Comparison of the Effectiveness of Monitoring Cisplatin-Induced Ototoxicity with Extended High-Frequency Pure-Tone Audiometry or Distortion-Product Otoacoustic Emission

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Background and Objectives: To compare the effectiveness of monitoring cisplatin-induced ototoxicity in adult patients using extended high-frequency pure-tone audiometry (EHF-PTA) or distortion-product otoacoustic emission (DP-OAE) and to evaluate the concurrence of ototoxicity and nephrotoxicity in cisplatin-treated patients.

Subjects and Methods: EHF-PTA was measured at frequencies of 0.25, 0.5, 1, 2, 3, 4, 6, 8, 9, 11.2, 12.5, 14, 16, 18, and 20 kHz and DP-OAE at frequencies of 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 kHz in cisplatin-treated patients (n=10). Baseline evaluations were made immediately before chemotherapy and additional tests were performed before each of six cycles of cisplatin treatment. Laboratory tests to monitor nephrotoxicity were included before every cycle of chemotherapy.

Results: Four of 10 patients showed threshold changes on EHF-PTA. Five of 10 patients showed reductions in DP-OAE, but one was a false-positive result. The results of EHF-PTA and DP-OAE were consistent in two patients. Only one patient displayed nephrotoxicity on laboratory tests after the third cycle.

Conclusions: In our study, the incidence rate of cisplatin-induced ototoxicity was 40% with EHF-PTA or DP-OAE. Although both EHF-PTA and DP-OAE showed the same sensitivity in detecting ototoxicity, they did not produce the same results in all patients. These two hearing tests could be used to complement one another. Clinicians should use both tests simultaneously in every cycle of chemotherapy to ensure the detection of ototoxicity.

KEY WORDS: Cisplatin · Ototoxicity · Otoacoustic emission · Pure-tone audiometry.

Introduction

The first-generation platinum drug cisplatin is widely and frequently used for the treatment of various cancers. It is an effective drug against many kinds of cancer but also has many associated adverse effects, including ototoxicity, nausea, vomiting, nephrotoxicity, bone-marrow suppression, and hepatotoxicity.¹ The ototoxicity of cisplatin is known to correlate with its cumulative dose. However, hearing loss (HL) after cisplatin treatment is difficult to predict based only on the cumulative dose because there is significant individual variability in susceptibility to ototoxicity.² However, cisplatin-induced ototoxic damage is usually considered irreversible once it has occurred.³ These facts justify the mandatory monitoring of ototoxicity to ensure its early detection.

Otototoxic effects often first appear at frequencies > 8 kHz. Numerous previous studies have demonstrated the value of extended high-frequency pure-tone audiometry (EHF-PTA) for the early detection of cisplatin-induced ototoxicity (Cis-OT), because Cis-OT begins in the most basal region of the cochlea.⁴ Distortion-product otoacoustic emission (DP-OAE) potentially reflects subclinical cochlear damage because DP-OAE am-
pli tude reduction arises from outer-hair-cell damage, which occurs before inner-hair-cell damage. Some clinicians advocate
the use of DP-OAE because this test is not affected by the
patient’s age or any deterioration in the patient’s general
condition caused by chemotherapy.

The first aim of our study was to investigate which of these
tests is the more sensitive method for detecting Cis-OT. We
performed both EHF-PTA and DP-OAE in every cisplatin-
treated patient and compared the ototoxicity detection rates of
the two tests. Our second aim was to assess the concurrence of
ototoxicity and nephrotoxicity in cisplatin-treated patients. Se-
rum blood urea nitrogen (BUN) and serum creatinine (Cr) lev-
els and the glomerular filtration rate (GFR) were measured to
detect nephrotoxic complications.

Subjects and Methods

This study was performed with the approval of the Institu-
tional Review Board of Eulji General Hospital and all the par-
ticipants gave their informed consent. A prospective study was
carried out in 17 patients who were undergoing chemotherapy
that included cisplatin from May 2011 to August 2013. Seven
of these patients discontinued their follow-up voluntarily or
dropped out of the study. The data for the 10 patients who com-
pleted the tests throughout all their cycles of chemotherapy
were collected.

All 10 patients were diagnosed with cancer by pathological
evaluation, including two with lung cancer, two with gastric
cancer, four with gynecological malignancies, one with gall
bladder cancer, and one with common bile duct cancer. Each
patient received several (2–6) cycles of cisplatin and i.v. dose
calculated from the body surface area of each patient. The hear-
ing levels of the patients were evaluated with EHF-PTA and
DP-OAE. The baseline evaluation was made immediately be-
fore chemotherapy commenced and additional tests were per-
formed immediately before each cycle of cisplatin treatment,
and one month after the end of treatment. None of our patients
had received any ototoxic drug other than cisplatin.

EHF-PTA was measured at frequencies of 0.25, 0.5, 1, 2, 3,
4, 8, 9, 11.2, 12.5, 14, 16, 18, and 20 kHz using an AC40 clini-
cal audiometer (Interacoustics, Assens, Denmark). All the pa-
tients were tested in both ears, and the pure-tone audiometric
thresholds, in decibels hearing level, were measured through
air and bone conduction. The presence or absence of a
change in the hearing threshold was based on published clini-
cal guidelines [American Speech-Language-Hearing Associa-
tion (ASHA) 1994] and included: 1) ≥20 dB change at any
one test frequency; 2) ≥10 dB change at any two consecutive
test frequencies at which responses were previously obtained
(ASHA 1994). Navigator PRO (Bio-logic Systems Corp., Mundelein, IL,
USA) was used to assess DP-OAE. The sound stimulus for
DP-OAE consisted of two simultaneous permanent pure tones
at different frequencies

\[ f_1: f_2 = 1.22 \]\text{ at } 60 \text{ dB SPL (L1} \geq \text{ L2)} \text{, and DP-OAE was measured at eight different frequen-
cies: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 kHz. Change in DP-OAE
was defined as a reduction in the signal-to-noise ratio (SNR) at
f_1 \text{ frequencies below 1 kHz, which is the difference between
the amplitude of DP-OAE and the noise floor at each test f_2
frequency. A reduction in SNR greater than 14 dB was regarded
as significant. At f_2 \text{ frequencies above 1 kHz, a reduction in
SNR greater than 7 dB was considered a significant clinical change.}^{3,6}

Serum BUN, serum Cr, and GFR were tested to monitor
nephrotoxicity. Blood samples were taken immediately before
each cycle of chemotherapy.

Statistical analyses were performed with the SPSS statistical
software package (SPSS, version 15.0 for Windows; SPSS
Inc., Chicago, IL, USA). The results of the blood tests before
each cycle were compared using multivariate analysis of vari-
ance. The correlations between the cumulative dose of cispl
atin and the risk factors for developing ototoxicity were cal-
culated using Pearson’s correlation analysis. Differences were
considered statistically significant at a p value of <0.05.

Results

Six of the 10 study subjects were men and four were wom-
en. The mean age of the group was 58.7 ± 10.3 years (range,
40–71 years). No child subject was included. The mean ini-
tial dose of cisplatin was 114.0 ± 40.3 mg/m² (range, 40–160
mg/m²) and the mean total infused dose was 610.0 ± 286.6
mg/m² (range, 80–960 mg/m²). Five patients received six cy-
cycles of chemotherapy, two of them received five cycles, an-
other two received four cycles, and one of them received two cy-
cycles (mean, five cycles; range, 2–6 cycles)(Table 1). One
patient (subject 10) had mixed-type HL on the right side and
a ventilation tube was inserted before the study. No other pa-
tient complained of HL, tinnitus, or aural fullness before
therapy. Four of the 10 patients [subjects 1, 3, 5, and 10 (left
er only), seven of 20 ears] revealed threshold changes on
EHF-PTA (Table 2). Five ears showed threshold changes be-
low 8 kHz (one ear at 3 kHz, two ears at 4 kHz, and another
two ears at 8 kHz), and another two ears showed changes at
frequencies over 9 kHz (one ear at 9 kHz and the other ear at
10 kHz). One patient (subject 10) with unilateral HL before
treatment showed a threshold change at 8 kHz on the healthy
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Table 1. Summary of ototoxicity and nephrotoxicity after cisplatin-based chemotherapy

| Age  | Sex | Initial dose (mg/m²) | Number of cycles | Side | Lowest frequency that showed threshold change (kHz) | Hearing loss time (cumulative dose: mg/m²) | Frequencies that showed DP-OAE value change (kHz) | Hearing loss time (cumulative dose: mg/m²) | Nephrologic laboratory changes |
|------|-----|---------------------|------------------|------|----------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|----------------------------------|
| 58   | F   | 160                 | 6                | R    | 10                               | After 3rd cycle (480)                     | 6                                        | After 3rd cycle (480)                     | Yes                              |
|      |     |                     |                  | L    | 9                                | After 3rd cycle (480)                     | 4, 6, 8                                  | After 3rd cycle (480)                     |                                    |
| 64   | M   | 105                 | 4                | R    | 3                                | After 6th cycle (780)                     | 4, 6, 8                                  | After 6th cycle (780)                     | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 53   | F   | 130                 | 6                | R    | 3                                | After 6th cycle (780)                     | 4, 6, 8                                  | After 6th cycle (780)                     | No                               |
|      |     |                     |                  | L    | 4                                | After 6th cycle (780)                     | 4, 6, 8                                  | After 6th cycle (780)                     |                                    |
| 65   | M   | 130                 | 6                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 40   | F   | 130                 | 6                | R    | 4                                | After 6th cycle (780)                     | 8                                        | After 6th cycle (780)                     | No                               |
|      |     |                     |                  | L    | 8                                | After 6th cycle (780)                     | 8                                        | After 6th cycle (780)                     |                                    |
| 44   | M   | 140                 | 5                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 62   | M   | 40                  | 2                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 71   | F   | 140                 | 5                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 70   | M   | 45                  | 4                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    |                                  |                                          |                                         |                                        |                                  |
| 60   | F   | 120                 | 6                | R    |                                  |                                          |                                         |                                        | No                               |
|      |     |                     |                  | L    | 8                                | After 4th cycle (480)                     | 6                                        | After 2nd cycle (240)                     |                                    |

*false positive result, †subject 10 already had unilateral hearing loss on her right side. PTA: pure-tone audiometry, DP-OAE: distortion-product otoacoustic emission

Table 2. Incidence of ototoxicity and nephrotoxicity after cisplatin-based chemotherapy

|                        | Patients (n=10) | Ears (n=20) |
|------------------------|-----------------|-------------|
| PTA threshold change   | 4 (40%)         | 7 (35%)     |
| DP-OAE value change    | 4 (40%)*        | 7 (35%)*    |
| Subjective hearing change | 0 (0%)         | 0 (0%)     |
| BUN, Cr, GFR change    | 1 (10%)         | –           |

*one ear showing a false-positive DP-OAE result was excluded. PTA: pure-tone audiometry, DP-OAE: distortion-product otoacoustic emission, BUN: blood urea nitrogen, Cr: creatinine, GFR: glomerular filtration rate

side only. Three ears (subjects 1 and 10) showed threshold changes during chemotherapy and another four ears (subjects 3 and 5) showed threshold changes after therapy ceased (Table 1, Fig. 1). To assess the overall changes in the hearing thresholds after chemotherapy, we plotted the average thresholds for all 10 patients at each frequency. There were no statistical differences in the hearing thresholds before and after treatment for either ear at any frequency measured (Fig. 2).

There was no significant correlation between the cumulative dose of cisplatin and the presence of hearing threshold changes on EHF-PTA (p > 0.05). There was also no significant correlation between the cumulative dose and the lowest frequency that showed hearing impairment (p > 0.05).

Five of the 10 patients (subjects 1, 3, 5, 8, and 10) showed a reduction in DP-OAE, but one of the results (subject 8) was a false positive, in which the DP-OAE change only occurred at 2 kHz, whereas no change was detected with EHF-PTA. The DP-OAE results were consistent with the EHF-PTA.
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Fig. 1. Results of pre-treatment and post-treatment EHF-PTA and DP-OAE for patients with hearing impairment. Two left audiograms show pre-treatment and post-treatment EHF-PTA in both ears, and four right DP grams show pre-treatment and post-treatment DP-OAE of right and left ears. Toward frequency that showed threshold change (kHz). *frequencies that showed DP-OAE value change (kHz). EHF-PTA: extended high-frequency pure-tone audiometry, DP-OAE: distortion-product otoacoustic emission, NF: noise floor.
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Subject 3

Fig. 1. Continued.
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OAE showed a false positive rate of 10% of chemotherapy, simultaneous with a hearing threshold change. According to the laboratory tests, which occurred after the third cycle or any otological problem during or after chemotherapy. Subjects complained of their newly developed hearing disturbance in-based chemotherapy were plotted in Fig. 3. None of the subjects showed bilateral HL on EHF-PTA. The sensitivity of EHF-PTA in detecting Cis-OT was 40% (Table 2). DP-OAE detected HL earlier than EHF-PTA in subject 10, in which DP-OAE detected HL earlier than EHF-PTA. The sensitivity of EHF-PTA in detecting Cis-OT was 40% (four of 10 patients) with a level of reduction at 2 kHz on DP-OAE only, although EHF-PTA detected no threshold change, it is reasonable to regard it as a false positive result. We could draw no conclusion from these data about which test is superior for the early detection of Cis-OT. The two tests seem to be mutually complementary. Therefore, clinicians should use both tests simultaneously in every cycle of chemotherapy to ensure the detection of otoxicity. There are no standard criteria for defining changes in DP-OAE, and we used the criteria that have been used in many previous studies. ASHA suggested the clinical criterion that DP-OAE changes should show a level reduction of 4 dB or that a loss of response at two adjacent frequencies indicates a “reduction” on DP-OAE. However, when this criterion was applied in our study, only three of 20 ears (15%) met the criterion (left ear of subject 1, both ears of subject 3). This implies that the ASHA criterion is too strict for the early detection of otoxicity.

The mean incidence of otoxicity was 33% when patients received a single dose of 50 mg/m² cisplatin. Coradini, et al. reported 52% bilateral HL in cisplatin-treated younger patients (median age, 12.3 years; median total dose of cisplatin, 406 mg/m²) using PTA, DP-OAE, and transient evoked otoacoustic emissions (TE-OAE). Another study using EHF-PTA detected HL in 42 of 55 ears (76.4%) after treatment. In the study of Eiamprapai, et al., the incidence rate of otoxicity detected with DP-OAE was 77.3% in adult patients after a cumulative dose of cisplatin of 156.1 ± 77.17 mg/m². Another study reported that the incidence of otoxicity was 81.3% in children (eight months to 20 years old) after a cumu-
Cisplatin can cause both ototoxicity and nephrotoxicity. The protein, kidney injury molecule 1, which is induced in the renal proximal tubular epithelium after cisplatin therapy, can also be expressed in the cochlea, and caused ototoxic effects in an animal study. Reports of the incidence of cisplatin-induced nephrotoxicity are relatively rare. An increase in the serum Cr concentration has been reported in 41% of patients treated with high doses of cisplatin (70–85 mg/m² for each cycle, 5.3 mean cycles). And Máthé, et al. reported that 23 of 38 patients with lung cancer showed pathological increases in serum Cr after 2–4 cisplatin infusions (75 mg/m²) per cycle. From our result, we infer that the incidence of cisplatin-induced nephrotoxicity (10%) is lower than the incidence of ototoxicity (40%). However, close monitoring must be mandatory for nephrotoxicity, because its consequences are lethal.

The purpose of monitoring ototoxicity during cisplatin chemotherapy is the early detection of sensorineural hearing impairment before the patient is himself/herself aware of it. If serious ototoxicity is detected, an alternative, less ototoxic drug, such as carboplatin, could be considered before ototoxicity progresses. The timing of the interruption of cisplatin should be considered based on various factors, including the amount of hearing deterioration, the hearing level before chemotherapy, the pathological type or grade of cancer, and the patient’s age. However, to the best of our knowledge, there is no specific criterion for the discontinuation of cisplatin therapy. The critical dose of Cis-OT is still controversial. The average cumulative dose of cisplatin to cause a threshold change in EHF-PTA was reported to be 400 or 343.6 mg/m² in two different studies. In one study using DP-OAE, the SNR amplitude decreased significantly when the patients received a cumulative dose of more than 200 mg/m². In the present study, ototoxicity was detected with EHF-PTA and DP-OAE after a total cumulative dose of 780 mg/m² in two subjects. Another subject displayed ototoxicity at a total cumulative dose of 480 mg/m² and another at 240 mg/m². The average cumulative dose of cisplatin during which ototoxicity developed was 570 ± 261.53 mg/m². However, three subjects who received a cumulative cisplatin dose > 700 mg/m² showed no change on either EHF-PTA or DP-OAE, implying that individual variability, such as genetic factors, affect the development of ototoxicity. In this study, there was no significant correlation between the cumulative dose of cisplatin and the presence of hearing threshold changes, which could be attributable to the small sample size. The four patients with HL after treatment showed threshold changes below 8 kHz, but none of them was aware of their hearing impairment during or after chemotherapy. This result justifies the monitoring of ototoxicity.

The limitation of this study was its small sample size. Only 10 patients completed all the scheduled follow-up evaluations. Because of the severity of the patients’ existing disease, some died during the research period, and some showed very poor compliance with the hearing test. Patients who did not feel their hearing was impaired tended to ignore the importance of the follow-up hearing tests. For this reason, seven patients discontinued regular hearing tests during and after their treatment with cisplatin. For the future, the study with larger
sample size will be necessary to clarify the effectiveness of EHF-PTA and DP-OAE for monitoring cisplatin-induced otoxicity. Several investigators argued that both EHF-PTA and OAE are problematic in patients with HL, particularly in the elderly, because of the limited responses to test due to pre-existing losses of outer hair cells in the cochlear basal region.\(^{21-30}\) For the cases of elderly patients, the baseline testing prior to ototoxic drug administration will be mandatory for the precise interpretation using “change of value”. Ress, et al.\(^{17}\) studied a greater number of patients including elderly subjects and DP-OAE showed effective sensitivity to detect ototoxicity. In the present study, all subjects performed EHF-PTA and DP-OAE before initial cisplatin infusion and the “change of value” after treatment were calculated.

As mentioned several times before, HL can occur without any subjective otological symptoms. It is also easy for oncologists to overlook the monitoring of hearing, because they consider the cancer therapy to be the most important issue. Detailed information about cisplatin-induced ototoxicity should be offered to patients and otologists should be involved in establishing a well-organized protocol for hearing tests for all cisplatin-treated patients.

**Conclusion**

In our study, the incidence rate of Cis-OT was 40% (four of 10 patients) when detected with either EHF-PTA or DP-OAE. Although both EHF-PTA and DP-OAE showed the same sensitivity in detecting ototoxicity, they did not produce coincident results in all cases. The two hearing tests complement one another, and clinicians should use both tests simultaneously in every cycle of chemotherapy to ensure the detection of ototoxicity. Cisplatin may induce nephrotoxicity less frequently than it induces ototoxicity.

**Acknowledgments**

This study was supported by Dong-A ST Co., Ltd, South Korea. Cisplatin administered in this study was not related with Dong-A ST Co., Ltd.

**REFERENCES**

1) Yilmaz S, Oktem F, Karaman E. Detection of cisplatin-induced ototoxicity with transient evoked otoacoustic emission test before pure tone audiometry. Eur Arch Otorhinolaryngol 2010;267:1041-4.
2) Lanvers-Kaminsky C, Krefeld B, Dinnesse AG, Deuster D, Seilert E, Würthwein G, et al. Continuous or repeated prolonged cisplatin infusions in children: a prospective study on ototoxicity, platinum concentrations, and standard serum parameters. Pediatr Blood Cancer 2006;47:183-93.
3) Schaefer SD, Post JD, Close LG, Wright CG. Ototoxicity of low- and moderate-dose cisplatin. Cancer 1985;56:1934-9.
4) American Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. ASHA 1994;36(11):9.
5) Beattie RC, Kemworthy OT, Luna CA. Immediate and short-term reliability of distortion-product otoacoustic emissions. Int J Audiol 2003;42:348-54.
6) Eiamprapai P, Yamamoto N, Hirauni H, Ogino-Nishimura E, Kitamura M, Hirano S, et al. Effect of cisplatin on distortion product otoacoustic emissions in Japanese patients. Laryngoscope 2012;122: 1392-6.
7) Komune S, Asakuma S, Snow JB Jr. Pathophysiology of the ototoxicity of cis-diamminedichloroplatinum. Otolaryngol Head Neck Surg 1981;89:275-82.
8) Brummert RE. Drug-induced ototoxicity. Drugs 1980;19:412-28.
9) Nakai Y, Konishi K, Chang KC, Ohashi K, Morisaki N, Minowa Y, et al. Ototoxicity of the anticancer drug cisplatin. An experimental study. Acta Otolaryngol 1982;93:227-32.
10) Konishi T, Gupta BN, Prazma J. Ototoxicity of cis-dichlorodiammine platinum (II) in guinea pigs. Am J Otolaryngol 1983:418-26.
11) Schweitzer VG, Hawkins JE, Lilly DJ, Litterst CJ, Abrams G, Davis JA, et al. Ototoxic and nephrotoxic effects of combined treatment with cis-diamminedichloroplatinum and kanamycin in the guinea pig. Otolaryngol Head Neck Surg 1984:92:38-49.
12) Arendberg JK. Dizziness and Balance Disorders. New York: Kugler Publications;1993.
13) Coradini PP, Cigan L, Selistre SG, Rosito LS, Brunetto AL. Ototoxicity from cisplatin therapy in childhood cancer. J Pediatr Hematol Oncol 2007:29:355-60.
14) Fausti SA, Larson RD, Neffinger D, Wilson RH, Phillips DS, Fowler CG. High-frequency audiometric monitoring strategies for early detection of ototoxicity. Ear Hear 1994;15:232-9.
15) Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol 2007:25:1190-5.
16) Littman TA, Magruder A, Strotcher DR. Monitoring and predicting ototoxic damage using distortion-product otoacoustic emissions: pediatric case study. J Am Acad Audiol 1998;9:257-62.
17) Ress BD, Srithar KS, Balkany TJ, Waxman GM, Stagner BB, Lonsbury-Martin BL. Effects of cis-platinum chemotherapy on otoacoustic emissions- the development of an objective screening protocol. Third place--Resident Clinical Science Award 1998. Otolaryngol Head Neck Surg 1999;121:693-701.
18) Stavroulaki I, Apostolopoulos N, Segas J, Tsakanikos M, Adamopoulos G. Evoked otoacoustic emissions--an approach for monitoring cisplatin induced ototoxicity in children. Int J Pediatr Otorhinolaryngol 2001;59:47-57.
19) Delehaye E, Capobianco S, Bertetto IB, Meloni F. Distortion-product otoacoustic emission: early detection in deoxeratmine induced ototoxicity. Auris Nasus Larynx 2006;35:198-202.
20) Dhooge I, Dhooge C, Geukens S, De Clerck B, De Vel E, Vinck BM. Distortion product otoacoustic emissions: an objective technique for the screening of hearing loss in children treated with platinum derivatives. Int J Audiol 2006;45:337-43.
21) Sakamoto M, Kaga K, Kamiyama T. Extended high-frequency ototoxicity induced by the first administration of cisplatin. Otolaryngol Head Neck Surg 2000;122:828-33.
22) Reavis KM, Phillips DS, Fausti SA, Gordon JS, Helt WJ, Wilmington D, et al. Factors affecting sensitivity of distortion-product otoacoustic emissions to ototoxic hearing loss. Ear Hear 2008;29:875-93.
23) Mukherjea D, Whitworth CA, Nandish S, Dunaway GA, Rybik LP, Ramkumar V. Expression of the kidney injury molecule 1 in the rat cochlea and induction by cisplatin. Neuroscience 2006;139:733-40.
24) de Jongh FE, van Veen RN, Veltman SJ, de Wit R, van der Burg ME, van den Bent MJ, et al. Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. Br J Cancer 2003;88:1199-206.
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25) Máthé C, Bohács A, Duffek L, Lukácsovits J, Komlosi ZI, Szondy K, et al. Cisplatin nephrotoxicity aggravated by cardiovascular disease and diabetes in lung cancer patients. Eur Respir J 2011;37:888-94.
26) Biro K, Noszéki L, Prekopp P, Nagyiványi K, Gécz 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;70:177-84.
27) Osterhammel D. High frequency audiometry. Clinical aspects. Scand Audiol 1980;9:249-56.
28) Kujansuu E, Rahko T, Punnonen R, Karma P. Evaluation of the hearing loss associated with cis-platinum treatment by high-frequency audiometry. Gynecol Oncol 1989;33:321-2.
29) Lonsbury-Martin BL, Cutler WM, Martin GK. Evidence for the influence of aging on distortion-product otoacoustic emissions in humans. J Acoust Soc Am 1991;89(4 Pt 1):1749-59.
30) Stover L, Norton SJ. The effects of aging on otoacoustic emissions. J Acoust Soc Am 1993;94:2670-81.