Purpose
Optimal assessment methods and criteria for reporting hearing outcomes in children who receive treatment with cisplatin are uncertain. The objectives of our study were to compare different ototoxicity classification systems, to evaluate the feasibility of including otoacoustic emissions and extended high frequency audiometry, and to evaluate a central review mechanism for audiologic results for cisplatin-treated children in the cooperative group setting.

Patients and Methods
Eligible participants were 1 to 30 years, with planned cisplatin-containing treatment. Hearing evaluations were conducted at baseline, before each cisplatin cycle, and at the end of therapy. Audiologic results were assessed and graded by the testing audiologist and by two central reviewers. Agreement was assessed using ICC 3,1, with 1 representing perfect agreement.

Results
At the end of treatment, the prevalence of any degree of ototoxicity ranged from 40% to 56%, and severe ototoxicity ranged from 7% to 22%. Compared with CTCAE, SIOP detected more ototoxicity (P = .004), whereas Brock criteria detected significantly fewer patients with any or severe ototoxicity (P < .001 for both). SIOP detected ototoxicity earlier than did the other scales. Agreement between the central reviewers and the institutional audiologist was almost perfect for ASHA and Brock, whereas the poorest agreement occurred with CTCAE.

Conclusion
The SIOP scale may be superior to ASHA, Brock, and CTCAE scales for classifying ototoxicity in pediatric patients who were treated with cisplatin. Future studies should evaluate inter-rater reliability of the SIOP scale.

INTRODUCTION
Cisplatin is a well-established chemotherapeutic agent that is used for several forms of childhood cancer, but its dose-limiting toxicity is hearing loss. Irreversible hearing loss occurs in approximately two thirds of children who are treated with cisplatin1 and is almost universal in specific subsets, such as young children with neuroblastoma who are treated with cisplatin and carboplatin.1-3 In children, cisplatin-induced ototoxicity has the potential to impact speech-language and social development, educational achievement, cognition, and quality of life.4,5

As survival has improved, strategies for mitigating or preventing the adverse effects of cancer therapy have assumed greater importance. As a result of differences in pediatric hearing assessment protocols, variability in hearing outcomes reporting, and differences in the mechanisms for collecting and reporting audiologic data in multicenter clinical trials, it is currently difficult to directly compare or pool ototoxicity data across studies. International standardization in the assessment and reporting of ototoxicity for pediatric patients is needed.
patients with cancer would advance patient care and ototoxicity research.

Ototoxicity is typically monitored with serial audiometry, measured for frequencies 0.25 to 8 kHz. Extended high-frequency audiometry (EHF) and otoacoustic emissions (OAEs) are more sensitive measures of ototoxicity.1-4 EHF audiometry is the measurement of hearing thresholds at frequencies > 8 kHz. It detects ototoxicity earlier because ototoxic damage initially occurs at the base of the cochlea where high frequencies are encoded.5 OAEs provide an objective evaluation of cochlear outer hair cell function, and changes in OAEs may precede loss of hearing sensitivity.6

Children’s Oncology Group (COG) study ACCL05C1 was designed to inform future ototoxicity studies by identifying the optimal criteria for ototoxicity reporting, to evaluate the feasibility of more sensitive measures of ototoxicity, and to gain pilot experience with a central ototoxicity review mechanism prospectively among pediatric patients who were treated with cisplatin in a cooperative group setting. The specific objectives were to compare contemporaneous ototoxicity scales, evaluate the feasibility of including OAEs and EHF, and assess central review for audiologic results.

PATIENTS AND METHODS

This study was a multi-institutional, multinational COG prospective observational cohort study.

Study Participants

Participants were enrolled between May 2007 and February 2012. Eligibility criteria were 1 to 30 years of age at enrollment, planned treatment with any cisplatin-containing regimen, no prior history of cisplatin therapy, and, for patients enrolled after February 9, 2009, intent to offer enrollment into a companion clinical trial (ACCL0431) for which cisplatin therapy, and, for patients enrolled after February 9, 2009, intent to

Ototoxicity Classification Systems Evaluated

Four ototoxicity systems were evaluated, the American Speech-Language-Hearing Association Ototoxicity Criteria (ASHA),18 Common Terminology Criteria for Adverse Events (CTCAE) version 3.0,19 the Brock Criteria (Brock),20 and the International Society of Pediatric Oncology Otoxicity Scale (SIOP).2 Specific definitions are listed in Appendix Table A1 (online only).

ASHA18 is a binary criterion (yes or no) that is designed for early ototoxicity detection. Ototoxicity is defined as a ≥ 20-dB decrease in pure tone threshold at one test frequency or a ≥ 10-dB decrease in pure tone threshold at two adjacent test frequencies. ASHA ototoxic change criteria exceed test-retest variability and indicates a loss of hearing as a result of ototoxicity.

CTCAE19 grading is the standard approach for toxicity reporting in National Cancer Institute clinical trials. Ototoxicity is graded on an ordinal scale from 1 to 4, with 4 being the most severe. Grades 1 and 2 are based on change in hearing thresholds from baseline, and grades 3 and 4 relate to recommendations for hearing intervention. CTCAE version 3.0 was the current version at the time of study activation.

Brock20 was developed to compare hearing outcomes at the end of treatment in international clinical trials; a statistically significant relationship has been established between cumulative cisplatin dose and Brock grade.21 Ototoxicity is graded on an ordinal scale of 1 to 4, where 4 is the most severe. Grades are based on hearing threshold levels ≥ 40 dB HL, rather than a change in threshold compared with baseline.

SIOP2 was also developed to report hearing outcomes in international clinical trials for pediatric patients who were treated with platinum chemotherapy. Grading is based on hearing thresholds ≥ 20 dB HL by using an ordinal scale of 1 to 4, where 4 is the most severe.

Procedures for Ototoxicity Determination

For each hearing evaluation, ototoxicity determination and grading was conducted by the testing audiologist and two central study audiologists (BB, KK). Raw audiologic data, including audiograms, tympanograms, OAE printouts, ABR waveforms, and the evaluation report, were faxed from the institutions to the COG Data Center and were then distributed to the study audiologists for independent central review. If the records indicated that specific tests were completed but the raw data were not submitted, missing data were requested from the institution. Central reviewers were blinded to the institutional audiologist’s assessment and to each other’s assessments. Any initial discrepancies between the two central reviews were discussed and resolved to achieve consensus. Because SIOP was added after completion of the study—as it was not available at the time of study development—it was only evaluated by one central reviewer (K.K.).

Audiograms were reviewed to determine if ototoxicity occurred according to ASHA and were graded for severity of hearing loss according to CTCAE, Brock, and SIOP. If middle ear pathology or conductive hearing loss was present, ototoxicity determination was based on bone conduction thresholds, and if bone conduction thresholds were not obtained, then the assessment was categorized as not evaluable. Ototoxicity for EHF was determined by using ASHA. When ABRs or ASSRs were measured, results were classified as normal or abnormal by the testing audiologist. If the ABR or ASSR was categorized as abnormal, ototoxic change in ABR and ASSR thresholds—relative to a previous ABR or ASSR—was determined according to ASHA. ABR and ASSR results and behavioral audiometric thresholds were not directly compared, and ototoxicity grading was not
applied to ABR and ASSR results. OAEs were classified as abnormal if a loss of OAEs occurred at any frequency within the 2- to 8-kHz range when middle ear function was normal.

Comparison of Ototoxicity Systems

Two approaches were used to compare the four different ototoxicity systems. First, within each patient, the earliest date of detection of ototoxicity was determined for each of the four measures (ASHA, CTCAE, Brock, and SIOP). These dates were ranked, with rank 1 for the earliest and rank 4 the latest. If more than one ototoxicity measure was met at the same time point, both were given a score that represented the mean of the corresponding ranks. For example, if three scales were second in detecting ototoxicity, each received a score of 3, which was the average of ranks 2 to 4. If none of the measures met ototoxicity criteria at any time point on study, the date was arbitrarily set as September 30, 2015, later than any study evaluation date. Rank scores among all patients were summarized for each measure; thus, a lower rank score indicates earlier detection of ototoxicity by that measure. Because not every audiogram was evaluable by all four scales, the rank score reflected a combination of sensitivity and feasibility.

Second, we reviewed false-positive rates for each ototoxicity system. A false positive was defined as identification of ototoxicity at one time point and normal hearing or no ototoxicity on a subsequent evaluation. If more than one false positive occurred in the same patient, each instance was counted. The last hearing assessment could never be designated a false positive as there would be no later assessment to confirm or change the assignment of ototoxicity.

Statistical Analysis

Descriptive statistics summarized patient characteristics, the number of evaluable assessments, and the prevalence of ototoxicity and severe ototoxicity (grades 3 or 4) by the different ototoxicity measures at the end of therapy and among all time points. McNemar’s test was used to compare the frequency of ototoxicity or severe ototoxicity by two different measures at the end of therapy. Two-sided nonparametric binomial sign test was used to compare rank scores for initial detection of ototoxicity between two measures; the scale with the lowest average rank was used as reference and compared with each of the other three scales. Bonferroni adjustment for the six possible pairwise comparisons would require a comparison between two scales to have a P value of < .0083 to be considered statistically significant. Initial agreement between the two central reviewers and between the institutional review and consensus central review was examined by using the simple Kappa statistic for comparisons between two categories and the weighted Kappa when data included more than two categories. Any ototoxicity, ototoxicity grade (1 to 4), and ototoxicity severity (severe vs none or mild) were compared.

Strength of agreement was defined as slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00). All analyses were performed by using SAS (SAS/STAT User’s Guide, Version 9.3; SAS Institute, Cary, NC).

RESULTS

During the study period, 301 participants from 53 institutions enrolled, of whom 131 coenrolled in ACCLO431. There were 17 participants who were ineligible (prior receipt cisplatin [n = 1], enrolled after February 9, 2009, and not eligible for ACCLO431 [n = 16]), which left 284 eligible participants. Table 1 lists the demographic characteristics of the cohort. Median age was 10.2 years (range, 0.1 to 21.3 years) and the median cumulative dose of cisplatin was 395 mg/m² (range, 48 to 623 mg/m²). There were 27 patients who underwent hematopoietic stem cell transplantation.

A total of 1,436 audiologic evaluations were reviewed. Hearing assessment methods and the number of evaluations that included OAEs and EHF are listed in Table 2. Central review for ototoxicity was not possible for 54 evaluations (4%) as a result of missing test data.

Table 3 lists the prevalence of ototoxicity and severe ototoxicity at the end of treatment by the four ototoxicity systems. A discordant pair occurred in the comparison of two systems when ototoxicity was classified by one system and not the other. Compared with CTCAE, SIOP detected significantly more ototoxicity (11 v 1 discordant pair; P = .004), whereas Brock criteria detected significantly fewer patients with any ototoxicity (0 v 19 discordant pairs) or severe ototoxicity (0 v 22 discordant pairs; P < .001 for both). In 19 patients who had ABR or ASSR at the end of treatment, ototoxicity occurred in eight and could not be determined in two patients due to lack of a prior comparison. Ototoxicity in EHF thresholds occurred in 69 (68%) of 101 patients and 25 patients (25%) had ototoxicity in EHF range but not in the conventional frequencies. DPOAEs were categorized as abnormal in 120 (60%) of 201 patients at the end of therapy.
Table 3. Incidence of Any Grade Ototoxicity and Severe Ototoxicity at the End of Treatment by Grading Criteria by Central Review

<table>
<thead>
<tr>
<th>Variable</th>
<th>ASHA</th>
<th>CTCAE*</th>
<th>Brock</th>
<th>SIOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ototoxicity at end of therapy†</td>
<td>117 (56%); $P = .0002$</td>
<td>109 (51%); Ref</td>
<td>85 (40%); $P &lt; .001$</td>
<td>118 (65%); $P = .004$</td>
</tr>
<tr>
<td>4 weeks post-cisplatin only</td>
<td>100 of 186 (54%)</td>
<td>90 of 189 (48%)</td>
<td>69 of 185 (37%)</td>
<td>97 of 189 (51%)</td>
</tr>
<tr>
<td>4 weeks post-transplantation only</td>
<td>17 of 23 (74%)</td>
<td>19 of 26 (73%)</td>
<td>16 of 25 (64%)</td>
<td>21 of 26 (81%)</td>
</tr>
<tr>
<td>Severe ototoxicity (grades 3 to 4) at end of therapy†</td>
<td>37 of 209 (18%); Ref</td>
<td>14 of 210 (7%); $P &lt; .001$</td>
<td>47 of 215 (22%); $P = .02$</td>
<td></td>
</tr>
<tr>
<td>4 weeks post-cisplatin only</td>
<td>25 of 185 (14%)</td>
<td>8 of 185 (4%)</td>
<td>34 of 189 (18%)</td>
<td></td>
</tr>
<tr>
<td>4 weeks post-transplantation only</td>
<td>12 of 24 (50%)</td>
<td>6 of 25 (24%)</td>
<td>13 of 26 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. $P$ values derived by using McNemar’s test compared with CTCAE are used as the reference (Ref) and are based on patients with both criteria available. Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; SIOP, International Society of Pediatric Oncology.

‡Six patients with grade not specified were excluded from the computation of severe ototoxicity using CTCAE.
†End of therapy means after the last dose of cisplatin or hematopoietic stem cell transplantation.

Table 4 lists the number of assessments that indicated ototoxicity for all audiometric evaluations combined. The number of evaluable audiograms was comparable between CTCAE, Brock, and SIOP, with slightly fewer by ASHA. Fewer patients had at least one audiogram that was evaluable by ASHA compared with the other scales. When evaluating time to detection of ototoxicity, on average, SIOP detected ototoxicity the earliest with the lowest mean rank score of 2.24, followed by ASHA, CTCAE, and Brock. Brock never detected ototoxicity before SIOP, ASHA, or CTCAE. Table 4 also illustrates that false positives were highest for ASHA and SIOP and lowest for Brock.

Agreement in the designation of ototoxicity and ototoxicity grade for all evaluations is shown in Table 5. Agreement between the two central reviewers was almost perfect. Agreement between the consensus central review and institutional audiologist was almost perfect for ASHA and Brock but was worst for CTCAE.

We found that SIOP might be the optimal criteria on the basis of the high number of evaluable assessments, sensitivity, and earliest time to detection of ototoxicity. ASHA had the lowest number of evaluable assessments, as it requires comparison with baseline and does not use a severity grading scale. Brock had the lowest false-positive rate and the highest inter-rater agreement; however, the scale identified ototoxicity in fewer patients, at a later time in treatment, and reported significantly fewer patients as having any ototoxicity and severe ototoxicity. Because Brock does not capture ototoxicity until hearing thresholds are ≤ 40 dB HL, it does not detect mild hearing loss that is communicatively important for developing children and adolescents. CTCAE was not the optimal measure by any evaluation and had the worst agreement between local and central audiologists.

In previous pediatric multicenter clinical studies, approximately 30% of hearing assessments were not evaluable for ototoxicity as a result of incomplete or missing test results or lack of a frequency-specific measurement. In contrast, only 4% of audiologic evaluations were missing data for central review and 3% of end-of-treatment audiograms were not evaluable for ototoxicity in this study. Our favorable results may have occurred because central review was completed soon after audiology results were submitted by the institution to COG and any missing test data were requested in real time. In addition, as the testing audiologist was asked to grade the results, he or she was aware of the information needed for ototoxicity grading.

Table 4. Comparison of Different Ototoxicity Criteria by Central Review

<table>
<thead>
<tr>
<th>Variable</th>
<th>ASHA</th>
<th>CTCAE*</th>
<th>Brock</th>
<th>SIOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of evaluable audiograms</td>
<td>969 of 1,042* (93%)</td>
<td>1,229 of 1,279 (96%)</td>
<td>1,228 of 1,279 (96%)</td>
<td>1,244 of 1,279 (97%)</td>
</tr>
<tr>
<td>Detection of ototoxicity, all evaluations</td>
<td>410 of 969 (42%)</td>
<td>367 of 1,223 (30%)</td>
<td>260 of 1,228 (21%)</td>
<td>429 of 1,244 (34%)</td>
</tr>
<tr>
<td>No. of patients with at least one follow-up evaluable audiogram</td>
<td>245</td>
<td>261</td>
<td>260</td>
<td>262</td>
</tr>
<tr>
<td>Detection of ototoxicity, all patients</td>
<td>139 of 282† (49%)</td>
<td>129 of 282 (46%)</td>
<td>100 of 282 (35%)</td>
<td>144 of 282 (51%)</td>
</tr>
<tr>
<td>Initial detection of ototoxicity, mean rank (range)</td>
<td>2.34 (1-4)</td>
<td>2.51 (1-4)</td>
<td>2.91 (1.5-4)</td>
<td>2.24 (1.3-5)</td>
</tr>
<tr>
<td>Initial detection rank comparison, $P$‡</td>
<td>.06</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>—</td>
</tr>
<tr>
<td>False positives (evaluations) identified§</td>
<td>21</td>
<td>13</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; SIOP, International Society of Pediatric Oncology.

*Does not include baseline evaluations.
†Otopathy could not be determined in two patients.
‡Initial detection rank score between SIOP and the other criteria were compared by binomial sign test.
§False positive was defined as the indication of ototoxicity at one time point but no ototoxicity in a latter study.

DISCUSSION

In this prospective, multi-institutional, multinational clinical trial among a large cohort of cisplatin-treated children and adolescents, variability of ototoxicity (40% to 56%) and severe ototoxicity (7% to 22%) reported by the different approaches was substantial. The current lack of an international standard for ototoxicity reporting prevents comparison of results within and across diseases and studies.

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There have been concerns about the reliability of institutional ototoxicity reporting. In a study of 120 children who were treated for hepatoblastoma, prevalence of CTCAE grade 3 and 4 ototoxicity was 4% by institutional reporting compared with 38% by central auditory specialist review. Having institutional audiologists review and report ototoxicity may have overcome these challenges as there was substantial to almost perfect agreement between institutional review and central review in our study. However, in light of its feasibility in the cooperative group setting demonstrated here, we believe central audiology review should be used in future clinical trials in which ototoxicity is a primary end point because it ensures consistency in the analysis of outcomes. This is important in the pediatric setting when test results may be incomplete or confounded by conductive middle ear pathology. In addition, collection of raw audiology data allows rescoring of ototoxicity by alternate approaches that might be developed in the future, as occurred in our study with SIOP.

OAEs were included in 84% of evaluations and are likely feasible for ototoxicity monitoring in future COG clinical trials; however, OAEs cannot estimate hearing thresholds, and, at this time, there are no accepted criteria for ototoxic change or grading of OAEs. Consistent with other studies, EHF was more sensitive to middle ear pathology. In addition, collection of raw audiology data allows rescoring of ototoxicity by alternate approaches that might be developed in the future, as occurred in our study with SIOP.

Agreement between central reviewers may be superior to ASHA, Brock, and CTCAE scales for classifying ototoxicity in pediatric patients who are treated with cisplatin. Future studies should evaluate inter-rater reliability of the SIOP scale.

Table 5. Agreement Between Central Reviewers and Between Central and Institutional Reviewers

<table>
<thead>
<tr>
<th>Variable</th>
<th>ASHA Kappa</th>
<th>95% CI</th>
<th>CTCAE Kappa</th>
<th>95% CI</th>
<th>Brock Kappa</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement between two central reviewers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ototoxicity incidence (yes v no)</td>
<td>0.92</td>
<td>0.89 to 0.95</td>
<td>0.92</td>
<td>0.90 to 0.95</td>
<td>0.98</td>
<td>0.97 to 1.0</td>
</tr>
<tr>
<td>Ototoxicity grade (1 to 4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.90</td>
<td>0.88 to 0.92</td>
<td>0.89</td>
</tr>
<tr>
<td>Ototoxicity severity (severe v none or mild)</td>
<td>NA</td>
<td>NA</td>
<td>0.80</td>
<td>0.74 to 0.87</td>
<td>0.93</td>
<td>0.86 to 1.0</td>
</tr>
<tr>
<td>Agreement between central and institutional reviewer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ototoxicity incidence (yes v no)</td>
<td>0.84</td>
<td>0.80 to 0.87</td>
<td>0.87</td>
<td>0.84 to 0.90</td>
<td>0.91</td>
<td>0.88 to 0.94</td>
</tr>
<tr>
<td>Ototoxicity grade (1 to 4)</td>
<td>NA</td>
<td>NA</td>
<td>0.84</td>
<td>0.81 to 0.86</td>
<td>0.89</td>
<td>0.86 to 0.92</td>
</tr>
<tr>
<td>Ototoxicity severity (severe v none or mild)</td>
<td>NA</td>
<td>NA</td>
<td>0.69</td>
<td>0.60 to 0.78</td>
<td>0.85</td>
<td>0.75 to 0.95</td>
</tr>
</tbody>
</table>

NOTE: Simple Kappa statistic was used for comparisons between two categories and weighted Kappa was used when data included more than two categories. Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.

Authors’ Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.
REFERENCES


Affiliations
Kristin R. Knight and Edward A. Neuwelt, Oregon Health and Science University, Portland, OR; Lu Chen and Ha Dang, Children’s Oncology Group, Monrovia; David Freyer, Children’s Hospital Los Angeles; Ha Dang, University of Southern California, Los Angeles; Lanie Lindenfeld, City of Hope, Duarte; Brad H. Pollock, University of California, Davis, Davis, CA; Richard Aplenc, Children’s Hospital of Philadelphia, Philadelphia, PA; Mary Bancroft, University of Gainesville, Gainesville; Dale F. Kraemer, University of Florida, Jacksonville, FL; Bonnie Bliss, Biljana Gillmeister, Jane Meza, and Lillian Sung, The Hospital for Sick Children, Toronto; and Eleanor Hendershot, McMaster Children’s Hospital, Hamilton, Ontario, Canada.

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Group-Wide, Prospective Study of Ototoxicity Assessment in Children Receiving Cisplatin Chemotherapy (ACCL05C1): A Report From the Children’s Oncology Group

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Lu Chen
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David Freyer
No relationship to disclose

Richard Aplenc
Honoraria: Sigma-Tau
Expert Testimony: Dana Wiggins
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Mary Bancroft
No relationship to disclose

Bonnie Bliss
No relationship to disclose

Ha Dang
No relationship to disclose

Biljana Gillmeister
No relationship to disclose

Eleanor Hendershot
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Dale F. Kraemer
Employment: 21st Century Oncology (I)

Lanie Lindenfeld
No relationship to disclose

Jane Meza
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Edward A. Neuwelt
Other Relationship: Fennec Pharmaceuticals

Brad H. Pollock
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Appendix

<table>
<thead>
<tr>
<th>Scale</th>
<th>Determination of Ototoxicity</th>
<th>Grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ASHA (ASHA 1994)</td>
<td>Change in hearing threshold compared with baseline</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NCI CTCAE v3</td>
<td>Change in hearing compared with baseline</td>
<td>Normal hearing, no change in hearing from baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Threshold shift or loss 15-25 dB compared with baseline, averaged at two or more contiguous frequencies in at least one ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Threshold shift of loss 25-90 dB, averaged at two or more contiguous frequencies in at least one ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brock (Brock 1991)</td>
<td>Bilateral threshold HL</td>
<td>≤ 40 dB at 8 kHz</td>
<td>≤ 40 dB at ≤ 4 kHz</td>
</tr>
<tr>
<td>SIOP ototoxicity scale (Brock 2012)</td>
<td>Threshold HL</td>
<td>Hearing threshold ≥ 20 dB at 1-8 kHz</td>
<td>Hearing thresholds ≥ 20 dB at 1-8 kHz</td>
</tr>
</tbody>
</table>

Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; HL, hearing level; NCI, National Cancer Institute; SIOP, International Society of Pediatric Oncology.