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Hearing evaluation of head and neck cancer patients (HNCP): Comparison of CTCAE, Brock and Chang adverse event (AE) criteria in patients receiving cisplatin (CDDP)

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Abstract

Purpose—To compare CTCAE, Brock and Chang hearing loss (HL) grading in HNCP receiving CDDP. Endpoints were baseline distribution of HL, inter-observer consistency, and sensitivity to HL following CDDP treatment.

Methods—460 single ear audiograms in 110 HNCP were graded. HL at baseline, inter-observer agreement rates, and changes in HL following CDDP were evaluated.

Results—The Chang and Brock tools' baseline HL distribution was concentrated at grade 0 (57 and 41%, respectively), whereas 47% per the CTCAE had grade 3 baseline HL. Inter-observer agreement was highest for the Brock scale (90%) followed by the Chang (89%) and CTCAE (75%) scales. Detection of change following CDDP was highest for Chang (48%) followed by Brock (45%) and the CTCAE (32%).

Conclusion—The Brock and Chang tools may be superior to the CTCAE in HNCP receiving CDDP using baseline HL distribution, inter-observer agreement and detection of HL grade change as performance indicators.

Keywords

ototoxicity; cisplatin; audiogram; hearing loss; adverse event; head and neck

Background

Cisplatin (CDDP) has been used for four decades as an integral part of the treatment for head and neck cancers. Hearing loss from CDDP is dose and schedule-related.¹²³ Because the representation of hearing loss by audiograms is complex, several auditory toxicity scales which reduce the complexity represented in the audiograms to integer scales of severity have been proposed.⁴⁻⁹¹⁰

The most commonly used tools to grade hearing loss in adult cancer patients are the US National Cancer Institute CTCAE criteria (see Table I).^{8,9} A major benefit of these scales is that they are widely available and familiar to the cancer clinical trials community. Because the CTCAE hearing impairment grades follow the uniform 0-4 point grading scale employed throughout the CTCAE, most clinicians are familiar with the interpretations of impairment levels: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = disabling. However, because the CTCAE hearing impairment scales do not discriminate between audiogram threshold shifts at frequencies critical to performance of activities of daily living (ADL) and frequencies less important to ADLs, these frequency-unbiased grade designations may not represent clinically relevant hearing impairment. An additional difficulty with the CTCAE is that it they are designed for patients with baseline evaluations and complex corrections of absolute change values using expected age-related threshold shifts are recommended.⁸¹¹ In our experience, such corrections are virtually never calculated when reporting AEs using the CTCAE because patients receiving CDDP are not typically enrolled prospectively in hearing monitoring programs.

In order to address these issues, alternative grading scales of audiogram-based hearing impairment have been proposed.^{5,7,10} The Brock scale, initially proposed to evaluate changes in audiograms in pediatric oncology patients receiving CDDP, weighs most heavily hearing threshold shifts occurring at frequencies critical to human speech recognition. In addition, the Brock scale assigns lower grades to shifts at higher frequencies and so assigns lower grades to the audiogram changes seen with early CDDP ototoxicity. The Brock scale also uses absolute thresholds to assign grades, eliminating the need for baseline or age-related corrections. However, because the Brock criteria do not account for any hearing losses less than 40 dB at any frequency, some audiograms by the Brock scale are graded zero (e.g. 35 dB loss at all frequencies = grade 0 by Brock) when in fact they could represent worse functional degrees of hearing loss than those assigned Brock grades one and two.⁵¹²

To address these concerns, the Chang grading system was developed to provide a more clinically consistent grading system in the pediatric population. This tool has been validated in the pediatric population and was found to correlate better than the CTCAE scale with clinical recommendations for assistive hearing devices in the pediatric population.⁵ There has been no analogous comparison of hearing grading systems for the adult population of cancer patients exposed to CDDP.

Materials and methods

We compared the CTCAE, Brock and Chang scales' sensitivity and inter-observer variability for detecting individual ear hearing loss in adult HNCP who were exposed to CDDP-based chemoradiation (CRT) based on audiometrically determined changes.

After obtaining IRB approval, we used an electronic database to identify HNCP who received concurrent CDDP and radiation (RT) between 2006-2010. We reviewed patient charts to identify patients with audiograms performed prior to treatment with CDDP. Each audiogram for each ear was assigned a hearing loss grade according to the CTCAE v.3, CTCAE v.4, Brock and Chang criteria (Table I). We did not use corrections based on the change from baseline or relative to expected age related threshold shifts as specified in the CTCAE because we were interested in comparing the CTCAE directly to the Brock and Chang criteria, which both classify the absolute hearing loss present in a patient rather than change from baseline. It is also our experience that the CTCAE is routinely applied this way in cancer clinical trials and therefore our comparison is a real world rather than idealized one. Audiograms were blinded to identity and timing relative to CDDP and independently graded by three evaluators: an otolaryngologist with expertise in hearing loss (K.W.C.), a medical oncologist who specializes in the treatment of HNCP (A.D.C.) and a clinical trial data manager trained by A.D.C. (R.R.L.). For purposes of comparison between scales at baseline and at follow-up, (Table III and Figure S1; Table IV and Figure S2) A.D.C.'s grade assignments were used since in our practice the treating medical oncologist is responsible for AE grading. We also examined inter-observer differences (Tables V and S1) to evaluate grading consistency among the evaluators.

In the subset of patients who had both baseline audiograms and audiograms following completion of RT, cochleae were contoured and RT doses were determined using Eclipse (Varian Medical Systems, Palo Alto, CA).¹³ Data were collected and analyzed using commercially available software, R version 2.15.0.

Results

We identified 236 HNCP who received concurrent CDDP and RT between 2006 and 2010 (Table II). There were a total of 460 ear-specific audiograms evaluable and 110 patients had at least one audiogram prior to receiving CDDP. The median age was 54(20-80) and there were 22 females. Sixty-seven patients had at least one follow-up audiogram and in all cases the first follow-up audiogram was after patient exposure to CDDP. Only 16 patients had both pre and post-radiation completion audiograms and therefore the influence of radiation on hearing loss was excluded from further analysis. The median dose of CDDP between the first and second audiograms was 150 mg/m² (range 40-450 mg/m²). The median interval between the baseline audiogram and first CDDP dose was 10 days (range 1-56) and the median interval between the last CDDP and first follow-up audiogram was 16 days (range 2-787). We were unable to consistently determine the reasons follow-up audiograms were obtained.

The CTCAE v.4 criteria specify that threshold shifts at 1, 2, 3, 4, 6 and 8 kHz must be evaluated in order for the CTCAE v.4 to be applied. 283/460 (62%) of the audiograms had at least one of these frequencies missing. Therefore we did not include the CTCAE v.4 in subsequent analyses.

We examined the distribution of hearing loss grades at baseline on an individual ear audiogram basis according to CTCAE v.3, Brock and Chang scales (Table III and Figure S1) using A.D.C.'s interpretations. Using CTCAE v.3, 47% of all audiograms demonstrated grade 3 hearing loss, with only 46% of audiograms with grade zero or one hearing loss. The Brock and Chang scales showed an inverse distribution relationship with the CTCAE v.3 distribution; 72% and 62% grade zero or one hearing loss and only 3% and 12% grade 3 hearing loss, respectively.

In Table IV and Figure S2 we compared the change in grade of hearing loss using the three scales between the baseline audiogram and the first audiogram after at least 40 mg /m² of CDDP. While the CTCAE v.3 detected changes in grade in 33% of the audiograms, the Brock and Chang scales detected 45% and 48%, respectively. Despite this decreased sensitivity of the CTCAE v.3 compared to the Brock and Chang scales, for the latter two scales there was a stepwise decline in incidence as the grade changes became larger, but the changes using the CTCAE v.3 demonstrated higher rates of more extreme change (2-2.5 grade change) than more moderate changes (1-1.5 grade change). For example, the CTCAE v.3 had the highest percentage of at least grade 2 changes from baseline, 21%, compared to 14% and 11% for the Brock and Chang scales (see Table IV and Figure S2).

We compared inter-observer differences in applying the grading scales to the audiograms. Table V shows the inter-observer agreement between R.R.L. and A.D.C., which were high for all grading tools: 92, 98, and 93% for the CTCAE v.3, Brock and Chang criteria, respectively. Inter-observer agreement between A.D.C. and K.W.C. was weaker, with 75, 90, and 89% agreement for the CTCAE v. 3, Brock and Chang scales, respectively. The A.D.C. and K.W.C. grading differences were congruent across all three scales 63% of the time, while grading differences were congruent between CTCAE v.3 and Brock, CTCAE v. 3 and Chang, and Brock and Chang in 68%, 65%, and 82% of instances, respectively (Table S1)

When we reviewed the discrepancies among ourselves, we found that the discordant grading by A.D.C. and K.W.C. according to CTCAE v.3 was largely explained by different applications of the grading criteria. Sixty percent of the discordant grades using CTCAE v.3 were because A.D.C. interpreted the criteria literally with respect to the “averaged at ... contiguous test frequencies” criterion in the CTCAE v.3 while K.W.C. interpreted the criteria to mean the discrete dB level at each of the two or three contiguous frequencies. For example, threshold detections at 4, 6 and 8 kHz of 10, 35, and 50 dB were interpreted as consistent with a grade 3 hearing loss by A.D.C. (average of three adjacent measurements= 32) and as grade 2 by KWC (only 2 adjacent values greater than 25). The second most common explanation for discrepancies in CTCAE v.3 (30%) was using air conduction versus bone conduction threshold measurements. Bone versus air conduction use is not specified in either the CTCAE v.3 nor Brock criteria, and the Chang criteria merely states

“bone conduction or air conduction with normal tympanogram”. Because tympanograms are not always available and most oncologists who translate audiograms into AE grades lack expertise in this area, A.D.C. consistently graded all audiograms using the higher threshold level if there was a discrepancy between bone and air conduction. K.W.C. graded the audiograms using the bone conduction threshold if it was lower, in order to specifically grade the sensorineural hearing loss, rather than also counting superimposed conductive overlay into the grading score. This differential grading criterion was responsible for 60% of the A.D.C. versus K.W.C. interpretation discrepancies using the Brock and Chang criteria. The few remaining discrepancies were explained by erroneous reads, most typically the misapplication of “greater than or equal to” criteria in the Chang and Brock criteria.

Discussion

This is the first report of a comparison of the CTCAE, Brock and Chang hearing assessment scales used on a large group of adult cancer patients receiving CDDP. We found that the CTCAE scales do not represent what we would expect to be a natural distribution of baseline hearing status in this population. A hearing loss scale which defines the largest percentage of patients as having severe hearing loss at baseline is probably one whose applicability is suboptimal (Table III and Figure S1). We found that both the Brock and Chang scales' distribution of hearing loss at baseline was much more consistent with what we would expect in a normal population. With the Brock and Chang scales, most patients at baseline had grade 0 hearing loss and hearing loss incidence was inversely related to the grade of hearing loss.

Hearing loss grading scales are often used not only to help clinicians evaluate which patients may not be appropriate for ototoxic agents such as CDDP, but also as part of the evaluation to determine the extent of hearing loss following treatment. The Brock and Chang scales were best at detecting changes from baseline prior to CDDP (Table IV and Figure S2).

Another important property of any scale for adverse event grading is an easy translation from measurements to grade assignments. Because many clinical trials are multi-institutional, inter-observer agreement of grade assignment is essential. We found that differences were least using the Brock and Chang scales. We also noted that while the grading assignments of a data monitor trained by a medical oncologist and medical oncologist interpretations were largely congruent, there was a greater difference between the medical oncologist and the otolaryngologist. Most of these differences were explained by specific, identifiable differences such as using air versus bone conduction thresholds and strict averaging versus absolute threshold levels at adjacent frequencies as discussed above. In the absence of more specific guidance concerning how to apply the various hearing AE scales, we discovered that we applied the scales differently based upon our underlying interests. In the case of the medical oncologist, alteration of the overall hearing experience of the patient was the primary question, while the otolaryngologist focused on the sensorineural component of hearing. Prior experience with pediatric audiogram evaluations suggests that the confounding effect from inclusion of hearing loss from non-sensorineural factors in the hearing evaluation is common.¹⁴ Potential ways to address this would be to ensure that all audiograms include masked bone thresholds in order to most specifically

quantify the sensorineural component of hearing loss and to have audiology specialists participate in the grading process. Specific guidance in AE grading tools such as the CTCAE could also guide trialists with respect to focusing on sensorineural rather than overall hearing evaluation.

For the purposes of this comparison we intentionally applied no correction to threshold shifts based upon age related norms for baseline audiograms using the CTCAE criteria. The Brock and Chang scales represent absolute hearing levels, whereas the CTCAE scale reports threshold shift from baseline. In pediatric oncology, only 1 in 500 children would be expected to have anything other than grade 0 pretreatment hearing loss. However, a large proportion of adult patients greater than 40 years old may begin with a baseline hearing loss. A scale which only focuses on change from baseline, like the CTCAE, is unable to correctly classify clinical impact on patients if the patients start from different baselines. Thus, an adult patient who had a pretreatment mild hearing loss sustaining 20 dB decrease in thresholds from chemotherapy is much less affected than an adult patient with pretreatment moderate hearing loss sustaining the same exact 20 dB decrease in threshold even though they would have been categorized as having the same CTCAE ototoxicity. In order to correctly assess true clinical impact to the patient, the hearing loss scale needs to reflect an absolute level of hearing, much like how hemoglobin level is graded in the CTCAE scale for anemia (i.e. absolute Hgb level determines the grade, not change in Hgb). Furthermore, in only a minority of cases are baseline audiograms routinely obtained in oncology patients, which makes it impossible to strictly apply CTCAE grading using change from baseline as the measure for a large proportion of patients in most study populations.¹⁴¹⁵

There are several weakness is to our study. First, because we have no external gold standard to which we can compare the ototoxicity grades using these scales, we cannot be certain whether any of them more closely approximate a gold standard of impairment severity. Pediatric studies have correlated hearing loss scale scores to hearing impairment and the subsequent developmental delay or use of hearing aids.¹⁶⁻¹⁸ We suspect that hearing aid use evaluation in our population would be problematic because of the substantial cost of hearing aids, which is often not covered by insurance. The social stigma of hearing aids could also confound hearing aid use as a gold standard. Additionally, recommendations for hearing aids in adults is a much more variable and subjective phenomenon than in children, and often incorporates considerations of the adult's job status and social status for example.

Another weakness of our study is its retrospective nature. Only 110 of 236 patients had a baseline audiogram and only 67 of these had subsequent audiograms. There were no standard criteria for timing or indication for follow-up audiograms. Our group does not take the position that obtaining audiograms at baseline or in follow-up after receiving CDDP is a well-accepted standard of care. Therefore, it is our impression that most of the follow-up audiograms were ordered for cause rather than as a routine, although we could not find this well documented in the patients' medical records. Because of this, any inference concerning the prediction of the extent and the number of patients experiencing hearing loss following CDDP is highly limited. Furthermore, the small number of patients with both pre and post RT completion audiograms prevented us from evaluating the contribution of radiation to hearing loss. It is worth noting that if we assume this is the worst-case scenario population

receiving CDDP, baseline hearing is likely no worse than documented here and CDDP-related hearing loss average is unlikely to be worse than documented here. These data could be useful to put worst-case scenario information on the frequency and severity one can expect from high-dose CDDP in this setting. Specifically, using the Brock and Chang scales, up to 39% of patients receiving CDDP have at least a grade 1 hearing toxicity and up to 10% experience a grade 2 or worse (Table IV and Figure S2). Finally, because this was a retrospective study, we could not control for comorbidities, the variable amounts of CDDP received, or the interval between CDDP and follow-up audiograms. Audiograms collected in the context of a prospective study of a uniformly treated population would be best to precisely determine hearing AE risk.

Conclusions

The Brock and Chang ototoxicity grading tools may be superior to the CTCAE in HNCP receiving CDDP as measured by their ability to score baseline hearing loss distribution, the degree of inter-observer grade assignment agreement, and by their ability to detect grade change following treatment. We do not know whether any of these tools are valid with respect to capturing patient relevant severity or long-term sequelae. Consensus meetings regarding prospective studies of the hearing loss grading tools coupled to validated hearing related quality of life instruments have been accomplished in pediatric oncology and should be considered for adult oncology as well.¹⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Audiogram – based hearing impairment scales, 5,7-9

CTCAE version 3	0	1	2	3	4
Hearing (monitoring program)		Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear	Profound bilateral hearing loss (>90 dB)
CTCAE version 4	0	1	2	3	4
Hearing Impaired		Adults Enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6 and 8 kHz audiogram): Threshold shift of 15-25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 Threshold shift.	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear.	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated.	Adults: Profound bilateral hearing loss (Threshold >80 dB HL at 2 kHz and above); nonservicable hearing
Brock	0	1	2	3	4
Hearing Threshold (dB HL)	< 40 dB at all frequencies	40 dB at 8 kHz	40 dB at 4 kHz and above	40 dB at 2 kHz and above	40 dB at 1 kHz and above
Chang	0	1a 1b	2a 2b	3	4
Sensorineural Hearing Threshold (dB HL): bone conduction or air conduction with normal tympanogram	20 dB at 1, 2 and 4 kHz	40 dB at any freq 6 to 12 kHz	40 dB at 4 kHz and above	40 dB at 2 or 3 kHz and above	40 dB at 1 kHz and above

Table II

Numbers of patients and evaluable audiograms

	Patients receiving cisplatin and radiation	Patients with at least one baseline audiogram	Total number of audiograms (right and left ear counted separately)	Patients with a baseline audiogram and at least one follow-up audiogram	Range of audiograms per patient	Patients with paired pre and post radiation audiograms	Median age in years (range)
Count	236	110 88 males, 22 females	460	67	1-6	16	54 (20-80)

Grade distribution (%) at baseline (no prior CDDP) based on audiogram data for ototoxicity on an individual ear basis according to AE scale according to readings by A.D.C. Grades 1 and 1b combined and grades 2 and 2b combined for graphical representation of Chang scale data.

Table III

Scale	Grade 0	Grade 1a	Grade 1b	Grade 2a	Grade 2b	Grade 3	Grade 4
CTCAE version 3	39 (18)	61 (28)		12 (5)		104 (47)	4 (2)
Brock	127 (58)	31 (14)		48 (22)		6 (3)	8 (4)
Chang	90 (41)	15 (7)	30 (14)	5 (2)	46 (21)	26 (12)	8 (4)

Changes in grade of ototoxicity per ear following at least 40 mg/m2 of cisplatin according to AE scale. For purposes of calculation, the Chang “1a and 2a”, “1b” and “2b” grades were assigned numbers of 1 and 2, 1.5 and 2.5 respectively.

Table IV

Difference in grade, follow-up minus baseline grade.	-3	-2.5	-2	-1.5	-1	-0.5	0	0.5	1	1.5	2	2.5	3
Percent changes with specified difference in grade following cisplatin													
CTCAE v 3	1%		0%		3%		67%		9%		13%		6%
Brock	1%		1%		3%		55%		28%		10%		1%
Chang	1%	2%	1%		3%		52%	10%	11%	12%	3%	2%	2%

Table V
Inter-observer differences in ototoxicity grading according to AE scale used. (sums not 100% due to rounding)

A.D.C. versus R. R. L								
Absolute grade assignment difference	0	1	2	3	4	kappa [#]		
CTCAE v3	92%	7%	0%	0%			0.868	
Brock	98%	2%	0%	0%			0.965	
Absolute grade assignment difference	0-0.5	1-1.5	2-2.5	3	4			
Chang	93%	5%	1%	0%			0.877	
A.D.C. versus K.W.C								
Absolute grade assignment difference	0	1	2	3	4	kappa [#]		
CTCAE v3	75%	23%	2%				0.623	
Brock	90%	6%	3%	1%	0%		0.862	
Absolute grade assignment difference	0-0.5	1-1.5	2-2.5	3	4			
Chang	89%	9%	2%				0.815	

[#]The unweighted kappa statistic for inter rater reliability was calculated using Cohen's method¹⁹