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Development and Validation of a Cisplatin Dose-Ototoxicity Model

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Abstract

Background—Cisplatin is effective in the treatment of several cancers but is a known ototoxin resulting in shifts to hearing sensitivity in up to 50–60% of patients. Cisplatin-induced hearing shifts tend to occur first within an octave of a patient's high frequency hearing limit, termed the sensitive range for ototoxicity (SRO), and progress to lower frequencies. While it is currently not possible to know which patients will experience ototoxicity without testing their hearing directly, monitoring the SRO provides an early indication of damage. A tool to help forecast susceptibility to ototoxic-induced changes in the SRO in advance of each chemotherapy treatment visit may prove useful for ototoxicity monitoring efforts, patient counseling, and therapeutic planning.

Purpose—This project was designed to (1) establish pretreatment risk curves that quantify the probability that a new patient will suffer hearing loss within the SRO during treatment with cisplatin and (2) evaluate the accuracy of these predictions in an independent sample of Veterans receiving cisplatin for the treatment of cancer.

Study Sample—Two study samples were used. The Developmental sample contained 23 subjects while the Validation sample consisted of 12 subjects.

Data Collection and Analysis—Risk curve predictions for SRO threshold shifts following cisplatin exposure were developed using a Developmental sample comprised of data from a total of 155 treatment visits obtained in 45 ears of 23 Veterans. Pure-tone thresholds were obtained within each subject's SRO at each treatment visit and compared with baseline measures. The risk of incurring an SRO shift was statistically modeled as a function of factors related to chemotherapy treatment (cisplatin dose, radiation treatment, doublet medication) and patient status

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(age, pre-exposure hearing, cancer location and stage). The model was reduced so that only statistically significant variables were included. Receiver-operating characteristic (ROC) curve analyses were then used to determine the accuracy of the risk curve predictions in an independent Validation sample of observations from over 62 treatment visits obtained in 24 ears of 12 Veterans.

Results—Only cumulative cisplatin dose and pre-exposure hearing were found to be significantly related to the risk for hearing shift. The dose-ototoxicity risk curve predictions developed from the Developmental sample yielded area under the ROC curve accuracy estimates of 0.85 when applied to an independent Validation sample.

Conclusions—Cumulative cisplatin dose in combination with pre-exposure hearing provides an indication of whether hearing will shift in the SRO in advance of cisplatin administration. The validated dose-ototoxicity risk curves described herein can be used before and during treatment to anticipate hearing loss. While having such a tool would not replace serial hearing testing, it would be of great benefit to an ototoxicity monitoring program. It would promote relevant pretreatment counseling. Furthermore, for those found to be at risk of SRO shifts within the speech frequencies, the oncology treatment plan could incorporate anticipated dosing adjustments that could stave off the impact that ototoxicity might bring.

Keywords

Cisplatin; ototoxicity; ototoxicity monitoring; Veterans

Cisplatin, a potent ototoxic chemotherapeutic agent, is highly effective against several cancers including head and neck, lung, testicular, bladder, brain, ovarian, uterine, and cervical. While highly effective, dose-limiting side effects of cisplatin include cochlear, renal, neurologic, hematologic, and gastrointestinal toxicities. Regarding the cochlear effects, incidence of hearing shifts in up to 60% and new tinnitus in up to 39% have been reported among those patients treated with the drug, and these effects are most often irreversible (Kopelman et al, 1988; Hallmark et al, 1992; Ress et al, 1999; Fosså et al, 2003; Dille et al, 2010a, 2010b).

Animal studies using rodent species have shown that within the cochlea, cisplatin damages outer hair cells (OHCs) within the organ of Corti and marginal cells within the stria vascularis (Schweitzer 1993; Laurell et al, 2000; Riedemann et al, 2008; Arora et al, 2009; Hellberg et al, 2009). The destructive pattern of OHC loss progresses lateral to medial starting at the cochlear base (high frequency coded) and progresses upward to the cochlear apex (low frequency coded) with each cisplatin treatment (Schweitzer 1993).

Because ototoxic hearing loss initially occurs at the highest frequencies, Fausti and colleagues (1999) have shown that testing an octave range of frequencies near each patient's high frequency limit of hearing, termed the sensitive range for ototoxicity (SRO), provides the earliest detection of cisplatin ototoxicity. Its intended application within an ototoxicity monitoring protocol is as a screening tool to be followed by a full audiometric exam if there is evidence of a change in hearing sensitivity.

The SRO overlaps conventional audiometric frequencies (.25–8 kHz) for most Veteran cancer patients in our studies to date but can be exclusively within the ultrahigh frequencies

for some patients (Fausti et al, 1999; Reavis et al, 2008). Monitoring the SRO therefore provides an opportunity to detect hearing shift before damage significantly impacts the speech (.5–4 kHz) frequencies. Once this opportunity is missed, it changes the goal of an ototoxicity monitoring program from prevention to rehabilitation of a handicapping hearing loss.

To predict when cochlear damage from cisplatin results in hearing loss is challenging because of variability in individual susceptibility, in part, due to the influence of numerous risk factors. There are reports in the literature of the synergistic effects of cisplatin with prior or concurrent radiation, doublet medication, age, and preexisting hearing loss (Hallmark et al, 1992; Bokemeyer et al, 1998; Ress et al, 1999; Bhandare et al, 2007). The objectives of this article are to establish pretreatment risk curves that quantify the probability that a new patient will suffer hearing loss within the SRO during treatment with cisplatin and to evaluate the accuracy of these predictions in an independent sample. The goal is to provide a tool to help forecast susceptibility to ototoxic-induced hearing loss within the SRO at each chemotherapy treatment visit that may prove useful for ototoxicity monitoring efforts and therapeutic planning. Having such a tool would promote relevant pretreatment counseling. Furthermore, for those at risk of SRO shifts in speech frequencies, the oncology treatment plan could incorporate anticipated dosing adjustment that could stave off the impact that ototoxicity might bring.

Risks for cisplatin ototoxicity can be generally divided into treatment and patient factors. Treatment factors reported in the literature to influence ototoxicity include cisplatin dose, infusion rate, regimen or treatment intervals, administration of chemotherapeutic medications given along with cisplatin (doublets), and radiation prior to or during treatment (Vermorken et al, 1983; Kopelman et al, 1988; Mencher et al, 1995; Bokemeyer et al, 1998; Ress et al, 1999; de Jongh et al, 2003; Marshall et al, 2006; Bhandare et al, 2007; Rybak, 2007).

Patient characteristics reported to increase individual susceptibility to cisplatin ototoxicity include the age of the patient and the presence of hearing loss prior to treatment (Hallmark et al, 1992; Seligmann et al, 1996; Bertolini et al, 2004; Li et al, 2004; Biro et al, 2006; Marshall et al, 2006; Bhandare et al, 2007; Rybak 2007; Truong et al, 2007). When age was found to increase risk, it was among children and adults over 40 yr. In contrast, however, several investigations found that neither of these patient characteristics influenced cisplatin ototoxicity (Laurell and Jungnelius 1990; Seligmann et al, 1996; Bokemeyer et al, 1998; de Jongh et al, 2003; Arora et al, 2009).

The aim of this report is to develop a statistical model to determine the contribution of several treatment and patient factors to cisplatin-related ototoxicity in an effort to find out which have the greatest influence on hearing outcomes. This model forms the basis of the proposed clinical approach to estimate ototoxicity risk using information obtainable prior to cisplatin treatment. Because it is important that this model be generalizable to other patients, it is subsequently validated on an independent sample of subjects. Validation of a model is a critical step in accurately assessing its diagnostic performance (Pepe, 2003; the interested reader may also want to refer to Gorga et al [2005] to see this approach applied to

development of distortion-product otoacoustic emission tests to separate normal from impaired ears). This article describes the findings of both the Developmental and Validation analyses.

METHODS

Part I: Developmental Study

Sample Subjects—Potential subjects receiving cisplatin were identified daily from the appointment list of the chemotherapy unit at the Portland VA Medical Center (PVAMC) or from an oncology nurse referral. They were prescreened using the electronic medical records for exclusionary criteria and to obtain treatment information. Criteria for excluding potential subjects from this study were (1) subject was cognitively, physically, or psychologically unable to participate; (2) retest thresholds must be within 5 dB at the baseline (pretreatment) evaluation; (3) subject or medical record report of Ménière's disease or retrocochlear disorder; (4) subject or medical record report of active or recent history of middle ear disorder, abnormal otoscopy, or abnormal tympanometric findings; (5) behavioral hearing thresholds were poorer than 70 dB HL 4 kHz. The Developmental study subjects were recruited as part of a larger project whose purpose was to compare objective measures (distortion product otoacoustic emission and auditory brainstem response testing) for early detection of ototoxicity. Defining maximum hearing loss was necessary to achieve the goal for that objective measures project.

Subjects were tested in a sound-treated room. All efforts were made to evaluate both ears of each patient at each visit. Hearing shifts are typically bilateral but are not identical in terms of the extent or the timing of the change. Therefore, the hearing result from each ear of a subject at each testing session, designated the subject-ear visit, constituted the unit of analysis to be used throughout.

Equipment and Measurements—A Virtual Corporation M320 audiometer was used for collecting all behavioral threshold data including 1/6 octave frequencies. KOSS Pro/4× Plus earphones, modified to improve the signal-to-noise ratio as described in Fausti et al (1990), were used for testing the frequencies 2 to 20 kHz. The earphones were calibrated twice monthly as described in Fausti et al (1979). The calibration procedure, specified by the earphone manufacturer, utilized a platform and silicone rubber coupler to tightly house the Bruel & Kjaer (B&K) 4134 microphone. The Koss earphones were centered and locked onto an aluminum spacer resulting in an effective volume of 6 cm³.

The tympanic membranes of each ear used in the analysis were fully visualized. Immittance testing was accomplished using a Grason-Stadler Tymptstar middle ear analyzer that was calibrated annually. Tympanograms were considered normal if compliance ranged from 0.2 through 1.8 cm³ and peak pressure ranged within −150 and +100 daPa.

Behavioral pure-tone thresholds were obtained using the modified Hughson-Westlake technique (Carhart and Jerger, 1959). All testing and calibration was done by an audiologist. Initial (baseline) testing was done prior to cisplatin administration to establish pretreatment hearing thresholds and to define each individual's SRO, a technique developed and verified

previously (Fausti et al, 1999; Vaughan et al, 2002). Specifically, subjects were tested from 2–8 kHz in 1/2-octave steps and in 1/6-octave steps in the extended high frequency range (9–20 kHz). The lowest frequency at which a threshold of 100 dB SPL was obtained constituted the top frequency of the SRO. This threshold plus the next six frequencies with thresholds of <100 dB SPL constituting each subject's individualized behavioral SRO were determined and tested. Subsequent testing was done using only SRO frequencies at each treatment interval unless this screen resulted in a hearing shift. All testing was completed within 24 hr of each chemotherapy treatment, immediately following cessation of treatment, and at 1 mo post-cessation of treatment.

There were other sessions in which the SRO thresholds were obtained on a subject but no cisplatin was administered. If a hearing shift was confirmed, testing was expanded to include the entire frequency range of 2–20 kHz to search for other frequencies that might be affected by the cisplatin treatment. Upon confirmation of hearing shift, weekly hearing thresholds were obtained until the behavioral SRO thresholds stabilized. If a hearing shift was confirmed, the oncology Volume 23, Number 7, 2012 team was notified of the shift and provided information about whether speech frequencies were compromised.

For the purpose of this study, significant threshold shifts were defined using American Speech-Language-Hearing Association (ASHA) clinical guidelines (American Speech-Language-Hearing Association Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulotoxic Drug Therapy, 1994) and included (1) 20 dB change at any one test frequency, (2) 10 dB change at any two consecutive test frequencies, or (3) loss of response at three consecutive test frequencies. Testing was limited to 105 dB SPL at all frequencies. Using these criteria, a binary indicator for the presence or absence of hearing shift in an ear within the SRO frequencies was obtained. This served as the primary outcome measure used in this study.

Part II: Validation Study

Sample Subjects—Patients receiving cisplatin were potential subjects recruited from adult inpatient and outpatient units at the PVAMC. Potential subjects receiving cisplatin were identified daily from the appointment list of the chemotherapy unit or from an oncology nurse referral. Subjects were prescreened using the electronic medical records for exclusionary criteria and to obtain treatment information. The subjects enrolled in the Validation study were part of a larger project to develop and evaluate a portable hearing testing device capable of measuring extended high frequency hearing. Except for the following two study-related differences, the same exclusionary criteria were used to recruit both groups of subjects (those participating in the Developmental or Validation studies). First, there was no exclusion for extent of hearing threshold loss in the Validation study sample. Second, subjects from the Validation study were tested on the chemotherapy unit or at bedside in the case of inpatients. There was no overlap of subjects in these two samples.

Equipment and Measurements—The subjects from the Validation study sample were tested using a handheld ototoxicity identification device. This device, the OtoID, was evaluated in an independent study for its ability to optimize the sensitivity, efficiency, and

cost-effectiveness of ototoxicity early identification practices (Wilmington et al, 2010). The OtoID was programmed to deliver up to 105 dB SPL stimuli output levels from 0.50 to 20 kHz.

Prior to testing, the tympanic membranes of all subjects were fully visualized. A Grason-Stadler GSI 33 Middle-Ear Analyzer was used to obtain tympanometric measures and was calibrated annually. Tympanograms were considered normal if compliance ranged from .2 through 1.8 cm³ and peak pressure ranged within -150 through +100 daPa.

The OtoID was validated as a testing device during earlier pilot work (Wilmington et al, 2010; Jacobs et al, forthcoming) by comparison to the Virtual M320 audiometer done during earlier pilot work. The two devices were shown (1) to have nearly identical stimulus characteristics, (2) to obtain comparable threshold measures, and (3) to provide test-retest reliability within ± 5 dB using healthy adults with both normal hearing and hearing impairment. Sennheiser HDA 200 earphones were used with the OtoID to reduce the detrimental effects of environmental noise. Prior to each testing session, the OtoID was calibrated using a B&K 4153 artificial ear equipped with the flat plate adaptor. A B&K 2250 sound level meter and a B&K 4192 microphone were used in the calibration.

Testing procedures used with the Validation study subjects were identical to the Developmental study subjects procedures except that subjects in the Validation study were tested across the entire range of .5–20 kHz at all sessions, done to achieve the goals of this research project. All testing was conducted by an audiologist. Initial (baseline) testing was done prior to cisplatin administration to establish pretreatment hearing thresholds and to define each individual's SRO. The seven frequencies constituting each subject's individualized behavioral SRO were evaluated at each treatment interval. Subjects were tested within 24 hr of each cisplatin dose (monitor evaluations). Subjects were also evaluated immediately following cessation of treatment and at 1 mo post-cessation of treatment. The criterion for hearing shift (previously described ASHA-defined significant hearing shift) was the same for both studies. If an ASHA-significant hearing shift was noted, repeat testing was conducted across the entire range of frequencies in order to verify the shift.

Part III: Data Analysis

Logistic regression was used to develop a statistical model, called the dose-ototoxicity model, relating risk of ASHA-significant hearing shift to treatment factors and patient features using logistic regression. This model would then test the importance of a variety of patient and treatment characteristics on the risk for hearing shift.

Cancer and Treatment Measurements—Subject characteristics were extracted from medical records. These included the subject's age, cancer location, and stage at diagnosis (American Joint Committee on Cancer [AJCC], 2010). Lung cancer stages I–IIIa were grouped into early-stage cancer, while stages IIIB–IV were grouped into late-stage cancer. Head and neck, skin, and bladder cancers diagnosed at stage I–III were grouped into early stage, and stages IVa–IVc were grouped into late stage.

Treatment factors were also identified from medical records and included whether radiation therapy was administered and the total dose of radiation in gray (Gy), and whether concomitant chemotherapy (doublet) medication, most commonly gemcitabine or etoposide, were given. In addition, the dose, dose given, and cumulative dose of cisplatin administered at each treatment appointment were determined from medical chart review. Dose was the prescribed level of cisplatin (mg/m^2) given each subject at each treatment visit. Dose given was the amount of cisplatin received at each treatment (in mg). Cumulative dose was the sum of the doses given (in mg) of cisplatin received up to, but not including, the date that hearing measures were taken on any particular visit. The dose administered on the date of the hearing measurement was not included since the ototoxic effect of cisplatin is not presumed to be immediate (Schweitzer 1993; Mukherjea et al, 2006). Finally, the measure of the cycles of chemotherapy was defined as the ratio of the number of cisplatin treatments completed up to the hearing measurement date divided by the number of months since the baseline measurement. Admittedly, some treatment factors may seem redundant since, for example, cumulative dose captures both dose given and cycles of chemotherapy.

Developmental Study Analysis—There were repeated measurements in this dataset: between ears at each monitoring appointment and across successive monitoring appointments within each ear. The effect of these sources of correlation was modeled using generalized estimating equations (GEE) (Fitzmaurice et al, 2004, p. 291–321). With very large sample sizes, it is feasible to build the regression model including all patient factors and treatment effects simultaneously, along with interaction effects, to test the importance of each effect on the fitted risk of hearing shift. However, this approach leads to computational difficulties in the GEE algorithm when sample sizes are as small as are commonly employed in cisplatin ototoxicity research, which appears to average about 40 subjects (Schaefer et al, 1985; Kopelman et al, 1988; Hallmark et al, 1992; Bokemeyer et al, 1998; Ress et al, 1999). To avoid these difficulties, a dose-ototoxicity model was built sequentially to achieve an accurate and parsimonious prediction of hearing shift from our sample of subjects. This model was built in three stages:

1. A “Patient Factor” model was first built and included subject age, cancer location (referenced to lung cancer), and cancer stage (referenced to early stage cancer). Lung cancer was used as the reference location for the model, and early stage cancer was used as the reference category. Pretreatment average pure tone threshold in the SRO was included, along with the upper limit frequency of the SRO obtained at the baseline evaluation. Pretreatment SRO average pure-tone threshold was standardized to a mean of zero and standard deviation using the following equation:

$$(\text{BaseSROAvg} - 70.2) / 12.3$$

BaseSROAvg is the average threshold in the SRO frequencies obtained before chemotherapy on each subject included in the study. The constants are the mean (70.2) and standard deviation (12.3) of the sample baseline SRO.

The Patient Factor model was reduced by backward elimination using p-values for the generalized score statistic to find the most important susceptibility factors predicting ototoxic hearing shift.

2. A “Chemotherapy Factor” model was built including cisplatin dose (mg/m^2), dose given (mg), and cumulative dose received, along with the important susceptibility factors determined in the model building of stage 1, above. We also included all two-way interactions between the cisplatin dose effects and the important patient factors. Cumulative dose of cisplatin was log transformed and standardized to a mean of 0 and standard deviation of 1 to improve computation. The transformation was $\log(\text{CumulativeDose}) - 5.70)/0.62$. The constants correspond to the sample mean log (dose) of 5.70 and standard deviation of 0.62. The Chemotherapy Factor model was reduced by backward elimination as per stage 1.
3. An “Other Cancer Treatment Factor” model was built on top of the results in stages 1 and 2. This model included presence/absence of prescribed radiation and presence/absence of doublet medication effects as categorical predictors and the dose of radiation prescribed as a continuous covariate. This model was reduced by backward elimination.

The model selected at the conclusion of stage 3 constitutes the final dose-ototoxicity model that best predicts ototoxic-induced hearing shift in this sample. The final GEE logistic regression model selected in this analysis provided an estimate of the average risk of hearing shift for each ear at any subject visit, given the covariates included in the final model. Risk curves are computed from the fitted model.

Validation Study Analysis—The risk curves fitted in the Developmental study were used to predict hearing shift at each monitoring appointment on each ear in the Validation sample. Risk Volume 23, Number 7, 2012 scores were compared to the observed hearing shifts at each appointment using receiver operating characteristic (ROC) curve analysis (Pepe, 2003, p. 79). The ROC is a plot of the true positive rate for predicting a hearing shift against the false positive rate of incorrectly identified nonshifts. The area under the receiver operating characteristic curve (AUC) is a measure of the average true positive rate over the range of false positive rates (Pepe, 2003, p. 79). High values of AUC indicate an accurate risk model. A 95% confidence interval for the AUC was estimated using the nonparametric standard error estimator proposed by Obuchowski (1997) for correlated measurements.

RESULTS

Developmental Analysis

One hundred and twenty-three potential subjects were identified from daily checks of the electronic medical records at the PVAMC. Fifty-six of the 123 potential subjects were ineligible according to one or more of the exclusionary criteria. Eleven subjects were ineligible based upon an interview with the subject or pre-interview with the oncology nurse regarding suitability of the subject for recruitment into the study. An additional 20 potential subjects declined to participate. Of the remaining 36, 13 had either baseline hearing that did

not meet the inclusionary criterion or did not provide any further visits beyond the baseline visit. The final sample was composed of 23 subjects with one or more follow-up measurements after the baseline visit.

Characteristics of these 23 subjects included in this analysis are shown in Table 1. These subjects provided an average of 3.5 (range = 1–14) hearing assessments. All subjects were male with a mean age of 62.4 yr (range = 51–79 yr). The majority (n = 15; 65.2%) presented with head and neck cancers, followed by lung cancer (n = 6; 26.1%). One subject each presented with skin and bladder cancer. Almost half of the subjects (n = 10; 43%) were diagnosed with late-stage cancer.

Cisplatin dose ranged from 50 to 100 mg/m² with a median dose of 100 mg/m² per treatment. The average initial dose given was 168.7 mg, and average final cumulative dose was 378.8 mg. (Final cumulative dose is the dose as of the last test session on that subject.) Six subjects (26%) were prescribed either gemcitabine or etoposide as concomitant chemotherapy medications. Most subjects were prescribed radiation therapy in conjunction with cisplatin (n = 18; 78%) with an average radiation total dose (in grays) of 54.9 (range = 14 to 70) among those prescribed radiation.

Forty-five ears (of the 23 subjects) were followed over a total of 155 monitor visits, shown in Table 2. From this group, one subject was subsequently removed from the analysis because his baseline thresholds were too variable upon retest. Pretreatment average pure-tone threshold at baseline in the SRO region was 70.2 dB SPL (range = 43.6–88.6 dB SPL). The highest test frequency in the SRO, which could be taken as a severity measure of each subject's high frequency hearing loss, averaged 11.6 kHz (range = 5.7–16 kHz).

Twenty-two of the 45 ears (49%) experienced a hearing shift during treatment with cisplatin, consistent with other reports of cisplatin-related ototoxicity from the literature (Fausti et al, 1999; Ress et al, 1999; Reavis et al, 2008; Reavis et al, 2010).

Table 3 shows results of the GEE logistic regression analysis. The final model was built sequentially from left to right in the table. The initial Patient Factor model included pretreatment SRO average pure tone threshold, highest frequency in the SRO, presence/absence of a late-stage cancer at diagnosis, location of the cancer, and age. Only pretreatment SRO average remained in the model after backward elimination. No other variables showed important effects on the risk of hearing shift (score statistic = 2.63, df = 4, $p = 0.62$). The Chemotherapy model included all chemotherapy metrics, along with an interaction between each metric, and pretreatment SRO average retained from the Patient Factor model. Backward elimination indicated that only the standardized log cumulative dose and the interaction between this and pretreatment hearing were the important predictors of hearing shift. The remaining effects had no statistically significant impact on the fit of the model (score statistic = 4.62, df = 6, $p = 0.59$). Finally, the effects of radiation therapy and doublet medications were tested on top of the Chemotherapy model. No statistically significant effect of radiation (score statistic = 2.44, df = 2, $p = 0.29$) or doublet medication was detected (score statistic = 1.45, df = 1, $p = 0.23$) though patients were tested only at treatment intervals and were not followed for long-term effects radiation on the cochlea.

These results indicate that the risk of hearing shift in this sample is best modeled using the standardized log cumulative dose and standardized baseline SRO average pure-tone threshold, and their interaction. The coefficients for these predictors are listed in the Final Model column of Table 3. The fitted intercept of the dose-ototoxicity model was -0.24 ; standard error of the intercept was 0.41 . As expected, parameter estimates indicate that increasing cumulative dose of cisplatin induces greater risks of hearing loss. Higher pretreatment pure tone thresholds in the SRO are associated with lower risks of hearing shift. The negative sign on the interaction term indicates a “dampening” effect of poorer hearing on the ototoxic effects of cisplatin.

Risk curves for cisplatin-induced hearing loss in the SRO frequencies are computed according to the following equations (Table 3):

$$StB = \frac{(\text{Baseline SRO PTA} - 70.2)}{12.3}$$

$$StDose = \frac{(\ln(\text{cumulative dose}) - 5.698)}{0.6202}$$

$$z = -0.24 + 0.84 StDose - 1.28 StB - 1.04 StDose \times StB,$$

so that the risk of a hearing shift, expressed as a probability, is $\exp(z)/(1 + \exp(z))$.

In order to illustrate the interaction between dose and hearing on cisplatin ototoxicity, we used these equations to compute risk curves for three different levels of pretreatment SRO average hearing thresholds (50 and 80 dB SPL and the sample mean of 70 dB SPL) in Figure 1. Figure 1 shows that better pretreatment hearing thresholds result in a much higher average risk of hearing shift over the course of treatment. Ears with pre-exposure average SRO thresholds of about 50 dB SPL are nearly certain to experience hearing shift by 400–500 mg/m² cumulative dose of cisplatin. Ears with poor average SRO thresholds (80 dB SPL) have flat, though nonnegligible, risks of hearing change as cumulative dose increases. Risk curves for the ears represented by the sample mean hearing (70 dB SPL) lie in between those constructed for better and worse hearing. The cumulative dose that is expected to cause hearing change in half of the subjects treated with cisplatin can be read directly from the curves in Figure 1. This is analogous to the median effective dose, or ED(50), used in dose-response studies (Collett, 1991, p. 96–97). For subjects with average hearing in our sample, the ED (50) is approximately 350 mg of cisplatin, which is consistent with previous studies. Subjects with particularly good hearing have a much lower ED(50) of about 190 mg, while subjects with particularly bad hearing actually never reach the 50% affected mark.

Validation Analysis

Twelve subjects in the Validation sample provided 62 monitoring appointments on 24 ears (Tables 1 and 2). Subjects in the Validation sample had a mean age of 65.1 yr (range = 48–80 yr). The majority ($n = 8$; 66.7%) presented with head and neck cancers, followed by lung cancer ($n = 3$; 25%) and bladder cancer ($n = 1$; 8.3%). This group had a considerably lower mean starting cisplatin dose given (mean = 85 mg vs. 168.7 mg) and had somewhat lower rates of radiation administered (58% vs. 78%). Table 2 shows that hearing loss occurred in 9 (38%) ears monitored in the Validation analysis.

Figure 2 shows histograms of the predicted risks in the Validation sample based on the regression results (shown in Table 3) and the risk curves (shown in Fig. 1) obtained from the Developmental sample. The factors employed to determine risk were the factors found to be significant from the analysis using the Developmental sample (i.e., cumulative cisplatin dose and baseline hearing thresholds). Hearing testing information obtained at each treatment interval was used only as a means of validating the dose-ototoxicity model when applied to this new, independent sample of subjects.

The top panel shows the hearing results obtained from each ear during a monitoring appointment in which there were no ASHA-significant shifts in the SRO frequencies while the bottom panel shows results in which a significant hearing shift occurred. Since subjects were tested multiple times across multiple monitoring appointments, the result from an individual ear might appear in the top panel at one visit and in the bottom panel at another. Among the ears without significant hearing change ($n = 38$) during treatment, the risk scores were clustered to the left side of the distribution indicating the model was highly accurate in predicting when no behavioral shift had occurred. Recall that 62% of ears in this sample did not have hearing change during treatment. Among the 38% of ears that experienced hearing shift ($n = 9$), the risk scores were more variable though they tended to cluster to the right (higher risk) side of the distribution, as would be expected. Though the Validation study sample was smaller, Figure 2 indicates a promising model since there is relatively good separation between histograms. This model is efficient since it determines risk solely on pretreatment hearing information and cisplatin cumulative dose.

The ROC curve provides a visual representation of a diagnostic binary classifier. The promising separation of risk scores provided by the ototoxicity model (Fig. 2) should result in a ROC curve that has a high degree of specificity (low false positive rate) and sensitivity (high true positive rate). The ROC curve of Figure 3 shows the accuracy of the diagnostic model (trained on the Developmental sample) when used to predict hearing shift on the Validation sample. The estimated AUC was 0.85 (95% confidence interval 0.62 to 1.0) indicating an accurate and robust model. More interesting is the high true positive rate (70%) with a concomitantly negligible false positive rate of 0% obtained with this model, improving to 80% at the cost of a low false positive rate of approximately 20%. Further, this elevated false positive rate could be successfully reduced with hearing threshold testing when risk scores for a patient become elevated with successive cisplatin dose.

DISCUSSION

Cisplatin has been used to treat cancer for over three decades. During that time, treatment regimens have varied to such an extent that it is not unusual to find conflicting reports regarding the significant variables that influence risk for ototoxicity (Helson et al, 1978; Vermorken et al, 1983; Hallmark et al, 1992; Bokemeyer et al, 1998). Cumulative dose generally emerges as the most important factor (Vermorken et al, 1983). The present study was designed with the purpose of determining the primary factors that influence cisplatin ototoxicity through the development of a risk model. Among the variables tested by this risk model, two primary factors emerge to predict hearing shift: cumulative cisplatin dose and pre-exposure hearing status. Specifically, hearing status prior to the start of chemotherapy,

above all other patient factors, is the important determinant and, in this case, moderates the dose effect. Those individuals with good pretreatment hearing are at greater risk for ototoxicity within the SRO than those with poor hearing. However, the risk score together with information about proximity of the SRO to the speech frequencies underlies the clinical interpretation. Those individuals with good pretreatment hearing may have an SRO that does not include speech frequencies and so may not be imminently handicapped.

In their guidelines for ototoxicity monitoring programs, the American Academy of Audiology (Academy) has early detection as one of two explicit goals of monitoring (the second goal is audiological intervention when a handicapping hearing loss has occurred) (American Speech-Language-Hearing Association Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulotoxic Drug Therapy, 1994; Academy, 2009). Protocols consistent with these guidelines include testing at extended high frequencies (>8 kHz) prior to treatment. A concern raised by some is that ototoxicity monitoring is relevant only to the extent that it identifies when speech communication is disrupted. This idea may have evolved from earlier reports that there exists an upper limit to hearing loss, a plateau phenomenon, that once reached will result in no further hearing shifts (Kopelman et al, 1988). This plateau phenomenon was contradicted by Helson et al (1978), who showed a clear trend in which ototoxicity “spreads” to lower frequencies, including the speech frequencies, with each additional treatment.

Early detection using the SRO technique in patients with good hearing is a “canary in the coal mine.” Once a hearing loss is confirmed, the SRO frequency range is expanded to include lower frequencies in order to facilitate identification of progression of the loss. The dose-ototoxicity risk curves described herein can be used throughout treatment to track risk as the SRO shifts, portending future permanent hearing shifts in frequencies that impact communication.

We have found that Veterans often have hearing loss prior to chemotherapy and as a result have SRO frequencies that extend into the conventional testing range. As an example, in this report *all* subjects had SRO frequencies that extended into the conventional testing range (8 kHz). Further, 74% had SRO frequencies extending down to 6 kHz, and 17% had SRO frequencies extending to 4 kHz. In this population, early changes due to ototoxicity can immediately impact hearing for speech that can adversely affect communication with family members and providers.

We have developed and validated this risk calculation for ototoxicity, which is in agreement with the preponderance of recent reports suggesting that dose and pre-exposure hearing status are related to cisplatin ototoxicity (Bokemeyer et al, 1998; Li et al, 2004; Reavis et al, 2008; Arora et al, 2009; Reavis et al, 2010; Dille et al, 2010a). The contribution of this validated risk model is that it allows ototoxicity risk to be determined for individual patients. Note also that risk for each individual is determined prior to any treatment or testing and that the model is as effective at predicting no hearing change as it is at predicting change.

In previous reports, age was commonly found to increase risk for ototoxicity (Helson et al, 1978; Hallmark et al, 1992; Bertolini et al, 2004). We did not find this to be an important

risk variable. One explanation for this inconsistency could be that age and hearing status are correlated. Children tend to have better hearing than adults while young adults typically have better hearing than older adults. In those studies that did find age to be a significant risk, the SRO technique was not employed. Rather, testing was done in the conventional range of hearing. Monitoring for change at each patient's high frequency hearing limit is known to provide the earliest detection of cisplatin-related hearing loss. Testing in the conventional range would have the appearance of early detection in patients with poorer hearing whose SRO is in the conventional range. But for patients with better hearing whose SRO is in the extended frequency range, monitoring in the conventional range would be the least sensitive region for early detection. In fact, it is entirely possible that several more cycles of cisplatin could be given to these better hearing patients before the hearing change that is occurring is detected in the conventional range. In an analysis using conventional range monitoring, age could masquerade as the important variable. In the end, using the SRO monitoring technique, we found hearing status prior to exposure to cisplatin to be the more relevant factor.

The dose-ototoxicity model developed and validated from two different samples of subjects is robust and stable. Recall that the testing environments for these two samples were quite different. The Developmental group was tested in a sound suite using a clinical audiometer while the Validation sample was tested in a quiet area of the chemotherapy unit using a portable testing device. As long as care is taken to obtain reliable results, typically confirmed by retest, this model provides an accurate equation by inputting pre-exposure hearing threshold and cumulative dose that will output a risk for hearing shift at each treatment session.

Predicting which patients will experience ototoxic hearing loss prior to treatment has been a clinical challenge. This tool can be used to estimate with better precision who will experience hearing shift and when hearing shift might occur. Pretreatment counseling of those patients and their families as they prepare for and undergo cancer treatment is invaluable. Further, for those found to be at risk of SRO changes within the speech frequencies, the oncology treatment plan could incorporate anticipated dosing adjustment that could stave off the impact that ototoxicity might bring. This prediction model may also improve efficiencies in monitoring programs by providing cost-effective strategies for hearing monitoring. In a time of rising healthcare costs, directing ototoxicity monitoring resources toward those patients most likely to experience hearing shifts near the speech frequencies is cost-effective, but only insofar as the risk of missing a patient who might experience a hearing shift is minimized.

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Abbreviations

Academy	American Academy of Audiology
ASHA	American Speech-Language-Hearing Association
AUC	area under the receiver operating characteristic curve
B&K	Brüel & Kjær
ED	effective dose
GEE	generalized estimating equations
PVAMC	Portland VA Medical Center
ROC	receiver-operating characteristic
SRO	sensitive range for ototoxicity

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Figure 1.

Risk curves were developed using the dose-ototoxicity model. Risk curves are shown for Developmental sample cisplatin-induced hearing shifts in the SRO frequencies. Separate curves are shown for ears with an SRO average hearing of 80 dB SPL (flat line) and 50 dB SPL (solid line) and 70 dB SPL (dotted line), which was the sample mean. The shaded area represents the 95% CI of risk for hearing shift.

Figure 2.

Histograms of the predicted risk for patient visits (PVs) associated with an ASHA-significant hearing shift in the SRO frequencies for the Validation sample. The top panel shows risks for monitoring appointments in which the ears did not actually show a shift. The bottom panel shows these risks for ears that had a significant shift. Predictions are based on the dose-ototoxicity model from a separate Developmental sample.

Figure 3.
ROC curve for dose-ototoxicity model predictions on the Validation sample.

Table 1

Characteristics of Subjects Administered Cisplatin from the Developmental and Validation Sample of Subjects

		Sample		
		Developmental	Validation	Total
Total subjects	N	23	12	35
Follow-up visits	Mean	3.5	2.6	3.2
	Min	1	1	1
	Max	14	7	14
Age	Mean	62.4	65.1	63.3
	Min	51.0	48.0	48.0
	Max	79.0	80.0	80.0
Cancer location				
Bladder	N	1	1	2
	%	4.3	8.3	5.7
Head/neck	N	15	8	23
	%	65.2	66.7	65.7
Lung	N	6	3	9
	%	26.1	25.0	25.7
Skin	N	1	-	1
	%	4.3	-	2.9
Average dose given	Mean	168.7	85.0	140.0
	Min	90.0	70.0	70.0
	Max	240.0	100.0	240.0
Highest cumulative dose of cisplatin	Mean	378.7	375.8	377.7
	Min	90.0	160.0	90.0
	Max	1320	660.0	1320
Subjects recommended radiation	N	18	7	25
	%	78%	58%	71%

Table 2

Characteristics of Ears in the Developmental and Validation Samples

		Sample		
		Developmental	Validation	Total
Total ears	N	45	24	69
Total # patient × ear visits	N	155	62	217
Pretreatment SRO avg (in dB SPL)	Mean	70.2	74.4	71.6
	Min	43.6	52.9	43.6
	Max	88.6	92.9	92.9
Ears with one or more hearing change events	N	22	9	31
	%	49%	38%	45%

Table 3

Results of the GEE Logistic Regression Analysis of Ears in Developmental Sample

Effect	Patient Factors			Chemotherapy Factors			Other Cancer Treatment Factors			Final Model (Dose-Ototoxicity Model)		
	Est.	SE	p	Est.	SE	p	Est.	SE	p	Est.	SE	p
Pretreatment SRO avg. **	-0.57	0.50	0.19	-1.62	1.28	0.25	-1.18	0.33	<.01	-1.28	0.36	<.01
SRO max	0.10	0.16	0.61									
Late-stage cancer	0.60	0.94	0.56									
Cancer location *												
Other	4.71	1.59										
Head/neck	0.65	0.71	0.20									
Lung			Reference									
Age	-0.12	0.08	0.20									
Log cumulative dose **				0.53	0.31	0.34	0.85	0.27	0.03	0.84	0.27	0.02
SRO avg. × Log cum dose				-1.06	0.30	0.08	-1.02	0.25	0.04	-1.04	0.25	0.02
Dose				-0.00	0.04	0.90						
SRO avg. × Dose				0.02	0.03	0.61						
Dose given				0.01	0.02	0.68						
SRO avg. × Dose given				-0.01	0.01	0.66						
Chemotherapy rate				0.19	0.16	0.36						
SRO avg. × Chemotherapy rate				-0.01	0.17	0.97						
Recommended radiation dose							0.03	0.03	0.24			
Any radiation prescribed							0.63	1.44	0.72			
Prescription of doublet medications							1.51	1.45	0.23			

Note: Columns are divided into estimate of the mean (Est.), standard error of the estimate (SE), and significance value (p).

* p-value for the cancer location effect based on 2 df generalized score statistic.

** Log cumulative dose and baseline SRO average pure tone thresholds were standardized, as described in the text.