International Journal of Science and Healthcare Research
Vol.6; Issue: 1; Jan.-March 2021
Website: ijshr.com
Original Research Article *ISSN: 2455-7587*

The Effect of Cisplatin Chemotherapy on Ototoxicity Event in Retinoblastoma Patients

Eka Savitri[1], Deti Fitria[2], Amsyar Akil[3], Dasril Daud[4], Nadhirah Rasyid[5], Abdul Kadir[6]

[1]Department of Ear, Nose, Throat, Head-Neck Surgery, Medical Faculty, Hasanuddin University, Makassar, Indonesia
[2]Department of Ear, Nose, Throat, Head-Neck Surgery, Medical Faculty, Hasanuddin University, Makassar, Indonesia
[3]Department of Ear, Nose, Throat, Head-Neck Surgery, Medical Faculty, Hasanuddin University, Makassar, Indonesia
[4]Department of Child Health, Medical Faculty, Hasanuddin University, Makassar, Indonesia
[5]Department of Child Health, Medical Faculty, Hasanuddin University, Makassar, Indonesia
[6]Department of Child Health, Medical Faculty, Hasanuddin University, Makassar, Indonesia

Corresponding Author: Eka Savitri

ABSTRACT

Background: Chemotherapy is one of the cancer treatments recommended as a first line in neck head cancer, one of which is cisplatin with frequent side effects ototoxic. Retinoblastoma is a neoplasm originating from neuroretina or glía cells that are malignant in children, especially under 5 years old. Various therapies are carried out, one of which is chemotherapy. Ototoxicity due to the use of cisplatin is a side effect that must be taken into account and requires the best early detection and monitoring.
Objective: This study aimed to assess and compare the function of cochlear hair cells with OAE examination before and after chemotherapy in retinoblastoma grade III and IV patients
Materials and Methods: This study was conducted using cohort prospective technique on 22 patients each sample was examined with OAE. OAE examination done before and after cisplatin chemotherapy in retinoblastoma stage III and IV
Results: The result showed that before and after administration of chemotherapy, all groups both stage III and stage lV did not change, the results were normal for all subjects with pass value
Conclusion: The function of the cochlear hair cell based on DPOAE examination in patients with stage III and IV retinoblastoma at each frequency obtained a pass value which meant that no cochlear hair cell damage which indicated no occurrence of ototoxicity and there were no significant differences of cochlear hair cell function between patients with stage III and IV retinoblastoma after receiving cisplatin chemotherapy.

Key words: Cisplatin, ototoxicity, retinoblastoma

1. INTRODUCTION

Head and neck cancer is a heterogeneous tumor and about 90-95% of squamous cells are the most common histology. The incidence half a million cases per year and continues to increase. In 2014 the incidence 55,070 cases in the United States while in Europe 139,000 of new cases of head and neck cancer.[1]

Chemotherapy is a cancer treatment using special drugs that can kill cancer cells. This chemotherapy aims to increase the cure rate in patients who are inoperable. Chemotherapy agents that have shown their activity in cancer therapy are recommended as the first line in neck head cancer, which is platinum type, one of them is cisplatin.[2] The use of anti-cancer drugs started since 1964 and generally anti-cancer drugs are very toxic so that their use must be very careful and with the right indication. One of the many toxic effects is ototoxic which is

characterized by a decrease in hearing in patients with head neck malignant tumors after chemotherapy.[3]

The ototoxic characteristic is associated with high frequency sensorineural hearing loss, because pathological findings occur that damage mainly to the basal part of the cochlea, although it can also extend to intermediate frequencies, can be transient but is generally irreversible.[3,4] Sensorineural hearing loss due to damage to the cochlea can be detected by Otoacoustic Emission (OAE) examination so information can be obtained about cochlear function which will affect the patient's ability to understand the conversation needed to communicate.[5]

Hawkins states that a ototoxicity is a tendency of drugs and chemical substances that cause disruption of function and cellular degeneration of the inner ear, especially the end organs and neurons of the cochlea and vestibular. The sensitivity of the inner ear to the toxic effects of a drug has long been recognized as a treatment side effect in medicine.[6,7] Reported ototoxic incidence of 33% in patients given single dose 50mg/m2 cisplatin.[4] In several studies there were differences in ototoxic incidents ranging from 11% to 33%.[6,8]

Retinoblastoma is a neoplasm originating from neuroretina or glía cells that are malignant, an intraocular malignant tumor in children, especially under 5 years of age.[9] Retinoblastoma occurs unilaterally or bilaterally. Manifestations that can arise include leukocoria, conjunctiva chemosis, strabismus, propotosis and even blindness.[10] Generally rertinoblastoma therapy is adjusted to the stage and according to the different needs of each patient. One of the various therapies performed is chemotherapy, even for selected extraocular retinoblastoma chemotherapy combined with external beam radiation or orbital exenteration or high-dose chemotherapy in metastatic retinoblastoma.[11,12] According to Miranda's 2015 study, the visit of retinoblastoma cases in the Adam Malik Haji Hospital in Medan was higher in cases of stage III and IV compared to cases of stage I and II retinoblastoma.[14]

Management of chemotherapy in the Department of Pediatric FK UNHAS Wahidin Sudirohusodo Hospital Makassar use cisplatin in the retinoblastoma. Ototoxicity due to the use of cisplatin is a side effect that must be taken into account before using it as cancer therapy, so this is important because this condition can become permanent and thus reduce the quality of life of patients and add psychological burden to patients and their families. So that it takes the best early detection and monitoring that can be done without reducing the anti neoplastic effect.

2. MATERIALS AND METHODS

2. 1. Ethics Statement

Written informed consent from all patients or patient's parent and permit was obtained from Biomedical Research Ethics Committee on Human Faculty of Medicine Hasanuddin University Makassar Indonesia (Register number : 1122 / H4.8.4.5.31 / PP36-KOMETIK / 2018).

2. 2. Patient selection

The research subjects were selected from samples are all affordable populations that meet the inclusion criteria. Sampling was done by consecutive sampling, ie all patients with retinoblastoma who received cisplatin chemotherapy. Each sample underwent an OAE examination before and undergoing cisplatin chemotherapy. At the time of admission to hospital before receiving cisplatin chemotherapy, patients with stage III and IV retinoblastoma were examined by DPOAE, and when they returned to undergo further chemotherapy DPOAE was examined during the period January 2019 - April 2019, which came to Wahidin Sudirohusodo Hospital. The sample received cisplatin chemotherapy 80 mg / m2.

2.3 DPOAE examination

The DPOAE examination using brand GSI, Grason Stadler Type Corti made

in USA, calibration in 2017, and gives results using the criteria of Pass or Refer. The frequency range examined is 2000 to 5000 Hz. Each frequency check from 2000 to 5000 Hz is rated in the range of 0 to 15 dB. Pass if there are waves where SN (signal to noise) ≥6 dB at each frequency means that there is no damage to the integrity of the cochlear outer hair cell. Refer if there are no waves where SN <6 dB at each frequency means that there is damage to the integrity of the cochlear outer hair cell.

2.4. Statistical analysis

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 24.0 for Windows. Samples were analyzed using the Kruskal Wallis test and the Mann Whitney test.

3. RESULTS

3. 1. Characteristics of Respondents

During the study period, 22 patients with stage III retinoblastoma and stage lV retinoblastoma. Of the 22 patients consisting of 7 patients with stage III retinoblastoma and 15 patients with stage IV retinoblastoma. The sexes in this study were male as many as female 11 patients each. The age characteristics of the sample varied between 1 to 8 years with the most patients in the 3-5 year age group. Based on the location of retinoblastoma, there were 6 patients with dextra retinoblastoma, 10 patients with sinistra retinoblastoma, 6 people with bilateral retinoblastoma (Table 1).

Table 1: Patient characteristics

Characteristics samples	Retinoblastoma	
	Stage III n = 7 (%)	Stage IV n = 15 (%)
Gender		
Male	4 (57,1 %)	7 (46,6%)
Female	3 (42,9 %)	8 (53,4%)
Location Retinoblastoma		
Dextra	2 (28,5%)	4 (26,7 %)
Sinistra	5 (71,6 %)	5 (33,3 %)
Bilateral	0 (0%)	6 (40,0%)
Age		
< 2 year	3 (42,9 %)	4 (26,7 %)
3- 5 year	4 (57,1 %)	7 (46,6 %)
>5 year	0 (0%)	4 (26,7 %)

3.2 Analysis of the occurrence of ototoxicity due to cisplatin chemotherapy

Examination in stage III and stage lV retinoblastoma patients using DPOAE to assess cochlear hair cell function showed that before and after chemotherapy, all groups both stage III and stage lV were no change, the results were normal for all subjects namely pass values (Table 2) .

Table 2: Function of cochlear hair cells before and after cisplatin chemotherapy

Stage	n	Before DPOEA		After DPOEA		*P-value**
		Pass	Refer	Pass	Refer	
		n (%)	n (%)	n(%)	n(%)	
III	7	7(100)	0(0)	7(100)	0(0)	0
IV	15	15(100)	0(0)	15(100)	0(0)	

3.3 The results of SN (Sound to Noise) examination at each frequency of OAE examination

Table 3: Results of dextra ear PASS Examination Stage III and stage IV subjects after cisplatin chemotherapy

Frekuensi Pemeriksaan OAE (Hz)	Dekstra		Beda Mean	P*
	Stadium III	Stadium IV		
PASS	Nilai SN dalam dB Mean±SD	Nilai SN dalam dB Mean±SD		
2000	13.28±4.535	14.40±1.805	1.12	0.945
3000	13.85±3.023	14.13±3.091	0.28	0.953
4000	15.00±0.000	15.00±0.000	0	1.000
5000	15.00±0.000	14.93±0.258	0.07	0.837

The results of the comparative analysis of all stages III and IV PASS examinations did not show significant differences (P> 0.05), however the biggest difference in the PASS value was in PASS 2000, which is 1.12 following PASS 3000, which is 0.28 (Table 3).

The results of the comparative analysis of all PASS tests in stage III and IV did not show significant differences (P> 0.05), however the biggest difference in the PASS value was at PASS 2000, which was 1.87 (Table 4).

Table 4: Results of sinistra ear PASS Examination Stage III and stage IV subjects after cisplatin chemotherapy

Frekuensi Pemeriksaan OAE (Hz)	Sinistra		Beda Mean	P*
	Stadium III	Stadium IV		
PASS	Nilai SN dalam dB Mean±SD	Nilai SN dalam dB Mean±SD		
2000	15.00±0.000	13.13±3.044	1.87	0.237
3000	15.00±0.000	15.00±0.000	0	1.000
4000	15.00±0.000	14.93±0.258	0.07	0.837
5000	15.00±0.000	15.00±0.000	0	1.000

4. DISCUSSION

The gender in this study was compared with men and women, 1: 1, 11 male patients (50%) and 11 female patients (50%). Pallysater (2018) research, the number of male with was 28 patients (58.3%), and female with was 20 patients (41.7%).[15] Al Hasan (2016) study also found a male to female ratio of 1.6.[16] Likewise, Gao et al. (2016) found that there were more men than women, 143 people (56.5%) compared to 110 people (43.5%).[17] There have been no reports on other studies regarding gender trends and race predilection.

Age of subjects between 1-8 years with a mean age of 3.5 years for all subjects. In the Pallysater study (2018) the average age for all samples was 3 years 7 months, higher than Selistre et al. (2016), which was 23.5 months.[15,18] The median age for all samples is 2 years 8 months, higher than Gao et al (2016), which is 25 months. However, the median value of retinoblastoma patients is consistent with Nelson (2011) is 2 years.[17] Age of samples ranged from the shortest (2 months) to the longest (13 years). The highest incidence in the first year of life, and the high initial mean age diagnosed may be related to the severity of retinoblastoma metastases.

OAE testing to assess cochlear hair cell function showed that before and after chemotherapy, all groups of patients with retinoblastoma Stage III and retinoblastoma Stage IV did not change; the researchers obtained 22 pass results for the sample. In a study conducted by Putri, et al. (2017) in 9 subjects studied by OAE before chemotherapy, 4 subjects after receiving cisplatin chemotherapy cycle lll there was a decrease in SNR (sound to noise ratio), but the Moucly's Test showed no significant difference in variance.[19] In contrast to the research conducted by Zainul, 2007, 5 (22.7%) patients from 22 samples experienced an ototoxic event after cisplatin chemotherapy cycle III.[20]

From the results of the study, in patients with Stage III retinoblastoma the results of the Pass from the OAE examination of the dextra ear show the Pass value at frequency 2000 and the frequency of 3000 is almost the same, the pass frequency value of 4000 and 5000 is the same, even though the results of the 2000-5000 examination with Pass values are not significantly different with P value 0.556, which is more than P> 0.05. Pass value for Sinistra ear from 2000-5000 shows the same Pass value. In patients with Stage IV retinoblastoma the results of Dextra ear pass show no different from the results of the examination in Stage III. The results of the Pass value in Sinistra ear indicate that the 2000 frequency is lower than the 3000-5000 frequency Pass value, but the Pass value of all frequencies is not significantly different.

Putri's Research, 2017 found that the number of frequencies that had decreased did not find a significant difference with a value of p = 0.866.[19] The study conducted by Zainul (2007) regarding the relationship of cisplatin chemotherapy with the occurrence of ototoxicity obtained p = 0.027 which means p <0.05 which showed a significant relationship between cisplatin chemotherapy and the incidence of ototoxicity.[20]

Delayed ototoxicity can occur in children. Maybe this is what happened in our study. In Kopelman's research, pediatric patients received cisplatin with a cumulative dose of 400 mg / m2. The median time for hearing loss after completing the first 135 days of significant therapy in children. New

6-44 month follow-up shows mild progression of hearing disorders 10-15 dB. Whereas in our study, patients received a cisplatin dose of 80 mg / m2.

Studies of scientific literature show that hearing loss mediated by cisplatin basically involves the generation of reactive / ROS oxygen species in the cochlea, outer hair cells, ganglia spirals, vascularis striae and spiral ligaments. There are various cytoprotective mechanisms for endogenous antioxidants such as glutathione and other antioxidant enzymes, protein heatshocks, adenosine A1, NRF2, kidney injury molecule 1 (KIM-1) receptors, to reduce the ototoxicity effects of cisplatin.[20] In the study by Caronia et al. (2009) Nucleotide excision repair genes play a key role in reversing DNA damage. Adenosine A1 (A1AR) receptors expressed endogenously have also been shown to provide protection against oxidative damage to the cochlea.[22] The local application of A1AR agonists results in an increase in the antioxidant glutathione peroxidase enzyme and superoxide dismutase.[22] Furthermore, A1AR agonists also reduce the increase in cisplatin-mediated malondialdehyde in the cochlea which results in protection against cisplatin-induced hair cell damage and hearing loss.[23] In Wang's (2004) study, one of the mechanisms of cisplatin-induced outside hair cell damage involved activation of the pro-apoptotic pathway. The use of caspase-3 and caspase-9 inhibitors prevents cisplatin-induced outside hair cell death. These autoprotective mechanisms support the results of our study.[24]

5. CONCLUSION

The function of the cochlear hair cell based on DPOAE examination in patients with stage III and IV retinoblastoma at each frequency obtained a pass value which meant that no cochlear hair cell damage was obtained which indicated no occurrence of ototoxicity. There were no significant differences of cochlear hair cell function based on DPOAE examination in patients with stage III and IV retinoblastoma after receiving cisplatin chemotherapy.

Conflicts of Interest: The authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

The authors very gratefully thank all retinoblastoma patients who were willing to be a respondent in this study.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A Cancer Statistics, 2014. CA Cancer J Clin 64(1):9-29, doi: 10.3322/caac.21208
2. Price KA, Cohen EE (2012) Current Treatment Option For Metastatic Head and Neck Cancer. Curr Treat Option Oncol 13(1):35-46, doi: 10.1007/s11864-011-0176-y
3. Riggs LC, 1998, Ototoxicity. In Bailey BJ. Head & Neck surgery-Otolaryngology. Second Edition. Philadelphia. Lippincott Raven. Pp 2165-2168.
4. Whitworth CA et al, 2004, Protection Against Ototoxicity by Adenosis Agonist, in Biochemical Pharmacology, pp. 1801-07.
5. Redemaker JM, et al, 2006, Relationship Between Cisplatin Administration and the Development of Ototoxicity. In Journal of Clinical Oncology. Vol 24. No. 6.pp. 918-924.
6. Soetirto, I., hendarmin, H. &bashiruddin, J. (2012) Hearing impairment and ear abnormalities in the health science textbook of the ear nose and throat, *FKUI*. Jakarta.
7. Wright A, 1997, Anatomy and Ultra structure of The Human Ear, Basic Science, in Scott Brown's, Otolaryngology, Sixth Edition, Vol 1, Buterworth, pp 1/1/1-1/1/49.
8. Dehne et al, 2001, Cisplatin Ototoxicity: Involvement of Iron Enhanced Formation of Superoxide Anion Radicals, in Toxicology and Applied Pharmacology, pp. 27-34
9. Duta A, Vankatesh MD, Kahsyap RC, 2005, Study of The Effects of Chemotherapy on Auditory Function, Indian Journal of Otolaryngology and Head Neck Surgery, Vol. 57, No.3, pp 226-8.
10. Dharmawidiarini D., Prijanto, dan Hendrian S. Ocular Survival Rate Retinoblastoma patients who have been enucleated or exentered at RSUD Dr. Soetomo Surabaya,

Jurnal Oftalmologi Indonesia, 2010; 7 (3): 94-102.
11. Kashyap S, Meel R, Pushker N, Sen S, Bakhshi S, Sreenivas V, Sethi S, Clinical Predictors of High Risk Histopathology in Retinoblastoma. Pediatr Blood Cancer. Wiley. Liss, Inc. 2011.
12. Shields, CL, Gorry T, Shields JA, Out Come of Eyes with Unilateral Sporadic Retinoblastoma Based on the Initial External Findings by the Family and the Pediatrician. J. Pediatric Ophtalmol and Strabismus 2004, 41; 143-149.
13. American Academy of Ophtalmology. Retinoblastoma In Pediatric Ophtalmology and Strabismus. 2015; 473-482).
14. Miranda G. 2015. Characteristics of Retinoblastoma Patients in Adam Malik Haji General Hospital January 2011-December 2013 Period. Sumatera utara University.
15. Pallysater, Dari. 2018. Profile of Retinoblastoma Patients in H. Adam Malik Hospital in 2014-2017. Sumatera Utara University.
16. Al hasan, A., Murad, R., Zaid, K. et al 2016, 'Epidemiological Characteristic of Retinoblastoma in Children Attending Almoussat University Hospital, Damascus, Syria, 2012-2016', Asia-Pacific of Journal of Cancer Prevemtion, vol.18,pp 421-424.
17. Gao, J., Zeng, J., Guo B, et al 2016,' Clinical presentation and treatment outcome of retinoblastoma in children od South Western China', Medicine, 95:42.
18. Salistre, S.G.A., Maestri, M.K., Silva, p.S., et al 2016,'Retinoblastoma in a pediatric oncology reference center in Southern brazil', BMC Pediatrics 16:48
19. Putri, Meyrna Heryaning. 2017. Relationship between ototoxicity and neoadjuvant chemotherapy in nasopharyngeal carcinoma based on ASHA, CTCAE, and DPOAE. ORLI Vol.47 No. 2
20. Sihotang, Zainul Bahri. 2007. Cisplatin Ototoxicity in Chemotherapy for Malignant Tumors and Neck in H. Adam Malik Hospital Medan. Sumatera utara University
21. Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicityand prevention. Hear. Res 2007; 226:157-167. [PubMed: 17113254]
22. Caronia D, Patino-Garcia A, Milne RL, Zalacain-Diez M, Pita G, Alonso MR, Moreno LT,Sierrasesumaga-Ariznabarreta L, Benitez J, Gonzaler-Neira A. Common variations in ERCC2 areassociated with response to cisplatin chemotherapy and clinical outcome in osteosarcoma patients. Pharmacogenomics J 2009; 9:347-353. [PubMed: 19434073]
23. Ford M. S., Maggirwar S. B., Rybak L. P., Whitworth C., Ramkumar V. (1997). Expression and function of adenosine receptors in the chinchilla cochlea. *Hear. Res.* 105 130-140. 10.1016/S0378-5955 (96) 00204-3
24. Wang Q., Steyger P. S. (2009). Trafficking of systemic fluorescent gentamicin into the cochlea and hair cells. *J. Assoc. Res. Otolaryngol.* 10 205-219. 10.1007/s10162-009-0160-4

How to cite this article: Savitri E, Fitria D, Akil A et.al. The effect of cisplatin chemotherapy on ototoxicity event in retinoblastoma patients. *International Journal of Science & Healthcare Research.* 2021; 6(1): 89-94.

******