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STUDY OF DETECTION OF HEARING LOSS IN PATIENTS UNDER CISPLATIN BASED CHEMOTHERAPY.

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ABSTRACT

Introduction- Cisplatin is extensively used as a chemotherapeutic agent for the management of several malignancies, including testicular, cervical, lung, and various head and neck cancers. However, it is also recognized as an ototoxic agent that may result in permanent bilateral sensorineural hearing loss. The objective of this study is to evaluate the incidence, consequences, and notable interindividual variability associated with cisplatin-induced ototoxicity. **Material And Methods -** Biopsy proven 52 cases of malignancy who were planned for cisplatin-based chemotherapy selected for study. All patients were divided into two groups depending on dose of cisplatin infused in 3 weeks. **Results-** The subjective hearing loss was found in 15 patients from group I with high dosage schedule and it was found in only 1 patient from group II low dosage schedule. Tinnitus was present in 5 patients with high dosage schedule. The hearing loss was sensorineural, dose dependent, symmetrical, bilateral and irreversible. Higher frequencies are first to be affected in cisplatin chemotherapy. **Conclusion-** Since high-frequency audiometry is primarily utilized in research contexts, there is a pressing need to develop a strict protocol for its integration into cisplatin-based chemotherapy regimens. This protocol should outline the appropriate timing, frequency, and methodology for conducting high-frequency audiometric assessments in patients undergoing treatment. Implementing such a framework will enable better monitoring of ototoxicity and facilitate timely interventions for hearing loss, ultimately improving patient care and outcomes. By formalizing this process, we can ensure a standardized approach that enhances the understanding of cisplatin's auditory effects while contributing to safer treatment practices.

KEYWORDS

Cisplatin, Ototoxicity, Chemotherapy, Sensorineural

INTRODUCTION

Cis-diamminedichloroplatinum (II) (cisplatin), a divalent platinum compound and potent cell cycle nonspecific chemotherapeutic agent, produces a dose limiting, permanent, high frequency Sensorineural hearing loss and peripheral neuropathy as well as dose related cumulative renal insufficiency with tubular necrosis and interstitial nephritis. The potential for dose limiting and permanent cochlear (neuro) toxicity remains despite present methods of hypertonic saline pre hydration, and mannitol diuresis prior to drug administration. Some of suggested mechanisms for cisplatin induced cytotoxicity may have potential application in the explanation of cochlear toxicity. They are (1) metalloenzyme mediated inhibition of carbonic anhydrase reaction with the resultant inhibition of endolymph production or generation of Endo cochlear potential (EP) presumably in the stria vascularis, (2) inhibition of cell based transport mechanism, (3) intra cellular binding of cisplatin to sulfhydryl groups of mitochondria and cytosolic fractions, and the subsequent disruption of DNA intrastrand and interstrand cross linking ,(4) sequestration of platinum by melanosomes with alteration of critical cellular enzyme activity , (5) cisplatin interaction with low molecular weight sulfhydryl containing compound (e.g. Glutathione and metallothionine), (6) cisplatin activation of oncogenes in vivo in renal tissues. None of these isolated findings, however, definitively account for the mechanism of cisplatin toxicity. Sarah Kohn et al Cisplatin inhibits adenyl cyclase in lateral wall of stria vascularis of dissected albino guinea pig cochlear tissues in vitro, hence suggesting that stria vascularis may be possible site of major platinum induced ototoxicity [1]. Further understanding of the inhibition of ATPase activity may be step in unravelling the mechanism of inner ear platinum toxicity.

Finally attempts to correlate peak plasma concentration of platinum with pathophysiology of ototoxicity are probably affected by several variables: individual host susceptibility of cochlear neuroepithelium, concentration of retained platinum between courses of chemotherapy treatment, and dose (mg/cm^2) interval between courses of platinum administration. The ototoxic effect of cisplatin is probably affected by not only peak plasma platinum concentration but also by the kinetics of elimination, inner ear platinum receptor binding, and changes in enzymatic activity. There is significant variability in the individual human presentation and susceptibility to cisplatin mediated ototoxicity. [2].

MATERIALAND METHODS

The subjects for the present study were drawn randomly from the patient population attending outpatient department of Govt. Cancer hospital and admitted in Cancer Hospital's wards. Biopsy proven 52 cases of malignancy who were planned for cisplatin-based chemotherapy for study. this study is carried out in 28 male and 24 female patients. Of these 17 patients had head and neck malignancy, 13 pt had carcinoma cervix ,5 of Ca lung and Ca Testis. 7 additional patients had other type of cancer.

Inclusion Criteria

- Patients with a histologically or serologically confirmed diagnosis of carcinoma.
- treated with cisplatin-based chemotherapy and without subsequent salvage chemotherapy
- Patients with normal hearing prior to chemotherapy treatment
- who have given informed consent.

Exclusion Criteria

- Active middle ear discharge
- History of ototoxic medications in the past
- Family history of deafness
- Patient not giving consent

The treatment protocol consisted of 2 different dosages of cisplatin in 2 different schedules

High Dosages >=100mg/m^2 body surface area, in divided dosages over 3-5 days. Courses of Cisplatin chemotherapy are spaced 3 weeks apart and repeated from 2 to 6 times.

Low dosages =50mg/m^2 body surface area per day or one over day or two over days, interval of 1 week to 3weeks in 1 to 5 courses

In addition to this they were also enquired about, diminished hearing, tinnitus, vertigo, unsteadiness before and after Cisplatin based chemotherapy.

- Distribution of patients according to the number of courses of chemotherapy received
- The variation in the number of courses, which ranged from one to six is explained by individual factors.

In several cases the chemotherapy was discontinued before entire planned dosage was given because of voluntary withdrawal, unwillingness to continue the project, cessation of chemotherapy, or combination of these.

Their clinical examination included routine general examination and local ENT check-up.

All selected patients had almost normal routine hemogram and renal function test before and after cisplatin-based chemotherapy.

Routine tuning fork test with 256 Hz, 512 Hz,1024 Hz i.e. Rinne Test, Weber test was done with 512Hz.

Hearing tests

- All patients were subjected to audiometry evaluation pure tone testing before and after of Cisplatin based chemotherapy.
- In ideal cases, audiogram was taken after each course of chemotherapy and in general after about 3 weeks.
- Audiometric Tests were performed on ALPS (Advanced Digital Audiometer) AD-2000 calibrated according to ISO standards.

Test Conditions

The audiological examination were carried out in ordinary chamber (not sound proof) but the test were carried out when the ambient noise was minimum.

- Routine Air Conduction threshold at 0.25, 0.5, 1,2,4,8 KHz pure tone frequencies was performed using TDH39 EAR phones with cushions
- Bone conduction threshold was established in the standard frequency range i.e. 0.25 to 4 KHz using Octicon Bone Vibrator (72923)
- Method Pure Tone Air conduction thresholds-the "up 5-down 10" method of threshold exploration was used

DISCUSSION

During the period of study, 52 patients were studied having various type of cancer with normal hearing. In our prospective study the patients were followed up after each course of chemotherapy for detection of development of cisplatin ototoxicity. Cisplatin was administered in combination with another cytotoxic drug.

In group I, patients Cisplatin was given in high dose i.e. 100-200 mg/m^2 in 2-6 courses, maximum number of patients (47.2%) were received total dose of 450 mg in 3 courses. Cumulative dose i.e. total dose ranges from 300 mg up to or more than 900mg. While in group II, cisplatin was given in low dose average 50 mg/m^2 in 2-5 courses. Cumulative dose ranges from 200 to 400 mg.

Pre-treatment Audiogram

Base line audiometry was done in all patients before starting Cisplatin chemotherapy in present series of study. In our study almost all patients all showed hearing threshold within normal limits.

Post-treatment Audiogram

All observed hearing loss on post-treatment audiometric evaluation in this series was Sensorineural type

Previous study by Zuur CL (2007) have showed Cisplatin induced hearing loss was sensorineural type. [3]

In our study 27 (75%) patients from group I and 4 (25%) patients from group II developed bilateral significant changes in Air Conduction hearing threshold after cisplatin therapy, the changes were differed only slightly between the sides.

In study by Laurel 1990 reported bilateral significant changes in air conduction hearing threshold in 37 patients of 54, and unilateral changes occurred in 7 patients. [4]

Another study by Water and Colleagues 1991 reported unilateral hearing loss is more common with low dose regimen, whereas bilateral involvement is predominant finding in the high dose regimen. [5]

In our study subjective change in hearing experienced by 15 out of 36 (41.1%) cases with high dose and only one out of 16 (6.2%) cases experienced with hearing impairment with low dosage.

In our study second common complaint by patients after cisplatin therapy was Tinnitus. The tinnitus was commonly transient mild disappearing a few hours to a week after discontinuation of treatment. Tinnitus was complained by 13% of patients who were receiving high dose (100-120 mg/m^2) cisplatin in our series. None of the patients from low dose cisplatin schedule in our series had experienced tinnitus during and after cisplatin chemotherapy.

In study of Arora et al (2009), about six patients out of fifty-seven patients had tinnitus irrespective of the dose of cisplatin.[6] and in study of Zuur CL et al (2007) 7% of the patients experienced tinnitus [2]

Our observations in present series of study showed 75% patients (i.e. 27 out of 36) who were receiving high dose of cisplatin developed significant thresholds shift i.e. objective hearing loss at high frequency. Pollera 1988 reported 75% of cases had significant threshold shift at high frequency after very high dose cisplatin. [7] Study by J.L Nagy 1998 demonstrated high frequency hearing loss in 36% (19 of 53) retested patients who were given high dose cisplatin. [8]. While our observation in present study with low dose cisplatin showed only 4 out of 16 patients (25%) had developed significant threshold shift at high frequency.

It was observed in our present series of study that the incidence of objective hearing loss at high frequency was maximum with total dose of 450mg i.e. after III courses of cisplatin chemotherapy. 15 out of 17(88.2%) cases who received courses i.e. total dose (450mg) of cisplatin developed high frequency significant threshold shift. 5 out of 6(83.3%) cases showed significant high frequency threshold shift on follow-up post treatment who received 300mg cisplatin i.e. after II course, while 2 out of 4(50%) cases showed significant high frequency threshold shift with 600mg(i.e. IV course) of cisplatin ,and 3 out of 5 (i.e. 60%) cases developed significant high frequency shift after 750mg(i.e. V course) of cisplatin and 3 out of 4 (i.e. 75%) cases developed significant high frequency shift after a maximum >=900mg (i.e. VI course)of cisplatin. This wide variations in high frequency threshold shift with different total dosage of cisplatin as observed in our study may be due to individual ototoxic susceptibility.

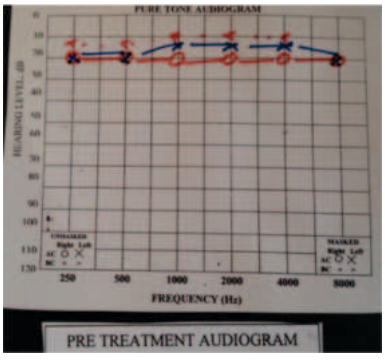

Fig 1: Pretreatment Audiogram Showing Normal Hearing In 18 Years Old Male.[14]

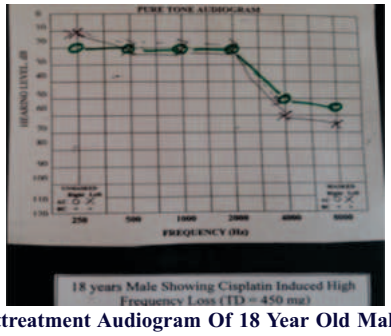

Fig 2: Posttreatment Audiogram Of 18 Year Old Male Showing Cisplatin Induced High Frequency Sensorineural Hearing Loss(TD=450mg) [14]

Wide variations in individual ototoxic susceptibility to cisplatin have been reported by Aguilar Markulis 1981. [9]

Mid frequency involvement was seen in 75% cases i.e. 3 out of 4 cases with 900mg cisplatin (i.e. after VI course). In 40% cases i.e. 2 out of 5 with 750mg cisplatin (i.e. after V course) and 29.4% cases (i.e. 5 out of 17) cases with 450mg cisplatin (i.e. III course). This observations from the present study that mid frequency hearing loss due to cisplatin ototoxicity is dose related.

One patient who received a total dose of 200mg cisplatin showed significant threshold shift as both high as well as mid frequency ranges.

Worawut Choeyprasert et al (2013) study showed that to ameliorate cisplatin-induced ototoxicity, the cumulative cisplatin dose <400mg/m2 should be a considerable benefit[10]

Only 1 out of 8 cases (12.5%) showed mid frequency involvement with very low dose (total dose 250mg).

Therefore, individual susceptibility of the person may be major factor in the development as well as the pattern of hearing loss.

In our study 8 (22.2%) patients had mild and 8(22.2%) patients had moderate degree of hearing loss with high dose cisplatin from group I, while 11 patients (30.5%) had developed moderate to severe degree of hearing loss after completion of high dose cisplatin chemotherapy. While in group II 1 patient developed mild degree of hearing loss, 2 had moderate degree and 1 patient had moderate to severe degree of hearing loss after completion of low dose cisplatin chemotherapy.

Myer reported that a significant number of patients treated with high dose cisplatin had moderate to severe hearing threshold shift. [11]

Prediction of Other Risk Factors

In our series of study, the maximum number of patients fall in 46–55-year age group from both high dose and low dose cisplatin. Advanced age showed highest incidence of significant threshold changes.

The incidence of significant threshold shift at mid frequency was progressively increased as age advanced with high dose cisplatin in group I. While group II with low dose cisplatin younger and middle age group i.e. 18-45 years were remained unaffected with cisplatin ototoxicity at both frequency ranges.

Laurell and Borg (1989) found that neither age nor pre-existing hearing loss was a risk factor in the development of cisplatin induced hearing loss. [12]

In our observational studies 87.5% cases had abnormal audiometric results were male and 50% were female with high dose cisplatin from group I, while from group II with low dose 25% cases had abnormal audiometric results were male and 25% were female. None of the previous study in literature showed any relation to sex of the patient with objective hearing loss after cisplatin.

It was observed in our study that significant threshold shift was associated with radiation in 8 out of 9 (88.8%) cases.

A Johnson et al found in their study that the subjects exposed to concurrent head and neck radiotherapy were grouped together to investigate the hearing loss within this cohort: 18 of the 31 received concurrent radiotherapy, and 11 of these 18 subjects experienced significant hearing loss following the concomitant use of cisplatin and radiation therapy. Of the 13 subjects who did not receive head and neck irradiation, only 4 developed significant hearing loss following cisplatin therapy.[13]

In present series of our study none of the patients developed any clinical symptoms and sighs of vestibular toxicity with both high as well as low dose cisplatin therapy.

In our prospective study total 58.8% patients developed significant bilateral symmetrical sensorineural hearing loss at high frequency with high and low dosages both

CONCLUSION

High dose Cisplatin treatment is associated with a risk of serious changes in hearing function. Ototoxicity affecting all age group but the most common age group is 56- 65 years and male patients having higher prevalence. The chief symptom of all patients were subjective change in hearing after Cisplatin chemotherapy and the second most common symptom was tinnitus which found only with higher dosage of Cisplatin. Pré-existing hearing loss may increase the risk of ototoxic changes perse, specially at advanced in old age slightly increases the risk.75% patient showed significant AC threshold shift in the higher frequency range after completion of Cisplatin therapy. All of this 33.2% of the patient showed significant changes in AC hearing thresholds in the middle frequency range of 5 to 2 KHz. Pure tone audiometry is most common method to diagnose ototoxicity of Cisplatin. The audiogram after the first course is of little value in predicting the development of the hearing function during further treatment. The ototoxic risk is determined more by the amount of the single dose than by cumulative dose. There is no specific cumulative threshold dose above which a rapid increase in hearing loss can be expected. Hearing loss was bilateral symmetrical and sensorineural type affecting higher frequency commonly.

Table 1: Post treatment objective hearing loss (STS) in relation to the total number of courses and total dose given (Group I)

No. Of courses	Total dose (mg)	No. Of patient	No. Of patient with no STS	No. Of patient with STS at Tm 4-8 KHz	No. Of patient with STS at Tm 0.5-2 KHz
2	300	6	1(16.6%)	5(83.3%)	--
3	450	17	2(11.7%)	15(88.2%)	5(29.4%)
4	600	4	2(50%)	2(50%)	--
5	750	5	2(40%)	3(60%)	2(40%)
>=6	>=900	4	1(25%)	3(75%)	3(75%)

Table 2: Post treatment objective hearing loss (STS) in relation to the total number of courses and total dose given (Group II)

No. Of courses	Total dose (mg)	No. Of patient	No. Of patient with no STS	No. Of patient with STS at Tm 4-8 KHz	No. Of patient with STS at Tm 0.5-2 KHz
2	200	1	--	1(100%)	1(100%)
3	300	3	3(100%)	--	--
4	400	4	3(75%)	1(25%)	--
5	250	8	6(75%)	2(25%)	1(12.5%)

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