Progression of Hearing Loss Following the Completion of Chemotherapy and Radiation Therapy: Case Report

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Abstract
There have been scattered accounts reported in the oncology literature of progressive hearing loss following the conclusion of chemotherapy. In this case study, we report the audiologic findings of such a case. These data underscore the need for post-therapy monitoring in cases where threshold shifts are discovered during the course of drug administration.

Key Words: Cisplatin, cranial radiation, high-frequency audiometry, ototoxicity, progressive hearing loss

Various medications have been associated with ototoxicity. The most common class of potentially ototoxic agents are the aminoglycosides, specifically neomycin, kanamycin, streptomycin, vancomycin, dihydrostreptomycin, and gentamicin. Other known potentially ototoxic drugs include loop diuretics such as ethacrynic acid and furosemide. Unlike salicylates or diuretics, which may produce a temporary hearing loss that is resolved when the medication is stopped, certain medications (e.g., neomycin) may continue to cause irreversible and progressive hearing loss even after administration of the drug is discontinued (Worthington, 1973).

Numerous antineoplastic medications are also known to be potentially ototoxic. Cisplatin (CDDP) has been the most thoroughly studied of the chemotherapeutic agents and is commonly included in a multiple drug treatment protocol. The reported prevalence of hearing loss associated with cisplatin therapy ranges from as high as 91 percent (Helson et al, 1978) to as low as 9 percent (Higby et al, 1974). Dose-limiting decisions are usually based on renal impairment. Cumulative dose exceeding 400 mg, concomitant use with other ototoxic medications, previous sensorineural hearing loss, and renal dysfunction appear to be predisposing factors increasing the probability of hearing loss (van der Hulst et al, 1988). In addition, younger patients tend to be more susceptible to audiologic changes associated with cisplatin (Weatherly et al, 1991). Similarly, and highly relevant to this case, there is a strong link between a previous history of cranial radiation and the likelihood of hearing loss occurring following cisplatin usage (Moretti, 1976; Schell et al, 1990).

Common symptoms reportedly associated with cisplatin ototoxicity include hearing loss (usually, but not always, symmetrical), tinnitus (ranging from transient to permanent), loudness recruitment, and otalgia (Reddel et al, 1982). Occasionally, vestibular symptoms are also reported (Schaefer et al, 1981; Kobayashi et al, 1987). Hearing loss initially occurs in the high frequencies (6000 and 8000 Hz for conventional audiometry) and may then progress to the lower frequencies, thus affecting speech intelligibility. Similar to aminoglycoside ototoxicity, the hearing loss may begin shortly after the initiation of treatment (Yung and Dorman, 1986) or may initially appear several days after treatment. Tange et al (1985) reported that 8 of the 23 cisplatin-treated patients they studied demonstrated significant auditory changes above
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8000 Hz. Thus, the inclusion of high-frequency audiometry in the monitoring of these patients is advisable.

Hearing loss due to cisplatin is usually permanent, but there may be some reversibility. Aguilar-Markulis et al (1981) recounted two patients who had demonstrated severe ototoxic changes (hearing loss into the speech frequencies). Follow-up testing 2 years later revealed total recovery for one patient, but continued deterioration for the other patient. Fausti et al (1984) reported on one patient whose audiograms indicated further deterioration of hearing across the frequency range during a follow-up test 5 weeks post treatment. The final follow-up, however, revealed no further changes.

Despite isolated cases such as these, which tend to be reported in the oncology literature, we were unable to find other references discussing the likelihood of progressive loss and/or recovery of auditory function following the cessation of chemotherapy in our review of the audiologic literature. Moreover, we found the following recommendation on monitoring in a respected textbook on ototoxicity: “assess cochlear and vestibular function before, during, and at the completion of parenteral drug treatment, whenever possible” (Shulman, 1979). Recall that hearing impairment due to antibiotic treatment usually occurs after 3 to 4 days, but unlike treatment with salicylates or loop diuretics, may be delayed for weeks or even months after completion of therapy. Thus, the practice of continued audiologic monitoring following the cessation of cisplatin with or without accompanying radiation treatment is not one that is universally accepted or followed.

In the present paper, we report the audiologic findings of a patient who demonstrated changes in auditory function following completion of chemotherapy. This case underscores the importance of continued post-therapy audiologic monitoring for patients presenting auditory symptoms.

CASE REPORT

History

This young female patient was first seen at the University of California San Francisco Medical Center at the age of 3 years, 8 months, presenting headache, vomiting, and ataxia. A computed tomography (CT) scan revealed a large posterior fossa mass, for which surgical debulking and placement of a VP shunt was performed. She received a subtotal resection, and the pathology report showed a low to intermediate grade ependymoma. She was placed on “8 to 1” chemotherapy (regimen B, protocol CCG-921). This consisted of eight sessions with 40–60 mG/m² of cisplatin administered over 6-hour periods, resulting in a total dose of 380 mG/m², along with concurrent cytotoxic therapy. Chemotherapy occurred over a 14-month period. Focal field irradiation therapy directed to the posterior fossa was given between the first and second chemotherapy sessions and was then terminated with no apparent side effects. Despite precautions taken to ensure that the cochlea was shielded from radiation, a review of the radiologic records indicated that the cochlea was unavoidably irradiated in order to encompass the tumor volume with adequate margin.

The patient’s first audiologic evaluation was ordered following her fourth chemotherapy session (1 year after initial diagnosis and initiation of chemotherapy). There were no indications of hearing impairment; however, the patient was complaining about discomfort to loud sounds. She had had one episode of otitis media treated successfully with antibiotics 5 months prior. The remainder of her otologic history was negative, and she did not present any risk factors for hearing loss.

Method

A total of six audiologic evaluations were performed. As stated above, the first was performed while she was still receiving chemotherapy. The second evaluation took place 1 month later on the final day of her therapy. The third evaluation was performed 3 months post therapy. The three subsequent sessions occurred at 2-month intervals. Thus, the final evaluation reported here occurred 9 months after the conclusion of cisplatin therapy. Pure-tone testing was completed using either conditioned play audiometry with the aid of a test assistant or with conventional, hand-raising techniques. Testing was performed on a Madsen OB 822 clinical audiometer using standard TDH-39 earphones in a double-walled, sound-treated booth. Immitance testing was also performed at each of the sessions, using a Grason-Stadler model 33 middle ear analyzer.

Test Results

Table I presents the audiometric pure-tone data. Speech reception thresholds were consist-
ent with these findings, and word recognition scores established using PBK word lists remained at 100 percent for both ears at each evaluation.

At the first visit (following the fourth cisplatin treatment), a slight loss was present at 6000 and 8000 Hz for both ears. It is impossible to pinpoint when the loss initially occurred, since the baseline audiogram was obtained so long after the initiation of treatment. An additional 10–20 dB decrease was seen in both ears at the conclusion of the drug administration (Test 2). At this time, however, the loss was confined to frequencies above 4000 Hz. The first indication of threshold shift below 6000 Hz was detected 3 months following the cessation of treatment (Test 3). These threshold shifts meet the multiple frequency criteria proposed by Simpson et al (1992) when measuring cisplatin ototoxicity. The loss continued to increase at 6000 and 8000 Hz (with 4000 Hz now stabilized) at the fourth visit. Then, unexpectedly, there was an improvement at 8000 Hz for the left ear (all other thresholds remaining with ±5 dB of Test 4). At the most recent follow-up evaluation, her thresholds again decreased at 8000 Hz, bilaterally, relative to Test 5, although there was an apparent improvement at 4000 and 6000 Hz in the right ear. It should be pointed out that threshold measurements were repeated at each visit, confirming the audiologists' belief that, despite her age, the patient was an extremely reliable test respondent. Air- and bone-conduction thresholds were equivalent above 500 Hz for both ears. There were slight air-bone gaps for the right ear at 250 Hz only, and the tympanograms for the right ear consistently indicated reduced compliance.

**DISCUSSION**

The results obtained in this case, in addition to others reported in the oncology literature, suggest that hearing loss associated with cisplatin therapy may be progressive beyond the conclusion of the drug administration. This may be especially true when other factors, in particular, radiation therapy, are used in conjunction with the chemotherapy. Therefore, audiologic monitoring may be appropriate for as long as 1 year beyond the completion of treatment. Extended monitoring may be even more important for children, who are reportedly more susceptible to these ototoxic effects and are less likely to recognize or report the onset of subtle symptoms. The earlier hearing loss is identified, the sooner an appropriate assistive listening device can be employed to minimize the effects of high-frequency hearing loss. Even when the hearing loss is limited to the very high frequencies (4000 Hz and above), the use of FM systems can alleviate the difficulties of listening in certain acoustic environments. Moreover, to a child, the unknown aspects of recruitment and/or tinnitus may be frightening and could be minimized through proper counseling.

We did not collect threshold data above 8000 Hz on this patient, because her threshold shifts were apparent during conventional audiometry. It is recommended, however, that monitoring during the course of chemotherapy include high-frequency testing whenever there

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**Table 1 Pure-Tone Air-Conduction Thresholds**

<table>
<thead>
<tr>
<th>Ear</th>
<th>Test</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>250 500 1000 2000 3000 4000 6000 8000</td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>10 10 5 0 0 5 15 20</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 5 5 0 0 5 25 30</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10 5 5 0 5 20 45 50</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>15 10 5 0 0 15 55 60</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10 10 5 0 0 20 60 60</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10 10 10 0 5 10 50 70</td>
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<tr>
<td>Left</td>
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<td>10 10 0 0 5 25 20</td>
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<td>2</td>
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<td>5 5 0 5 5 35 50 70</td>
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<tr>
<td></td>
<td>5</td>
<td>5 5 0 5 10 40 50 50</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10 5 0 5 0 35 50 60</td>
</tr>
</tbody>
</table>

*Test 1 was conducted following the fourth session of chemotherapy; Test 2 took place 1 month later on the final day of therapy; Test 3 was performed 3 months post therapy; Test 4 was performed 5 months post therapy; Test 5 was performed 7 months post therapy; Test 6 was performed 9 months post therapy.
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is no apparent loss for the conventional frequencies.

For patients such as the one reported in this paper, it is difficult to determine whether the chemotherapy, the radiation therapy, or both are responsible for the subsequent hearing loss. While most reports agree that the use of radiation therapy predisposes the patient to a greater likelihood of hearing loss when receiving cisplatin, there are some reports that suggest that the cisplatin is the primary ototoxic agent. Schell et al (1990) prospectively tested a large group of patients who received either cisplatin, cranial irradiation, or both. They reported that there was a significantly greater potentiation of ototoxicity when these therapies were used together, but that hearing acuity was either not affected or only minimally affected for the irradiation-only group.

Redell et al (1982) indicate that routine audiometry in cisplatin patients may be omitted, since dose modifications are based on symptoms, rather than audiometric findings. They state that following a baseline audiogram, it may be wise to delay follow-up testing until the first symptoms develop. We do not agree, particularly with children, for the reasons discussed above. While it is evident that threshold shifts can continue post therapy, it is not clear whether auditory symptoms will initially appear post therapy when there are no symptoms (as measured with conventional audiometry, high-frequency audiometry, or otoacoustic emissions) shown during the course of drug administration. We are currently collecting data on this matter. For cost-containment considerations, it is possible that if threshold shifts, measured with conventional or high-frequency audiometry, do not appear by the conclusion of therapy, continued monitoring may not be necessary. If there are threshold shifts or auditory symptoms present during therapy, however, continued post-therapy monitoring at 3-month intervals for up to 1 year is advised.

REFERENCES


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