Decrease of Sensorineural Hearing Frequency and Cochlear Hair Cell Function in Malignant Head and Neck Tumor Post Cisplatin Chemotherapy Series II

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Abstract

Background: Malignancy in head and neck is mostly squamous cell carcinoma which are relatively radiosensitive. Giving chemotherapy combination of cisplatin-5 fluorouracil most frequently used in Lotus inpatients unit of Dr. Soetomo General Hospital Surabaya.

Purpose : This study aimed to prove the decrease of sensorineural hearing frequency and cochlear hair cells function in malignant head and neck tumors patients post- cisplatin chemotherapy series II.

Method: The samples were malignant head and neck tumor patients that would receive cisplatin chemotherapy. The inclusion criteria wereaged 18 to 65 years, malignant head and neck tumors planning to get cisplatin chemotherapy, intact tympanic membrane, ANM checks within normal limits. Tympanogram type A, DPOAE examination with pass results.

Results: Pre-and post-cisplatinchemotherapy series I did not obtain any changes, those were pass on all frequencies. Mc Neymar test on DPOAE post-cisplatin chemotherapy I obtained p = 0.250 in 6 kHz frequency (p>0.05). DPOAE post-cisplatin II in 6 kHz frequency showed no significant difference (p>0.05)

Conclusion: There was no decrease of outer cochlear hair cells function in malignant head and neck tumors patients who received cisplatin chemotherapy series II.

Keywords: *cisplatin-5 fluorouracil chemotherapy, sensorineural hearing, intact tympanic membrane, cochlea.*

Introduction

Head and neck malignancy is a major health problem in the world. In America 2006 it is estimated about 500,000 new cases[1]. Head and neck malignancy (>75%) is a type of squamous cell carcinoma which is relatively radiosensitive. Approximately one-third is still in early stage that can be treated with surgery or radiotherapy. Therefore chemotherapy is an alternative choice in the treatment of malignant head and necktumors[2].

Combination chemotherapy of cisplatin-5 fluorouracil is frequently used in Lotus inpatients unit of Dr. Soetomo General Hospital Surabaya[3]. Along with this fact, chemotherapy toxicity is now a concern. one of them is ototoxic. Chemotherapy drugs that have ototoxic effects are cisplatin, carboplatin, nitrogen mustard, metrotrexat, vincristine, dactinomicyn, and bleomicyn[4].

Cisplatin (*cis-diamminedichloroplatinum*-CDPP) is one of the most widely used and most potent chemotherapeutic drugs for malignant head and neck tumors treatment. Giving high doses of cisplatin 100-120 mg/m^2 of body surface could cause progressive sensorineural hearing loss, Irreversible, and bilateral starting at a frequency above 8000 Hz which will eventually affect the lower frequencies if therapy is continued and accompanied by tinnitus[5]. A research in America reported that cisplatin chemotherapy led to sensorineural hearing loss of 82.6% at a frequency of

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3 kHz, 45.3% at 4 kHz, 81.0% at 6 kHz and 90.5% at 8 kHz with pure tone audiogram examination[6]. Another study on malignant tumors patients using Distortion Product Otoacoustic Emissions (DPOAE) obtained outer hair celldamage of 63.4% (6.7% at 6-10 kHz, 56.7% at 8-10 kHz) post-first chemotherapy and 70% post-second chemotherapy (8.3% at 4-10 kHz, 31.7% at 6-10 kHz, 30% at 8-10 kHz)[7]. Hearing loss at high frequency may not cause communication disorder but continuesly there will interfere conversations frequency resulting patient's communication disorder[5]. Cisplatin damages the cochlear outer hair cells progressively from the base to the apex therefore sensorineural hearing loss occurs starting at high frequency. Apoptosis causes death of cochlear outer hair cells resulting in sensorineural hearing loss[8]. On the condition of outer hair cells damaged, the damage can affect the inner hair cells and supporting cells. The cisplatin ototoxicity is not limited to the cochlear outer hair cells but also reported to occur atrophy of vascular stria, collapse of reisnerr membrane and the degeneration of spiral ganglion[5, 9, 10].

Cochlear hair cells play a role in improving or sharpening the peak of traveling waves by increasing basilar cellular activity on a particular frequency. Cochlear outer hair cells damage due to cisplatin occurs from the third day in the basal to apex[11]. An objective diagnose tool of cochlear outer hair cell damage is otoacoustic emission. Distortion product otoacoustic emission can evaluate cochlear response at high frequency which is the sensitive frequency to detect muscle otoxicity[10].

Method

This study was an observational study with a non-comparable longitudinal approach conducting at Audiology inpatient unit of Otolaryngology Department Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Hospital Surabaya, Indonesia. The samples were malignant head and neck tumor patients who would receive cisplatin chemotherapy. The sampling technique used in this study was consecutive sampling

The inclusion criteria wereaged 18 to 65 years, malignant head and neck tumors planning to receive cisplatin chemotherapy, intact tympanic membrane, ANM checks within normal limits, Tympanogram type A, and DPOAE examination with pass results. While the exclusion criteria werea presence history of noise exposure, radiotherapy in the temporal bone area, previous otoxic drugs, hypertension and diabetes mellitus.

This research used the following tools and materials; tools for ear examination cosisting ofhead lamp, cotton wool, cotton and otoscope. ANM checking tool consisted of Audiometer AD type 229E, a tympanometry type Inter acoustic AT 35. DPOAE examination tool used 100 mg/m^2 body surface and data collection sheet.

The samples were patients with tympanogram A. This study used one ear sample but if both ears met the criteria, the sample used was right ear. ANM and DPOAE I (pre chemotherapy)/cisplatin chemotherapy I used100 mg/m2 body surface. After 3 days, ANM and DPOAE II (post-chemotherapy I) were performed. Administration of cisplatin chemotherapy II was given 3-4 weeks after cisplatin chemotherapy I. After 3 days of cisplatin II series, ANM and DPOAE III (post cisplatin II chemotherapy) were performed.

The data were tabulated and analysed statistically using SPSS (SPSS. Inc. Chicago IL). The data obtained was then examined and processed statistically by paired sample t test to analyze high frequency sensorineural hearing loss and Mc Neymar test to analyze the decrease of cochlear outer cell function pre and post cisplatin chemotherapy.

Result

Table 1 showed age, sex and diagnosis distribution.

Table 1. Age, Sex and Diagnosis Distribution

Variable	Total	%
Age (year)		

***Cont.*. Table 1. Age, Sex and Diagnosis Distribution**

<35 35-45 >45	1 9 2	8.33 75.00 16.67
Sex		
Male Female	8 4	66.67 33.33
Diagnosis Distribution		
Nasopharyngeal Carcinoma Sinonasal Carcinoma Laryngeal Carcinoma	8 3 1	66.67 25.00 8.33
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A paired sample t test on ANM results post-cisplatin chemotherapy I and II obtained p = 0.339 at 4 kHz, p = 0.053 at 6 kHz and p = 0.809 at 8 kHz that meant ANM post cisplatin chemotherapy I and II has no significant difference (p> 0.05). Based on statistical calculation using paired sample t test obtained p = 0.339 at 4 kHz, p = 0.002 at 6 kHz and p = 0.166 at 8 kHz that meant ANM pre and post cisplatin chemotherapy II at 4 kHz and 8 kHz had no significant difference (p> 0.05) while at 6 kHz had a significant difference (p <0.05). DPOAE pre-and post-chemotherapy cisplatin I obtained pass at all frequencies, therefore the data obtained were homogeneous and could not be done a statistical test. DPOAE examinationpre-chemotherapy was 12 patients (100%) and 12 patients (100%) post-chemotherapy (Table 2).

Table 2. ANM Result

ANM	Pre-Chemotherapy		Chemotherapy I		Changes		T	p
	Average	SD	Average	SD	Average	SD		
ANM Result Pre and Post Cisplatin Chemotherapy I								
4 KHz 6 KHz 8 KHz	22.50 22.08 22.92	5.000 6.557 3.965	22.50 24.17 24.17	5.000 6.86 4.174	- -2.083 -1.250	- 3.343 3.108	- -2.159 -1.393	- 0.054 0.191
ANM Result Post Cisplatin Chemotherapy I and II								

Cont... **Table 2. ANM Result**

4KHz 6KHz 8KHz	22.50 24.17 24.17	5.00 6.686 4.174	23.33 26.67 24.58	3.257 3.892 4.502	-.8.33 -.250 -.417	2.887 3.989 5.823	-1.000 -2.171 -0.248	0.339 0.053 0.809
ANM Result pre and Post Chemotherapy II								
4 KHz 6 KHz 8 KHz	22.50 22.08 22.92	5.00 6.557 3.965	23.33 26.67 24.58	3.257 3.892 4.502	-.833 -4.583 -1.667	2.887 3.965 3.892	-1.00 -4.005 -1.483	0.339 0.002* 0.166

Mc Neymar test obtained p = 0,250 at 6 kHz while at 1,2,3 and 4 kHz, DPOAE results were pass, no changes post- cisplatin chemotherapy I and II (homogeneous), thus the data could not be tested. DPOAE post-cisplatin chemotherapy I and II at 6 kHz had nosignificant difference (p>0.05). Mc Neymar test obtained p = 0.250 at 6 kHz while at 1,2,3 and 4 kHz, DPOAE results were pass, no changes post-cisplatin chemotherapy II (homogeneous). DPOAE post-cisplatin chemotherapy II at 6 kHz showed no significant difference (p>0.05).

Table 3. DPOAE Result

DPOAE	**Pre**	**Post I**
DPOAE Result Pre and Post Cisplatin Chemotherapy		
Pass (1.2.3.4.6 kHz) Refer (1.2.3.4.6 kHz)	12 (100%) -	12 (100%) -
DPOAE Result Post Cisplatin Chemotherapy I and II		
Pass freq. 1.2.3.4.6 kHz Refer freq. 1.2.3.4 kHz freq. 6 kHz	12 (100%) - -	9 (75%) - 3 (25%) *
DPOAE Result Pre and Post Cisplatin Chemotherapy II		
Pass freq. 1.2.3.4 kHz Refer freq. 1.2.3.4 kHz Freq. 6 kHz	12 (100%) -	9 (75%) - 3 (25%) *

Discussion

The results indicated that the most patients based on age distribution aged 35-45 years. Most patients with nasopharyngeal carcinoma were on 4-6th decade and the climax was on 5th decade that was between 41-50 years[12]. In 2009, most sinonasal carcinoma patients in Dr. Soetomo General Hospital aged>40 years[13]. Age over 50 years is very influential on the incidence of malignant head and neck tumor due to a decrease in physiological capacity and reduced ability to deal with environmental stress[14].

The ratio of male versus female was 2: 1. This result was in accordance with the data of Oncology Unit of Otolaryngology Department, Dr Soetomo General Hospital that nasopharyngeal carcinoma was the most malignant head and neck tumor. The ratio of male versus femele were 2: 1 in nasopharyngeal carcinoma, 3: 2 in sinonasal carcinoma, and 11: 1 in laryngeal carcinoma[12, 13]. Male is the most suspected gender because they often go out of the house to work therefore the risk of carcinogenic substances exposure and other environmental factors are higher[1].

ANM pre and post cisplatin chemotherapy I at 4 kHz had no changes therefore the data could not testedstatistically. While at 6 and 8 kHz obtained no significant different. This was different with other studies that obtained sensorineural hearing loss as much as 33% post-cisplatin chemotherapy I but it was not stated at what frequency the sensorineural hearing loss happened[15]. This difference could also be affected by the effects of chemotherapy combined with radiotherapy, thus increasing toxicity. This study was consistent with another study that stated the cisplatin ototoxicity with conventional ANM examination obtaining 1 person (35.7%) with sensorineural hearing loss, if with the extended high frequency (EHF) audiometry obtaining 88.1% with the range of 40-60 dB[16].

The researchers have not been able to find the reason why the significance only occured at 6 kHz while at 4 kHz and 8 kHzpre and post cisplatin chemotherapy II obtained no significance difference.This result was inconsistent with other studies suggesting sensorineural hearing loss occurring since the administration chemotherapy Iand being progressive with larger cumulative doses[15]. Based on comparative studies between audiogram and cochlear damage, cochlear outer hair cell damage caused hearing loss between 55-65 dB.Cochlear inner hair cells caused a very heavy hearing loss of 95 dB[14].

There was no decrease in cochlear outer hair cell function in patients with head and neck tumor post-cisplatin chemotherapy I. This was not in accordance with the theory that cisplatin would cause disturbance after cisplatin chemotherapy I.Other studies showed the results of DPOAE post cisplatin chemotherapy Iobtaining refer at 6 kHz frequency as much as 6.7% and at 8 kHz as much as 56.7%. Another difference was the number of samples of 30 people that was more than this study[7].

DPOAE post-cisplatin chemotherapy I and II obtained no significant difference. This is different from other research obtaining refer at 4 kHz frequency as much as 8.3%, 6 kHz as much as 31.7% and 8 kHz as much as 30%[7]. This difference could be due to the differences of sample size and the weakness of the tools used in this study. Research on Testicular Carcinoma in Hungary showed SNHL in samples receiving cumulative doses>400 mg/m^2 while in samples with cumulative doses <300 mg/m^2 obtained no significant difference[17].

Pre and post cisplatin chemotherapy II results obtained no significant difference. The cisplatin ototoxicity was highly dependent on cumulative doses. Ototoxicity increased at doses>400 mg, with DPOAE examination obtained referral data at lower frequencies. In this study chemotherapy I used accumulative dose between 120-170 mg, post-chemotherapy II used cumulative dose between 240-340 mg.Research on testicle carcinoma in Hungarian obtained an impaired function of cochlear outer hair cells in samples receiving cumulative doses>400 mg/m^2 while in samples with cumulative doses <300 mg/m^2, there was no significant impaired function of cochlear hair cells[17]. This inadequacy of this study with other studies might be due to several factors that induce cisplatin ototoxicity. Many things could be an induced factors of cytotoxicity such as cumulative dose (>400 mg), long-term administration (≥6months), administration method, individual susceptibility variation, extreme age, previous hearing loss, anemia, radiation history, and the use ofother ototoxicity drugs[17]. Chemotherapy affects the body cells. Continuous exposure causes damage to hair cells in the cochlea that cause cochlear dysfunction and will increase the hearing threshold.[18] Chemotherapy has physical and psychological side effects.[19] There was a correlation between the increased dose of cisplatin with the cytotoxicity effects on NPC stem cell.[20]

Conclusion

It was obtained sensorineural hearing loss at 6 kHz frequency, while at 4 and 8 kHz frequencies were still in normal state (no hearing loss). Malignant head and neck tumor patients who received cisplatin chemotherapy II. There was no decrease in cochlear outer hair cells in malignant head and neck tumor patients who received cisplatin chemotherapy II.

Ethical Clearance : This research is approved by Ethical Clearance from Universitas Airlangga dan Dr

Soetomo Teaching Hospital

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