Paediatrica Indonesiana

VOLUME 55 May • 2015 NUMBER 3

Original Article

Prevalence and risk factors of hearing loss in children with solid tumors treated with platinum-based chemotherapy

Eka D. Edward[1], Nelly Rosdiana[1], Farhat[2], Olga R. Siregar[1], Bidasari Lubis[1]

Abstract

Background The platinum-based chemotherapy drugs, cisplatin and carboplatin, are widely used in the treatment of several types of solid tumors. However, the treatment has side effects including hearing loss.

Objective To evaluate the prevalence of hearing loss related to platinum-based chemotherapy and to identify associated factors.

Methods A cross-sectional study was performed in Adam Malik Hospital, Medan, North Sumatera, from April to July 2012. Twenty-two subjects who fulfilled the eligibility criteria underwent otoacoustic emission evaluations. Eleven children had received cisplatin and eleven had received carboplatin. The association between hearing loss and risk factors was assessed using Fisher's exact and Chi-square tests.

Results Seven subjects with hearing loss were identified. Five of these patients (5 out of 11) had received cisplatin and 2 patients (2 out of 11) had received carboplatin. There was no statistically significant difference between carboplatin- and cisplatin-associated hearing loss (P=0.361). Neither gender (P=0.452) nor age (P=0.212) was related to hearing loss. However, higher cumulative chemotherapy doses (cisplatin >600 mg/m^2 and carboplatin >1800 mg/m^2) were associated with hearing loss (P=0.022 and P=0.004, respectively).

Conclusion Patients who had higher cumulative doses of platinum-based chemotherapy are at risk for developing hearing loss. **[Paediatr Indones. 2015;55:121-5.]**

Keywords: *platinum, children, solid tumor, hearing loss*

Survival rates for childhood cancer are likely to increase over the next few decades. This growing population remains vulnerable to a variety of long-term, therapy-related sequelae as some anti-cancer drugs have adverse side effects that reduce their quality of life.[1]

Platinum-based cheumotherapeutic agents such as cisplatin and carboplatin are widely used for the treatment of several pediatric solid tumors.[2] The treatment, however, often causes harmful, long-term side effects, such as nephrotoxicity, neuropathies, and ototoxicity. Platinum-induced ototoxicity usually manifests as a permanent, bilateral, high frequency, sensorineural hearing loss. Initially, hearing in the high frequency range is affected, progressing to the lower frequencies

This study was presented at the 5th Annual Pediatrics Scientific Meeting (PIT V), Indonesian Pediatrics Society, Bandung, Indonesia, October 15 – 17, 2012.

From the Department of Child Health[1] and Department of Otolaryngology[2], University of North Sumatera Medical School/H. Adam Malik General Hospital, Medan, Indonesia.

Reprint requests to: Eka D. Edward, Department of Child Health, University of North Sumatera Medical School/RS. H. Adam Malik, Jl. Bunga Lau No.17, Medan, 20136 Indonesia. Tel. +62-618-361721, +62-618-365663, Fax. +62-618-361721. E-mail: eka_far@yahoo.com.

during later treatment. The incidence of hearing loss from cisplatin, a first generation platinum-based chemotherapy treatment, ranges from 26% to more than 90%.[3] Carboplatin is a second-generation platinum compound which is less toxic than cisplatin. Studies have reported 0-19% incidence of hearing loss from carboplatin.[4,5]

Several risk factors have been identified to predict hearing loss in children treated with platinum-based chemotherapy.[6] Children under 5 years of age tend to experience hearing loss.[7] High cumulative doses and cranial irradiation also cause hearing loss.[8-10] Other studies found that genetic factors and gender influence the incidence of ototoxicity.[6,11]

The aim of this study was to evaluate the prevalence and identify risk factors of hearing loss in children who received platinum-based chemotherapy.

Methods

A cross-sectional study was conducted from April to July 2012 in H. Adam Malik Hospital, Medan, North Sumatera Indonesia. Consecutive sampling was done on children who met the inclusion criteria, which were as follows: children aged 6 months – 17 years with solid tumors who received at least two cycles of cisplatin or carboplatin, and the absence of recurrent ear infections. Subjects who had a history of hearing impairment before therapy, had undergone radiotherapy of the head, or had tumors in the central nervous system, were excluded. All children which their parents approve to informed concern were evaluated by an audiologist using *Oto Read*®, a portable otoacoustic emissions (OAE) screener, made by *Interacoustics A/S Assens*, Denmark 2003. This equipment has 86.4% sensitivity and 99.4% specificity.

This study was approved by the Medical Ethics Committee of the University of North Sumatera Medical School.

Possible associations between hearing loss and risk factors were analyzed by Chi-square and Fisher's exact tests. A value of $P < 0.05$ was accepted to be statistically significant. Data were analyzed using *SPSS version 15*.

Results

Of 24 children who had received platinum-based chemotherapy, 2 children excluded from the study because of recurrent ear infections. The 22 children who met the inclusion criteria consisted of 11 children who received cisplatin and 11 children who received carboplatin.

The largest group of subjects by age was the <5-year-old group (11/22). Retinoblastoma was the most common type of tumour (15/22) followed by nasopharyngeal carcinoma (2/22), osteosarcoma (2/22), hepatoblastoma (1/22), fibrosarcoma (1/22), and ovarian cancer (1/22) (**Table 1**). None of the patients received additional ototoxic drugs, such as certain antibiotics or diuretics. None of the children or parents reported subjective hearing loss before the chemotherapeutic treatment.

Of 7 subjects with hearing loss, 5 had received cisplatin and 2 had received carboplatin. However, Fisher's exact test revealed no significant association between the chemotherapy used and hearing loss (P=0.361). Hearing loss was most commonly found in the < 5 years age group of children (5/7). However, Chi-square test revealed no significant differences between age groups as they related to hearing loss (P=0.35). Nor was there a significant relationship between gender and the occurrence of hearing loss (P=0.652), as shown in **Table 2**.

Table 1. Subjects' characteristics

Characteristics	Chemotherapy groups	
	Cisplatin (n=11)	Carboplatin (n=11)
Age, n		
< 5 years	3	8
> 5 – 10 years	1	2
> 10 – 15 years	5	1
> 15 years	2	-
Gender, n		
Male	4	6
Female	7	5
Diagnosis, n		
Retinoblastoma	4	11
Nasopharyngeal carcinoma	2	-
Osteosarcoma	2	-
Hepatoblastoma	1	-
Fibrosarcoma	1	-
Ovarian cancer	1	-

With regards to cumulative doses, both cisplatin and carboplatin regimens had significant relationships between higher cumulative dose and hearing loss (P=0.022 and P=0.004, respectively), as shown in **Table 3**.

Table 2. Relationship of hearing loss and risk factors

Risk factors	Otoacoustic emissions results		P value
	Hearing loss (n=7)	No hearing loss (n=15)	
Chemotherapy, n			
Cisplatin	5	6	0.361*
Carboplatin	2	9	
Age, n			
< 5 years	5	6	0.35#
> 5 - 10 years	0	3	
> 10 – 15 years	1	5	
> 15 years	1	1	
Gender, n			
Male	3	9	0.652*
Female	4	6	

* Fisher's exact test , # Chi-square test

Table 3. The relationship between hearing loss and cumulative dose of platinum-based chemotherapy

Cumulative dose (mg/m^2)	Otoacoustic emissions results		P value
	Hearing loss (n=7)	No hearing loss (n=15)	
Cisplatin, n			
200 – 400	1	5	0.022*
401 – 600	0	1	
> 600	4	0	
Carboplatin, n			
300 - 800	0	7	0.004*
801 – 1300	0	2	
1301 – 1800	0	0	
> 1800	2	0	

*Chi-square test

Discussion

A 1983 study in nine children found an 88% rate of hearing loss at high frequencies after treatment with cisplatin.[12] Another study reported hearing loss in 37% of children treated with cisplatin.[13] The first study on carboplatin in children was conducted in 1990 and found that 19% suffered hearing loss.[14] However, another study in the Netherlands in 2005 found that no hearing loss was detected in children after carboplatin administration.[4] In our study, 7 out of 22 patients had hearing loss after using platinum-based chemotherapy. Although this difference was not statistically significant (P=0.361), it shows tendency that cisplatin was more toxic than carboplatin.

We analyzed 10 males and 12 females, but found no relationship between gender and hearing loss. The result differed from that of a previous study which showed that males were more susceptible to cisplatin-associated hearing loss by as much as 4 times more than females. Since they could not elucidate the reason, they suggested that the difference was due to genetic factors.[6]

In 2004, a study found that children < 5 years of age at the time of treatment were 21 times more likely to have hearing loss than patients aged 15-20 years.[7] Another study showed that children aged < 12 years were at higher risk compared to those aged > 12 years.[15] Most of our subjects (11/22) were children under 5 years of age. Five out of 7 children who had hearing loss in this study was under 5 year-age group, but no significant difference in hearing loss was observed between age groups (P=0.35).

The cumulative cisplatin dose is considered to be the main risk factor for hearing loss. A German study found 12% hearing loss appeared at a dose range of 1–200 mg/m^2.[8] Other studies have reported that wide ranges of cisplatin doses (120–450 mg/m^2) were correlated with a progressive risk of developing severe hearing loss.[13,15,16] Carboplatin, at the standard dose, does not appear to be a significant risk factor for hearing loss.[13] A Netherlands study showed that of 25 children treated with carboplatin, none had hearing loss afterwards, while a Washington study showed that only 4% of children who received carboplatin had hearing loss.[4,17] Although ototoxicity might be lower, high doses (total dose 2 g/m^2) of carboplatin may cause high and low frequency hearing loss.[18] In an animal study, carboplatin damaged inner hair cells at a low dose and outer hair cells at a high dose.[19]

In our study, we divided cisplatin into three dosage groups. Subjects who received cumulative doses above 600 mg/m^2 had the highest prevalence of hearing loss. We found only 1 patient with hearing loss who received a cisplatin dose in the range of 200 to 400 mg/m^2 and 4 patients with hearing loss who received >600 mg/m^2 cisplatin. The one patient with hearing loss in the 200 to 400 mg/m^2 group was a teenager diagnosed with carcinoma of the ovary. She often listened to music using headphones at a

high volume. We could not rule out the possibility that her hearing loss occurred as a result of exposure to loud noise. Eleven subjects with solid tumors received carboplatin. Two patients who received higher cumulative doses (2680 mg/m^2 and 4955 mg/m^2) suffered hearing loss. Both cases required higher doses due to retinoblastoma relapse. Further study is needed with a larger sample size to more accurately analyze for an association between cumulative doses of carboplatin and hearing loss. Platinum-based chemotherapy agents induce dose-dependent death of cochlear hair cells, with outer hair cells more susceptible to cisplatin and inner hair cells more susceptible to carboplatin.[19,20] Platinum agents target the DNA of proliferating cells to exert tumoricidal effects.[21] In contrast to tumor cells, cochlear cells proliferate slowly, and mammalian cochlear cells not at all. [22] As such, permanent and bilateral hearing loss may result. A study revealed that no improvement was observed with time. Instead, worsening or progression of hearing loss in the lower frequencies was detected during follow-up.[13]

We found that 7 patients had bilateral hearing loss. We did not assess for a worsening or permanent effect of platinum-based chemotherapy on hearing loss, as this study had a cross-sectional design. Further longitudinal studies with a large sample size is needed to investigate this effect.

Hearing loss can be detected by audiometry, OAE and brainstem-evoked response audiometry. Otoacoustic emission directly assesses the function of hair cells. The OAE can be used as a screening test for ototoxicity, but does not determine the threshold of hearing as well as audiometry.[23] Most subjects were <5 years of age which is an obstacle for audiometric examinations, as it is difficult for these patients to cooperate with the examiner.

In a previous study, hearing loss in children affected their speech, language, educational and social-emotional development. Auditory capability for children aged <5 years is very important because at this age children learn language. High frequency hearing loss impacts their academic achievement.[24,25] A US study involving 1,228 subjects with minimal sensorineural hearing loss showed hearing difficulty in educational test compared to normal children.[26] In our study, most patients were < 5 years of age and had not attended school, but we received two reports from parents that their children had difficulty hearing in crowded areas. Two subjects with hearing loss were in school-aged. One subject stopped attending school due to financial problems, while the other attended school and continued the chemotherapy protocol. This latter patient was able to attend school, participate in academic activities, and had no difficulty in communication. We recommended that she undergo regular hearing exams, since she would complete the chemotherapy protocol later, as additional treatments would affect the cumulative dose.

A limitation of the study was that we did not perform OAE examinations prior to chemotherapy administration, so we could not compare subjects' initial auditory function to that after chemotherapy. Other limitations were the small sample size and lack of long-term monitoring for the possibility of permanent hearing loss.

In conclusion, hearing loss is common in children with solid tumors who receive platinum-based chemotherapy. Higher cumulative doses of platinum-based chemotherapy are a risk factor for hearing loss.

Conflict of interest

None declared.

References

1. American Academy Pediatrics Section of Hematology/Oncology Children's Oncology Group. Long-term follow-up care for pediatric cancer survivors. Pediatrics. 2009;123:906-15.
2. Sukardja IDG. Dasar-dasar Kemoterapi Kanker. In: Sukardja IDG, editor. Onkologi Klinik. 2nd ed. Jakarta: Airlangga University Press; 2000. p. 239-55.
3. Schultz C, Goffi-Gomez MV, Liberman PH, Carvalho AL. Report on hearing loss in oncology. Braz J Otorhinolaryngol. 2009;75:634-41.
4. Smits C, Swen SJ, Theo Goverts S, Moll AC, Imhof SM, Schouten-van Meeteren AY. Assessment of hearing in very young children retinoblastoma receiving carboplatin for retinoblastoma. Eur J Cancer. 2006;42:492-500.
5. Kennedy IC, Fitzharris BM, Colls BM, Atkinson CH.

Carboplatin is ototoxic. Cancer Chemother Pharmacol. 1990;26:232-4.
6. Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59:144-8.
7. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 2004;40:2445-51.
8. Simon T, Hero B, Dupuis W, Selle B, Berthold F. The incidence of hearing impairment after successful treatment of neuroblastoma. Klin Padiatr. 2002;214:149-52.
9. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. Hearing loss in patients with nasopharyngeal carcinoma after chemotherapy and radiation. Kaohsiung J Med Sci. 2003;19:163-9.
10. Chan SH, Ng WT, Kam KL, Lee MC, Choi CW, Yan TK, *et al*. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. Int J Radiat Oncol Biol Phys. 2009;73:1335-42.
11. Ross CJ, Katzov-Eckert H, Dube MP, Brooks B, Rassekh SR, Barhadi A, *et al*. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009:41;1345-9.
12. McHaney VA, Thibadoux G, Hayes FA, Green AA. Hearing loss in children receiving cisplatin chemotherapy. J Pediatr. 1983;102:314-7.
13. Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, *et al*. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26:649-55.
14. Stohr W, Langer T, Kremers A, Bielack S, Lamprecht-Dinnesen A, Frey E, *et al*. Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system. Cancer Invest. 2005;23:201-7.
15. Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer. 2006;107:417-22.
16. Lewis MJ, DuBois SG, Fligor B, Li X, Goorin A, Grier HE. Ototoxicity in children treated for osteosarcoma. Pediatr Blood Cancer. 2009;52:387-9.
17. Dean JB, Hayashi SS, Albert CM, King AA, Karzon R, Hayashi RJ. Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens. J Pediatr Hematol Oncol. 2008;30:130-4.
18. Rybak LP. Ototoxicity and antineoplastic drugs. Otolaryngol Head Neck Surg. 1999;7:239-43.
19. Hofstetter P, Ding P, Powers N, Salvi RJ. Quantitative relationship of carboplatin dose to magnitude of inner and outer hair cell loss and the reduction in distortion product otoacoustic emission amplitude in chinchillas. Hear Res. 1997;112:199-215.
20. Laurell G, Bagger-Sjoback D. Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol. 1991;20:158-67.
21. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. Oncogene. 2003;22:7265-79.
22. Garcia-Berrocal JR, Nevado J, Ramirez-Camacho R, Sanz R, Gonzalez-Garcia JA, Sanchez-Rodriguez C, *et al*. The anticancer drug cisplatin induced an intrinsic apoptotic pathway inside the inner ear. Br J Pharmacol. 2007;152:1012-20.
23. Skinner R. Best practice in assessing ototoxicity in children with cancer. Eur J Cancer. 2004;40:2352-4.
24. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005;23:8588-96.
25. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing loss, quality of life and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. Pediatrics. 2007;120:1229-36.
26. Bess FH, Dodd-Murphy J, Parker RA. Children with minimal sensorineural hearing loss: prevalence, educational performance and functional status. Ear Hear. 1988;19:339-54.