Auditory Function in Pediatric Osteosarcoma Patients Treated with Multiple Doses of cis-Diamminedichloroplatinum(II)

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ABSTRACT

Serial auditory evaluations were performed in 54 pediatric patients (5 to 18 yr) treated with cis-diamminedichloroplatinum(II) for osteosarcoma. Each course of cis-diamminedichloroplatinum(II) comprised 150 mg/m² and was administered initially at two weekly intervals for seven courses (3 mo) and subsequently at three monthly intervals for 15 to 21 mo. Overall, 604 courses were administered, and observations were conducted from diagnosis to 6 yr. Bilateral hearing loss was detected in all patients. The loss varied from mild (20 to 40 dB) to profound (>90 dB). Initial losses occurred in the higher frequencies and were also greater at these frequencies. Significant loss was first observed after 300 mg/m² for frequencies over 4000 Hz and gradually shifted to incorporate the lower frequencies. Hearing loss was permanent.

INTRODUCTION

CDP is a highly effective therapeutic modality for the treatment of osteosarcoma (1-3). Its major drawback resides in its potential to cause nephro- and ototoxicity. The latter includes tinnitus, otalgia, and alterations in vestibular function (4-11). The incidence and severity of ototoxicity are a function of dose, rate of drug delivery, concurrent administration of diuretics or aminoglycosides, dehydration, and pre-existing sensorineural hearing loss (4-15). Only a limited number of reports have appeared in relation to ototoxicity in the pediatric age (7, 10).

We report auditory evaluations in 54 pediatric patients (108 ears) who were treated with a standardized dose and regimen of CDP for osteosarcoma.

PATIENTS AND METHODS

The primary tumor in 54 patients, aged 5 to 18 yr (median, 13; mean, 13), was treated preoperatively with intraarterial CDP. The dose was 150 mg/m² and was administered at 2 weekly intervals with heparin and mannitol diuresis as outlined in Fig. 1. The first 12 patients received 3 to 4 courses, and as experience accumulated, an attempt was made to administer a total of 7 courses (12 wk). The primary tumor was then extirpated, and patients who responded were treated with an adjuvant chemotherapy regimen comprising 2 courses of high-dose MTX-CF followed by ADR or i.v. CDP (Fig. 2). Each agent was administered at weekly intervals with a 3-wk rest period interposed between courses. The dose of i.v. CDP was also 150 mg/m² and was administered in a manner similar to the intraarterial method but without heparin. The total projected duration of treatment, including the preoperative phase, was 15 mo. This resulted in the delivery of a maximum of 12 CDP courses. Patients also received supplemental magnesium gluconate and allopurinol throughout the period of treatment.

During the course of treatment, 17 patients who achieved an initial dramatic response to CDP requested that surgery be eliminated and an attempt be made to eradicate tumor exclusively with chemotherapy. As a result, 2 consolidating periods of 5 and 6 to 7 courses of intraarterial CDP were administered. The intervals between CDP courses in the consolidating periods, were 2 to 3 wk, and between each consolidating period, 4 mo, during which MTX-CF-ADR was interposed. The pro-

RESULTS

Six hundred four CDP courses (range, 1 to 23; mean, 10; median, 10) were administered to 54 patients without evidence of renal and audiological abnormalities at initiation of treatment (Table 1). Thirty patients remained free of disease, completed the prescribed courses of therapy, and were followed up to 6 yr (median, 3).

Bilateral hearing loss was observed in all patients. The initial losses were in the high frequency range and were also more profound in these frequencies. Hearing loss was first noted after 300 mg/m² for frequencies over 4000 Hz and gradually shifted to incorporate lower frequencies with accumulated dosage. The losses varied from mild (20 dB to 40 dB) to profound (over 90 dB), the deficits progressing with cumulative treatments (Table 2; Fig. 3). The hearing loss at 250 Hz as compared to 8000 Hz was statistically significant (P < 0.05, x²). Repeat testing after discontinuation of treatment revealed that all auditory deficits were permanent.

The magnitude of change, i.e., the mean difference in hearing between sequential levels with cumulative CDP dosages at each frequency, is illustrated in Table 3. At 2000 Hz, in the frequency range for speech communication, the mean difference between 300 mg/m² and 450 mg/m² was 7.8 dB, and from 750 mg/m² to >1500 mg/m², with the exception of 1050 mg/m² to 1200 mg/m², it varied from 24.0 to 38.5 dB. In contrast, at the higher frequencies (4000 and 8000 Hz), little change was detected with cumulative CDP dosages in excess of 750 mg/m². Hearing aids were recommended for children with a hearing loss in the range of normal speech (loss greater than 30 dB at 2000 Hz in the better ear).

The relationship of age to hearing loss in the pre- and postpubertal period (over 12 yr) was also investigated. The incidence was comparable in both groups, but the degree was

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The abbreviations used are: CDP, cis-diamminedichloroplatinum(II); MTX, methotrexate; CF, citrovorum factor; ADR, Adriamycin.
CDP AND AUDITORY FUNCTION IN PEDIATRIC OSTEOSARCOMA PATIENTS

Fig. 1. Schedule for CDP treatment. Patients received a maintenance i.v. infusion of 3000 ml/m² of 5% dextrose in 0.5% saline solution. This infusion was interrupted for 9 h to permit administration of the following: 250 ml/m² of 5% saline solution (1 h); 50 ml of 20% mannitol (15 min); and 200 ml of 50% mannitol dissolved in 1000 ml/m² of 5% dextrose in 0.5% saline solution (8 h). Intraarterial CDP was administered over 2 h concurrently with the initiation of the latter infusion. The maintenance infusion was then reinstituted. CDP was dissolved in 300 ml of normal saline to which 3000 IU of heparin were added. The depicted volumes of 20% mannitol (50 ml, 10 g, and 200 ml, 40 g) were utilized for a surface area of 1 to 1.5 m². Appropriate adjustments were made for patients with smaller surface areas.

Table 1 Patients, time interval, and cumulative number of CDP courses

<table>
<thead>
<tr>
<th>Patients</th>
<th>Interval from diagnosis (mo)</th>
<th>Courses</th>
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<tr>
<td>54</td>
<td>0-3</td>
<td>3-6</td>
</tr>
<tr>
<td>52</td>
<td>0-6</td>
<td>7-8</td>
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<td>6-12</td>
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<td>12-18</td>
<td>1-15</td>
</tr>
<tr>
<td>22</td>
<td>&gt;18</td>
<td>&gt;15</td>
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</tbody>
</table>

Fig. 2. Chemotherapy treatment schema. Patients were assigned to receive 7 courses of intraarterial CDP at 2 weekly intervals as induction therapy (in the initial phases, 12 patients received 3 to 4 courses). This was followed by a surgical procedure. MTX, high-dose methotrexate (12.5 g/m²); 4DR, Adriamycin (25 mg/m²/day for 3 days); CDP, cis-diaminedichloroplatinum(II) (150 mg/m²).

Table 2 Dosage and mean decibel level at different frequencies

<table>
<thead>
<tr>
<th>Base-line dosage (mg/m²)</th>
<th>Mean decibel level at the following frequencies (Hz)</th>
<th>8000</th>
<th>4000</th>
<th>2000</th>
<th>1000</th>
<th>500</th>
<th>250</th>
</tr>
</thead>
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<td>18.3 9.4 0 4.2 0 4 5.6 9.4</td>
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<tr>
<td>150</td>
<td>16.1 15 6.8 0 5.0 0 3.9 3.6 10.4</td>
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<tr>
<td>300</td>
<td>35.0 42.1 21.6 12.5 8.2 25 7.3 8.2 13.6</td>
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<tr>
<td>450</td>
<td>47.5 26.5 40.0 12.0 25 2.0 4.0 7.0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>40.5 25.8 28.1 25.0 15.5 50 7.5 6.4 9.1</td>
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<tr>
<td>750</td>
<td>65.5 58.3 51.5 25.7 17.5 40 2.5 3.0 5.5</td>
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<tr>
<td>900</td>
<td>69.1 60.0 58.1 38 28.2 20 15.7 10.9 13.4</td>
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<tr>
<td>1050</td>
<td>67.9 70 52.3 30.0 28.4 15.4 9.4 10.0</td>
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<td>1200</td>
<td>63.2 23.3 46.8 45.6 15.3 38.7 3.2 5.4 10.3</td>
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<tr>
<td>1350</td>
<td>67.7 52.5 45 29.8 30.0 15.4 11.5 12.2</td>
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<tr>
<td>1500</td>
<td>65.9 27.5 54.0 39.3 26.1 19.3 14.7 7.5 9.7</td>
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<tr>
<td>&gt;1500</td>
<td>70.0 60.8 55.5 51.1 42.7 47.1 26.1 11.6 12.0</td>
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</table>

Fig. 3. Hearing threshold at different frequencies with cumulative doses of CDP.

Table 3 Magnitude of change (mean difference in sequential levels of hearing) with escalating dosage and frequency

<table>
<thead>
<tr>
<th>Dosage escalation (mg/m²)</th>
<th>Mean difference (dB) at the following frequencies (Hz)</th>
<th>8000</th>
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<th>2000</th>
<th>1000</th>
<th>500</th>
<th>250</th>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
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<tr>
<td>0-150</td>
<td>3.4 -2.6 -1.2 -0.1 -2.0 1.0 14</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150-300</td>
<td>22.3 12.2 4.0 3.3 2.6 4.2 22</td>
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<tr>
<td>300-450</td>
<td>34.3 17.1 7.8 -2.0 -1.6 -2.4 10</td>
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<tr>
<td>450-600</td>
<td>27.8 18.7 11.3 3.5 0.8 -0.3 28</td>
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<tr>
<td>600-750</td>
<td>52.8 42.1 13.3 -1.5 -2.6 -3.9 10</td>
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<tr>
<td>750-900</td>
<td>56.4 48.7 24.0 11.7 5.3 4.0 16</td>
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<tr>
<td>900-1050</td>
<td>55.2 43.3 32.4 11.4 3.8 0.6 26</td>
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<tr>
<td>1050-1200</td>
<td>50.5 37.4 11.1 -0.8 -0.2 0.9 14</td>
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<tr>
<td>1200-1500</td>
<td>55.0 43.6 25.6 11.4 5.9 2.8 26</td>
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<tr>
<td>1350-1500</td>
<td>53.2 44.6 21.9 10.7 1.9 0.3 31</td>
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<tr>
<td>&gt;1500</td>
<td>57.3 46.1 38.5 22.1 6.0 2.6 32</td>
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DISCUSSION

The potential to develop CDP ototoxicity is related to cumulative dosage, rate of drug delivery (bolus versus more prolonged administration), subsequent or concurrent administration of specific diuretics, aminoglycosides, and dehydration (12, 13, 15). These confounding factors were eliminated from our study which comprised children and adolescents with normal baseline audiological and renal function treated with a fixed CDP dosage and regimen.

Our results demonstrated that CDP caused a mild (20 to 40 dB) to profound (over 90 dB) hearing loss with cumulative doses. The complication developed in all patients who received CDP in excess of 300 mg/m². Initially, the losses occurred at the higher frequencies (6000 to 8000 Hz) and were also greater in these frequencies. Most reports concur that CDP markedly increased losses also occurred for frequencies over 4000 Hz.

greater in those under 12 yr. For example, at a dosage of 300 mg/m², at 2000 Hz, children under 12 had a mean decibel hearing loss of 45 dB compared to 8.2 dB for those over 12 (Table 3).

With the development of a hearing loss, a concurrent and progressive deterioration in renal function was also noted. This manifested as an elevation in the serum creatinine and a reduction in the corrected creatinine clearance. This finding was attributed to the renotoxic effects of CDP and has previously been documented (16). However, the renal abnormalities were not considered to be a causative factor in the development of hearing loss.
and gradually shifted to incorporate the lower frequencies. With incremental dosages above 750 mg/m² additional losses at the lower frequencies still occurred, but at the higher frequencies the deficits appeared to stabilize (see magnitude of change). Thus, at certain frequencies, after a specific dosage of CDP, auditory losses may be finite.

The pattern of early and severe loss in the higher frequencies has previously been reported in patients who received CDP by bolus administration (5). In contrast our patients developed similar hearing losses with a 2-h constant infusion. The latter produces a steady state lasting 2 to 3 h (1) and contradicts the supposition that short peak plasma levels of filterable platinum, which are characteristics of bolus administrations, are probably responsible for the initial pattern of audiological abnormalities (5).

Our results also demonstrated increased hearing losses in the younger child; this is consistent with the observation that the complication is inversely related to age (10). Hearing loss was also permanent. This finding contradicts that of Aguillar-Markulis et al. (14) who reported occasional reversibility of the process.

In previous studies, evaluation of CDP ototoxicity was complicated by inclusion of different patient populations, multiple agent chemotherapy, variable methods of administration, exposure to audiotoxic agents, and preexisting renal and other complications. Our study eliminated most of these factors and confirmed that initial losses occur at higher frequencies, are proportional to cumulative dosage, and may be anticipated at dosages in excess of 300 mg/m².

REFERENCES
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