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Original Article

The Relationship between Cumulative Platinum-Based Chemotherapy Dose and The Occurrence of Ototoxicity in Head and Neck Malignancies

Hendro Purnomo[1], Dwi Marliyawati[1], Zulfikar Naftali[1], Dian Ayu Ruspita[2], Muyassaroh[2]

[1]Department of Otorhinolaryngology, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[2]Department of Otorhinolaryngology, Kariadi Hospital Semarang, Indonesia

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Author Affiliation:
Department of Otorhinolaryngology, Faculty of Medicine, Diponegoro University Semarang, Indonesia

Author Correspondence:
Dwi Marliyawati
Dr. Sutomo Street No. 16, Semarang, Central Java 50244, Indonesia

E-mail:
dwimarliyawati@yahoo.com

Abstract

Background : Chemotherapy is a treatment for head and neck malignancies. Hearing impairment is a side effect of chemotherapy, especially caused by platinum-based chemotherapy. Hearing impairment generally occurs at high frequencies after the administration of chemotherapy. The aims of this study was to prove assosciation between cumulative doses of platinum-based chemotherapy and ototoxic events in head and neck malignancies.
Methods : This is a cross-sectional study. The sample is patients with head and neck malignancy receiving platinum–based chemotherapy at Dr. Kariadi Hospital Semarang from March to June 2023. Hearing assessment using pure tone audiometry was performed randomly at all chemotherapy cycles. Data was analyzed with a chi-square test.
Results : Eighty-one subjects (52 male, 29 female), consisting of 71 subjects received cisplatin, and 10 subjects received carboplatin. Ototoxicity occurs in 91.7% of subjects receiving cumulative doses of cisplatin >300mg/m^2 and carboplatin >1500mg/m^2 compared to cumulative doses of cisplatin <300mg/m^2 and carboplatin <1500mg/m^2, which was 46.7% (p = 0.001, CI 1.416–2.725).
Conclusion : There was a significant association between cumulative doses of platinum-based chemotherapy and ototoxicity incidence of head and neck malignancy patients.

Keywords : ototoxic, pure tone audiometry, chemotherapy, platinum

INTRODUCTION

Head and neck malignancies account for 5.3% of the total incidence of tumors worldwide annually. It is estimated that over 800,000 new cases and nearly 500,000 deaths.[1,2] Surgical procedures, radiotherapy, and chemotherapy in various combinations are used to treat head and neck malignancies, depending on the stage and primary location. Chemotherapy, as one of the multimodal curative therapies, can be given concomitantly with radiotherapy to provide a good therapeutic response. Platinum-based chemotherapy is the most widely used and globally accepted chemotherapy drug.[3,4]

Hearing loss is a sensorineural, bilateral, and permanent ototoxic side effect of platinum-based drugs.[5,6] The prevalence of cisplatin chemotherapy-induced ototoxicity varies widely between 11–97% in several studies.[7,8] The prevalence of ototoxicity due to cisplatin chemotherapy in a previous study was 32%.[8] Hearing loss occurs primarily at high frequencies following the administration of high-dose cisplatin. One study mentioned that a cumulative dose of cisplatin over 300 mg/m² and carboplatin over 1500 mg/m² can cause ototoxicity.[8–10] Ototoxicity is assessed using ASHA criteria measured by pure-tone audiometry. The aim of this study is to prove the relationship between the cumulative dose of platinum-based chemotherapy and chemotherapy-induced ototoxicity in patients with head and neck malignancies at Dr. Kariadi Hospital.

METHODS

This research is an observational analytic study with a cross-sectional design. The subjects of the study were patients with head and neck malignancies who visited the Oncology Clinic and Clinical Diagnostic Centre of Dr. Kariadi Hospital and met the research criteria. Subjects underwent pure-tone audiometry examinations at random chemotherapy session. The study period was from March to July 2023. Sampling was conducted using consecutive sampling. Inclusion criteria included subjects who received at least one cycle of platinum-based chemotherapy, aged ≥18 – 65 years, had a baseline audiogram before chemotherapy, and were willing to participate in the study. Exclusion criteria consisted of long-term use of medications (antibiotics, NSAIDs, quinine), patients with chronic otitis media, a history of hemodialysis, changes in chemotherapy regimens, a history of head and neck radiation, and a history of noise exposure. Ototoxicity was assessed using ASHA criteria, defined as an increase in hearing threshold of 20 dB at one frequency or 10 dB at two consecutive frequencies observed in the audiogram. Confounding factors in this study included gender, age, and history of anemia. Data analysis was performed using the chi-square test with SPSS 25.

This study received ethical clearance and approval from the Research Ethics Committee of Dr Kariadi Hospital and the Medical Council of Dr Kariadi Hospital.

RESULTS

Eighty-one subjects who met the inclusion and exclusion criteria were outpatients at the ENT Oncology Department of Dr Kariadi Hospital during the period from March to July 2023. The characteristics of the subjects are listed in Table 1.

Table 1 shows that the percentage of subjects who

TABLE 1
Characteristics of Subjects

Variable		Ototoxicity		Total
		Positive	Negative	
		54 (66.7%)	27 (33.3%)	81 (100%)
Gender	Male	36 (44.4%)	16 (19.8%)	52 (64.2%)
	Female	18 (22.2%)	11 (13.6%)	29 (35.8%)
Age	>40 years old	36 (44.4%)	20 (24.7%)	56 (69.1%)
	≤40 years old	18 (22.2%)	7 (8.6%)	25 (30.9%)
History of anemia	anemia +	11 (13.6%)	3 (3.7%)	14 (17.3%)
	anemia -	43 (53.1%)	24 (29.6%)	67 (82.7%)
Chemotherapy drugs	Paclitaxel-Cisplatin	49 (60.5%)	22 (27.2%)	71 (87.7%)
	Paclitaxel-Carboplatin	5 (6.2%)	5 (6.2%)	10 (12.3%)
Cumulative Dose	Cisplatin > 300mg/m^2, Carboplatin > 1500mg/m^2	33 (40.7%)	3 (3.7%)	36 (44.4%)
	Cisplatin ≤ 300mg/m^2, Carboplatin ≤ 1500mg/m^2	21 (25.9%)	24 (29.6%)	45 (55.6%)

TABLE 2
Relationship between Cumulative Chemotherapy Dose and Ototoxicity

Variable	Ototoxicity						*p*	PR	*r*	CI 95%
	Positive		Negative		Total					
	n	%	n	%	n	%				
Cumulative dose							0.001	1.964	0.404	1.416–2.725
Cisplatin >300 mg/m^2, Carboplatin >1500 mg/m^2	33	91.7	3	8.3	36	100				
Cisplatin ≤300 mg/m^2, Carboplatin ≤1500 mg/m^2	21	46.7	24	53.3	45	100				

TABLE 3
The relationship between gender, age, and history of anemia with ototoxicity

Variable		Ototoxicity						*p*	PR	CI 95%
		Positive		Negative		Total				
		n	%	n	%	n	%			
Gender	Male	36	69.2	16	30.8	52	100	0.512	1.115	0.796–1.563
	Female	18	62.1	11	37.9	29	100			
Age	> 40 years old	36	64.3	20	35.7	56	100	0.496	0.893	0.653–1.221
	≤ 40 years old	18	72	7	28	25	100			
History of anemia	anemia +	11	78.6	3	21.4	14	100	0.496	1.224	0.883–1.698
	anemia -	43	64.2	24	35.8	67	100			

experienced ototoxicity (66.7%) was higher compared to those who did not experience ototoxicity (33.3%). Male gender and age over 40 years were more likely to experience ototoxicity, among which 60.5% used the cisplatin.

Table 2 shows that ototoxicity in the subjects occurred mostly in the group of subjects who received a cumulative dose of Cisplatin >300 mg/m² and Carboplatin >1500 mg/m². The analysis results indicate a significant relationship between the cumulative dose of chemotherapy and ototoxicity (*p-value* ≤0.05). The correlation value obtained, 0.404, indicates a positive relationship, with the strength of the relationship between the cumulative dose and the incidence of ototoxicity being moderate.

Table 3 shows that ototoxicity occurs frequently regardless of gender (both male and female), all age ranges, and whether there is a history of anemia or not. The analysis results indicate that there is no significant relationship between gender, age, and history of anemia with ototoxicity.

DISCUSSION

The characteristics of subjects with head and neck malignancies in this study were predominantly male (64.2%). This is consistent with previous research indicating that males are 2–4 times more likely to develop head and neck malignancies compared to females.[11] The patients in this study were mostly in the age group >40 years (69.1%) compared to the age group ≤40 years (30.9%), which aligns with research suggesting that head and neck malignancies are more common in the over 50 age group than in younger age groups. This could be attributed to advanced age and higher exposure to smoking and alcohol in males compared to younger individuals and females.[12] On the contrary, other studies have suggested that head and neck malignancies can occur at any age, with no differences across age groups.[13] Regarding the variable of anemia, the presence of a history of anemia (17.3%) was smaller compared to the group with no history of anemia (82.7%), which is consistent with other research indicating that 10.1% of patients receiving chemotherapy experience anemia.[14]

The incidence rates of nephrotoxicity, leukopenia, and anemia are higher with cisplatin administration, whereas carboplatin administration is associated with a higher incidence of thrombocytopenia.[15] Many derivatives of cisplatin have been developed, such as carboplatin, oxaliplatin, nedaplatin, hepteplatin, and

lobaplatin, but none have surpassed cisplatin in terms of effectiveness and spectrum of action.[16] Subjects in this study mostly received cisplatin regimen (87.7%) compared to carboplatin therapy regimen (12.3%), which is because cisplatin is recognized as the first-line therapy for head and neck malignancies and is considered the most effective neoadjuvant or concomitant therapy with radiotherapy.[17]

One of the common complications after chemotherapy is the decline in hearing function, which is one of the effects of chemotherapy-induced ototoxicity. Research indicates that platinum-based chemotherapy, both cisplatin and carboplatin, is the leading cause of ototoxicity compared to other chemotherapy drugs. Although carboplatin has similar anti-tumor effects as cisplatin, it has milder ototoxic effects. Studies have reported ototoxicity rates ranging from 45–83.3% for cisplatin and varying from 16.6–75% for carboplatin.[18] Another study on decreased bone conduction in nasopharyngeal carcinoma post-platinum-based chemotherapy found that 53% of the cisplatin group experienced decreased bone conduction, and 42.3% in the carboplatin group.[19]

The results of this study indicate that the cumulative dose of platinum-based chemotherapy drugs, both cisplatin and carboplatin, is significantly associated with the occurrence of chemotherapy-induced ototoxicity (p=0.001), with a moderate correlation between cumulative dose and ototoxicity (r=0.404). Consistent with previous research, hearing impairment occurs in 26% of patients at cumulative cisplatin doses between 300–600 mg/m^2, and around 12% at doses <200 mg/m^2.[5] This study found that ototoxicity appears (4%) after the first cycle of cisplatin regimen, indicating that ototoxicity begins to occur after receiving a chemotherapy dose of 80mg/m^2. This aligns with previous research indicating that high-frequency hearing impairment can occur with individual cisplatin doses exceeding 60 mg/m^2.[2,20]

Gender, age, and history of anemia are confounding factors in this study, so bivariate analysis was conducted on gender, age, and history of anemia to determine their relationship with chemotherapy-induced ototoxicity. The analysis revealed no relationship between gender, age, and history of anemia with chemotherapy-induced ototoxicity. This is consistent with previous research indicating that gender does not influence chemotherapy drug toxicity.[21] Other researchers have suggested that advanced age (>65 years) does not affect the incidence and severity of chemotherapy drug toxicity compared to younger ages.[22,23] However, contrary findings suggest that advanced age and low hemoglobin levels are associated with platinum-based chemotherapy-induced ototoxicity.[24]

CONCLUSION

There is a moderate positive relationship between cumulative dose of platinum-based chemotherapy and the occurrence of ototoxicity in head and neck malignancies. Confounding factors such as gender, age, and history of anemia do not affect the occurrence of ototoxicity in this study.

REFERENCES

1. Aupérin A. Epidemiology of head and neck cancers: an update. Curr Opin Oncol. 2020;32(3):178–86. DOI:https://doi.org/10.1097/CCO.0000000000000629
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. DOI:https://doi.org/10.3322/caac.21492
3. To'bungan N, Aliyah SH, Wijayanti N, Fachiroh J. Epidemiologi, stadium, dan derajat diferensiasi kanker kepala dan leher. Biog J Ilm Biol. 2015;3:47–52. DOI:https://doi.org/10.24252/bio.v3i1.566
4. Cohen N, Fedewa S, Chen AY. Epidemiology and Demographics of the Head and Neck Cancer Population. Oral Maxillofac Surg Clin North Am. 2018;30(4):381–95. DOI:https://doi.org/10.1016/j.coms.2018.06.001
5. Rottenberg S, Disler C, Perego P. The rediscovery of platinum-based cancer therapy. Nat Rev Cancer. 2021;21(1):37–50. DOI:https://doi.org/10.1038/s41568-020-00308-y
6. Dilruba S, Kalayda G V. Platinum-based drugs: past, present and future. Cancer Chemother Pharmacol. 2018;77(6):1103–24. DOI:https://doi.org/10.1007/s00280-016-2976-z
7. Biro K, Noszek L, Prekopp P, Nagyiványi K, Géczi L, Gaudi I, *et al*. Characteristics and risk factors of cisplatin-induced ototoxicity in testicular cancer patients detected by distortion product otoacoustic emission. Oncology. 2006;70(3):177–84. DOI:https://doi.org/10.1159/000093776
8. Monfared ZE, Khosravi A, Safavi Naini A, Radmand G, Khodadad K. Analysis of Cisplatin-Induced Ototoxicity Risk Factors in Iranian Patients with Solid Tumors: a Cohort, Prospective and Single Institute Study. Asian Pac J Cancer Prev. 2017;18(3):753–8. DOI:https://doi.org/10.22034/APJCP.2017.18.3.753
9. Sriyapai T, Thongyai K, Phuakpet K, Vathana N, Buaboonnam J, Sanpakit K. Ototoxicity and long-term hearing outcome in pediatric patients receiving cisplatin. Turk J Pediatr. 2022;64(3):531–41. DOI:https://doi.org/10.24953/turkjped.2021.5012
10. Edward ED, Rosdiana N, Farhat F, Siregar O, Lubis B. Prevalence and risk factors of hearing loss in children with solid tumors treated with platinum-based chemotherapy. Paediatr Indones. 2015;55(3 SE-Articles). DOI:https://doi.org/10.14238/pi55.3.2015.121-5
11. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Prim. 2020;6(1):92. DOI:https://doi.org/10.1038/s41572-020-00224-3
12. Gormley M, Creaney G, Schache A, Ingarfield K, Conway DI. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. Br Dent J. 2022;233(9):780–6. DOI:https://doi.org/10.1038/s41415-022-5166-x
13. Guo K, Xiao W, Chen X, Zhao Z, Lin Y, Chen G.

Epidemiological Trends of Head and Neck Cancer: A Population-Based Study. Biomed Res Int. 2021;2021:1738932. DOI:https://doi.org/10.1155/2021/1738932

14. Razzaghdoust A, Mofid B, Peyghambarlou P. Predictors of chemotherapy-induced severe anemia in cancer patients receiving chemotherapy. Support Care Cancer. 2020;28(1):155–61. DOI:https://doi.org/10.1007/s00520-019-04780-7
15. Tang L-L, Chen Y-P, Chen C-B, Chen M-Y, Chen N-Y, Chen X-Z, *et al*. The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. Cancer Commun (London, England). 2021;41(11):1195–227. DOI:https://doi.org/10.1002/cac2.12218
16. Tsvetkova D, Ivanova S. Application of Approved Cisplatin Derivatives in Combination Therapy against Different Cancer Diseases. Molecules. 2022;27(8). DOI:https://doi.org/10.3390/molecules27082466
17. Aguiar PNJ, Tadokoro H, da Silva GF, Landgraf MM, Noia Barreto CM, Filardi BA, *et al*. Definitive chemoradiotherapy for squamous head and neck cancer: cisplatin versus carboplatin? A meta-analysis. Future Oncol. 2016;12(23):2755–64. DOI:https://doi.org/10.2217/fon-2016-0068
18. Patatt FSA, Gonçalves LF, Paiva KM de, Haas P. Ototoxic effects of antineoplastic drugs: a systematic review. Braz J Otorhinolaryngol. 2022;88(1):130–40. DOI: https://doi.org/10.1016/j.bjorl.2021.02.008
19. Apriliana C, Naftali Z, Yusmawan W. Decreased bone conduction value among nasopharing carcinoma with platinum based-cemotherapy: Combination of neoadjuvant paclitaxel-cisplatin and paclitaxel-carboplatin. J Kedokt Diponegoro. 2019;8(1). DOI:https://doi.org/10.14710/dmj.v8i1.23300
20. Santosa YI, Samiadi D, Aroeman NA, Fianza PI. The effect of Tocoferol on Ototoxic effect of Cisplatin. Bandung Med J. 2012;44(4). DOI:https://doi.org/10.15395/mkb.v44n4.176
21. Marcu LG. Gender and Sex-Related Differences in Normal Tissue Effects Induced by Platinum Compounds. Pharmaceuticals (Basel). 2022;15(2). DOI:https://doi.org/10.3390/ph15020255
22. Argyriou AA, Polychronopoulos P, Koutras A, Iconomou G, Gourzis P, Assimakopoulos K, *et al*. Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy? Support care cancer Off J Multinatl Assoc Support Care Cancer. 2006;14(3):223–9. DOI:https://doi.org/10.1007/s00520-005-0868-6
23. Barginear M, Dueck AC, Allred JB, Bunnell C, Cohen HJ, Freedman RA, *et al*. Age and the Risk of Paclitaxel-Induced Neuropathy in Women with Early-Stage Breast Cancer (Alliance A151411): Results from 1,881 Patients from Cancer and Leukemia Group B (CALGB) 40101. Oncologist. 2019;24(5):617–23. DOI:https://doi.org/10.1634/theoncologist.2018-0298
24. Mizrahi D, Park SB, Li T, Timmins HC, Trinh T, Au K, *et al*. Hemoglobin, Body Mass Index, and Age as Risk Factors for Paclitaxel- and Oxaliplatin-Induced Peripheral Neuropathy. JAMA Netw open. 2021;4(2):e2036695. DOI:https://doi.org/10.1001/jamanetworkopen.2020.36695