshold seen in these patients. In all these cases hearing loss affected the higher frequencies above 4 KHz.

DISCUSSION

This study assessed and analysed the audiological functions of 60 patients undergoing chemotherapy with Cisplatin.

15% of the patients receiving Cisplatin developed hearing loss which was sensorineural, bilateral and predominantly affecting frequencies above 4 KHz. This correlates with the findings of McHaney et al.[3]

High dose of Cisplatin produced a higher incidence of ototoxicity compared to patients receiving lower dosage of Cisplatin. This was 33% in the high dosage group compared to 12% in the low dosage group [Table 1]. Similar observations have been made by Water et al[4] who assessed in their studies that regimens using low dose Cisplatin were less ototoxic than high dosage regimens.

A single higher dosage of Cisplatin (22%) produced a higher incidence of ototoxicity than a single lower dosage (2%) at the end of 1 cycle [Table 2]. Similar observations have been made by Laurel et al[5] who reported that higher single dosage led to an increased hearing loss.

It was observed in this study that with an increase in number of cycles in chemotherapy there appeared to be an increase of severity of hearing loss [Table 2]. It was also found that hearing thresholds at higher frequencies were elevated in patients with a cumulative dosage of more than 300 mg /sq m of Cisplatin which is similar to other studies.[6] No further shift in hearing threshold was observed in 3 patients when more than 500 mg / sq m was given (1 patients in low dosage group and 2 in higher dosage group between 3 and 6 courses) [Table 2]. There appeared to be a plateau for the hearing loss in the higher frequencies between 45 to 55 dB (3 patients in low dosage group and 1 in the high dosage group) Kopelman et al[7] in their study found an upper limit to the hearing loss caused by Cisplatin called the plateau between 3000 and 8000 Hz at hearing impairment of 40-60dB. This is explained by the fact that once all outer hair cells of cochlea have been destroyed there can be no further hearing loss expected by

Table 1: Hearing loss in patients receiving chemotherapy

	No.of patients	Patients with moderate SNHL	Patients with severe SNHL	Total No. of patients with SNHL
Low dosage group	51	3(6%)	3(6%)	6(12%)
High dosage group	09	1(11%)	2(22%)	3(33%)

Table 2: Change in degree of hearing threshold with dose and duration of chemotherapy

	End of 1 course		End of 3 courses		End of 6 courses		During follow up	
Dosage	Low	High	Low	High	Low	High	Low	High
Mild SNHL	1	-	-	1	-	-	-	-
Moderate SNHL	-	2	3	-	3	1	3	1
Severe SNHL	-	-	-	2	3	2	3	2

Table 3: Symptoms in patients with SNHL

	Tinnitus	Hearing loss	Tinnitus and hearing loss	Vertigo
Low dosage group	2	1	1	-
High dosage group	2	-	1	-

Table 4: Relationship of renal function with ototoxicity

	Pts with elevated serum creatinine (>20%) at the end of 6 cycles	Pts with SNHL at the end of 6 cycles	Percentage
Low dosage group	10	3	30%
High Dosage group	3	1	33%
Total	13	4	31%

subsequent administration of cisplatin.

Patients undergoing chemotherapy with Cisplatin who showed an increase in their serum creatinine of greater than 20% on completion of chemotherapy course showed a higher incidence of ototoxicity [4 out of 13(32%)] [Table 4]. A similar observation was found in other studies by Piel et al[8] in which they found patients on Cisplatin with a higher creatinine clearance had a higher percentage of ototoxicity.

Regular audiometric examination was helpful in detecting hearing loss in 9 out of 60 (15%) patients undergoing chemotherapy in this study. It was seen that 2 patients who developed SNHL remained asymptomatic and audiometry was useful in detecting hearing loss in these patients [Table 4]. We thus recommend regular audiological monitoring as an essential part of monitoring of ototoxicity in patients receiving Cisplatin.

CONCLUSION

This study concluded that a significant number of patients who were subjected to chemotherapy based on Cisplatin developed hearing loss (9 out of 60 (15%). The hearing loss was sensorineural affecting frequencies more than 4000Hz, permanent and irreversible in nature. The patients receiving higher dosages of Cisplatin and cumulative dosages of more than 300mg/sqm of Cisplatin had increased chances of ototoxicity and metabolic parameters like deterioration of renal function have a bearing on the ototoxicity. Regular audiometric evaluation during chemotherapy and follow up were instrumental in detecting hearing loss and are therefore to be recommended both pretreatment and after every course of chemotherapy to detect any ototoxicity.

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