Original Article

Iraqi National Journal of Medicine. July 2023, Volume 5, Issue 2

Ototoxicity in Cancer Patients on Cisplatin Therapy Attending Basrah Oncology Centre: A Cohort Study

Hasanain M. Al-Ali[1], Jasim N. Al-Asadi[2], Abdulrazzaq J. Alrubaye[3], Hasson M. Hasson[4]

[1]Community medicine specialist, ENT practitioner doctor, public health unit, Al-Sadr teaching hospital. [2]College of medicine, Basrah university. [3]Al-Sadr teaching hospital. [4]Basrah oncology center, Basrah, Iraq.

ABSTRACT

Background: Cisplatin is a chemotherapeutic agent that is used extensively for the treatment of a broad spectrum of tumors. However, progressive irreversible side effects of Cisplatin, including ototoxicity, have been reported. **Methods**: A cohort study was implemented from 1 April to 30 August 2015 to study the association between Cisplatin chemotherapy and sensory-neural hearing loss as the major and most important sign of ototoxicity. The cohort group included cancer patients treated with Cisplatin, while patients on Carboplatin were the control group. Cisplatin and Carboplatin belong to alkylating platinum chemotherapy drugs, which are used to treat various malignant solid tumors. Data collection was done through a questionnaire, including information related to sociodemographic characteristics and current and past medical history. Hearing loss was assessed using pure tone audiometry at the time of starting chemotherapy and one month later. **Results:** The total number of patients was 50, with male to female ratio 1:1 and a mean age of 49.7±14.7 (range 18–80 years): 27 patients were on Cisplatin with a mean age of 50.3±13.5 and 23 patients were on Carboplatin chemotherapy with a mean age of 51.9±15.1 with no significant difference in age (P=0.695). A highly significant association between Cisplatin use and sensory-neural hearing loss (RR, 5.13; P <0.001) was noted. No significant association was found between hearing loss and sociodemographic characteristics or other clinical conditions. **Conclusions:** Ototoxicity represents a significant clinical sequel of Cisplatin chemotherapy in patients with cancer. A future study using a larger sample size aiming at the evaluation and prevention of Cisplatin induced ototoxicity is recommended.

Keywords: ototoxicity, cisplatin, cancer therapy, Basrah

Corresponding author: Hasanain M. Al-Ali, Email: h80iraq@yahoo.com

Disclaimer: The authors have no conflict of interest.

DOI: https://doi.org/10.37319/iqnjm.5.2.2

Received: 18 Dec 2022 Accepted: 9 Mar 2023 Published online: 15 Jul 2023

INTRODUCTION

Hearing loss is a global health problem. According to WHO estimates (2012), 360 million people (5.3%) worldwide suffer from hearing loss.[1]

Various etiological factors can cause hearing loss, including usage of chemotherapy drugs, which have been found to have ototoxicity effect. Cisplatin is one of the widely used chemotherapeutic agents to treat several cancers, which leads to ototoxicity induction causing hearing loss by affecting inner ear leading to sensory neural hearing loss (SNHL), depending on its dose.[2] Cisplatin ototoxicity was known for four decades.[3] Cisplatin with a single dose of 50 mg/m² received by patients is associated with about 33% incidence of ototoxicity.[4] Cisplatin can be replaced by carboplatin,

which belongs to the same group of alkylating chemotherapy agents with no or less hearing loss rates.[5,6]

Justification

Although SNHL is a common public health problem and was found to be associated with cisplatin use in comparison with carboplatin use,5,6 such issue was not studied in Basrah. Therefore, this study was implemented.

Objective

To study the association between cisplatin chemotherapy and sensory-neural hearing loss in cancer patients.

Literature review

Definition and types of hearing loss

Hearing can be measured in units of decibels (dB) via pure tone audiometry (PTA) through which at a distance of 1 m from the source of sound 0 (dB) represents the threshold of hearing, 60 (dB) conversional voice and 90 (dB) shouting, and 120 (dB) represents discomfort.[7] So, hearing loss measured by decibels hearing loss (dB HL) is as follows: mild: 26–40 (dB HL), moderate: 41–55 (dB HL), severe: 56–70 (dB HL), and profound: 71–89 (dB HL).[8] The types of hearing loss are as follows:

1. Conductive hearing loss: occurs because of a mechanical defect in the external ear canal and middle ear.
2. SNHL: a defect in the vestibulocochlear system.
3. Mixed hearing loss: a combination of 1 and 2 as mentioned above.

Etiological factors of hearing loss

Hearing loss can be due to the following etiological factors in which about 50% are preventable and/or treatable via hearing aids, hearing assisting therapy and surgery[1]: congenital, occlusion of external ear, infection, tumor, noise induced. presbycusis (aging hearing loss), trauma, Ménière disease., neurological, diabetes mellitus, drugs, such as Aminoglycosides, Aspirin, and chemotherapy, e.g., cisplatin, and other factors, such as iatrogenic, autoimmune, and idiopathic.[7–10]

Role of cisplatin and carboplatin in hearing loss

Cisplatin is one of the alkylating agents that is composed mainly of ethyleneimines and nitrogen mustards. These groups of cytotoxic drugs act by preventing the synthesis of DNA by either two strands cross-linking or breaking of DNA strand in the cell division phase in the guanine position of N-7 of DNA by alkyl group transfer to that position.[11] Cisplatin is indicated as a chemotherapy for malignant tumors of the testicles, ovary, bladder, cervical, head and neck, and lung. It is used either alone or in combination with other chemotherapy drugs. The route of administration is intravenous infusion with high amount of fluid.[12] The side effects of cisplatin include acute nausea, vomiting, and diarrhea, as well as delayed ototoxicity, nephrotoxicity, bone marrow suppression, electrolytes disturbance, peripheral neuropathy, hemolysis, sterility, Raynaud's disease.[11] In animal studies Cisplatin is teratogenic.[12] SNHL and tinnitus are clearly dose-limiting adverse effects of Cisplatin.13 Clinically if these adverse effects occurred, the course of chemotherapy by cisplatin can be stopped or shifted to other drugs that have less ototoxicity, e.g., Carboplatin.[14] Despite the assumed immune response of inner ear,[15] Cisplatin causes inner ear ototoxicity through outer hair cells (OHCs), stria vascularis marginal cells, and spiral ganglion cells, by damaging through apoptosis.[16,17] These changes associated with inner ear antioxidant enzymes changing and glutathione concentrations decrease can be prevented by administering diethyldithiocarbamate.[18] Factors that may aggravate cisplatin ototoxicity are first dose, summation of doses, high communitive dose, extreme age, renal failure, preexisting hearing loss, noise exposure, nutritional deficiency, radiotherapy, and regime method,19 and if treatment by cisplatin is accompanied by radiotherapy of cranium.[20]

Cisplatin ototoxicity is a bilateral progressive irreversible hearing loss at high frequencies.[21] Carboplatin belongs to the same alkylating group of Cisplatin, but there is a huge difference between the two drugs in chemical, pharmacological, and toxicological characteristics.[22] It is well tolerated with fewer side effects than that of cisplatin, including ototoxicity, nausea, neurotoxicity, and nephrotoxicity. Even in accumulative doses, carboplatin has less ototoxicity than cisplatin.[22,23] Ototoxicity can occur in patients receiving high-dose chemotherapy that contains cisplatin and carboplatin.[24] The usage of auditory brainstem response (ABR) monitoring of malignant tumor patients who received two cycles of chemotherapy revealed that 30% of cisplatin treated and 0% of carboplatin revealed hearing loss.[25]

In pediatric patients of different malignancies showed that 86% of patients on cisplatin and 33% of those on carboplatin had ototoxicity.[26] Patients who had received

Carboplatin in its standard dose, even in those who have started their treatment with cisplatin, did not experienced ototoxicity, whereas patients who had received cisplatin alone experience hearing loss in long-term chemotherapy.[27]

Pure tone audiometry

Manual (conventional) PTA is a subjective measurement of an individual's hearing sensitivity as a diagnostic and monitoring tool depending on pure tones calibration.[28] The American Speech-Hearing-Language Association (ASHA) sets the standardization of PTA of measuring air-conduction at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz (125 Hz under some circumstances) and bone-conduction at fixed intervals from 250 Hz to 4000 Hz and at 3000 Hz. PTA is calibrated during standardized test environment. Early changes cannot be detected by conventional PTA, therefore usage of high-frequency audiometry and distortion product otoacoustic emissions (HFA + DPOAES) is better for ototoxicity monitoring. But unavailability of (HFA+ DPOAES) in our hospital obliged us to use PTA. The standardized PTA examination room is made as regard to standards of safety, emergency, ventilation, temperature, disinfection, and sound-isolation to achieve accurate results[29] (Fig. 1 and 2).

Figure 1: The standard pure tone audiometry room of examination. *Photo credit: denoc hearing*

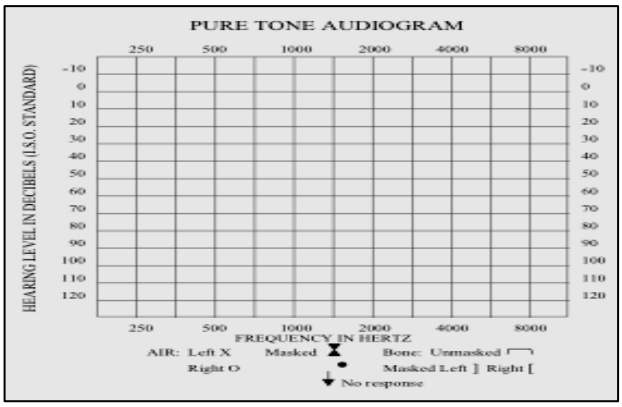

Figure 2: The standard pure tone audiogram recording sheet**.**

MATERIALS AND METHODS

This research was a cohort study carried out at the Oncology Centre and the ENT department in Al-Sadr Teaching Hospital in Basrah city, south of Iraq, from April 1 to August 30, 2015. Official and ethical permissions of Basrah General Health Directorate and the ethical and Research Committees of College of Medicine were obtained before carrying out this study. The study population included adult patients who were newly diagnosed with cancer attending the Oncology Centre for chemotherapy who were put on cisplatin alone as a cohort group and those who were put on carboplatin alone as a control group. The exclusion criteria were children and patients who already had hearing difficulty. A total of 50 patients were eligible: 27 patients were on cisplatin and used as cohort group and 23 patients were on carboplatin and used as control group. Both groups were followed up for one month. Recording of data was performed on sheets that were given code numbers and then were transferred to computer with daily checking. Data were collected using a special questionnaire designed for the purpose of the study to enquire about information related to

1. Personal information.
2. Medical and surgical history.
3. Ear, Nose and Throat (ENT) clinical symptoms and signs, such as hearing difficulty, ear discharge, tinnitus, vertigo, and headache.
4. Type of chemotherapy: Either Cisplatin or Carboplatin
5. Audiometric examination: The entire participants underwent audiometric examination, using the manual (conventional) PTA before and one month after usage of chemotherapy. PTA is a subjective measurement of an individual's hearing sensitivity as diagnostic and monitoring tool depending on pure tones calibration

depending on the ASHA setting. Hearing loss was defined as pure tone average (the mean of thresholds at speech frequencies) greater than 20 dB hearing level in the worse ear.

RESULTS

Sociodemographic characteristics of the study population:

Table 1 shows that 52% of patients were aged 50 years and above: Male to female ratio 1:1. About 52% of patients were from urban area. Unemployed patients were 50% of the study population, and 30% were either illiterate or were able to read and write. Current smokers constituted 12%. Only 1 patient (2%) reported having a family history of hearing loss.

Relationship between chemotherapy type and SNHL:

Table 2 shows that the incidence rate of SNHL in one or both ears was 66.7% among Cisplatin-treated patients, whereas the incidence rate of SNHL in one or both ears was only 13% among Carboplatin-treated patients. The relative risk equals to 5.13 with $P < 0.001$.

Association of sociodemographic characteristics with hearing loss:

Table 3 shows that there is no statistically significant association between sociodemographic characteristics and hearing loss. The risk of hearing loss increased with increasing age and was slightly more among males than females. Patients with low educational level (illiterate and only read and write) had a higher risk of hearing loss.

Table 1: Sociodemographic characteristics of the study population.

Character	No.	%
Age (years)		
≤ 35	11	22.0
36 - 49	13	26.0
50 - 64	19	38.0
≥ 65	7	14.0
Gender		
Male	25	50.0
Female	25	50.0
Residency		
Urban	26	52.0
Rural	24	48.0
Occupation		
Governmental employed	12	24.0
Private job	13	26.0
Unemployed	25	50.0
Education		
Illiterate & just read and write	15	30.0
Primary &intermediate	18	36.0
Secondary &above	17	34.0
Smoking		
Non smoker	44	88.0
Current smoker	6	12.0
Family history of hearing loss		
Positive	1	2.0
Negative	49	98.0
Total	50	100

Table 2: Medical history of the study population

Medical condition	No.	%
Hypertension		
Negative	49	98.0
Positive	1	2.0
Diabetes Mellitus		
Negative	49	98.0
Positive	1	2.0
Head or Ear Trauma		
Negative	50	100.0
Positive	0	0.0
Ear Surgery		
Negative	50	100.0
Positive	0	0.0
Ear Discharge		
Negative	50	100.0
Positive	0	0.0
Loud noise and explosion		
Negative	50	100.0
Positive	0	0.0
Chronic drug intake		
Negative	49	98.0
Positive	1	2.0
Total	50	100

Table 3: Association of Cisplatin with hearing loss

Type of chemotherapy	Hearing loss		No hearing loss		Total No. (%)
	No.	%	No.	%	
Cisplatin	18	66.7	9	33.3	27 (100)
Carboplatin	3	13.0	20	87.0	23 (100)
X^2 = 14.661 DF= 1 P <0.0001 RR= 5.13					

Table 4: Association of socio-demographic characteristic with hearing loss.

Character	Hearing loss		No hearing loss		RR	P-Value
	No.	%	No.	%		
Age (years)						
≤35	3	27.3	8	72.7	1	0.135
36-49	3	23.1	10	76.9	0.846	
50-64	11	57.9	8	42.1	2.120	
≥65	4	57.1	3	42.9	2.091	
Gender						
Female	9	36.0	16	64.0	1	0.390
Male	12	48.0	13	52.0	1.333	
Residency						
Urban	10	38.5	16	61.5	1	0.598
Rural	11	45.8	13	54.2	1.189	
Occupation						
Governmental employed	4	33.3	8	66.7	1	0.249
Private job	8	61.5	5	38.5	1.846	
Unemployed	9	36.0	16	64.0	1.018	
Education						
Secondary &above	6	35.3	11	64.7	1	0.555
Illiterate& just read and write	8	53.3	7	46.7	1.509	
Primary &intermediate	7	38.9	11	61.1	1.101	
Smoking						
Non smoker	19	43.2	25	56.8	1	0.647
Current smoker	2	33.3	4	66.7	0.771	
Family history of hearing loss						
Negative	20	40.8	29	59.2	1	0.420
Positive	1	100.0	0	0.0	2.450	

DISCUSSION

Sociodemographic characteristics of the population and their relations with SNHL

In this study, sociodemographic characteristics showed that the people aged 50–64 years were the most frequent age group. It is well known that advanced age is a risk factor for malignancy.[30] In addition, patients who were less than 15 years were already excluded from the study, because they did not attend Basrah Oncology Centre. SNHL is most frequent with increasing age, although there is no significant association between age and SNHL.

SNHL is more in males than in females with a relative risk of 1.333 and P = 390, which indicates that there is no statistically significant difference between males and females. This result is in agreement with that of a study carried out in the USA in 1997, which found that females were generally better than males in hearing at high frequencies.[31]

The approximate urban to rural number of cancer patients may be because of pollution, bombing by depleted Uranium, and changes in eating and life style habits, which have affected both urban and rural residential places evenly, whereas the study carried out in Basrah in 2005 revealed that urban patients constituted 42% and rural patients 58%.[32] Such

difference cannot be relied because both the studies differ in setting and sample size.

SNHL is more in rural residential places with a relative risk of 1.189 and P = 0.598, which indicates that there is no statistically significant difference between rural and urban residential places with SNHL, especially in rural areas, where there is less noise than urban residential places (table 4).

SNHL is most frequent in private jobs with a relative risk of 1.846 but without significant association (P = 0.249). It is assumed that most private jobs need dealing with external environment with exposure to high noise than governmental employs, which are often held inside bureaus.

SNHL is most frequent in lower educational level groups with a relative risk of 1.509 (P = 0.553), which indicates that there is no statistically significant difference. The effect of low educational level may be confounded by age, because elderly people are likely to have low educational level.

The majority of patients in this study were nonsmokers, and nonsmokers showed a high rate of SNHL than smokers, which is an unexpected result, and no plausible explanation for this result can be drawn from such small sample size.

Relation between chemotherapy type and SNHL

Cisplatin showed itself as a very high-risk factor for SNHL compared with carboplatin. About two-thirds (66.7%) of cisplatin-treated patients have SNHL compared with 13% of carboplatin-treated patients, giving a relative risk of 5.13 (P < 0.001).

According to a 1992 literature review, carboplatin has less emetogenic and nephrotoxic effects than cisplatin and lacks ototoxicity and neurotoxicity.[33]

In 1998, a review of the characteristics of cisplatin and carboplatin using clinical trials on various malignancies from 1966 to 1997 revealed that cisplatin can replace carboplatin in several malignancies while having less activity is in others. The differences between the two drugs require further studies.[34]

In a study carried out in 1999 with monitoring of ototoxicity effects of standard doses of Cisplatin and Carboplatin to 9 patients and 12 patients, respectively, via usage of ABR. After 5–6 cycles of administration of the two drugs, ABR showed normal hearing pattern in all the patients who were administered carboplatin, whereas two patients who were administered cisplatin therapy had SNHL.[25]

A retrospective study in 2002 was carried out on 26 children with malignant tumor, of whom 14 received Cisplatin and 12 received Carboplatin with monitoring of hearing via PTA. After several cycles of this chemotherapy, it was found that typical bilateral SNHL occurred in 86% of cisplatin-received patients and in 33% of carboplatin-received patients.[26]

In a cohort study done in 2004, after 10 years follow up in the Gustave Roussy Institute on 120 young children suffering from various malignancies, including hepatoblastoma, osteosarcoma, germ cell tumors, or neuroblastoma, receiving cisplatin and/or carboplatin, hearing loss was observed in 37% of cisplatin alone received patients. carboplatin alone received patients did not show hearing loss, and 43% of patients treated with cisplatin plus carboplatin showed hearing loss, thus carboplatin has not significant ototoxicity effects in comparison with cisplatin at standard dose.[27]

In a cohort study on 23 medulloblastoma patients treated with carboplatin from 1999 to 2006, there were only two patients with hearing loss so supposing that carboplatin protocols are successive alternative to cisplatin.[5]

In 2012, a longitudinal prospective trial since 1998 about ototoxicity Platinum drugs on 17 adults and 112 pediatrics soft tissue sarcoma and osteosarcoma patients in Germany, Switzerland, and Austria. From a total 108 patients treated using cisplatin, 13 were treated using carboplatin and 8 using both. About 42.1% of adults and 49.1% of children have hearing difficulty. A total of 6 of the 13 Carboplatin-treated patients (who were all children) had hearing loss, suggesting that carboplatin ototoxicity in children is much more than adults.[23]

cisplatin ototoxicity is because of its DNA integration by its cochlear tissue accumulations leading to proteins and enzyme protein formation dysfunction. cisplatin toxins in cochlea cause overload of reactive oxygen species in

addition to antioxidant system decreasing causing cell apoptosis.

The superoxides generated by the various cochlear tissues can (a) interact with nitric oxide and form peroxynitrites which nitrosylate and inactivate proteins, (b) form free hydroxyl radicals, which on interaction with iron (Fe), react with polyunsaturated fatty acids in the bilipid bilayer of the cell membranes to generate highly toxic aldehyde 4-hydroxynonenal (4-HNE) leading to cell death. This increase in 4-HNE has been associated with increased Ca2+ influx into the OHC and apoptosis, (c) inactivate antioxidant enzymes, and (d) cause cytosolic migration of Bax, leading to release of cytochrome c from injured mitochondria, which is responsible for the activation of caspase 3 and caspase 9. Caspase-activated deoxyribonuclease is then activated causing DNA breakdown (and cleavage of fodrin in the cuticular plates of injured hair cells).[35]

CONCLUSIONS

Cisplatin is a very high-risk factor for developing SNHL at its standardized chemotherapy dose just after one month of starting chemotherapy. carboplatin has very much less risk for SNHL at its standardized chemotherapy dose for the same period of usage of cisplatin. Factors such as age, gender, residential places, occupation, educational status, smoking, hypertension, diabetes mellitus, and chronic drug intake have no significant relationships with SNHL

RECOMMENDATIONS

The recommendations the participants of this study suggest are as follows:

1. carboplatin can be the drug of choice instead of cisplatin in many tumors to get rid of ototoxicity of cisplatin.
2. Replacement of cisplatin therapy by carboplatin whenever noticing of early signs of ototoxicity in tumors those must be started with cisplatin.

REFERENCES

1. World Health Organization (WHO). Deafness and hearing loss. Fact sheet N°300. Updated March 2015.
2. Bokemeyer C, Berger CC, Hartmann JT, Kollmannsberger C, Schmoll HJ, Kuczyk MA, et al. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer. 1998; 77:1355–1362.
3. Piel IJ, Meyer D, Perlia CP, Wolfe VI. Effects of cisdiamminedichloroplatinum (NSC-1 19875) on hearing function in man. Cancer Chemother Rep. 1974; 58:871–875.
4. Kaufman A. Dizziness and Balance Disorder: An Interdisciplinary Approval. Kugler, New York, NY, 1993.
5. Musial-Bright L, Fengler R, Henze G, Hernáiz Driever P. Carboplatin and ototoxicity: Hearing loss rates among survivors of childhood medulloblastoma. Childs Nerv Syst. 2011; 27(3):407–413.
6. Stohr W, Langer T, Kremers A. Hearing function in soft tissue sarcoma patients after treatment with carboplatin: A report from the Late Effects Surveillance System. Oncol Rep. 2004; 12:767–771.
7. Warner G, Burgess A, Patel S, Martinez-Devesa P, Cobridge R (Eds). Otolaryngology and Head and Neck Surgery, 1st Edition, Oxford University Press, China, 2009; pp. 288–824.
8. Smith R, Shearer A, Hildebrand M, Camp G. Deafness and Hereditary Hearing Loss Overview, Gene Reviews, University of Washington, Seattle, 2014.
9. Pasha R, Golub JS (Eds). Otolaryngology head & neck Surgery Clinical Reference Guide, 3rd Edition, Plural Publishing, USA, 2011; pp. 362.
10. Roland N, McRae R, McCombe A. Key topics in otolaryngology and head and neck surgery, 2nd Edition, Tylor & Francis e-Library, UK, 2005; pp. 315.
11. Laurence D, Bennet P, Brown M (Eds). Clinical Pharmacology, 8th Edition, Churchil Livingstone, Singapore, 1997; pp. 547–555.
12. Khanderia S, Jordan B, Martin J, Ryan R, Wagle S, Amin S, et al (Eds). British National Formulary (BNF) 66, BMJ Group and Pharmaceutical Press, Germany, 2013; pp. 575–576.
13. Bokemeyer C, Berger CC, Hartmann JT. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer. 1998; 77:1355–1362.
14. Hill G, Morest K, Parham K. Cisplatin-induced ototoxicity: Effect of intratympanic dexamethasone injections. Otol Neurotol. 2008; 29(7): 1005–1011.
15. Satoh H, Firestein GS, Billings PB, Harris JP, Keithley EM. Proinflammatory cytokine expression in the endolymphatic sac during inner ear inflammation. J Assoc Res Otolaryngol. 2003; 4:139–147.
16. So H, Kim H, Kim Y. Evidence that cisplatin-induced auditory damage is attenuated by downregulation of proinflammatory cytokines via Nrf2/HO-1. J Assoc Res Otolaryngol. 2008; 9:290–306.
17. Kim HJ, Lee JH, Kim SJ. Roles of NADPH oxidases in cisplatin-induced reactive oxygen species generation and ototoxicity. J Neurosci. 2010; 30:3933–3946.
18. Rybak L, Husain K, Morris C, Whitworth C, Somani S. Effect of protective agents against cisplatin ototoxicity. Am J Otol. 2000; 21(4):513–520.
19. Allen GC, Tiu C, Koike K, Ritchey AK, Kurs-Lasky M, Wax MK. Transient evoked otoacoustic emissions in children after cisplatin chemotherapy. Otolaryngol. Head Neck Surg. 1998; 118:584–588.
20. Huang Z, Timerbaev AR, Keppler BK, Hirokawa T. Determination of cisplatin and its hydrolytic metabolite in human serum by capillary electrophoresis techniques. J Chromatogr A. 2006; 1106(1-2):75–79.
21. Rademaker-Lakhai J, Crul M, Zuur L, Baas P, Beijnen J, Simis Y, et al. Relationship Between Cisplatin Administration and the Development of Ototoxicity. J Clin Oncol. 2006; 24(6):918–924.

22. Brunton L, Lazo J, Parker K. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Eleventh edition. McGraw-Hill companies. 2006; pp. 1333–1334.
23. Nitz A, Kontopantelis E, Bielack S, Koscielniak E, Klingebiel T, Langer T, et al. Prospective evaluation of cisplatin- and carboplatin mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients. Oncol Lett. 2013; 5(1):311–315.
24. Freilich R, Kraus D, Budnick A, Bayer L, Finlay J. Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. Med Pediatr Oncol. 1996; 26(2):95–100.
25. De Lauretis A, De Capua B, Barbieri M, Bellussi L, Passàli D. ABR evaluation of ototoxicity in cancer patients receiving cisplatin or Carboplatin. Scand Audiol. 1999; 28(3):139–143.
26. Montaguti M, Brandolini C, Ferri GG, Hatzopoulos S, Prete A, Pession A. Cisplatin and carboplatin-induced ototoxicity in children: clinical aspects and perspectives for prevention. Acta Otorhinolaryngol Ital. 2002; 22(1):14–18.
27. 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(10):649–655.
28. American Speech-Language-Hearing Association. (1990). Sound Field Measurement Tutorial II-371. Rockville, MD.
29. American National Standards Institute. (2004). Methods for Manual Pure-tone Threshold Audiometry (ANSI S3.21-2004). New York, NY.
30. Hildebrand MS, Husein M, Richard JH. Genetic Sensorineural Hearing Loss. Cummings Otolaryngology: Head & Neck Surgery. 5th edition, Mosby Inc: An Imprint of Elsevier. 2010: 94–95.
31. Murphy MP, Gates GA. Hearing Loss: Does Gender Play a Role? Medscape Women's Health.1997; 2(10):2.
32. Habib OS, Al-Ali JK, Al-Wiswasi MK, Ajeel NAH, Al-Asadi OG, Khalaf AA, et al. Cancer in Basrah 2005: preliminary results. Health and health care service in Basrah A set of performance indicators, University of Basrah College of Medicine, Basrah. 2011. Chapter Nine. pp. 103–104.
33. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: An analysis of the literature. Kluwer Academic Publishers, Netherlands, 1998.
34. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of Cisplatin and Carboplatin. J Clin Oncol. 1999; 17(1):409–422.
35. Rybak L, Mukherjea D, Jajoo S, Ramkumar V. Cisplatin ototoxicity and protection: Clinical and experimental studies. Tohoku J Exp Med. 2009; 219(3):177–186.