Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus After Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer.

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Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus After Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer


See accompanying editorial on page 2687

ABSTRACT

Purpose

Cisplatin is widely used but highly ototoxic. Effects of cumulative cisplatin dose on hearing loss have not been comprehensively evaluated in survivors of adult-onset cancer.

Patients and Methods

Comprehensive audiological measures were conducted on 488 North American male germ cell tumor (GCT) survivors in relation to cumulative cisplatin dose, including audiograms (0.25 to 12 kHz), tests of middle ear function, and tinnitus. American Speech-Language-Hearing Association criteria defined hearing loss severity. The geometric mean of hearing thresholds (0.25 to 12 kHz) summarized overall hearing status consistent with audiometric guidelines. Patients were sorted into quartiles of hearing thresholds of age- and sex-matched controls.

Results

Increasing cumulative cisplatin dose (median, 400 mg/m²; range, 200 to 800 mg/m²) was significantly related to hearing loss at 4, 6, 8, 10, and 12 kHz (P trends, .021 to < .001): every 100 mg/m² increase resulted in a 3.2-dB impairment in age-adjusted overall hearing threshold (4 to 12 kHz; P < .001). Cumulative cisplatin doses > 300 mg/m² were associated with greater American Speech-Language-Hearing Association–defined hearing loss severity (odds ratio, 1.59; P = .0066) and worse normative-matched quartiles (odds ratio, 1.33; P = .093) compared with smaller doses. Almost one in five (18%) patients had severe to profound hearing loss. Tinnitus (40% patients) was significantly correlated with reduced hearing at each frequency (P < .001). Noise-induced damage (10% patients) was unaffected by cisplatin dose (P = .59). Hypertension was significantly related (P = .0066) to overall hearing threshold (4 to 12 kHz) in age- and cisplatin-dose–adjusted analyses. Middle ear deficits occurred in 22.3% of patients but, as expected, were not related to cytotoxic drug dosages.

Conclusion

Follow-up of adult-onset cancer survivors given cisplatin should include routine inquiry for hearing status and tinnitus, referral to audiologists as clinically indicated, and hypertension control. Patients should be urged to avoid noise exposure, ototoxic drugs, and other factors that further damage hearing.

INTRODUCTION

The current 5-year relative survival rate for all cancers taken together approximates 66%. As a result, there are 14.5 million cancer survivors in the United States. This number will increase to 19 million by 2024, with 97% representing survivors of adult-onset cancer. Given these increasing numbers, in-depth investigations of treatment toxicities that affect functional status, such as cisplatin-related hearing loss and tinnitus, are increasingly important. Cisplatin is one of the most ototoxic drugs in clinical use, causing permanent, bilateral sensorineural hearing loss in substantial numbers of patients, with many experiencing permanent tinnitus. Nonetheless, few comprehensive audiometric data exist for cisplatin-associated hearing loss in adult-onset cancer survivors. Several investigations of
patients with head and neck cancer were confounded by cranial radiotherapy; limitations of other studies included small numbers, concomitant vincristine, and restriction of audiometric testing to just a few frequencies. To our knowledge, only one series evaluated hearing loss in terms of cumulative cisplatin dose, and none included audiometric assessments of noise-induced damage, middle ear function, or evaluation of speech processing.

To fill important gaps in these areas, we conducted comprehensive audiometric testing in relation to cumulative cisplatin dose in 488 men with adult-onset germ cell tumors (GCT), testing all frequencies between 0.25 and 12 kHz and evaluating audiologically defined noise-induced damage, speech processing, tinnitus, patient-reported outcomes, and middle ear function.

**PATIENTS AND METHODS**

**Patients**

All patients were enrolled in the Platinum Study, which includes eight cancer centers in the United States and Canada. Eligibility criteria included: men with a diagnosis of histologically or serologically confirmed GCT, age younger than 50 years at diagnosis and age 18 years or older at study consent, consent with cisplatin-based chemotherapy, and no subsequent salvage chemotherapy. Study procedures were approved by the Human Subjects Review Board at each institution. This report covers all 488 patients who completed audiometric testing through April 16, 2015.

**Data Abstracted From Medical Records**

For each patient, standardized forms were used to collect demographic and clinical data, including treatment information. Dose data were collected from cancer centers in the United States and Canada. Eligibility criteria included: men with a diagnosis of histologically or serologically confirmed GCT, age younger than 50 years at diagnosis and age 18 years or older at study consent, consent with cisplatin-based chemotherapy, and no subsequent salvage chemotherapy. Study procedures were approved by the Human Subjects Review Board at each institution. This report covers all 488 patients who completed audiometric testing through April 16, 2015.

**Audiometric Testing**

Pure-tone air conduction thresholds were obtained bilaterally for each patient at frequencies of 0.25 to 12 kHz as in prior studies, covering the speech frequency range, including those important for perceiving vowels and consonants. Frequencies of 10 and 12 kHz were included, given their importance in the early diagnosis of pediatric cisplatin-induced hearing loss. Otoscopy and bone-conduction thresholds (0.25 to 4 kHz) evaluated middle ear function. Speech reception thresholds (SRTs), which use speech stimuli consisting of two-syllable words, quantified speech processing.

**Classification of hearing loss and assessment of severity.** International American Speech-Language-Hearing Association (ASHA) criteria defined hearing loss as a hearing threshold at any frequency (0.25 to 12 kHz) that exceeded 20 dB for either ear. ASHA criteria defined hearing loss severity as follows: mild: 21 to 40 dB; moderate: 41 to 55 dB; moderately severe: 56 to 70 dB; severe: 71 to 90 dB; and profound: > 90 dB; for at least one tested frequency for either ear.

**Statistical analysis.** Cumulative cisplatin dose (mg/m²) was compared with the air conduction threshold at each frequency in the 0.25 to 12 kHz range, with statistical significance defined as P < .05 for dose in the linear regression model: hearing threshold = dose + age at audiometry. No evidence for nonlinearity of the cisplatin dose-response relationship was observed, as evaluated by comparisons of the linear model with cubic and quadratic models at each frequency. For each patient, we compared the geometric mean of hearing thresholds (4, 6, 8 kHz) to the expected geometric mean in the age-specific normative sample for 25th, 50th, and 75th percentiles. Each patient was allocated to the respective quartile (1 to 4) of the reference population, with quartile 4 representing the most severe hearing impairment. Cumulative cisplatin dose groups (≤ 300 mg/m² and > 300 mg/m²) were tested for association with age-matched normative quartiles (quartile = dose group) and with ASHA-defined severity classes (severity class = dose group + age at audiometry) by ordinal regression. The 300 mg/m² cut point was chosen, given its correspondence to the most commonly used study regimen (BEP), with the standard three cycles resulting in a cumulative cisplatin dose of 300 mg/m².

**Patient-Reported Outcomes**

Patients completed questionnaires concerning neurotoxic symptoms, lifestyle habits, comorbidities, and medication use. The Scale for Chemotherapy-Induced Neurotoxicity (SCIN), validated in testicular cancer survivors (TCS) given cisplatin-based chemotherapy, was used to query tinnitus and hearing: this was supplemented with validated hearing questions from Ventry and Weinstein regarding noise exposure, hearing aid use, and problems hearing words or language in crowds.

**Statistical analyses.** SCIN results, smoking status (current smoker, ever smoker), and hypertension (defined as prescription medication for hypertension) were compared with the overall hearing threshold (4 to 12 kHz) and SRT. To test whether each variable (response) was associated with hearing thresholds, we fit the following linear regression model: overall hearing threshold = response + age at audiometry. All statistical models were fit using R version 3.1.1 (http://www.R-project.org/). Plots were...
Median age at diagnosis was 31 years (range, 15 to 49 years), and median interval between chemotherapy and audiometry was 4.25 years (range, 1 to 30.3 years; Table 1). Chemotherapy consisted largely of BEP (60.5%) or EP (32.0%). Median cumulative cisplatin dose was 400 mg/m² (range, 198 to 800 mg/m²). Hypertension largely of BEP (60.5%) or EP (32.0%). Median cumulative cisplatin dose correlated (threshold (0.25 to 12 kHz). Because these variables were highly correlated, only the former was subsequently applied.

**Overall Hearing Loss**

Audiogram shapes showed a largely high-frequency, sloping hearing loss, with substantial interindividual variation (Fig 1). Only 20% of patients had normal hearing (ie, flat audiogram; Fig 1A), whereas others had differing degrees of hearing loss, with ASHA-defined mild, moderate, moderately severe, or severe/profound hearing loss, in 25%, 16%, 21%, and 18%, respectively (Figs 1B to 1F).24 For two patients with ear asymmetry, data were averaged.

Most patients (388 of 488, 80%) had a hearing loss of > 20 dB (Fig 2).24 The overall pattern of kHz-specific hearing thresholds accentuated its high-frequency nature, with the largest reductions at 12 kHz. Age at either audiometry (P < .001) or GCT diagnosis (P < .001) strongly associated with impaired overall hearing threshold (0.25 to 12 kHz). Because these variables were highly correlated (R = 0.79), only the former was subsequently applied.

**Cumulative Cisplatin Dose**

Statistically significant age-adjusted relationships between increasing cumulative cisplatin dose and increasing (worse) hearing thresholds (dB) existed for 4 kHz (P = .021), 6 kHz (P = .0017), 8 kHz (P < .001), 10 kHz (P < .001), and 12 kHz (P = .0013), but not for other frequencies (Appendix Fig A1, online only). Cumulative cisplatin doses > 300 mg/m² were associated with increased ASHA severity classes compared with ≤ 300 mg/m² after age adjustment (Fig 3; odds ratio [OR], 1.59; 95% CI, 1.14 to 2.21; P = .0066). Moderately severe to profound hearing loss occurred in 29.5% and 44.6% of patients, respectively, after ≥ 300 mg/m² and > 300 mg/m² of cisplatin. Dose group did not correlate with age (P = .24).

**Comparisons to Normative Population**

Figure 4A shows subject distribution by age and normative hearing quartile. Patients administered > 300 mg/m² cisplatin were more likely to be in a higher quartile (worse hearing) than those given ≤ 300 mg/m² (Fig 4B; OR, 1.33; 95% CI, 0.95 to 1.85; P = .093). For every 100-mg/m² increase in cumulative cisplatin dose, a 3.2-dB decline in overall hearing threshold (4 to 12 kHz) occurred after age adjustment (Fig 5A; P < .001). Time from chemotherapy to audiometry correlated with worse overall hearing

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**Table 1. Demographic Features, Clinical Characteristics, and Patient-Reported Outcomes for 488 Male Germ Cell Tumor Survivors at the Time of Enrollment Onto the Platinum Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>488</td>
</tr>
<tr>
<td>Age at GCT diagnosis, years</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>31 (15-49)</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>24 (4.9)</td>
</tr>
<tr>
<td>20-29</td>
<td>187 (38.3)</td>
</tr>
<tr>
<td>30-39</td>
<td>182 (37.3)</td>
</tr>
<tr>
<td>40-49</td>
<td>95 (19.5)</td>
</tr>
<tr>
<td>Age at audiometry, years</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>38 (20-68)</td>
</tr>
<tr>
<td>20-29</td>
<td>88 (18.0)</td>
</tr>
<tr>
<td>30-39</td>
<td>180 (38.9)</td>
</tr>
<tr>
<td>40-49</td>
<td>138 (28.3)</td>
</tr>
<tr>
<td>50-59</td>
<td>75 (15.4)</td>
</tr>
<tr>
<td>60-69</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Time from chemotherapy to audiometry, months</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>51 (5-364)</td>
</tr>
<tr>
<td>&lt; 24</td>
<td>105 (21.8)</td>
</tr>
<tr>
<td>24-47</td>
<td>121 (25.2)</td>
</tr>
<tr>
<td>48-71</td>
<td>72 (15.0)</td>
</tr>
<tr>
<td>72-119</td>
<td>81 (16.8)</td>
</tr>
<tr>
<td>≥ 120</td>
<td>102 (21.2)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>428 (87.7)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>54 (11.1)</td>
</tr>
<tr>
<td>Not available</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Calendar year of diagnosis</td>
<td></td>
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<tr>
<td>1980-1989</td>
<td>5 (1.0)</td>
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<tr>
<td>1990-1999</td>
<td>57 (11.7)</td>
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<tr>
<td>2000-2009</td>
<td>207 (42.4)</td>
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<tr>
<td>2010-2015</td>
<td>219 (44.9)</td>
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<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>139 (28.5)</td>
</tr>
<tr>
<td>Nonseminoma/mixed GCT</td>
<td>344 (70.5)</td>
</tr>
<tr>
<td>GCT, not otherwise specified</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>138 (28.3)</td>
</tr>
<tr>
<td>II</td>
<td>184 (37.7)</td>
</tr>
<tr>
<td>III</td>
<td>102 (20.9)</td>
</tr>
<tr>
<td>Other</td>
<td>63 (12.9)</td>
</tr>
<tr>
<td>Not specified</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Site of GCT</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>435 (89.1)</td>
</tr>
<tr>
<td>Extragonadal</td>
<td>52 (10.7)</td>
</tr>
<tr>
<td>Not specified</td>
<td>1 (0.2)</td>
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<tr>
<td>Chemotherapy regimen</td>
<td></td>
</tr>
<tr>
<td>BEP: total cycles</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>295 (60.5)</td>
</tr>
<tr>
<td>3</td>
<td>183 (37.5)</td>
</tr>
<tr>
<td>4</td>
<td>99 (20.3)</td>
</tr>
<tr>
<td>5+</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>EP: total cycles</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>156 (32.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>4</td>
<td>150 (30.7)</td>
</tr>
<tr>
<td>5+</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Cisplatin, etoposide, ifosfamide: total cycles</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>4</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>5+</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Other cisplatin-based regimens: total cycles</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>3</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>4</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td>Cumulative dose of cisplatin, all patients, mg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt; 300</td>
<td>25 (5.1)</td>
</tr>
<tr>
<td>300</td>
<td>165 (33.8)</td>
</tr>
</tbody>
</table>

(continued on following page)
Table 1. Demographic Features, Clinical Characteristics, and Patient-Reported Outcomes for 488 Male Germ Cell Tumor Survivors at the Time of Enrollment Onto the Platinum Study (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>301-399</td>
<td>22 (5.0)</td>
</tr>
<tr>
<td>400</td>
<td>254 (52.1)</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>22 (4.5)</td>
</tr>
</tbody>
</table>

- **Education**
  - High school or less: 48 (9.8)
  - After high school but not college\(h\): 96 (19.7)
  - College/university graduate: 222 (45.5)
  - Postgraduate level: 112 (23.0)
  - Other/prefer not to say/not answered: 10 (2.0)

- **Smoking status**
  - Current smoker: 29 (5.9)
  - Former smoker: 149 (30.5)
  - Never smoker: 294 (60.2)
  - Not answered: 16 (3.3)

- **Hypertension and on prescription medication**
  - Not at all: 287 (58.8)
  - A little: 115 (23.6)
  - Quite a bit: 38 (7.8)
  - Very much: 39 (8.0)
  - Not answered: 9 (1.8)

- **Reduced hearing**
  - Not at all: 335 (68.7)
  - A little: 108 (22.1)
  - Quite a bit: 24 (4.9)
  - Very much: 12 (2.5)
  - Not answered: 9 (1.8)

- **Problems hearing in crowds**
  - Yes: 145 (29.7)
  - No: 316 (64.8)
  - Don’t know/not sure: 20 (4.1)
  - Not answered: 7 (1.4)

- **Require hearing aid**
  - No: 476 (97.5)
  - In one ear: 1 (0.2)
  - In both ears: 5 (1.0)
  - Not answered: 6 (1.2)

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide, and cisplatin; GCT, germ cell tumor; IV, intravenously.

\(h\)Includes 59 patients for whom data were indicated as unavailable/not applicable and eight for whom this variable was not available/blank.

- **Median cumulative cisplatin doses among patients given three and four cycles of BEP** were 300 mg/m\(^2\) (range, 272 to 400 mg/m\(^2\)) and 400 mg/m\(^2\) (range, 198 to 800 mg/m\(^2\)), respectively. For all BEP-treated patients, the median cumulative cisplatin dose was 300 mg/m\(^2\) (range, 198 to 800 mg/m\(^2\)). Corresponding median doses of etoposide were 1,500 mg/m\(^2\) (range, 1,014 to 1,677 mg/m\(^2\)), 2,000 mg/m\(^2\) (range, 500 to 2,645 mg/m\(^2\)), and 1,500 mg/m\(^2\) (range, 500 to 2,645 mg/m\(^2\)), respectively, with median doses of bleomycin 270 units (range, 64 to 330 units), 360 units (range, 60 to 360 units), and 270 units (range, 60 to 540 units), respectively. Of all men treated with BEP, 215 received standard dosages for each cycle (bleomycin 30 units IV weekly; etoposide 100 mg/m\(^2\) IV once per day, 5 days; cisplatin 20 mg/m\(^2\) IV once per day, 5 days), and 80 received a modified dose for at least one cycle.

- **Median cumulative dose of cisplatin among patients given four cycles of EP** was 400 mg/m\(^2\) (range, 200 to 600 mg/m\(^2\)), and among all patients given EP it was 400 mg/m\(^2\) (range, 200 to 600 mg/m\(^2\)). Corresponding median doses of etoposide were 2,000 mg/m\(^2\) (range, 1,000 to 2,000 mg/m\(^2\)) and 2,000 mg/m\(^2\) (range, 500 to 3,000 mg/m\(^2\)), respectively. Of men receiving EP, 99 received standard dose (etoposide 100 mg/m\(^2\) IV once per day × 5 days, cisplatin 20 mg/m\(^2\) IV once per day × 5 days), and 57 received a modified dose for at least one cycle.

(R = 0.23; 95% CI, 0.14 to 0.32), likely a result of the strong positive correlation with age (R = 0.48; 95% CI, 0.41 to 0.55). On adjustment for both age and time since chemotherapy, we still observed for every 100-mg/m\(^2\) increase in cumulative cisplatin dose a 3.3-dB decline in overall hearing threshold (4 to 12 kHz; P < .001). In this multivariate model, time from chemotherapy was not significant (P = .42), whereas age was highly significant (P < .001).

### Noise-Induced Hearing Loss

Of 388 patients with hearing loss (> 20 dB) at any frequency, 39 (10%) also displayed audiometrically defined noise damage. Risk did not differ for patients given a cumulative cisplatin dose of > 300 mg/m\(^2\) or ≤ 300 mg/m\(^2\) (P = .59), nor did noise damage affect normative quartile assignment (P = .42). Work-related noise exposure was associated with a noise notch in the audiogram (OR, 1.89; 95% CI, 0.96 to 3.69; P = .062), as observed by others.\(^{38}\)

### Conductive Hearing Loss (middle ear deficit)

Of all 488 patients, 58% (283) had pure sensorineural hearing loss, 0.4% (two) had pure conductive hearing loss, and 21% (103) had mixed hearing loss. As expected, no association with cumulative dose of cisplatin, etoposide, or bleomycin was evident for the 105 patients with conductive hearing loss (P = .78, 0.69, 0.42, respectively).

### Other Risk Factors

In analyses adjusted for age and cisplatin dose, impaired overall hearing threshold (4 to 12 kHz) was significantly associated with hypertension (n = 60; P = .0066). No significant association was evident for current smoking (n = 29; P = .079) or ever smoking (current plus former; n = 178; P = .095).

### Associations With Patient-Reported Outcomes

Approximately 30% and 40% of patients, respectively, reported reduced hearing or tinnitus (Table 1). Impaired overall hearing threshold (4 to 12 kHz) was strongly associated with degree of self-reported hearing loss (P < .001) and with tinnitus (P < .001) after age adjustment (Fig 5B). Statistically significant relationships between tinnitus and impaired hearing thresholds were observed at each frequency: 0.25 kHz (P = .012), 0.5 kHz...
To our knowledge, this is the largest and most comprehensive study of cisplatin-associated ototoxicity in survivors of adult-onset cancer, including quantitative comparisons of frequency-specific audiometric findings with patient-reported outcomes. New findings include statistically significant associations between increasing cumulative cisplatin dose and hearing loss at each of 4, 6, 8, 10, and 12 kHz and with severity of hearing loss defined by ASHA criteria.24 Highly significant associations between hearing loss at each kHz frequency and tinnitus were observed, in addition to significant correlations between SRT and tinnitus and self-reported hearing loss. Cumulative cisplatin dose was not related to audiometrically defined noise-induced hearing loss. Impaired overall hearing threshold (4 to 12 kHz) was significantly associated with hypertension but not smoking status. Middle ear deficits were observed.

There are few audiometric data in survivors of adult-onset cancer treated with cisplatin-based chemotherapy without cranial radiotherapy. Among 86 TCS, Bokemeyer et al6 tested frequencies of 0.5 to 8 kHz at a median of 4.8 years after cisplatin-based chemotherapy. Hearing loss was reported in 66% of patients, but frequency-specific associations with cumulative cisplatin dose were not examined. Glendenning et al11 evaluated frequencies of 1, 2, 4, and 8 kHz among 260 TCS, with cumulative cisplatin dose associated with hearing loss only at 8 kHz. An investigation of several hundred cisplatin-treated TCS in Norway restricted audiometric testing to 4 kHz and compared hearing loss with a normative population.10 Although TCS given larger numbers of cycles of cisplatin-based chemotherapy were assigned to greater hearing-impaired normative quartiles, the effect of cumulative cisplatin dose was not addressed.10

More than 90% of our 488 patients received modern cisplatin-based chemotherapy consisting largely of BEP or EP; thus, results are relevant to current practice. Hearing deficits were observed throughout the speech perception range, including the higher frequencies reported in pediatric studies,21,23,40,41 likely accounting for the strong correlation we observed for overall hearing threshold (4 to 12 kHz) and SRT and patient-reported hearing deficits (Fig 5B).
One in five patients had severe or profound hearing loss, a level at which hearing aids are typically recommended, but few used them, likely because of high cost, lack of insurance coverage, low performance/price ratio, or appearance. It is noteworthy that awareness of this problem and the patient’s acceptance of hearing loss typically increases hearing aid use. An additional 37% of patients with moderate or moderately severe ASHA-defined hearing loss would benefit from additional audiological follow-up, as clinically indicated. Worsening of audiometrically assessed cisplatin-associated hearing loss with time has been reported in childhood cancer survivors but has not been longitudinally studied in survivors of adult-onset cancer to our knowledge. The effect of cumulative cisplatin dose on hearing loss in our cross-sectional investigation remained statistically significant for many decades ($P < .001$), although the effect of increasing age was even stronger. Because higher frequencies are also disproportionately affected by age-related hearing loss, it will be critical to evaluate the extent to which survivors of adult-onset cancer given cisplatin-based chemotherapy may experience accelerated age-related sensory deficits.

**Tinnitus**

Tinnitus was significantly associated with impaired hearing at all frequencies, including 10 and 12 kHz, and reflects neural changes in the brain’s central auditory system. Hearing loss perturbs normal input to this area, a mismatch between excitatory and inhibitory networks occurs, and neurons underlying sound perception become abnormally activated, even without external stimulation. In some patients, tinnitus becomes debilitating as a sensory, anxiety-producing, and communication deficit. Few treatments are effective, with most relying on behavioral modification.

**Noise Damage**

The presence of noise notches in audiograms has not been previously evaluated in cancer survivors given cisplatin or cranial radiotherapy. The proportion (10%) of our patients with audiograms suggestive of noise damage is comparable to, or slightly less than, normative data assembled by the US Centers for Disease Control and Prevention, which reports that 17% of adults (20 to 69 years) demonstrate permanent noise-induced hearing damage. Our slightly lower prevalence may reflect the younger age distribution compared with population norms.

**Conductive Hearing Loss (middle ear deficits)**

The prevalence of conductive hearing loss is approximately 8% in adults without cancer and generally attributed to infection- or treatment- or age-related damage to sound conduction mechanisms. An explanation for the increased
Fig 5. (A) Comparison of overall hearing threshold (4 to 12 kHz) to cumulative cisplatin dose. The $P$ value is for the dose term in the following linear regression model: $\text{dB} = \text{dose} + \text{age at audiometry}$. (B) Comparison of overall hearing threshold (4 to 12 kHz) to the Scale for Chemotherapy-Induced Long-Term Neurotoxicity items for ringing in ears and reduced hearing. The $P$ value is for the response term in the following linear regression model: $\text{dB} = \text{response} + \text{age at audiometry}$. (C) Comparison of speech recognition threshold to the Scale for Chemotherapy-Induced Long-term Neurotoxicity items for ringing in ears and reduced hearing. The $P$ value is for the response term in the following linear regression model: $\text{dB} = \text{response} + \text{age at audiometry}$. 

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Frisina et al
prevalence we observed is not readily apparent and, as expected, was not related to cytotoxic drug exposure dosage levels.

**Comment**

Strengths of our study include large numbers of patients, detailed treatment data, thorough hearing evaluations, adjustment for age-related hearing loss, and consideration of covariates. Our quantitative assessment of cumulative cisplatin dose and frequency-specific hearing loss is not confounded by vinca alkaloids. Although pediatric investigations of cisplatin-induced hearing loss have yielded valuable perspective on classification approaches, pediatric scales do not take into account age-related hearing loss. To adjust for this effect, we not only included age in multivariate analyses but also compared hearing thresholds with age-matched normative data, because as in previous studies of ototoxicity in adult-onset cancer survivors, baseline hearing measures were not available. Because suitable data were unavailable for a North American cohort, we used normative data from a National Institutes of Health–sponsored study of 40,541 Norwegian men (97% white). Although we found expected relationships between higher cisplatin dose and assignment to worse age-matched hearing quartiles, we were not able to adjust for potentially differing distributions of hypertension, smoking, and other potential confounders. Any differences, however, are unlikely to materially affect our conclusions.

**Cancer Survivor Plans and Future Research**

Although follow-up hearing assessment guidelines exist for children given cisplatin-based chemotherapy, we found no similar recommendations for adult-onset cancer survivors. For children, a complete audiological examination at entry into long-term follow-up is recommended by the Children's Oncology Group, with annual testing if hearing loss is detected or as recommended by an audiologist, as well as yearly questioning about hearing status. Similarly, for adult-onset cancer survivors after cisplatin-based chemotherapy, our findings suggest that health care providers should conduct a minimum annually audiology patients about hearing status, consulting with audiologists as indicated. Patients should also be urged to avoid noise exposure, ototoxic drugs, and other factors that may further damage hearing. As recommended by national regulatory agencies for the general population, patients should be advised to wear hearing protection in noisy environments and take advantage of new, digital hearing aids and other innovative auditory therapies that are emerging. Given the significant relationship we found between hypotension and hearing loss and reported in other studies for tobacco use, health care providers should monitor blood pressure and encourage smoking cessation.

Because alterations in the highly successful GCT regimens are unlikely, our results point to the importance of ongoing research aimed at the identification of genetic variants associated with cisplatin-related ototoxicity. It is possible that genomic analysis may be able to eventually identify patients with newly diagnosed testicular cancer susceptible to ototoxicity. These findings could affect decisions with regard to the administration of adjuvant chemotherapy for high-risk clinical stage I disease or adjuvant chemotherapy after initial orchectomy and retroperitoneal lymph node dissection with positive lymph nodes to prevent recurrence.

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Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus after Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer

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The Platinum Study Group consists of Howard D. Sesso (Brigham and Women’s Hospital, Boston, MA); Clair J. Beard and Stephanie Curreri (Dana-Farber Cancer Institute); Lawrence H. Einhorn, Lois B. Travis, Mary Jacqueline Brames, Somer Case-Eads, and Shirin Ardeshir-Rouhani-Fard (Indiana University); Jeri Kim (MD Anderson Cancer Center); Darren R. Feldman, Erin Jacobsen, and Deborah Silber (Memorial Sloan Kettering Cancer Center); Lynn Anson-Cartwright and Robert Hamilton (Princess Margaret Hospital); Nancy J. Cox (Vanderbilt University); M. Eileen Dolan (University of Chicago); David J. Vaughn, Linda Jacobs, Sarah Lena Panzer, and Donna Pucci (University of Pennsylvania); Debbie Baker, Cindy Casaceli, Chunkit Fung, and Eileen Johnson (University of Rochester); Heather E. Wheeler (Loyola University Chicago); and Robert D. Frisina (University of South Florida). The Platinum Study Group Advisory Committee consists of George Bosl (Memorial Sloan Kettering Cancer Center); Sophie D. Fossa (Norwegian Radium Hospital); Mary Gospodarowicz (Princess Margaret Hospital); and Leslie L. Robison (St. Jude Children’s Research Hospital). Enrolling sites for the Platinum Study as of April 16, 2015 were Memorial Sloan Kettering Cancer Center, Indiana University, Princess Margaret Hospital, University of Pennsylvania, University of Rochester, and Dana-Farber Cancer Institute.
Fig A1. Comparison of hearing thresholds at each audiometric frequency to cumulative dose of cisplatin (mg/m²). The $P$-value represents the dose term in the following linear regression model: hearing threshold = dose + age at audiometry. The dose term effect size ($\beta$) and 95% CIs for each frequency are shown at lower right.