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ORIGINAL ARTICLE

Audiological Profile of Cancer Patients Under Treatment of a Cisplatin Chemotherapy at Zagazig University Hospitals

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ABSTRACT

Background: Ototoxicity refers to the hearing disorder which results from the temporary or permanent inner ear dysfunction after treatment with an ototoxic drug. One such drug class that produces ototoxicity is the cancer chemotherapeutic agents. Chemotherapy is a core component of treatment for advanced cancers, when early metastasis is known to occur. **Objectives**: The current study is to evaluate the cisplatin-associated ototoxicity in cancer patients receiving chemotherapy and evaluate the feasibility of an audiological monitoring program.

Patients & Methods: Eighteen cancer patients were treated with cisplatin chemotherapy in this cohort in Oncology Department & audiologically evaluated in Audiovestibular Medicine Unit, Otorhinolaryngology Department, Faculty of Medicine, Zagazig University Hospital. **Results**: significant changes in hearing thresholds (250 through 8000Hz) in pure tone audiometry after cisplatin therapy. Extended high frequency audiometry revealed highly significant increasing in hearing thresholds at frequencies (10, 12.5,16KHZ) after cisplatin therapy in the study group. Transient evoked otoacoustic emission (TEOAE) revealed significant decrease in signal to noise ratio after cisplatin therapy. Extended high frequency audiometry and Transient evoked otoacoustic emissions had the highest sensitivity in the early detection of cisplatin ototoxicity.

Conclusions: Cisplatin produces a bilateral, symmetrical hearing loss, mainly affecting the high-frequency range which could be monitored by Extended high frequency audiometry and Transient evoked otoacoustic emissions.

Keywords: Audiological - Ototoxicity- a Cisplatin - Chemotherapy.

INTRODUCTION

Ototoxicity refers to the hearing disorder which results from the temporary or permanent inner ear dysfunction after treatment with an ototoxic drug. One such drug class that produces ototoxicity is the cancer chemotherapeutic agents. Chemotherapy is a core component of treatment for advanced cancers, when early metastasis is known to occur[1] , [2].

Cisplatin chemotherapy, a highly effective chemotherapeutic is associated with high incidence of ototoxicity. Chemotherapy side effects in routine care are common and can be serious[3]. Cisplatin-associated ototoxicity usually manifests as bilateral irreversible, progressive, high frequency sensorineural hearing loss associated with tinnitus[4]. The degree of hearing loss is often variable and is related to the dose.

An audiological monitoring program can avert, to a large extent, the reduced quality of life as a result of hearing loss, since patients on such drugs can be identified early, counseled, monitored and managed appropriately through interventions in a logical, systematic and coherent manner [5].

knowledge of the epidemiology of hearing loss associated with cisplatin chemotherapy would be basically considered for the implementation of such a program [6]. It is important to do further studies customized for each area, therefore this study was organized to help in this critical issue.

The aim of the current study is to evaluate the cisplatin-associated ototoxicity in cancer patients receiving cisplatin chemotherapy and evaluate the feasibility of an audiological monitoring program.

PATIENTS AND METHODS

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Eighteen cancer patients were treated with cisplatin chemotherapy in this cohort in Oncology Department and audiologically evaluated in Audiovestibular Medicine Unit, Otorhinolaryngology Departments, Faculty of Medicine, Zagazig University Hospital during the period 2018/2019.

Inclusion criteria: Patients in any age. Patients had histopathologically confirmed diagnosis of cancer and underwent cisplatin chemotherapy. Commencing with the first cycle of chemotherapy. Patients had not received prior radiotherapy or not undergoing radiotherapy treatment.

Audiological criteria: No history of ear disease. Normal tympanic membrane. Normal pure-tone thresholds (250-8000 Hz).

Equipment: Sound treated room locally made. Two channel audiometer Madsen (orbiter 922) caliberated according to ANSI (1969) [7]. The air conduction stimulus was delivered via supra aural headphone model TDH 49. The bone conduction stimulus was delivered via bone conduction vibrator model B71, with extended high frequency facility delivered via supra aural headphone model Sennheiser HAD 200. Immittancemeter (Zodiac 901). Otoacoustic emission (ILO version 6).

Methods:

All subjects of this study were submitted to:

Full history taking. Otological examination. Basic audiological evaluation before starting cisplatin chemotherapy treatment. Audiological evaluations were obtained at Audiovestibular Medicine Unit, Otorhinolaryngology Department.

The course of follow up:

Audiological assessment was done for 18 cancer patients after 3 months of treatment with cisplatin chemotherapy. audiological assessment in pretreatment results are compared with hearing threshold changes in post-treatment. Pure-tone audiometry (PTA) including air conduction for octave frequencies 250Hz through 8000 Hz and bone conduction for octave frequencies 500Hz through 4000 Hz using ascending and descending techniques. Speech audiometry including speech reception threshold (SRT) using Arabic spondee words [8] and Word discrimination score using Arabic phonetically balanced words[9] .

Extended high frequency including pure tone air conduction audiometry for octave frequencies of 10000, 12500 and 16000HZ.

Immittancemetry: Tympanometry. Acoustic reflex threshold measurements using pure tones of 500, 1000, 2000 and 4000 HZ elicited ipsi and contra laterally. Transient evoked otoacoustic emissions (TEOAEs).

Statistical analysis

Data were checked, entered and analyzed using SPSS version 20 for data processing. The following statistical methods were used for analysis of results of the present study.

Data were summarized using:

I-The arithmetic mean ($\overline{X}$)

II- The standard deviation (SD)

The comparison was done using:

I- Paired sample T test.

II- Wilcoxon signed rank test.

III- Pearson and spearman correlation coffiecient test.

IV- McNemmar test.

RESULTS

This study included 18 patients under cisplatin chemotherapy in oncology department. There was statistically significant changes in hearing thresholds (250 through 8000Hz) in pure tone audiometry after cisplatin therapy. Extended high frequency audiometry revealed highly significant increasing in hearing threshold at frequencies (10, 12.5,16KHZ) after cisplatin therapy in the study group (Table 1,2). Transient evoked otoacoustic emission (TEOAE) revealed significant decrease in signal to noise ratio after cisplatin therapy (Table 3). There was Significant positive correlation between age and hearing loss in pure tone audiometry at (4,8KHz) and in extended high frequency audiometry at (10,12.5Khz) (Table 4). Effect of cycles shows statistically Significant positive Correlation between number of cycles of cisplatin chemotherapy and hearing loss at 4000 and 8000 Hz in pure tone audiometry and at all frequencies in Extended high frequency audiometry (10, 12.5 and 16KHz) (Table 5). (Ear effect), there was no significant difference between level of hearing loss in right & left side in pure tone audiometry (250 through 8000Hz) and in extended high frequency audiometry (10,000 through 16000Hz) (Table 6).

Table (1): Comparison of pure tone audiometry, Extended high frequency audiometry on the right side before and after cisplatin in the study group;

	Before cisplatin (18) mean ± SD (Range) Median	After cisplatin (18) mean ± SD (Range) Median	Paired t- test	p-value
Pure tone audiometry at different frequencies				
250 (HZ)	10.8±1.9 (10-15) 10	15.8±5.5 (10-25) 15	4.1	**<0.001****
500(HZ)	10.9±1.7 (10-15) 10	18.3±3.8 (15-25) 17.5	12.3	**<0.001****
1(KHZ)	12.5±2.5 (10-15) 12.5	25±2.9 (20-30) 25	13.4	**<0.001****
2(KHZ)	15±5.9 (10-25) 12.5	23.3±3.8 (15-25) 25	6.2	**<0.001****
4(KHZ)	19.2±10.4 (10-40) 17.5	32.5±11.4 (20-55) 30	Wilcoxon=14.7	**<0.001****
8(KHZ)	27.5±22.5 (10-75) 20	45±23.5 (25-95) 37.5	Wilcoxon=15.1	**<0.001****
Extended high frequency audiometry (10 through 16KHz)				
10 (KHZ)	40±24.8 (15-90) 32.5	53.5±24.7 (30-105) 47.5	11.6	**<0.001****
12.5(KHZ)	46.7±20.5 (30-90) 40	68.3±13.8 (55-95) 62.5	7.2	**<0.001****
16(KHZ)	77.5±12.2 (60-95) 75	89.2±5.5 (80-95) 90	4.5	**<0.001****

*** *Statistically highly significant difference (P ≤ 0.001)**

Table (2): Comparison pure tone audiometry, Extended high frequency audiometry on the left side before and after cisplatin in the study group;

Pure tone audiometry at different frequencies	*Before cisplatin* (18) mean ± SD (Range) Median	*After cisplatin* (18) mean ± SD (Range) Median	Paired t- test	p-value
250 (HZ)	12.5±3.9 (10-20) 10	17.5±4.9 (10-25) 17.5	5.1	**<0.001****
500(HZ)	12.5±2.5 (10-15) 12.5	20±2.9 (15-25) 20	12.4	**<0.001****
1(KHZ)	15±4.2 (10-20) 15	26.5±2.4 (25-30) 25	12.9	**<0.001****
2(KHZ)	14.2±4.6 (10-20) 12.5	25.8±4.6 (20-30) 27.5	20.4	**<0.001****
4(KHZ)	23.3±13.5 (10-50) 20	35±12.6 (25-60) 30	Wilcoxon=8.7	**<0.001****
8(KHZ)	31.6±22.9 (10-80) 25	48.3±17.9 (30-85) 42.5	Wilcoxon=11.1	**<0.001****
Extended high frequency audiometry				
10 (KHZ)	42.5±22.7 (20-90) 35	53.3±19.8 (35-95) 47.5	13	**<0.001****
12.5(KHZ)	49.2±20.3 (30-90) 40	76.7±10.9 (60-95) 77.5	9.1	**<0.001****
16(KHZ)	77.5±12.1 (55-95) 80	93.3±3.8 (85-95) 95	5.1	**<0.001****

Wilcoxon signed rank test.

* *Statistically highly significant difference ($P \leq 0.001$)

Table (3): Comparison transient evoked oto-acoustic emission (TEOAE) on the right side and left side before and after Cisplatin in the study group;

	Before cisplatin (18) mean ± SD (Range) median	*After cisplatin* (18) mean ± SD (Range) median	Paired t- test	p-value
***TEOAE at different frequencies* in right side**				
1 (HZ)	7.3±8.2 (0.8-21.7) 2.8	2.1±3.3 (0.0-9.3) 0.85	3.04	**0.007***
1.4(HZ)	15.9±3.7 (4.6-25.8) 6.7	3.2±2.4 (0.6-7.6) 3.2	7.4	**0.001****
2(KHZ)	13.2±5.3 (8.6-23.1) 11.3	7.4±3.1 (2.1-10.1) 8.8	4.3	**0.001****
2.8(KHZ)	13.4±7.7 (5-23.5) 14.3	3.9±1.2 (2.4-5.9) 4.1	Wilcoxon=5.4	**0.001****
4(KHZ)	13.9±6.1 (3-18.9) 16.9	4.1±3.7 (0.1-11.1) 3.5	Wilcoxon=4.9	**0.001****
***TEOAE at different frequencies* in left side**				
1 (HZ)	11.5±8.3 (2.6-24.5) 10.2	5.4±3.9 (1-13) 4.2	3.3	**0.004***
1.4(HZ)	11.9±7.1 (1.9-22) 9.9	4.5±4.1 (0.2-11.8) 4.05	3.01	**0.008***
2(KHZ)	11.3±3.9 (7.2-17.1) 10.2	6.9±3.9 (1.3-11.9) 6.1	3.3	**0.004***
2.8(KHZ)	14.6±7.7 (0.9-25.1) 14.3	5.1±4.1 (0.6-12) 4.35	Wilcoxon=4.9	**0.001****
4(KHZ)	13.5±4.9 (6.9-20.1) 14.5	2.8±2.6 (0.3-7.1) 2.5	Wilcoxon=6.6	**0.001****

*** *Statistically highly significant difference (P ≤ 0.001)**

Table(4): Correlation between age and pure tone audiometry & Extended high frequency audiometry(Effect of age).

		Age
250	R	-.194-
	P	.439
500	R	.454
	P	.062
1kh	R	.435
	P	.071
2h	R	.155
	P	.539
4kh	R	.737**
	P	.000
8kh	R	.592**
	P	.010
HF10kh	R	.762**
	P	.000
HF12.5kh	R	.586**
	P	.010
HF16kh	R	.308
	P	.213

Table (5): Correlation between cycles of cisplatin chemotherapy and pure tone audiometry & Extended high frequency audiometry(Effect of cycles).

		Cycle
250kh	R	-.257-
	P	.302
500kh	R	.385
	P	.111
1kh	R	.366
	P	.135
2kh	R	.227
	P	.366
4kh	R	.671**
	P	.002
8kh	R	.591**
	P	.010
HF10kh	R	.736**
	P	.000
HF12.5kh	R	.554**
	P	.017
HF16kh	R	.476*
	P	.042

Table (6): Comparison of level of hearing loss between right and left side(Ear effect).

		Right	Left	Paired t/ Sign	P
	250	10.83±1.91	12.3±3.5	-1.458	0.163
		10 (10-15)	10 (10-20)		
	500	10.83±1.91	12.4±2.92	-1.915-	0.058
		10 (10-15)	12.5 (10-15)		
	1 KH	13.5±2.53	15.0±4.2	-1.853	0.066
		12.5 (10-15)	15 (10-20)		
	2 KH	15.0±5.93	14.16±4.61	Z=0.644	0.528
		12.5 (10-25)	12.5 (10-20)		
	4 KH	20.16±10.46	22.33±13.50	Z=-1.949	0.055
		17.5 (10-50)	20 (10-50)		
	8 KH	28.5±22.57	30.66±22.94	Z=-1.847	0.068
		20 (10-75)	25 (10-80)		
	10 KH	40.0±24.85	42.50±22.76	Z=1.625	0.122
		32.5 (15-90)	35 (20-90)		
	12.5 KH	46.66±20.5	49.16±20.23	Z=-0.986	0.362
		40 (30-90)	40 (30-90)		
	16 KH	77.51±12.15	77.53±12.35	Z=-0.015	0.998
		75 (60-95)	80 (55-95)		

DISCUSSION

Li et al., 2004 [10] stated that the use of cisplatin has contributed to increase in the long-term survival in patients with cancer. Unfortunately, ciplatin has adverse effects including ototoxicity and associated permanent hearing loss.

In this study, Pure tone audiometry results showed statistically significant changes in hearing thresholds at (2000-8000 HZ) after cisplatin treatment. Table (1,2), the hearing loss were sensorineural with overlapping bone conduction on air conduction.

These results agree with **Liberman et al.** [11] who report the audiologic profile of patients who had cancer in childhood. The hearing loss identified in cancer patients, examined years after the completion of treatment was bilateral, sensorineural and symmetrical, predominantly affected the frequencies of 4, 6, and 8 kHz.

This happened due to affection of cisplatin chemotherapy on basal turn of cochlea as degeneration of the outer hair cells and stria vascularis**, Lauterman J.** [12] also has suggested there is decrease in the level of cochlear glutathione and formation of reactive oxygen species.

Greenee et al.[13] also reported that, the incidence of cisplatin induced ototoxicity was even more prevalent in patients receiving both cisplatin and radiation to their cochlea.

In this study, Extended high frequency audiometry revealed highly significant increasing in hearing thresholds at frequencies (10, 12.5, 16KHZ) after cisplatin therapy in the study group .Table(1,2)

It is clear that, the result of this study supports the previous report that demonstrated the vulnerability of high frequencies affection to ototoxic drugs [15] .

These finding agree with **Ravi et al.,** [14] who reported that cellular equivalent for cisplatin- related ototoxicity seems to be the loss of the outer hair cells in the organ of corti. As the onset of ototoxic damage effects the basal cochlea that could be detected at very high frequencies of hearing. extended high frequency audiometry (8-20KHZ) which is a favourable test for the early evaluation of ototoxicity.

In this study, Tympanometry type (A) was found in study group in all patients except 3 patients were type (C) after cisplatin therapy.

Transient evoked oto-acoustic emission (TEOAE) results in study group revealed statistically significant decreasing in signal to

noise ratio at frequencies from (1-4KHZ) after cisplatin therapy on the right side and left side .Table(3), Signal to noise ratio (SNR) in TEOAEs were failed in 15 patients after cisplatin therapy, 2 are partial pass and one patient is passed, middle ear disease accounted for abnormal Transient evoked otoacoustic emission in 3 patients with significant negative middle ear pressure, the other patients with normal middle ear pressure revealed correlation between TEOAEs reproducibility and PTA threshold.

These results agree with **Beck et al., [15]** who found TEOAE amplitude decrease in different frequencies in 86% of the cisplatin received patients.

Also agreed with **Plinkert and Krober [16]** who reported that 31%of the patients' emission amplitude decrease in frequencies who received 100mglm^2 cisplatin.

In this study, there was Significant positive correlation between age and hearing loss in pure tone audiometry at (4,8KHz) and in extended high frequency audiometry at (10,12.5Khz).Table (4)

The patients of old age group (40-50 years) more vulmerable to increase hearing loss more than lower age group. Effect of cycles shows statistically Significant positive Correlation between number of cycles of cisplatin chemotherapy and hearing loss at 4000 and 8000 Hz in pure tone audiometry and at all frequencies in Extended high frequency audiometry (10, 12.5 and 16KHz).Table (5)

In this study, The patients with number of 5 cycles (C5) and 6 cycles (C6) are showed more increase hearing loss at 4,8KHz in PTA and at all frequencies of extended high frequency audiometry (10, 12.5 and 16KHz) than those patients who received 3 cycles and 4 cycles of cisplatin treatment in this study.

These results are consisted with **American Speech-Language-Hearing Association [17]** that reported the individual and cumulative dose affects of cisplatin Ototoxicity, Particularly cumulative doses greater than 400 mg/m2 seem to be directly related to the incidence and severity of ototoxicity.

In this study, (Ear effect), there was no significant difference between level of hearing loss in right & left side in pure tone audiometry (250 through 8000Hz) and in extended high frequency audiometry (10,000 through 16000Hz) .Table (6).

CONCLUSION

Transient evoked otoacoustic emission and high frequency audiometry (4 through 16 KHz) are the most sensitive audiological monitoring test. There was positive correlation between age and symmetrical sensorineural hearing loss in pure tone audiometry at 4,8KHz and extended high frequency audiometry at 10,12.5 KHz. There was positive correlation between numbers of cycles of cisplatin and hearing threshold in pure tone audiometry at 4,8KHz and extended high frequency audiometry at (10 through 16KHz).

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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