VOLUME 23 · NUMBER 34 · DECEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development

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Submitted November 11, 2004; accepted August 26, 2005.

Supported by a Veteran's Administration Merit Review Grant and by NIH Grants No. NS33618, NS34608, and NS44687 from the National Institute of Neurological Disorders and Stroke (to E.A.N.).

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2334-8588/$20.00

DOI: 10.1200/JCO.2004.00.5355

ABSTRACT

Purpose
To describe the frequency and severity of ototoxicity in a series of pediatric patients treated with platinum-based chemotherapy.

Patients and Methods
Serial audiologic evaluations were conducted for 67 patients aged 8 months to 23 years who received platinum-based chemotherapy. Audiologic data was analyzed to determine time to hearing-loss using American Speech-Language-Hearing Association (ASHA) criteria, and the effects of treatment and patient characteristics on the incidence and severity of ototoxicity.

Results
Bilateral decreases in hearing were seen in 61% of patients (median time to hearing loss, 135 days). Children treated for medulloblastoma, osteosarcoma, and neuroblastoma had greater incidence and severity of hearing loss. Agreement between the usually reported National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and ASHA criteria was inadequate.

Conclusion
Traditional reporting of toxicity data (CTCAE) has under-reported ototoxicity and minimized the significance of hearing loss in children. As pediatric patients experience improved survival, the effects and implications of high-frequency hearing loss with regard to academic achievement and speech and language development are important considerations, especially in patients younger than 5 years.

J Clin Oncol 23:8588-8596.

INTRODUCTION

The platinum compounds cisplatin and carboplatin are essential components in the chemotherapeutic treatment of a variety of pediatric malignancies. The use of platinum drugs has contributed to increases in the long-term survival in children with cancer. Unfortunately, platinum agents have adverse effects including ototoxicity and associated permanent hearing loss.[1-6] The effect of hearing loss in young children is significant and can influence speech and language development, educational achievement, and social-emotional development.[7] Clinical trials of chemoprotective agents (eg, thiols[8]) to protect children against platinum-induced hearing loss are needed.

Platinum ototoxicity is typically manifested as bilateral high-frequency sensorineural hearing loss.[1] With continued administration and increasing cumulative dose, the hearing loss tends to increase in severity and progressively spreads to affect hearing at

lower frequencies.[1] Progression of hearing loss after completion of treatment has been reported in 15% to 20% of patients.[9]

The reported incidence of cisplatin ototoxicity in children ranges from 26% to more than 90%,[1-6] with the variation influenced by treatment and patient-related factors. Data from clinical trails can be difficult to compare due to differences in patient populations, dosages, treatment schedules, and method of administration. Larger cumulative doses, prior cranial radiation, younger age, pre-existing hearing loss, and kidney dysfunction have been cited as factors that increase a child's risk for ototoxicity.[2-4,6,10]

Carboplatin is considerably less ototoxic than cisplatin. However, the use of stem-cell transplant or hematopoietic growth factors allows for the administration of higher doses to increase the efficacy of therapy,[10] which can lead to greater ototoxicity. When carboplatin is administered in alternate cycles with cisplatin, or after cisplatin chemotherapy, significant hearing loss can result.[10]

Variability in the criteria used to define ototoxicity also affects the reported incidence. Clinical trials list ototoxicity as an adverse event based on a numeric grading system, the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[11] A definition of the CTCAE ototoxicity criteria and grades is provided in Table 1. The appropriateness of this classification system has been questioned because it does not specifically consider high-frequency hearing loss.[2] By tradition, many published clinical trials report only grade 3 and 4 CTCAE toxicities. In the case of hearing loss, this would leave grades 1 and 2 ototoxicity unreported, thereby underestimating the magnitude of ototoxicity in children treated with platinum agents. We believe that CTCAE grade 1 and 2 hearing losses are significant in children and should therefore be considered and reported.

The primary objectives of this report are to summarize the baseline and treatment characteristics of a series of pediatric cancer patients treated with platinum-based chemotherapy, to characterize the incidence of and time to ototoxicity in these patients, and to explore the agreement of hearing loss assessment tools.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board at the Oregon Health and Science University (Portland, OR).

Study Design

Serial audiologic data were collected for 82 children and young adults who received platinum chemotherapy according to Children's Oncology Group protocols through the Oregon Health and Science University Department of Pediatric Hematology and Oncology between June 2000 and December 2003.

Patients assigned to platinum therapy were referred to the Pediatric Audiology Program at Oregon Health and Science University Doernbecher Children's Hospital. The audiologic and medical records were reviewed retrospectively. Of the 82 patients reviewed, 67 had baseline and serial audiologic evaluations. Baseline testing was completed before the first platinum treatment. Monitoring evaluations occurred before

Table 1. Definition of the Ototoxicity Criteria and Grades

ASHA Ototoxicity Criteria	NCI CTCAE Ototoxicity Grades	Brock's Hearing Loss Grades
(A) 20 dB or greater decrease in pure tone threshold at one test frequency	Grade 1: threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear	Grade 0: hearing thresholds less than 40 dB HL at all frequencies
(B) 10 dB or greater decrease at two adjacent test frequencies		
(C) Loss of response at 3 consecutive test frequencies where responses were previously obtained*		
	Grade 2: threshold shift or loss of > 25-90 dB, averaged at two contiguous test frequencies in at least one ear	Grade 1: thresholds 40 dB or greater at 8,000 Hz
	Grade 3: hearing loss sufficient to indicate therapeutic intervention, including hearing aids (eg, > 20 dB bilateral HL in the speech frequencies; > 30 dB unilateral HL; and requiring additional speech-language related services)	Grade 2: thresholds 40 dB or greater at 4,000-8,000 Hz
	Grade 4: indication for cochlear implant and requiring additional speech-language related services	Grade 3: thresholds 40 dB or greater at 2,000-8,000 Hz
		Grade 4: thresholds at 40 dB or greater at 1,000-8,000 Hz

Abbreviations: ASHA, American Speech-Language-Hearing Association; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; HL, hearing level.
*Changes are computed relative to baseline assessment. Results indicating significant change in hearing must be confirmed by repeat testing.

additional platinum cycles, typically at 1- to 4-month intervals. Seven patients had an initial audiologic assessment after the first platinum dose (between 1 and 57 days after the start of therapy). In these patients, this initial evaluation indicated normal hearing thresholds and thus was used as the baseline for comparisons to subsequent examinations. Fifteen patients were excluded due to either a missing baseline audiologic examination (eight patients) or follow-up examinations (seven patients).

Main Outcome Measurements

All patients received standard audiologic assessment including otoscopy, immittance, and pure tone audiometry. The method of evaluation was selected based on the age and developmental status of the patient, the child's ability to cooperate, and state of health. Conventional audiometry, conditioned play audiometry, and visual reinforcement audiometry were used to measure pure tone thresholds in 63 patients. Frequency-specific auditory brainstem response testing (ABR) was used to measure baseline peripheral auditory function and determine change in hearing in four patients who were too ill to cooperate with behavioral assessment. Details regarding the audiologic assessments are described in Appendix 1.

A subset of patients also received baseline and serial measurement of evoked distortion product otoacoustic emissions and extended high-frequency audiometry (9,000 to 16,000 Hz). Evoked otoacoustic emissions and extended high-frequency audiometry are more sensitive to initial ototoxic changes than standard pure tone audiometry,[12,13] and these results will be reported in a future article.

Patients served as their own controls for ototoxic change relative to baseline measures. An example of sequential audiologic results is shown in Figure 1. Decreases in hearing were considered significant for ototoxicity only when American Speech-Language-Hearing Association (ASHA) criteria were met, the patient had no indication of middle ear pathology, and decreases in thresholds were confirmed by repeat testing. Patients were observed longitudinally until the therapy protocol was changed to a nonplatinum therapy, completion of chemotherapy, or death. A subset of 14 patients with hearing loss was observed poststudy to monitor for progression of hearing loss.

Clinical End Points

The primary definition of ototoxicity is the criteria published by the ASHA.[14] The intent of the ASHA criteria is to detect ototoxicity early in the treatment process so that hearing loss may be minimized or prevented, if possible. Ototoxicity is thus defined in absolute terms as a decrease in hearing thresholds relative to baseline testing and indicates evidence of decrease in hearing due to treatment, but does not necessarily suggest the presence of a communicatively

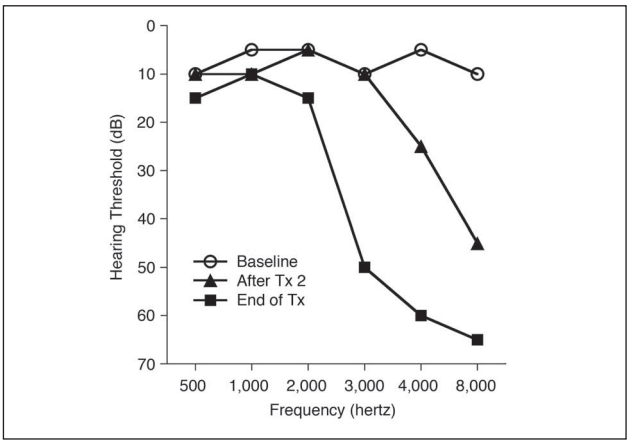

Fig 1. Sequential audiometry in a 4-year-old male with neuroblastoma during platinum treatment (Tx). After the second treatment (400 mg/m^2 cisplatin) hearing loss met American Speech-Language-Hearing Association criteria for ototoxic change. After completing treatment (400 mg/m^2 cisplatin; 1,700 mg/m^2 carboplatin), he sustained moderate to severe high-frequency hearing loss, Common Terminology Criteria for Adverse Events grade 3 ototoxicity, and Brock's grade 2 hearing loss.

significant hearing loss. To evaluate the severity of acquired hearing loss, the end-of-treatment audiologic results were assigned numeric grades using the classification system of Brock et al[2] grades 0 to 4 and by the CTCAE grades 1 to 4.[11] Although the three criteria specify different domains of ototoxicity, for ease of reference the definitions and grades are listed in Table 1. In cases of asymmetric hearing loss the numeric grade assigned corresponded to audiometric results from the ear with better hearing.

Statistical Methods

Descriptive statistics are provided as means and standard deviations for numeric variables and percentages for categoric variables. Kaplan-Meier time-to-event estimates were used for time to initial ototoxic change in hearing according to ASHA criteria. Comparisons between stratifications were made using the log-rank test. Potential stratification variables included age group, sex, race, Hispanic ethnicity, tumor type, and prior cranial radiation. To assess the simultaneous impact of potential predictor variables, Cox proportional hazards models were fit to these data using backward and stepwise variable selection from among the stratification variables. Both methods of variable selection arrived at the same best model. The Akaike's information criteria (smaller values indicate a better fit) suggested inclusion of a model term that approached significance ($P = .0521$), so this variable was included in the best model.

Comparisons of Brock's grades were made across the potential stratification variables using the Kruskal-Wallis nonparametric analysis of variance. Spearman nonparametric correlation coefficients were estimated to compare the association of the cisplatin and carboplatin dosages with the Brock's grades. Given the relatively small sample size

and the large number of tests performed, multiple analyses, such as the assessment of individual stratification variables, should be viewed as descriptive rather than definitive. Comparisons were made among the three definitions of toxicity (that is, ASHA, CTCAE, and Brock's grade). For each of CTCAE and Brock's grade, toxicities were classified as present if the grade was $\geq$ 1, 2, or 3. This generated a binary (that is, yes or no) classification similar to the ASHA criteria. A κ statistic was estimated to compare agreement (beyond chance) for each possible pair among the three binary classifications (CTCAE, Brock's, and ASHA) with respect to agreement. This allows comparison of each approach as a present/absent criterion. We consider a good κ to be at least 0.70. All analyses were performed using SAS version 8 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics are summarized in Table 2. Patients ranged in age from 8 months to 23 years at the time of the baseline hearing evaluation. The majority of children were treated for medulloblastoma, osteosarcoma, and neuroblastoma; others were treated for primitive neuroectodermal tumor (PNET) of the CNS, germ cell tumors, gliomas, and other extra-axial tumors.

Patients with neuroblastoma and glioma tended to be younger, whereas patients diagnosed with germ cell, extra-axial tumor, and osteosarcoma tended to be older. The majority of patients were male. Three patients were Asian and the remaining patients were white. About one third of patients received cranial radiation before platinum-based chemotherapy.

Platinum agent used, dosage levels, and frequency of chemotherapy varied according to the protocol, age, and medical condition. Forty patients received only cisplatin, 19 received both cisplatin and carboplatin, and eight were treated with only carboplatin. Mean cumulative dosages are listed in Table 3. Target doses, timing of administration, and other protocol details are listed in Appendix Table 1.

Sixteen patients had reductions and/or withdrawal of cisplatin during chemotherapy treatment including children treated for medulloblastoma (n = 11), osteosarcoma (n = 3), PNET (n = 1), and glioma (n = 1). With the exception of one patient (with nephrotoxicity), reductions and/or deletions of cisplatin were due to ototoxicity.

Three children treated for osteosarcoma received prolonged intravenous gentamicin for treatment of infectious complications. Concurrent administration of platinum drugs with aminoglycoside antibiotics, furosemide, and possibly acetaminophen can contribute to increased ototoxicity.[10,15]

Six children had otitis media and associated and conductive hearing loss during the course of audiologic monitoring. In four children, the otitis media and conductive hearing loss resolved spontaneously by the next monitoring evaluation. Two children had chronic otitis media and conductive hearing loss for a period greater than 90 days. They were referred to the otolaryngology department and they received bilateral tympanostomy tubes, resulting in the resolution of the conductive hearing loss. The changes in auditory thresholds due to conductive hearing loss were not considered in the indication for ototoxicity and were not included in the determination of severity of acquired hearing loss.

Of the 67 patients, 41 (61%) experienced a decrease in hearing sensitivity secondary to ototoxicity (Table 4). Incidence of ototoxicity was highest in children treated for medulloblastoma and osteosarcoma. Median time to the first significant decrease in hearing (ASHA criteria) was 135 days (95% CI, 107 to 188 days; Fig 2). Comparisons of time to hearing loss by tumor type, age group, and prior cranial radiation are in Figures 3, 4, and 5, respectively.

Table 2. Patient Characteristics

Sample	No.	Age (years)		Females		White		Hispanic Ethnicity		Prior Radiation	
		Mean	SD	No.	%	No.	%	No.	%	No.	%
Overall	67	9.65	6.19	22	32.8	64	95.5	9	13.4	23	34.3
Tumor type											
Germ cell	9	16.28	2.83	3	33.3	9	100.0	1	11.1	3	33.3
Glioma*	7	5.43	4.98	3	42.9	7	100	2	28.6	2	28.6
Medulloblastoma	17	8.64	5.76	5	29.4	15	88.2	4	28.6	13	76.5
Neuroblastoma	12	3.25	2.09	4	33.3	12	100.0	0	0.0	0	0.0
Non-CNS tumor†	4	13.24	5.32	2	50	4	100.0	0	0.0	0	0.0
Osteosarcoma	12	13.98	3.20	2	16.7	11	91.7	2	16.7	0	0.0
PNET	6	9.20	6.75	3	50	6	100.0	0	0.0	5	83.3

Abbreviations: SD, standard deviation; PNET, primitive neuroectodermal tumor.
*Ependymoma (n = 3), glioblastoma multiforme (n = 1), astrocytoma (n = 1), and chiasmatic glioma (n = 1).
†Wilms' tumor (n = 2), nasopharyngeal carcinoma (n = 1), and pleuropulmonary blastoma (n = 1).

Table 3. Treatment Characteristics

Tumor Type	No.	Days From Baseline to First Dose		Days From Diagnosis to First Dose		Total Cisplatin Dose (mg/m^2)		Total Carboplatin Dose (mg/m^2)		Cisplatin Dose to Hearing Loss* (mg/m^2)		Carboplatin Dose to Hearing Loss* (mg/m^2)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
All combined	67	7.8	29.1	53	88	493	174	4701		274	135	2,048	1,104
Germ cell	9	−0.2†	22.9	−3.3‡	98	711	314	None		450	212	None	
Glioma	7	10.9	18.7	19	143	438	109	5,049	2103	315	210	1,373	590
Medulloblastoma	17	17.4	49.0	91	66	430	107	3,552	702	212	97	3,000	(n = 1)§
Neuroblastoma	12	13.1	20.6	89	107	457	86	1,700	0	331	144	1,700	(n = 1)
Non-CNS	4	6.2	9.3	38	42	493	81	9,600	(n = 1)	270	0	None	
Osteosarcoma	12	0.8	1.3	16	7	490	80	5600	(n = 1)	267	131	800	(n = 1)
PNET	6	−6.7	19.3†	85	52	418	145	3,568	691	225	64	3,000	(n = 1)

Abbreviations: SD, standard deviation; PNET, primitive neuroectodermal tumor.
*Only among patients who experienced hearing loss.
†A negative mean value includes one or more patients for whom the baseline followed the first dose (see Patients and Methods).
‡A negative value denotes a diagnosis that occurred after the first treatment.
§When based on a sample size of 1, there is no standard deviation.

The difference in time to ototoxicity between patients of white race and those of Asian race was significant ($P = .012$), although there are only three patients of Asian race. The median time to hearing loss for Asians was 86 days (95% CI, 44 to 95 days), whereas the median was 139 days (95% CI, 121 to 206 days) for whites. The difference between time to hearing loss for those of Hispanic ethnicity and not of Hispanic ethnicity approached statistical significance ($P = .059$), with median time to hearing loss of 108 days (95% CI, 71 to 185 days) in those of Hispanic ethnicity and 135 days (95% CI, 107 to 476 days) in those not of Hispanic ethnicity. There were no differences between the sexes ($P = .19$) with respect to time to hearing loss, although the median time to hearing loss was 185 days (95% CI, 135 days or more) in females and 124 days (95% CI, 95 to 188) in males. The best proportional hazards model to predict time to hearing loss includes white race (hazard ratio, 0.15; 95% CI, 0.04 to 0.53; $P = .0034$), Hispanic ethnicity (hazard ratio 3.07; 95% CI, 1.29 to 7.30; $P = .011$), female sex (hazard ratio, 0.40; 95% CI, 0.18 to 0.86; $P = .020$), and age 15 years or older (hazard ratio, 0.45; 95% CI, 0.20 to 1.01; $P = .052$). This means that white, non-Hispanics, females, and those age 15 years or older had longer times to hearing loss.

The severity of hearing loss acquired at the end of treatment, by Brock's and CTCAE grades, is summarized in Table 4. There was a significant difference among the diagnoses with respect to Brock's grades ($P = .039$). Children treated for medulloblastoma, osteosarcoma, and neuroblastoma acquired more severe hearing loss. There was a significant correlation between the Brock's grades and the cumulative dose of cisplatin ($r = 0.33$; $P = .010$) but not between the Brock's grades and the cumulative dose of carboplatin ($r = 0.12$; $P > .5$). Fifteen patients had dose reductions of cisplatin during treatment due to significant ototoxicity. These dose reductions may confound the correlation between the cumulative dose of cisplatin and the Brock's grades. There was a significant difference between the sexes ($P = .043$), with females having lower grades than males.

Table 4. Outcomes

Tumor Type	No.	With Ototoxicity		Median Time to Hearing Loss in Days	No. of Patients With Brock's Grade 1/2/3/4	No. of Patients With NCI CTCAE Grade 1/2/3/4	Referred for Hearing Aids	
		No.	%				No.	%
All combined	67	41	61.2	135	12/13/1/2	6/18/17/0	17	25.4
Germ cell	9	1	11.1	NA	0/0/0/0	1/0/0/0	0	0.0
Glioma	7	4	57.1	332	1/1/0/0	1/3/0/0	1	14.2
Medulloblastoma	17	15	88.2	121	5/2/1/1	1/10/4/0	4	23.5
Neuroblastoma	12	8	67.7	132	0/7/0/0	1/0/7/0	7	58.3
Non-CNS	4	1	25	NA	0/0/0/0	0/1/0/0	0	0.0
Osteosarcoma	12	9	75	122	4/2/0/1	2/3/4/0	4	33.3
PNET	6	3	50.0	188	2/1/0/0	0/1/2/0	1	16.6

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NA, median not attained in sample; PNET, primitive neuroectodermal tumor.

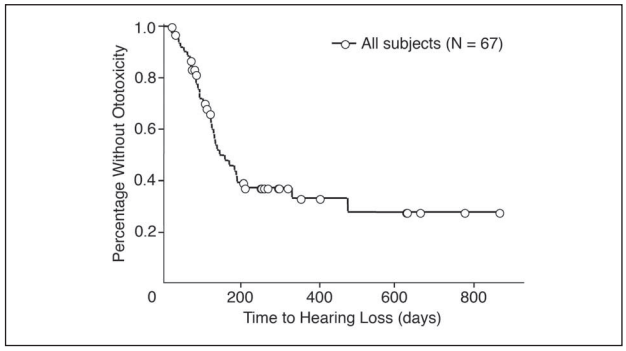

Fig 2. Kaplan-Meier plot of time to first significant hearing change by American Speech-Language-Hearing Association criteria (in days) in all patients. Median time to hearing loss is 135 days (95% CI, 107 to 188 days). Symbols on line represent patients without hearing loss at their last observation.

There was no difference in the Brock's grades with respect to history of prior cranial radiation ($P > .5$), age group ($P = .11$), white race ($P = .24$), or Hispanic ethnicity ($P > .5$).

Hearing aids were recommended for 17 patients (41% of patients with ototoxicity). Among patients with ototoxicity, children treated for neuroblastoma were most frequently referred for hearing aids. Children treated for medulloblastoma, osteosarcoma, PNET, and glioma were also referred for amplification.

When the CTCAE toxicity grades 1 and greater were compared with the ASHA criteria, the agreement was perfect ($\kappa = 1.0$) by definition. However, if CTCAE toxicity grade is 2 or greater, the agreement with ASHA criteria decreases to 0.82, and if CTCAE toxicity grade is 3 or greater, the agreement with ASHA decreases to 0.35. The agreement between ASHA criteria and Brock's grade is 0.63 for Brock's grades 1 or greater, 0.33 for Brock's grade 2 or greater, and 0.06 for Brock's grade 3 or greater. When the CTCAE toxicity grades are compared with the Brock's grades, the only categorizations for which the agreement exceed 0.65 are when CTCAE toxicity grade is 3 or greater and Brock's grade is 2 or greater ($\kappa = 0.88$).

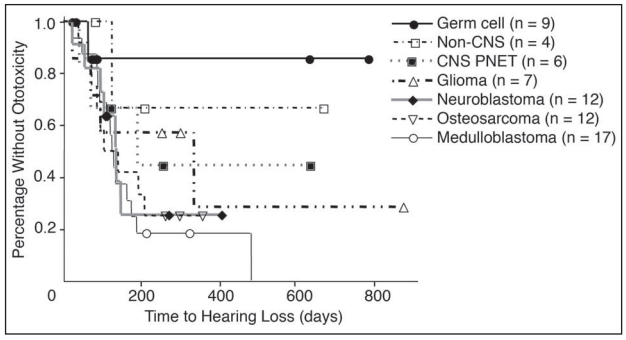

Fig 3. Kaplan-Meier plot of time to first significant hearing change by American Speech-Language-Hearing Association criteria (in days) classified by tumor type. Differences across tumor types were not statistically significant ($P = .29$) although sample sizes are small. Medians were medulloblastoma, 121 days; osteosarcoma, 122 days; neuroblastoma, 132 days; primitive neuroectodermal tumor, 188 days; glioma, 332 days; and germ cell and non-CNS, not reached. Symbols on lines represent patients without hearing loss at their last observation.

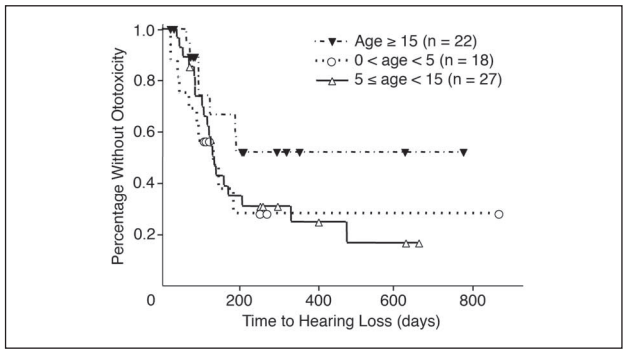

Fig 4. Kaplan-Meier plot of time to first significant hearing change by American Speech-Language-Hearing Association criteria (in days) classified by age group. There were no differences among the age groups ($P = .21$) although the trend is for shorter times to ototoxicity in younger patients. Age 15 years or older, median 191 days; 5 to younger than 15 years, 131 days; younger than 5 years, 114 days. Symbols on lines represent patients without hearing loss at their last observation.

Fourteen children who had hearing loss during treatment have been observed to monitor for progressive hearing loss. Length of follow-up ranged between 6 to 44 months after completion of treatment, with an average of 20.7 months. In all patients, there has been no improvement in hearing. Three children have had mild progression of their hearing loss, with a 10- to 20-dB decrease in hearing thresholds relative to results obtained at the completion of platinum chemotherapy. These three children were treated with cranial radiation followed by cisplatin for medulloblastoma.

DISCUSSION

In this study 55% of children (22 of 40) treated with cisplatin, 38% of children (three of eight) treated with carboplatin, and 84% of children (16 of 19) treated with both agents

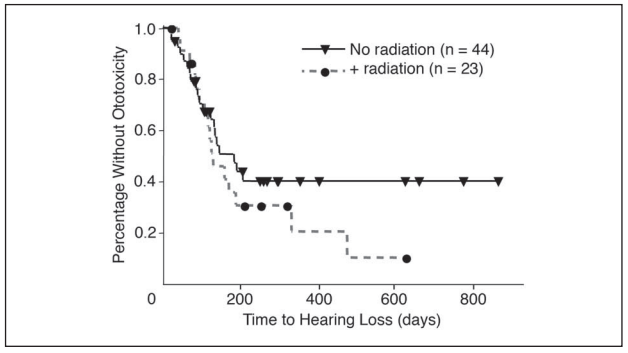

Fig 5. Kaplan-Meier plot of time to first significant hearing change by American Speech-Language-Hearing Association criteria (in days) classified by prior radiation. There was no difference in time to ototoxicity ($P = .56$) in children who had cranial radiation (median, 131 days) before chemotherapy and those who did not have cranial radiation (median, 139 days). Symbols on lines represent patients without hearing loss at their last observation.

acquired sensorineural hearing loss secondary to treatment. Several studies have reported that the individual and cumulative dose of cisplatin, particularly cumulative doses greater than 400 mg/m^2, and the cumulative dose of carboplatin seem to be directly related to the incidence and severity of ototoxicity[2-4,6] (see Appendix Table 2 online). Individually, children in this series first showed decreases in hearing after cumulative cisplatin doses ranging between 75 and 600 mg/m^2 and carboplatin doses between 800 and 3,420 mg/m^2. Patients treated for germ cell tumors (Children's Oncology Group 8882) received the highest cumulative doses of cisplatin. These patients were older and they received cisplatin as divided doses during 5 days, which may account for the lower incidence of ototoxicity in this group.

Prior or concurrent craniospinal radiation has been found to enhance the ototoxicity of cisplatin and hearing loss can be seen at lower cumulative doses.[16] In this study, 23 patients received cranial radiation before platinum chemotherapy and 16 (70%) acquired hearing loss. There were no significant differences in the incidence of ototoxicity or the time to hearing loss in children with and without cranial radiation.

Young age at the time of treatment has also been found to increase a child's risk for ototoxicity.[2-4] Li et al[3] found that children younger than 5 years of age at the time of treatment were 21 times more likely to acquire moderately severe high-frequency hearing loss than patients aged 15 to 20 years. In this study there was a trend for shorter times to ototoxicity in younger children (age younger than 15).

Children treated with both cisplatin and carboplatin can sustain significant hearing loss.[10] Of the 19 children who received a combination of cisplatin and carboplatin, 16 had ototoxicity. As a group, children treated for neuroblastoma acquired the most severe hearing losses. These children were young at the time of treatment (mean age, 3.25 years), and seven received carboplatin conditioning for bone marrow transplantation after cisplatin chemotherapy; these factors substantially increase the risk for communicatively significant hearing loss.[3,4,10] Of the eight children with neuroblastoma who had ototoxicity, seven acquired moderate to severe hearing loss at 3,000 to 8,000 Hz.

Hearing aids were recommended for 17 children, nine of whom were treated with cisplatin and eight of whom were treated with both cisplatin and carboplatin. Two children who acquired severe ototoxicity required long-term intravenous gentamicin during chemotherapy. The concurrent administration of both of these ototoxic agents likely contributed to increased hearing loss in these children. A referral for hearing aids was based on several factors. The severity and frequency range of the acquired hearing loss and its impact on speech perception was a significant consideration, and children who acquired Brock's grade 2 hearing loss or worse were consistently referred for hearing aids. Other factors included delayed or decreased speech and language development in young children, compromised communicative function, and decreased educational performance associated with hearing difficulty.

Of 14 children who had long-term audiologic follow-up, three children had additional deterioration of their hearing. Hearing loss progression was seen up to 26 months after completion of chemotherapy in these patients. There are several reports in the literature of delayed-onset or progressive hearing loss years after completion of chemotherapy and/or cranial radiation therapy.[17,18] Bertolini et al[18] evaluated the evolution of hearing loss in 120 survivors of childhood cancer with histories of cisplatin and/or carboplatin-based chemotherapy. Median follow-up was 7 years after completion of treatment. Deterioration of hearing was observed in 37% of patients treated with cisplatin and in 43% of patients treated with both agents. Progression of hearing loss was seen up to 136 months after discontinuation of chemotherapy and worsening of hearing was not only evident in patients who sustained ototoxicity during treatment, it was also seen in patients who had normal audiometry at the end of chemotherapy. The length of time required for stabilization of hearing loss following discontinuation of chemotherapy is not known.

Three different measures of ototoxicity were evaluated. CTCAE toxicity grades 1 or greater are equivalent to the ASHA criteria by definition. Literature reports, however, often focus on only CTCAE toxicity grades 3 or higher, which agree poorly with (and underestimate) the impact of ototoxicity as assessed by ASHA criteria ($\kappa = 0.35$). In this series, 24 patients (36%) would not have been reported as having ototoxicity if only CTCAE grades 3 and 4 were considered. The Brock's grades do not agree well with the ASHA criteria (largest $\kappa = 0.63$) or with the CTCAE toxicity grade. This was expected, given that the Brock's grades indicate severity of hearing loss and not a specific change in hearing. Children with hearing loss whose thresholds were less than 40 dB met criteria for Brock's grade 0. It should be noted that Brock's grade 0 hearing loss does not suggest normal hearing sensitivity. Normal hearing in children is defined as hearing thresholds at or less than 15 dB HL across the entire speech spectrum of 250 to 8,000 Hz.[19] In addition, Brock's grade 0 does not indicate that the child did not have a significant change in hearing due to treatment. To avoid confusion, it may be helpful to consider adding another step to the Brock's hearing loss grades to indicate when a child has had a mild decrease in hearing from baseline.

Ototoxicity is a common toxicity of platinum chemotherapy. The current standards for reporting ototoxicity data from clinical trials inadvertently underestimate the magnitude of the problem. The authors argue that hearing loss at frequencies above 2,000 Hz is highly significant in young children. Even minimal and mild hearing loss in high-frequency regions above 2,000 Hz considerably increases a child's risk for

academic difficulties and social-emotional problems, and increased levels of fatigue in the learning environment.[20]

To properly build their language foundation, children must be able to hear all of the sounds of speech. The high-frequency speech phonemes contain the least acoustic power; yet provide the major contribution to speech intelligibility.[21] High-frequency hearing impairment reduces the audibility and recognition of the speech sounds (*s, f, th, sh, h, k,* and *t*), which contain primary acoustic energy above 2,000 Hz. High-frequency hearing is important for the perception of fricative phonemes, which constitute approximately 50% of the consonant sounds in English. The phoneme /*s*/ is the third to fourth most frequently occurring consonant.[22] The sounds *s, t,* and *z* are also linguistic markers, used to indicate tense, plurals, possession, and sex. Reduction in audibility of these sounds can cause errors in the development of noun-verb morphology. Without high frequency speech information above 4,000 Hz, children may not hear plural forms of words or they may hear them inconsistently, especially when listening to the voices of women or other children.[23] Finally, high-frequency hearing loss may also reduce the audibility of low-frequency speech cues.[24]

In adolescents and adults, high-frequency hearing loss does not typically affect speech recognition until the loss involves frequencies below 3,000 to 4,000 Hz.[25] Having already attained language competence, they can use redundant semantic and syntactic cues to compensate for decreased audibility or distortion of speech information. Young children who are in the process of learning language do not have enough experience to use these cues as accurately.

Noise and reverberation have a significant effect on the transmission of speech sounds. Young children with normal hearing have greater difficulty than do adults in understanding speech in noisy and reverberant environments due to developmental factors and inexperience with language.[23,26] Understanding speech in noise is further degraded by high-frequency hearing loss.[27]

Hearing loss that does not cause difficulty when the child is close to and facing the speaker may interfere with perceiving and distinguishing speech when the speaker is at a distance or facing away from the child. Children learn vocabulary and the rules of language through repeated exposures over different contexts. Much of this learning occurs incidentally, by overhearing the conversations of others,[22] and these opportunities are diminished when a child has high-frequency hearing loss.

There is limited research investigating language development, psychosocial development, and academic achievement, specifically in children with high frequency hearing loss with or without prior platinum-based chemotherapy. Bess et al[20] evaluated the educational performance and social-emotional functioning of 1,218 children with minimal sensorineural hearing loss: 37% of the children with minimal hearing loss failed at least one grade in school compared with a normative rate of 3%. They also experienced greater dysfunction in social-emotional domains including behavior, energy, stress, self-esteem, and social support than did their normally hearing peers.

A child's parents, physicians, or teachers may not immediately recognize the functional impact of high-frequency hearing loss. Listening conditions at home, or in a clinical setting, are often relatively good, with close proximity to the speaker, casual and predictable conversation topics, and familiar vocabulary and context. The listening demands required for success in educational situations are much greater than those needed for casual conversation. The effects of high-frequency hearing loss, while subtle, are significant. It is important that children treated with platinum agents receive careful, continued, long-term audiologic management. Research is needed to identify long-term educational and social outcomes in pediatric patients treated with platinum-based chemotherapy.

Several agents have been studied for potential protection against ototoxicity.[28-30] Clinically, sodium thiosulfate (STS) has been found to reduce ototoxicity in adult patients receiving high-dose carboplatin with blood-brain barrier disruption.[8] STS may also reduce the incidence and severity of ototoxicity in children treated with high-dose carboplatin in conjunction with blood-brain barrier disruption.[31] Dickey et al[32,33] studied STS otoprotection for cisplatin-induced hearing loss in a rat model and found that animals who received STS 8 hours after cisplatin showed no significant change from baseline ABR values, whereas control animals showed marked ototoxicity. In a PNET brain tumor animal model using two high-dose otoprotective thiol drugs, Neuwelt et al[34] showed that the efficacy of chemotherapy was not influenced if the timing of intravenous administration was optimized. Because of the high incidence of platinum-induced ototoxicity, especially in young children, and the efficacy of thiol otoprotection in animal models and in adults with brain tumors, protocols using thiols for otoprotection are being developed.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Edward A. Neuwelt				Adherex Technologies, Inc (C)				Adherex Technologies, Inc (C)
Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required								

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