Cancer Chemother Pharmacol (1988) 21: 61–64

Cancer Chemotherapy and Pharmacology



# Very high-dose cisplatin-induced ototoxicity: a preliminary report on early and long-term effects*

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**Summary.** Acute and subacute audiometric hearing changes were evaluated in 12 patients receiving 35 courses of very high-dose (vhd) cisplatin (200 mg/m$^2$ per course) in hypertonic saline at 4 or 8-week intervals. Audiogical evaluations were performed both before and immediately after each course of chemotherapy, and again after the discontinuation of treatment. A significant drop of the mean hearing threshold ($P < 0.01$) at high frequencies was observed even within 48 h from the end of the first course of therapy, with 50% of the patients presenting a hearing loss of more than 15 dB. At the same total dose (200 mg/m$^2$), one course of this regimen provided an incidence of hearing loss of more than 15 dB, which was four times greater than that reported with two courses of standard-dose regimens. The incidence and severity of the hearing impairment progressed further with subsequent courses of chemotherapy. Compared with baseline levels, most patients (75%) receiving at least two courses had a moderate to severe hearing loss, especially involving 4 and 8 kHz. At the end of treatment, 33% of the patients complained of a nondisabling functional hearing impairment. No recovery occurred after chemotherapy had been discontinued for 9–28 weeks. At this dose level cisplatin is markedly ototoxic. The use of hypertonic saline and vigorous hydration are effective means of minimizing the risk of nephrotoxicity, but seem to have no effect on cisplatin-related ototoxicity.

## Introduction

Ototoxicity is a well-recognized side effect of cisplatin, being observed in 7%–90% of patients receiving standard doses (up to 120 mg/m$^2$ per course) [5, 7].

With the improved methods of administration now available, higher doses (up to 200 mg/m$^2$ per course) can be delivered with an acceptable risk of nephrotoxicity and better antitumor effects [12]. At these dose levels, however, other kinds of toxicity appear (retinal [13], hepatic [15]), while others become more severe (myelosuppression) and even dose-limiting (neurotoxicity) [2, 12, 13].

The aim of the present study was the better definition of the incidence and severity of both early and long-term ototoxicity related to very high-dose (vhd) cisplatin (200 mg/m$^2$) in hypertonic saline [12].

* Supported in part by a grant from the Ministero della Sanita: 'Controllo dell'emesi indotta da agenti antineoplastici'

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## Materials and methods

Since June 1985, a total of 12 patients (median age 51 years, range 33–58) affected with advanced ovarian cancer and receiving vhd cisplatin as part of the primary (5 cases) or salvage (7 cases) treatment have been included in this study. Only patients receiving at least two courses of chemotherapy (400 mg/m$^2$) with serial audiometric testing (at least 5 evaluations) have been considered.

There was no prior history of ototoxic drug therapy in any of the patients, except for 3 with prior exposure to standard-dose cisplatin (50 mg/m$^2$ at 4-week intervals up to a total dose of 300 mg/m$^2$ in 2 patients, and 550 mg/m$^2$ in the 3rd, discontinued 2, 4 and 3 months earlier, respectively).

In 7 cases (2 with prior cisplatin), however, the initial audiological evaluation revealed a preexisting stable hearing loss exceeding 30 dB (ranging between 35 and 55) at one or more frequencies (2, 4 and 8 kHz in 1 patient, 4 and 8 kHz in 2 patients, and 8 kHz only in the remaining cases).

Cisplatin (40 mg/m$^2$ per day for 5 days) was given either alone every 4–5 weeks as salvage therapy or as primary treatment at 8-week intervals with sequential Adriamycin (40 mg/m$^2$ on day 1) and cyclophosphamide (200 mg/m$^2$ per day on days 3–5).

Hydration with 6 l/day (250 ml/h) normal saline with potassium and magnesium supplements was begun 12 h before the first cisplatin dose and continued for 12 h after the fifth dose. Each single dose (40 mg/m$^2$) was dissolved in 250 ml 3% NaCl and infused over a 30-min period. Furosemide (20 mg i.v.) was given 30 min before each cisplatin dose. Standard regimens including high-dose metoclopramide and dexamethasone were also administered in an attempt to control emesis.

An adequate urine output was maintained in all the patients. The patients were also carefully monitored to avoid fluid overload and severe electrolyte disturbance.

Pre- and post-treatment audiometric testing were performed within 2 days before the first and after the last day of cisplatin for each course of chemotherapy. When possible, the patients were periodically evaluated after completion of the treatment.

**Table 1.** Mean (± SD) hearing threshold levels (dB) observed in patients receiving cisplatin (200 mg/m² per course) in hypertonic saline

| | | Frequency | | |
|---|---|---|---|---|
| | No. of pts | 2 kHz | 4 kHz | 8 kHz |
| a) Acute effects | | | | |
| 1st course Before | 12 | 19.3± 8 | 23.2±13 | 35.0±14 |
| After | 12 | 27.8± 8** | 43.1± 8** | 61.2±13** |
| 2nd course Before | 12 | 21.9± 8 | 30.6±14 | 52.7±17 |
| After | 12 | 31.3±14 | 46.0±13* | 64.6± 8 |
| 3rd course Before | 10 | 19.4±11 | 37.2±19 | 57.5±17 |
| After | 10 | 23.9± 8 | 33.6±12 | 67.8±16 |
| b) Cumulative effects | | | | |
| Baseline | 12 | 19.3± 8 | 23.2±13 | 35.0±14 |
| 1st course | 12 | 21.9± 8 | 30.6±14* | 52.7±17** |
| 2nd course | 12 | 19.9±12 | 37.8±19** | 58.5±16** |
| 3rd course | 12 | 22.5±10 | 40.2±16*** | 67.2±15*** |
| Follow-up | 12 | 30.5±12* | 45.6±16*** | 65.6±11*** |

For acute effects, comparisons are between pre- and post-treatment levels for each course
For cumulative effects, comparisons are between the baseline audiometric evaluation (before the 1st course) and controls at 4–8 weeks after each subsequent course as well as after discontinuation of cisplatin (follow-up: 9–28 weeks after the end of treatment)
* $P<0.05$; ** $P<0.01$; *** $P<0.001$ (Student's paired $t$-test)

Pure tone thresholds were obtained bilaterally at 0.25, 0.5, 1, 2, 4 and 8 kHz. The audiometric assessment was conducted in a sound-controlled testing booth under standard clinical conditions [7]. Any subjective hearing difficulty and tinnitus was recorded.

On the basis of previous reports [1, 10], the mean hearing threshold of the two ears was considered reliable for the statistical analysis.

A decrease of more than 15 dB at one or more frequencies on serial audiography was considered significant and referred to as moderate (>15–30 dB) or severe (>30 dB).

To evaluate the acute audiometric changes, comparisons were made of the mean hearing threshold levels before and after each course. Serial audiological tests performed 4–8 weeks after each subsequent course were compared with the baseline levels (before the start of vhd cisplatin) to evaluate the subacute ototoxic effects. Finally, the long-term effects were studied by comparing both the baseline hearing level and that after the last course with those found 9–28 weeks after the discontinuation of treatment.

Student's paired $t$-test was used for the statistical analysis.

## Results

A total of 82 audiograms were obtained during chemotherapy. Additional tests were conducted after the discontinuation of cisplatin (median follow-up 10 weeks, range 9–28 weeks) in all cases. In two patients the treatment was discontinued before the third course of cisplatin because of disease progression. One patient received a fourth course of vhd cisplatin as salvage treatment after achieving complete pathological remission. The median number of vhd cisplatin courses was three (range two to four), and the mean cumulative dose (previous standard dose included), 737.5 mg/m² (range 400–1150 mg/m²).

An analysis of each frequency, providing a characterization of the drug-induced hearing loss, is shown in Table 1. The proportion of patients with moderate and severe hearing loss at each point in the study has also been reported (Fig. 1).

At lower frequencies (0.25, 0.5, 1 kHz), neither severe nor moderate shifts in the hearing thresholds were detected at any time during the subsequent courses of vhd cisplatin or at the end of the treatment.

The audiometric changes observed at higher frequencies are reported below.

### *Acute toxicity*

At higher frequencies (2, 4, 8 kHz), a significant shift in hearing threshold was evident within 48 h from the end of the first course. Compared with baseline levels a statistically significant increase of the mean hearing thresholds occurred at 2, 4 and 8 kHz ($P<0.01$, Table 1a).Three out of six patients with audiological impairment of more than 15 dB presented a severe hearing loss. Changes occurred at 4 and 8 kHz in two cases, while in another patient hearing loss was also found at 2 kHz.

Comparison of post-treatment audiometric levels with those found prior to the second cisplatin course showed that acute changes in mean hearing threshold were statistically significant only at 4 kHz ($P<0.05$, Table 1a). Four patients showed a further moderate hearing loss at this point, involving more than one frequency in one case.

No significant acute audiometric changes were found in the ten patients receiving a third course of vhd cisplatin, although a further slight worsening of the mean hearing threshold was evident (Table 1a). No patient had a post-treatment hearing loss of more than 15 dB.

### *Subacute and long-term toxicities*

As regards baseline levels, audiometric testing performed 1 or 2 months after the first course of cisplatin (just prior to

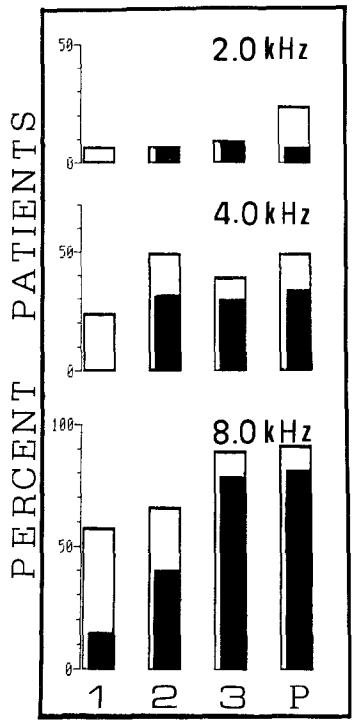


**Fig. 1.** Percentage of subjects with hearing loss (□, >15 dB; ■, >30 dB) after one, two, and three courses of vhd cisplatin and 9–28 weeks after the end of treatment (P), compared with baseline levels

the second course) showed statistically significant changes in the mean hearing threshold at both 4 ($P < 0.05$) and 8 ($P < 0.01$) kHz, but not at 2 kHz (Table 1b).

Compared with baseline levels, seven patients (58%; Fig. 1) showed hearing losses of more than 15 dB (severe at 8 kHz in two patients), affecting at least two frequencies in three cases. Three of the four patients with tinnitus showed hearing loss at both 4 and 8 kHz.

At this time a complete recovery of the early hearing loss at 4 kHz in three patients and at 8 kHz in one patient, and a reduction of the severity of hearing drop at 8 kHz in another case were found. Three out of four patients showing any recovery, however, retained the audiometric impairment at at least one more frequency. Two more patients with no acute changes after the first course of cisplatin showed a moderate hearing loss at 8 kHz.

At 1 or 2 months after the second course of cisplatin, a further worsening in the audiometric values was observed. Compared with baseline values the mean hearing levels were statistically significantly higher at both 4 and 8 kHz ($P < 0.01$, Table 1b). At this time nine patients (75%) showed a hearing loss of more than 15 dB. Two patients with no ototoxicity with the previous course of vhd cisplatin developed a severe hearing loss at 8 kHz, while three out of seven patients with established ototoxicity after the first course (including those who had any recovery) showed worsening of the hearing loss at 4 kHz in two cases and also at 2 kHz in another. In six cases more than one frequency was involved. In five out of eight patients with loss at 8 kHz and all four patients with loss at 4 kHz the hearing loss was severe. Two patients complained of tinnitus.

At 1 or 2 months after the third course of vhd cisplatin, highly statistically significant changes ($P < 0.001$) were found in the mean hearing threshold levels at both 4 and 8 kHz (Table 1b).

Two additional patients developed severe hearing loss at 8 kHz, and one of these also complained of tinnitus. Of the patients with established ototoxicity with prior courses of vhd cisplatin, two experienced worsening of the severity of the hearing loss, in one the range of frequencies involved was extended, and no changes were found in the remaining six patients (including the two patients who discontinued treatment after the second course).

At the same time, all but one patient (with a baseline hearing loss after standard-dose cisplatin) had either moderate (one patient) or severe (ten patients) hearing loss (92%; Fig. 1) affecting one (8 kHz in five cases) or more frequencies (8 and 4 kHz in five cases and 2 kHz in addition in three).

At this time four patients (33.3%) had functional hearing loss with more difficulty in hearing high-frequency sounds, such as a telephone bell, than normal voice tones.

Compared with mean baseline levels, the hearing loss observed 9–28 weeks after discontinuation of therapy (Table 1b) was similar to that observed 4–8 weeks after the last course of cisplatin, except at 2 kHz ($P < 0.05$).

Except for one patient with worsening of the hearing loss at 2 kHz, no further differences were found in the remaining ten patients since the previous evaluation. No recovery could be detected within the limits of the observation period (Fig. 1).

## Discussion

Studies conducted by Litterest [11] and Earhart et al. [4] have provided the experimental basis for administration of cisplatin in hypertonic saline, permitting the clinical use of doses higher than the conventional ones. Preliminary studies suggest significant therapeutic advantages related to higher plasma platinum levels achieved with this regimen [3], and promising clinical trials are currently in progress.

At the dose levels used in this study, cisplatin toxicity becomes more frequent and severe. At the present time, the dose-limiting peripheral neurological toxicity makes this treatment unsuitable for long-term use [2, 12, 13]. Ototoxicity has also been described, but there are few data available on this subject [2, 12, 13].

On the other hand, several reports describe in detail the characteristics of ototoxicity induced by standard-dose cisplatin. Hearing loss has been reported to be bilateral [1, 8, 10], symmetrical [1, 10], dose-related and cumulative [10, 14], particularly involving high frequencies above the speech range [1, 6, 8, 10]. Rapid drug delivery, the concurrent use of diuretics, dehydration and probably preexisting hearing loss [16, 19], may increase this toxicity to even a greater extent.

The data presented in the present paper indicate that at the dose levels that can now be administered (200 mg/m$^2$ per course), cisplatin is markedly ototoxic despite the use of a 5-day schedule, which has been reported as less ototoxic than a 1-day schedule with standard-dose cisplatin [17]. In 50% of our patients, a significant hearing loss occurred even within 48 h from the end of the first course. At the same cumulative dose (200 mg/m$^2$) and schedule (five daily doses) the incidence of the hearing loss induced by

one course of vhd cisplatin was approximately four times higher than that observed by Vermorken et al. after two courses of 100 mg/m$^2$ [17].

Both the incidence and the severity of the hearing changes progressed even more with subsequent treatments, so that most of the patients (75%) receiving two courses and nearly all the patients (92%) receiving three courses of vhd cisplatin showed significant hearing losses (83% severe) compared with baseline levels.

However, in spite of significantly lower hearing levels, the ability to understand speech was only slightly impaired. No patient suffered a disabling hearing loss requiring the use of a hearing aid.

The ototoxicity observed in this study was bilateral and symmetrical ($R$, Spearman: $P < 0.0001$) and nearly always and more severely involved high frequencies beyond the speech range. The early hearing recovery observed in four patients after the first course of vhd cisplatin was lost at the subsequent course. No recovery occurred after two or more courses. Most of the patients complained occasionally of transient tinnitus unrelated to the severity of the hearing loss.

No relationship was found between the course of the ototoxicity and either the interval between the cisplatin administration (4 versus 8 weeks) or a preexisting hearing loss. Because of the limited number of patients considered, definite conclusions cannot be made on this point.

For the first course of cisplatin, a highly statistically significant correlation (Spearman test) was found between hearing level changes and cisplatin-induced anemia ($R = -0.79$; $P < 0.002$). A slight but significant relationship ($P < 0.05$) was observed between the acute hearing loss and serum creatinine level changes as an index of nephrotoxicity. This finding, however, could be indicative of a simultaneous but independent toxicity of cisplatin affecting both the inner ear and the kidney. In fact, in this study hearing loss was clearly dose-dependent, cumulative, and irreversible, whereas creatinine changes, according to previous observations [13], always returned to normal values within a few weeks after treatment, even when pathologic values were reached (three patients, 8.6% of courses, with creatinine $> 1.5$ g/dl). No relationship could be observed between either acute or subacute hearing loss and the electrolyte changes at the end of the hydration after the first course of vhd cisplatin.

The use of hypertonic saline and vigorous hydration are effective means of minimizing the risk of nephrotoxicity, but seem to provide no effect on cisplatin-related ototoxicity.

Further studies must be made to establish the therapeutic index of vhd cisplatin compared with standard-dose regimens.

*Acknowledgement.* We thank Mr E. Neve for his technical assistance and cooperation.

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Received April 2, 1987/Accepted October 7, 1987