Sensorineural Hearing Loss and Cochlear Outer Hair Cell Function Nasopharyngeal Carcinoma Due to Influence of Cisplatin

Fira Sofia[1], H.M.S Wiyadi[1], Achmad Chusnu Romdhoni[1]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Academic Medical Center, Surabaya, Indonesia

Abstract

Background: Nasopharyngeal carcinoma is a type of tumor sensitive to chemotherapy and radiotherapy. One of the various chemotherapy drugs is cisplatin. However, the cisplatin effects on sensorineural hearing loss and cochlear outer hair cell dysfunction in patients with nasopharyngeal carcinoma have not been evidently discovered. **Objective**: This research aims to prove the cisplatin effects on sensorineural hearing loss and cochlear outer hair cell dysfunction in patients with nasopharyngeal carcinoma. **Materials and Methods**: This research adopted analytical observation by employing a prospective cohort study approach. In addition, the sampling technique implemented consecutive sampling. This research was conducted at the ENT-HN Outpatient Unit (URJ) of the Neuro-otology Division of Dr.Soetomo Public Hospital during September-November 2020 period. The auditory test was executed by Pure-Tone Audiometry (ANM) and Distortion Product Otoacoustic Emission (DPOAE). Meanwhile, the statistical analysis was assessed by the Wilcoxon and McNemar test. **Results**: This research involved 22 samples. The cumulative dose of cisplatin up to chemotherapy series III ranged from 260-270 mg with an average of 265.45+5.10 mg. The results of the ANM test before and after chemotherapy series III employing Wilcoxon test indicated significant differences in frequency of 500 Hz (p-value =0.014), 6000 Hz (p-value = 0.011), 8000 Hz (p-value = 0.019),10000 Hz (p-value = 0.000), and 12500 Hz (p-value = 0.002). The frequency of 125 Hz with a p-value = 0.343, the frequency of 250 Hz with a p-value = 0.690, the frequency of 1000 Hz with a p-value = 0.179, the frequency of 2000 Hz with a p-value = 0.459, and the frequency of 4000 Hz with a p-value = 0.125 indicated no significant difference witha p-value greater than 0.05. Meanwhile, the DPOAE test results before and after chemotherapy series III utilizing the McNemar test demonstratedthe frequency of 1000 Hz (p-value = 1.000), 2,000 Hz (p-value = 0.453), 4000 Hz Hz (p-value = 1.000), 6000 Hz (p-value = 0.388), 8000 Hz (p-value = 0.754), and 1000 Hz (p-value = 1.000). The comparative analysis of the DPOAE test results before and after chemotherapy Series 3 suggested no significant difference, with a p-value greater than 0.05 at all frequencies. **Conclusion**: There were cisplatin effects on sensorineural hearing loss in patients with nasopharyngeal carcinoma after chemotherapy series 3 based on ANM test at the frequencies of 500 Hz, 6000 Hz, 8000 Hz, 10000 Hz, and 12500 Hz. There were no cisplatin effects on cochlear outer hair cell dysfunction in patients with nasopharyngeal carcinoma after chemotherapy series 3.

Corresponding author:
Dr. A.C. Romdhoni,
dr., Sp. T.H.T.K.L (K), FICS

Keywords*: cisplatin, sensorineural hearing loss, cochlear outer hair cell dysfunction, nasopharyngeal carcinoma*

Introduction

High-frequency sensorineural hearing loss and cochlear outer hair cell dysfunction are some of the clinical manifestations of ototoxicity after cisplatin administration.[1]Ototoxicity is a condition where there is damage to the cochlea or the vestibular apparatus, caused by exposure to chemicals, including drugs.[2]Hearing loss may occur at lower frequencies if the chemotherapy is continued. One of the causes of hearing loss severity is the cumulative dosage of cisplatin. Cisplatin administered at a high dose of 100-120 mg/m^2 based on body surface area, can cause progressive, irreversible, and bilateral sensorineural hearing loss starting at a frequency of 8000 Hz.[3]

Cisplatin damages the cochlea outer hair cells progressively from the base to the apex, which causes sensorineural hearing loss at high frequencies. Ototoxicity occurs through necrosis, apoptosis, or a combination of both. Cisplatin causes an increase in reactive oxygen species (ROS), which will trigger apoptosis. Apoptosis causes the death of the cochlea outer hair cells, resulting in sensorineural hearing loss.[3]

Research conducted in Tamil Nadu, India, in 2018, reported that 63% of nasopharyngeal carcinoma patients experienced hearing loss due to cisplatin use,but 37% of patients did not experience hearing loss. An audiometry test was performed after administration of chemotherapy series 3 and series 6.[3] Another study in India reported that after receiving cisplatin administration, 22% of the patients experienced hearing loss at a frequency of 4000 Hz to 6000 Hz and 71% of the patients experienced it at a frequency of more than 8000 Hz.[4]

Auditory tests to detect the cisplatin effects on sensorineural hearing and cochlear outer hair cell dysfunction employs pure tone audiometry (ANM) and distortion product otoacoustic emission (DPOAE). The degree of hearing loss was determined by calculating the hearing threshold of air conduction (AC) on pure tone audiometry. Distortion product otoacoustic emission could evaluate the cochlear response at high frequency, a sensitive frequency for detecting ototoxicity.[5]

This study aims to prove the effect of cisplatin on sensorineural hearing loss and identify the function of outer hair cells in patients with nasopharyngeal carcinoma.

Materials and Methods

The research was done on an analytic observational basis.The research design utilizeda prospective cohort study.The study population included nasopharyngeal carcinoma patients, who received cisplatin chemotherapy up to series 3 at the"Teratai" Surgical Inpatient Care Unit of ENT-HN Polyclinic at RSUD, headed by Dr. Soetomo Surabaya from September until November 2020. The research sample covered all accessible populations that met the inclusion and exclusion criteria. The inclusion criteria required patients aged from 18 to 60 years old, while the exclusion criteria included patients with nasopharyngeal carcinoma with hypertension and diabetes mellitus and patients with nasopharyngeal carcinoma who had received radiotherapy. Additionally, the criteria for dropout patients included the replacement of the cisplatin chemotherapy regimen by another platinum-based group (carboplatin).Sampling was conducted by consecutive sampling.

This research has fulfilled ethical clearance (Ref. No: 0112/LOE/301.4.2/IX/2020). The variables analyzed included sensorineural hearing loss and the functions of outer hair cells. The procedure of this study encompassed recording and examination of ANM and DPOAE before and after cisplatin chemotherapy series 3. The cumulative dose of

cisplatin until the chemotherapy series 3 in patients with nasopharyngeal carcinoma in this study ranged from 260 to 270 mg with a mean value of 265.45 + 5.10 mg.

Sensorineural hearing loss is a hearing loss in one ear caused by damage to outer hair cells in the cochlea. The examination involved pure tone audiometry at each frequency. The audiometer employed in this study was Astera II of Madsen, produced in Denmark in 2017. Audiogram of AC and BC values reached more than 25 dB which coincide (negative air-bone gap). The ANM examination resulted in an audiogram with AC and BC curves. AC examination was performed at the frequencies of 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz, 8000 Hz, 10000 Hz, and 12500 Hz, while BC examination was at the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. The PTA examination was performed before receiving chemotherapy series 1 and after chemotherapy with cisplatin series 3.

Cochlear outer hair cell dysfunction is a disorder of the function of transmitting sound waves from the inner ear to the auditory nerve cells. The cochlear outer hair cell dysfunction was detected through the DPOAE examination. The DPOAE examination in this study was performed at six frequencies, namely 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz, 8000 Hz, and 10000 Hz. The criteria for the examination results were"pass" and "refer."

All data collected in data collection sheets were then arranged in a tabular form and then analyzed statistically. Analysis of the effect of cisplatin on sensorineural hearing loss and impaired cochlear outer hair cell function in patients with nasopharyngeal carcinoma utilized Wilcoxon and McNemar statistical tests.The results of this study were determined by a significance level (α) of 0.05.

Results and Discussion

The results indicated more male patients than females with a ratio of 4.5:1 (Table 1). The age distribution of the samples displayed that most of the patients belonged to the 40-50 year age group.

Table 1. Age and Sex distribution of the Karsinoma Nasofaring patients

Age	n	%
<20	1	4.55
>20 - 30	1	4.55
>30 - 40	2	9.10
>40 - 50	12	54.55
>50 - 60	6	27.25
Total	22	100
Gender		
Male	18	81.82
Female	4	18.18
Total	22	100

Table 2. Sensorineural hearing loss before and after chemotherapyseries 3

Before chemotherapy	After chemotherapy		Total	Percentage (%)
	Normal	SNHL		
Normal	1	8	9	40.91
SNHL	0	13	13	59.09
Total	1	21	22	100.00
Percentage (%)	4.55	95.45	100.00	

Sensorineural hearing loss before chemotherapy was detected in 13 patients (59.09%), and normal hearing was detected in 9 patients (40.91%). Sensorineural hearing loss before chemotherapy series 3 was detected in 21 patients (95.45%), and normal hearing was detected in 1 patient (4.55%).

Table 3. Comparison of PTA examination results before and after chemotherapy Series 3

Frequency (Hz)	Shapiro-Wilk		Wilcoxon (p)
	Before chemotherapy (p)	After chemotherapy series 3 (p)	
125	0.000	0.000	0.343
250	0.002	0.000	0.690
500	0.000	0.002	0.014*
1000	0.003	0.092	0.179
2000	0.057	0.001	0.459
4000	0.049	0.166	0.125
6000	0.043	0.443	0.011*
8.000	0.017	0.006	0.019*
10000	0.000	0.004	0.000*
12500	0.000	0.000	0.002*

Comparative analysis of PTA examination results before and after chemotherapy series 3 using the Wilcoxon test indicated significant differences at frequencies of 500 Hz (p = 0.014), 6000 Hz (p-value = 0.011), 8000 Hz (p-value = 0.019), 10000 Hz (p-value = 0.000) and 12500 Hz (p-value = 0.002). The frequency of 125 Hz with a p-valueof 0.343, the frequency of 250 Hz with a p-valueof 0.690, the frequency of 1000 Hz with a p-value of 0.179, the frequency of 2000 Hz with a p-value of 0.459, and the frequency of 4000 Hz with a p-value of 0.125 indicated no significant difference, where the p-value of was greater than 0.05.

The age of the patients as the samples ranged from 18-60 years. The minimum age was determined based on the lowest age for adult patients, while the maximum age of 60 years was applied to avoid bias from presbycusis. Presbycusis is a hearing loss due to a degeneration process at 65 years or more, characterized by decreased hearing sensitivity in both ear.[6]

The most affected age group ranged > 40-50 years. This age group was the initial age for exposure to carcinogenic agents. That is because it takes several decades to develop malignant cells of nasopharyngeal carcinoma until they appear clinically. Therefore, exposure to carcinogens has a significant effect on the incidence of malignancy. Old age affects the incidence of head and neck malignant tumors, related to a decrease in physiological capacity and a reduced ability to deal with environmental stress. Thus, they are easily exposed to oncogenic viruses, carcinogenic substances, and other environmental factors.[7]

The cumulative dosage of cisplatin to chemotherapy series 3 in patients with nasopharyngeal carcinoma in this study ranged from 260 to 270 mg. The cumulative dosage of cisplatin given was an important factor in chemotherapy. The cumulative dosage of cisplatin providing chemotherapy effects to nasopharyngeal carcinoma was an average of 200 mg/m Cisplatin administered at a high dosage of 100-120 mg/m^2 based on body surface area could cause progressive, irreversible, and bilateral sensorineural hearing loss starting at a frequency of 8000 Hz.[3] The cumulative dosage of cisplatin also affected the severity of the hearing loss. An audiometry test was performed after administration of chemotherapy series 3 and series 6.[3]

An audiometry test was performed after administration of chemotherapy series 3 and series 6.[3]It was in accordance with the literature stating that high-frequency sensorineural hearing loss and cochlear outer hair cell function were one of the clinical manifestations of ototoxicity after cisplatin administration.[1,3]

High-frequency hearing loss is synonymous with SNHL because of damage to the cochlear hair cells. Acoustic energy entered the cochlea through the footplate of the stapes at the foramen ovale and was amplified in the perilymph of the scala vestibuli. Sound waves traveled along the basilar membrane from the base to the apex. The High-frequency sound waves (10000 Hz) traveled maximally at the base and did not reach the apex. However, the low-frequency sound waves (125 Hz) could travel up to the apex. Sound waves travel caused deflection of the stereocilia, causing ion channels at the ends of the stereocilia to open and close. This explained that high-frequency sounds were sensitive at the base of the cochlea and low frequencies at the cochlear apex. It caused hearing loss which usually occurs at high-frequency first and then the low-frequency.[8]

The analysis of the DPOAE examination result before and after cisplatin chemotherapy series 3 utilized the McNemar test on all frequencies indicated no significant difference. This result contrasts with the study of Teotia et al. reported that 90.00% of patients had ototoxic on DPOAE examination after cisplatin

chemotherapy series 3. The study of Eiamprapai et al. suggested that the administration of cumulative dose in laboratory animals causes cochlear outer hair cells loss on cochlea basal turn. Therefore, it more apparent at high frequency.[9,10]These differences could be attributable to the dissimilarity in the sample and utilized tools size in this study. Many things could be the factor of induced ototoxicity, namely cumulative dose more than 400mg, long-term administration of greater than or equal to 6 months, administration techniques, individual variations in susceptibility, extreme age, previous hearing loss, anemia, history of radiation exposure, and other ototoxic medication use.[11]

Conclusion

There were cisplatin effects on sensorineural hearing loss in patients with nasopharyngeal carcinoma after chemotherapy series 3 based on ANM test at the frequencies of 500 Hz, 6000 Hz, 8000 Hz, 10000 Hz, and 12500 Hz. There were no cisplatin effects on cochlear outer hair cell dysfunction in patients with nasopharyngeal carcinoma after chemotherapy series 3.

Conflict of Interest: No conflict of interest.

Ethical Approval: All procedures performed in this study that involved human participants are in accordance with the ethical committee standards of Dr. Soetomo Hospital, Surabaya, with ethical number 0112/LOE/301.4.2/IX/2020.

Informed Consent

Informed consent was obtained from all samples of individuals included in this study.

References

1. Oun R, Moussa YA, Wheate NJ. The side effect of platinum-based chemotherapy drugs: a riview for chemists. *Dalton Transactions*.2018; 47:6645-53.
2. Chang KW, 2014. Ototoxicity. In Johnson JT, Rosen CA.(eds.)*Bailey's head and neck surgery-otolaryngology*, 5th edition, Philadelphia: Lippincott Willias & Wilkins, p.2542-55.
3. Sivasankari L, Subramanian L. A study of cisplatin chemotherapy and hearing loss. *Internasional Journal of Otorhinology and Head and Neck Surgery*. 2018; 4:1297-1300.
4. Kalyanam B, Sarala N, Mohiyuddin SMA, Diwakar R, 2018. Auditory function and quality of life in patients receiving cisplatin chemotherapy in head and neck cancer: a case series follow up study. *Journal of Cancer Research and Therapeutic***.** 2018; 14: 1099-1104.
5. Yu KK*, et al*. Comparison of the effectiveness of monitoring cisplatin-induced ototoxicity extended high-frequency pure-tone audiometry or distortion-product otoacoustic emission. *The Korean Audiological Society*.2014; 58-68.
6. Busis SN, 2006. Presbycusis. In: Calhoun KH, Eibling DE, (eds.)*Geriatric otolaryngology*, New York: Taylor and Francis, p.77-90.
7. Salehiniya H, Mohammadian M, Hafshejani AM, Mahdavifar N. Nasopharyngeal cancer in the world : epidemiology, incidence, mortality and risk factors. *World Cancer Research Journal*. 2018; 5: 1-8.
8. Weber PC, Khariwala S. Anatomy and physiology of hearing. In Johnson JT, Rosen CA, (eds.) *Bailey's head & neck surgery otolaryngology*, 5thedition, Philadelphia: Lippincott Williams & Wilkins, p. 2014; 2253-73.
9. Teotia M, Bist SS, Agarwal VK, Gupta M, 2017. Distortion product otoacoustic emissions and high frequency audiometry for early detection of cisplatin induced ototoxicity. *Internasional Journal of Contemporary Medical Research***.** 2017; 6: 1315-18.
10. Eiamprapai P, Yamamoto N, Hiraumi H, Nihimura EO, Kitamura M, Hirano S, *et al*. Effect of cisplatin on distortion product

otoacoustic emissions in Japanese Patients. *The Laryngoscope*. 2012; 122: 1392-6.

11. Biro K, Noszek L, Prekopp P, Nagyivanyi K, Geczi L, Gaudi I, Bodrogi I. Characteriristic and risk factors of cisplatin-induced ototoxicity intesticular cancer patients detected by Distortion Product Otoacoustic Emission. *Oncology*. 2006; 70: 177-184.