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RESEARCH ARTICLE

Cisplatin associated ototoxicity in patients receiving cancer chemotherapy in a tertiary care hospital

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ABSTRACT

Background: Cisplatin-based treatment regimen has been a gold standard in the treatment of various solid tumors. Ototoxicity is a very serious adverse effect of cisplatin therapy in either high or low dose regimens. Cisplatin selectively damages the outer hair cells within the organ of Corti, spiral ganglion cells, and cells within the stria vascularis and produce hearing loss in higher frequencies. **Aims and Objectives:** The objective of the study is to estimate the extent and severity of ototoxicity in cancer patients receiving cisplatin based chemotherapy. **Materials and Methods:** All the patients irrespective of age and sex diagnosed with cancer and receiving cisplatin chemotherapy were included in the study. The otoscopic examination and puretone audiogram taken before each cycle of cisplatin therapy were recorded in the data collection form. The data collected were statistically analyzed using descriptive statistics and expressed in percentage. **Results:** Twenty-five patients were enrolled in the study and sequential audiogram was taken before each cycle of cisplatin therapy and post-treatment and it showed that there was a gradual increase in threshold of hearing in speech frequency and high frequency when compared to pre-treatment audiogram in both ear. The audiogram of speech frequency after treatment showed that 52% and 56% of patients had moderate hearing loss in the right and left ear, respectively. **Conclusion:** Early identification of ototoxicity by sequential monitoring of hearing loss might help in early rehabilitation of the cancer survivors thereby improving their quality of life.

KEY WORDS: Cisplatin; Ototoxicity; Chemotherapy; Audiogram; Pure Tone Average

INTRODUCTION

Cisplatin is a widely used chemotherapeutic agent since its approval in 1978 for the treatment of various cancers.[1] Cisplatin-based treatment regimen has been a gold standard in the treatment of various solid tumors such as ovarian, testicular, cervical, lung, head, neck, and bladder cancers.[2,3]

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However, treatment with cisplatin is associated with drug resistance and several adverse effects such as ototoxicity, nephrotoxicity, and neurotoxicity.[1,3] To prevent this, combination therapy of cisplatin with other chemotherapeutic agents has been used as novel therapy for the treatment of many cancers.[4]

Ototoxicity is a very serious adverse effect of cisplatin therapy in either high or low dose regimens. A study had shown that cisplatin was retained in human cochlea for about 18 months after past cycle of cisplatin therapy.[5] Cisplatin chemotherapy causes permanent hearing loss in 40–80% of adults and 50% of children.[5] Ototoxicity can occur anytime from hours to days following cisplatin therapy.[3] The hearing loss produced by cisplatin therapy is bilateral, permanent, dose related, and

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cumulative and it is particularly serious in pediatric population as loss of hearing at the developmental stage affects the speech, cognitive, and social development of the child.[2,3]

Cisplatin selectively damages the outer hair cells within the organ of Corti, spiral ganglion cells, and cells within the stria vascularis and produces hearing loss in higher frequencies.[3] Early diagnosis of hearing loss can be done by monitoring of high frequency audiograms.[6] The main symptoms of ototoxicity includes subjective hearing loss, ear pain, and tinnitus.[2] Hearing loss can progress for up to 2 years in 15–20% of patients.[3]

There are several publication suggesting genetic susceptibility to cisplatin ototoxicity and gene polymorphism playing an important role in increasing the likelihood of ototoxicity in patients treated with cisplatin chemotherapy.[2,7] It is not yet possible to identify the genetically susceptible individuals before cisplatin therapy.[6] Ototoxicity monitoring is very important in patients on cisplatin chemotherapy as hearing loss decrease the quality of life and will have impact on social and academic development of pediatric patients.[5]

Cancer survivors continue to grow hence it is important to address the long-term sequelae of cancer chemotherapy. Studies related to cisplatin associated ototoxicity are scarce; hence, the present study will monitor the cisplatin associated ototoxicity in patients receiving cancer chemotherapy in a tertiary care hospital.

Objective

The objective of the study is to estimate the extent and severity of ototoxicity in cancer patients receiving cisplatin chemotherapy.

MATERIALS AND METHODS

The study was commenced after obtaining approval from Institutional Ethical Committee (IEC - Reference number: 1246/MBBS/2018), Tirunelveli Medical College, Tirunelveli, South India. Written informed consent was obtained in local vernacular language from all the patients or their guardian before including them in the study.

Study Design

Descriptive type of prospective observational study was done for a period of 6 months between March 2019 and August 2019 in the department of oncology in a tertiary care hospital. The study population were the male and female patients diagnosed with cancer and on cisplatin chemotherapy.

Selection Criteria

All the patients irrespective of age and sex diagnosed with cancer and receiving cisplatin chemotherapy were included in the study. Patients with cancer having hearing loss before starting cisplatin chemotherapy, cancer patients receiving or received other ototoxic drugs, patients receiving radiation to head and neck tumors, and patients with brain metastasis were excluded from the study.

Study Procedure

Study participants were enrolled as per the selection criteria. Demographic details, disease details, and drug details were recorded from the case sheet of the enrolled study participants. Clinical assessment was also done and recorded. The otoscopic examination and puretone audiogram taken before each cycle of cisplatin therapy were recorded in the data collection form from the case sheet. During each visit symptoms of ototoxicity such as hard of hearing (HOH), tinnitus, and ear pain were asked for and recorded. After treatment audiogram and follow-up were be done 4 weeks after the past cycle and the related data were recorded. The study participants were categorized on the basis of degree of hearing loss as normal (−10–15), slight (16–25), mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB), and profound (>90 dB) according to American Speech-Language-Hearing Association guidelines (ASHA). Laboratory investigation such as complete blood count, liver function test, and renal function test was recorded. The data collected were tabulated and statistically analyzed using descriptive statistics and expressed in percentage.

RESULTS

During the 6 month study period, a total of 40 patients were screened and 25 patients were enrolled in the study as per the selection criteria. Among 25 patients, 14 (56%) were males and 11 (44%) were females. The age of the study population was ranging from 23 to 72 years; the mean age of male and female patients was 57 years and 47 years, respectively [Table 1]. The most common age group among the males was 61–80 years, followed by 41–60 years and among females the most common age group was 41–60 years, followed by 20–40 years [Figure 1]. The most common comorbid condition seen among the study participants were diabetes (32%) and hypertension (24%). Regarding the personal habits, 28% of the patients were both alcoholic and smoker [Table 1]. The most common cancer in the study participants was carcinoma lung (56%) and the least common was carcinoma gall bladder, liver, and urinary bladder (4%) [Table 2]. The stage of carcinoma was stage four in 48% and stage three in 36% of the study participants [Table 2]. The combination regimen of cisplatin and gemcitabine was given to 64% and cisplatin and etoposide was given to 36% of study participants [Table 3].

Hearing loss in decibels (db) after treatment in the right ear in the frequency of 1000 Hz, 2000 Hz, 4000 Hz, 80,000 HZ, 10,000 Hz, and 12,000 Hz was 38 db, 45 db, 51 db, 56 db, 76 db, and 79 db, respectively [Table 4]. Similarly, in the

Table 1: Baseline characteristics

Variable	Value *n* (%)
Total study population (*n*)	25
Males (%)	14 (56)
Females (%)	11 (44)
Mean age of study population (years)	52
Males (years)	57
Females (years)	47
Personal history	
Smoker	4 (16)
Alcoholic	2 (8)
Both	7 (28)
Nil	12 (48)
Comorbidity	
Diabetes mellitus	8 (32)
Hypertension	6 (24)
Bronchial asthma	2 (8)
No comorbidity	9 (36)

n is number of patients

Table 2: Diagnosis and stage of cancer

Variables	Value *n* (%)
Diagnosis	
Carcinoma lung	14 (56)
Carcinoma ovary	6 (24)
Periampullary cell carcinoma	2 (8)
Carcinoma urinary bladder	1 (4)
Carcinoma liver	1 (4)
Carcinoma gall bladder	1 (4)
Stage of cancer	
Stage - I	NIL
Stage - II	4 (16)
Stage - III	9 (36)
Stage - IV	12 (48)

n is number of patients

Table 3: Chemotherapy drug regimen

Drug regimen	Value *n* (%)
Cisplatin and gemcitabine	16 (64)
Cisplatin and etoposide	9 (36)

n is number of patients

left ear in the frequency of 1000 Hz, 2000 Hz, 4000 Hz, 80,000 HZ, 10,000 Hz, and 12,000 Hz and the hearing loss were 42 db, 48 db, 55 db,626 db, 79 db, and 88 db, respectively [Table 5]. The pure tone average (PTA) of the right ear after treatment was 42 db in speech frequency and 70 db in high frequency. Similarly, in the left ear the PTA for speech frequency was 45 db and for high frequency was 75 db [Figure 2].

According to ASHA defined hearing loss, the PTA of speech frequency after treatment showed that 52% and 56% of patients had moderate hearing loss in the right and left ear respectively [Figure 3]. About 52% and 48% of patients had moderately severe hearing loss in the high frequency in the

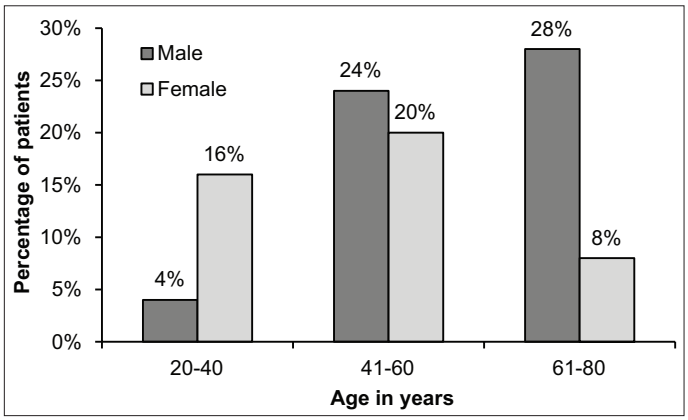

Figure 1: Age distribution of study participants

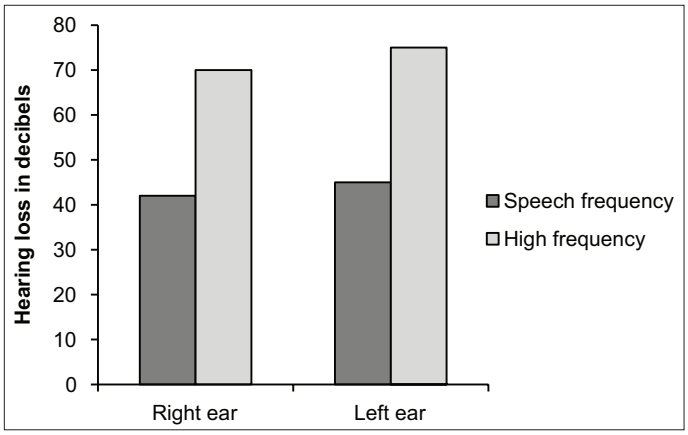

Figure 2: Puretone average of speech frequency and high frequency in the right and left ear after treatment

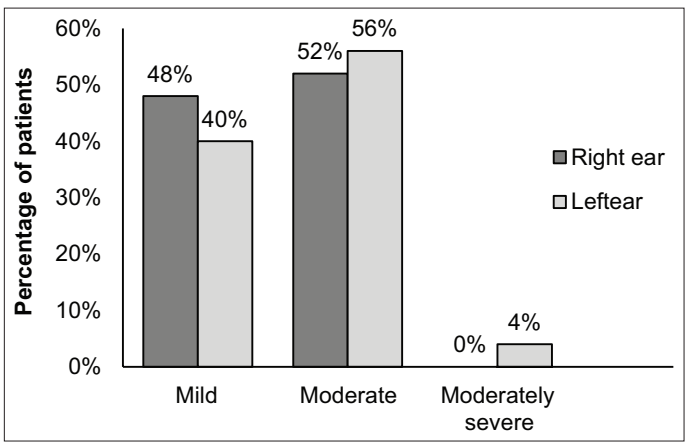

Figure 3: ASHA defined hearing loss with PTA of speech frequency after treatment. PTA: Puretone average, ASHA: American Speech-Language-Hearing Association

right and left ear, respectively [Figure 4]. About 32% and 28% of patients had severe hearing loss in high frequency in the right and left ear, respectively, and 4% of patients had profound hearing loss in the left ear [Figure 2]. About 44% of study participants complained of HOH and tinnitus, 32% of study participants had ear pain and tinnitus and finally 24% of patients had HOH alone [Figure 5].

DISCUSSION

In the 6 months study period conducted in oncology department the most common age group taking cisplatin chemotherapy were 61–80 years among the males and 41–60 years among females. The sequential audiogram of study participants taken before each cycle of cisplatin therapy and post-treatment showed that there was a gradual increase in threshold of hearing in both speech frequency and high frequency when compared to pre-treatment audiogram in the both right and left ear [Tables 4 and 5]. In this study, the hearing loss is more in the high frequency than speech frequency in the both right and left ear. High frequency hearing is initially affected because high frequency region in the cochlea is more susceptible to cisplatin. In the present study, according to ASHA defined hearing loss the study participants had bilateral sensorineural hearing loss in both the ears ranging from moderately severe, severe, to profound hearing loss. The normal frequencies of a human ear that can appreciate is between 20 and 20,000 Hz and the speech frequency is in the range from 500 to 4000 Hz and the normal conversation is in between 45 and 60 dB.[8] The symptoms of ototoxicity are subjective hearing loss, ear pain, and tinnitus. In the present study, 11 patients (44%) out of 25 study participants complained of HOH and tinnitus.

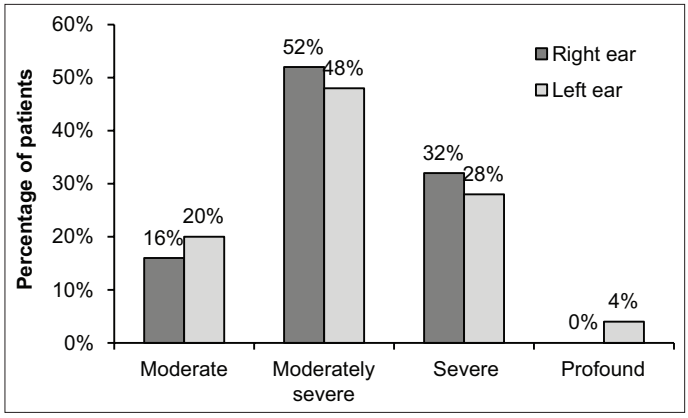

Figure 4: ASHA defined hearing loss with PTA of the high frequency after treatment. PTA: Puretone average, ASHA: American Speech-Language-Hearing Association

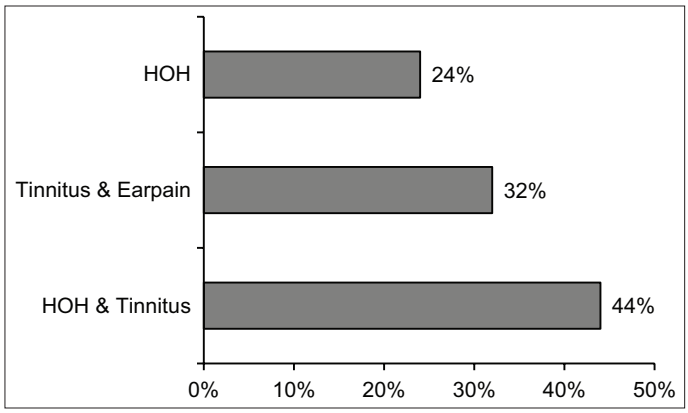

Figure 5: Symptoms related to ototoxicity

Young children are at high risk of developing moderate to severe hearing loss from cisplatin therapy than adults. The incidence of cisplatin associated ototoxicity in children ranges from 22% to 70%.[9] When the exposure to cisplatin is continued that the severity of hearing loss is increased, later spreads progressively affecting the lower speech frequency.[6] Cisplatin therapy is known to cause ototoxicity and the risk factors are high cumulative dose of cisplatin, extreme ages of life, renal failure, pre-existing hearing loss, noise exposure, ototoxic drugs exposure, nutritional status, and cranial irradiation.[2,3,9] Many studies have shown high incidence of permanent bilaterally symmetric sensorineural hearing loss involving higher frequencies.[2,6,10] The hearing loss may not be always symmetrical, Jenkins *et al*. have documented that 75% of women after cisplatin therapy had an asymmetry of hearing threshold of at least ten decibels between ears.[10] A study has documented that 2–36% of patients treated with cisplatin therapy complained of tinnitus[2]. Clinical manifestation of cisplatin ototoxicity appears within hours to days after exposure.[8] An interindividual difference in ototoxicity following cisplatin therapy is described by several genetic variant traits. It would be very useful to identify the genetic variant that predispose to cisplatin ototoxicity thereby reducing the risk of ototoxicity.[7,11] The simple molecular mechanism related to cisplatin ototoxicity is acute and chronic generation of reactive oxygen species (ROS) in organ of Corti, stria vascularis, and spiral ganglionic cells which leads to depletion of cochlear

Table 4: Sequential hearing loss in decibels of the right ear after cisplatin therapy

Variable	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz	10,000 Hz	12,0000 Hz
Pre treatment	16	17	19	19	22	23	25	30
Before cycle 2	23	25	28	32	38	42	46	49
Before cycle 3	24	28	32	36	38	41	50	62
Before cycle 4	24	28	33	36	38	42	55	65
Before cycle 5	28	29	35	42	45	49	62	68
Before cycle 6	30	31	38	43	47	50	70	74
After treatment	30	33	38	45	51	56	76	79

Hz: Hertz

Table 5: Sequential hearing loss in decibels of the left ear after cisplatin therapy

Variable	250 Hz	500Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz	10,000 Hz	12,0000 Hz
Pre treatment	15	16	19	20	21	23	28	29
Before cycle 2	24	26	31	36	38	44	52	56
Before cycle 3	26	30	33	38	42	45	62	70
Before cycle 4	26	30	34	39	42	46	68	72
Before cycle 5	27	32	38	44	48	52	70	75
Before cycle 6	32	35	40	45	51	56	75	85
After treatment	32	36	42	48	55	62	79	88

Hz: Hertz

antioxidant enzymes that help in scavenging and neutralizing generated superoxides. Chronic increase in ROS generation leads to increase in pro-inflammatory cytokine formation and superoxide generation in the cochlea leading to activation of pro-apoptotic pathway.[7] One of the approaches tried for the treatment of cisplatin ototoxicity is the use of systemic or local administration of antioxidants or drugs that activate endogenous antioxidant system and use of anti-inflammatory agents targeting the pro-inflammatory mechanisms associated with cisplatin treatment.[12] Most of the studies are in the experimental animal stage and they are yet to be studied in human clinical trial for validation.[12] However, it is important that the antitumor activity of cisplatin should not be interfered.[6]

The limitation of the present study is that the sample size is small and single-centered study, duration of study was short- and long-term follow-up and was not done and the cumulative cisplatin dose associated with ototoxicity is not assessed. To prevent cisplatin-induced ototoxicity the physician should limit the total dose per cycle and limit the cumulative dose but this might reduce the efficacy of cisplatin. Hence, sequential audiometric monitoring will help to detect the hearing loss earlier thereby the cisplatin dosage may be modified or can be substituted with other safer platinum compounds.[6] Modern treatment of cancer has improved the survival rates of cancer patients. Hence, the adverse effects of chemotherapeutic drugs should not adversely affect the quality of life of the cancer survivors.

CONCLUSION

We conclude that early identification of ototoxicity by sequential monitoring of hearing loss might help in early rehabilitation of the cancer survivors. In future, high risk patients may be identified earlier with pharmacogenomic study by identifying the genetic variants responsible for ototoxicity. It is essential to develop otoprotective agents with cisplatin therapy thereby reducing the prevalence of ototoxicity and improve quality of life of cancer survivors.

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