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Late onset and asymmetric sensorineural hearing loss in pediatric cancer survivors following treatment with cisplatin containing chemotherapy regimes

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LATE ONSET AND ASYMMETRIC SENSORINEURAL HEARING LOSS IN PEDIATRIC CANCER SURVIVORS FOLLOWING TREATMENT WITH CISPLATIN CONTAINING CHEMOTHERAPY REGIMENS

by

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Abstract: This study aims to determine the prevalence of asymmetric hearing loss (AHL) and late onset hearing loss (LOHL) in pediatric cancer patients treated with cisplatin and the risk factors for both AHL and LOHL. This study will also examine the relationship between AHL and LOHL.

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Disclosures

Research reported in this publication received Institutional Review Board approval from the Washington University Medical Center Human Research Protection Office, ID # 201504118, approved 6/1/2015.

Dedication

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LIST OF ABBREVIATIONS

CDDP = cisplatin

ABR = auditory brainstem response testing

VRA = visual reinforcement audiometry

CPA = conditioned play audiometry

SNHL = sensorineural hearing loss

ASHA = American Speech-Language-Hearing Association

CTCAE = National Cancer Institute Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events

SIOP = Society of Pediatric Oncology (SIOP) Boston Ototoxicity Grading Scale

QOL = quality of life

UHL = unilateral hearing loss

AHL = asymmetric hearing loss

LOHL = late onset hearing loss

TDH39 = Telephonics Dynamic Headphone 39

ER-3A = Etymotic Research 3A Insert Earphones

With the advances in treatment of pediatric cancer, the survival rate for children and adolescents has increased to over 80% (Bertolini et al., 2004; Siegal, Naishadhamc, & Jemal 2013; Spix, Pastore, Gankila, Stiller, & Steliarova-Foucher, 2006). Multimodality therapy has contributed to the increased survival rates in this patient population (Siegal, et al., 2013). Unfortunately, there are a number of adverse long-term effects due to cancer treatment that need to be identified and addressed.

Risk Factors and Incidence of Platinum-induced Ototoxicity

Ototoxicity or hearing loss is one of the major side effects of chemotherapy treatment with platinum compounds, such as cisplatin (CDDP) or high dose carboplatin (Coradini, Cigana, Selistre, Rosito, & Brunetto, 2007; Dean, et al., 2008; Knight, Kraemer, & Neuwelt, 2005; Punnet et al., 2004). The presence and degree of ototoxicity varies in this population depending on a variety of factors. In general, the most severe ototoxicity has been reported in patients receiving CDDP, while patients receiving only carboplatin alone have less risk of hearing loss (Dean et al., 2008). Risk factors for developing hearing loss include: diagnosis at a younger age (especially younger than five years old), diagnoses such as central nervous system tumors and neuroblastoma, treatment with prior or concomitant cranial radiation, treatment with cumulative doses of cisplatin greater than 400 mg/m2, renal dysfunction, and pre-existing hearing loss. Other contributors to ototoxicity are the concomitant use of aminoglycoside antibiotics and loop diuretics (Grewal et al., 2010; Knight, Kraemer, Winter, and Neuwelt, 2007).

The reported incidence of ototoxicity in pediatric oncology patients varies, ranging from as low as 4% to as high as 85% (Helt-Cameron & Allen, 2009; Dean, et al., 2008; Einarsson et al., 2010; Kolinsky, Hayashi, Karzon, Mao, & Hayashi, 2010; Kushner, Budnick, Kramer,

Modak, & Cheung, 2006; Massimino et al., 2010; Orgel et al., 2011). This large range reflects a combination of factors, including: 1.) The age and developmental level of the patients studied necessitating the use of different testing modalities across the population, [auditory brainstem response testing (ABR), visual reinforcement audiometry (VRA), conditioned play audiometry (CPA), and/or conventional behavioral testing], influencing the observed rate of hearing loss; 2.) Different studies require different amounts and type of data for a patient to be evaluable; 3.) Varying definitions of hearing loss, including whether the better hearing ear, the worse ear, or averaged ear data is used to classify a patient; 4.) Varying age groups, influencing the reliability of testing; 5.) The unique challenges of the pediatric oncology patient, who are often not in ideal test states due to pain, sickness, fear, and/or fatigue, with the youngest patients constituting the most complicated ones. Both the age and the state of the patient have an affect not only on the reliability of the test, but also the number of frequency thresholds obtained in each test session.

Additionally, the inclusion of various types of hearing loss as a result of treatment can lead to a wide range of results. Some studies include conductive and mixed hearing loss in the reported incidence of ototoxicity, while other studies solely link sensorineural hearing loss (SNHL) to the treatment (Brock et al., 2012; Jereczek-Fossa, Jarowski, Milani, & Orecchia, 2003; Kolinsky et al., 2010). Another factor contributing to the variability in incidence reports is that oto-protectant studies are often intermingled in the literature. Studies clearly identifying patients with SNHL free of other confounding factors are rare. Historically, a variety of grading scales have been used to report the incidence of ototoxicity, including the Brock grading scale, American Speech-Language-Hearing Association (AHSA) criteria, and the National Cancer Institute Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse

Events (CTCAE) (Bass et al., 2014; Grewal et al., 2010). All of these factors make comparing data across the literature difficult (Bass et al., 2014; Kolinsky et al., 2010).

More recent attempts to standardize grading systems include the Society of Pediatric Oncology Boston Ototoxicity Grading Scale (SIOP) and the Chang grading systems. These were developed to define pediatric sensorineural ototoxic hearing loss from platinum chemotherapies, with the goal to report the severity of hearing loss at the end of therapy and improve the correlation of the toxicity grade with functional outcomes. Both scales are based on absolute hearing thresholds and focus on high frequency hearing loss, which is the characteristic pattern observed in patients receiving platinum based chemotherapy. Authorities in the areas of oto-protection have expressed the need for such grading systems to help standardize data across institutions and to improve the analysis of specific groups. Such systems will aid in assessing the impact of oto-protectants (Brock et al., 2012). A recent comparison of the SIOP and the Chang scale revealed that the SIOP scale appears to be more sensitive to identifying mild hearing losses and clinically significant hearing loss. Furthermore, the SIOP scale has been reported to be easier to use and comprehend (Bass et al., 2014).

Sensorineural Hearing Loss in Patients Treated with Platinum Compounds

Hill and colleagues, (1972) were the first to report ototoxicity due to CDDP in adults. Hearing loss due to CDDP occurs due to damage to structures within the organ of Corti; CDDP specifically and simultaneously damages the outer hair cells and their associated stereocilia, spiral ganglion cells, and the stria vascularis (Schmidt, Knief, Lagosch, Deuster, & Zehnhoff-Dinnesen, 2008; Schweitzer et al., 1984; Van Ruijven, de Groot, Klis, & Smoorenburg, 2005; Wright and Schaefer, 1982). Deterioration of outer hair cells within the organ of Corti begins in

the basocochlear region, but damage can spread to the inner hair cells and lower frequency regions of the cochlea with continued exposure to platinum agents (Li, Womar, & Silber, 2004). Thus, platinum-induced hearing loss typically presents as a permanent, bilateral, usually symmetric, SNHL, with hearing loss beginning in the high frequencies (Blakey & Meyers 1993; Kushner et al., 2006; Schell et al., 1989). The hearing loss may also be accompanied by peripheral neurotoxicity and permanent or temporary tinnitus (Alberts & Noel, 1995; Rybak, 2005; Schmidt et al., 2008; Stavroulaki, Apostolopoulos, & Segas, Tsakanikos, & Adamopoulos 2001).

Hearing Loss in Children

Acquired hearing loss in children and adolescents has a significant impact on communication, especially for young children who are developing or have not yet developed speech and language skills. It is important to note that acquired and/or progressive SNHL can be a challenge to identify in the pediatric population due to the high prevalence of conductive hearing loss.

Yoshinago-Itano, Sedey, Coulter, & Mel, (1998) demonstrated that hearing loss in children often leads to delays in speech and language. Other reports have noted negative effects of hearing loss in children such as difficulties in auditory processing, communication, school performance, and social interaction, as well as reduced quality of life (QOL) measures (Barr et al., 2000; Bess, Dodd-Murphy, & Parker 1998; Knight et al., 2005; Moeller, Tomblin, Yoshinago-Itano, Connor, & Jerger, 2007). The presentation of high frequency hearing loss associated with platinum-induced ototoxicity causes some consonants, mainly fricatives, to be inaudible. Especially for young children, missing out on high frequency speech information

makes speech recognition and understanding particularly difficult (Knight et al., 2005; Li et al., 2004; Stelmachowitz, Pittman, Hoover, Lewis, & Moeller, 2004).

Gurney et al. (2007) observed that neuroblastoma patients with acquired hearing loss versus normal hearing were at least twice as likely to experience difficulties with reading skills, math skills, and/or attention issues and had a greater risk of having a general learning disability in addition to special educational needs. Even mild high frequency hearing loss above 2,000 Hz has been correlated with increased fatigue in the classroom environment in addition to increased academic and social-emotional problems (Bess et al., 1998). From a general pediatric perspective, Lieu (2004) reported that even a mild unilateral hearing loss (UHL) can have detrimental effects on a child's language development as that child loses the typical advantages of hearing with both ears - localization abilities, loudness perception, enhanced speech perception, and improved ability to hear in noisy and quiet environments (Cadieux, Firszt, & Reeder, 2013; Ching, van Wanrooy, & Dillon, 2007). Children with minimal and UHL are also at risk for speech and language, academic, and behavioral problems (Hindley, 1997; Stein, 1983).

It is important to note the fine distinction between UHL and asymmetric hearing loss (AHL), both of which are seen in the pediatric population. UHL is used to describe a patient whose better-hearing ear is normal, while AHL is used when the better-hearing ear is impaired (Vila & Lieu, 2015). UHL affects approximately three to six percent of school-age children in the United States (Ross, Visser, Holstrum, Qin, & Kenneson, 2010) and this percentage increases with age (Uwiera et al., 2009). There is currently no documented prevalence of AHL because estimates for this type of loss are consolidated under the prevalence of bilateral hearing losses.

Recent estimates of any type of hearing loss (bilateral, UHL, AHL) in the adolescent population in the United States are approximately 20% (Shargorodsky, Curhan, Curhan, & Eavey, 2010).

Current Study

The literature substantiates that there is a critical need for early identification and intervention regarding any type (i.e., conductive or SNHL) and degree of hearing loss in children (Downs & Yoshinago-Itano 1999). Monitoring air and bone conduction thresholds both during and after treatment is essential in the pediatric oncology population to provide the necessary services to ensure that children advance and develop normally (Bass, White, & Jones, 2013). Kolinsky et al. findings revealed that pediatric cancer survivors are at risk for hearing deterioration years after the cessation of chemotherapeutic therapy (2010). Continued audiologic follow-up at regular intervals both during and long after the completion of therapy is crucial in order to identify and manage both chronic and late onset hearing loss (LOHL).

It is well recognized that ototoxic hearing loss can present during the course of CDDP treatment (Li et al., 2004; Montaguti et al., 2002; Skinner, Pearson, Amineddine, Mathias, & Craft, 1990). Less documented, but also reported, are auditory complications due to treatment with platinum compounds and radiotherapy that can progress beyond the cessation of treatment (Bertolini et al., 2004; Kolinsky, et al., 2010). Whelan et al. (2011) reported that hearing loss due to cancer treatment could manifest or progress greater than five years following diagnosis. Similar results regarding worsening of auditory thresholds years after completion of treatment with CDDP were reported by Bertolini et al. (2004) and Einarsson et al. (2010) finding progressive hearing loss from 136 months to up to 22.3 years respectively. For these reasons,

and because of the impact of hearing loss on a child's global development, long-term follow-up beyond the completion of treatment is necessary.

Another less documented, but significant complication in this patient population is AHL. Asymmetric and unilateral hearing losses due to treatment with CDDP and/or radiation have been reported in the literature (Aguilar-Markulis, Beckley, Priore, & Mettlin, 1981; Hayashi, Wheeler, King, Mansur, & Hayashi, 2014; Knight et al., 2007; Schmidt et al., 2008; Waters, Ahmad, Katsarkas, Stanimir, & McKay, 1991). Schmidt et al. (2008) specifically found left ears to be significantly more affected in terms of high frequency hearing loss in patients receiving CDDP. AHL, especially in patients with medulloblastoma or neuroblastoma, may also be linked to the development of LOHL in this population (Hayashi et al., 2014). Given its impact on language and speech development, better characterization of AHL in pediatric patients is needed.

The aim of this project is to determine the prevalence of AHL and LOHL in pediatric cancer survivors treated with CDDP. Despite the extensive effort to investigate this topic, the variability in testing, the inconsistent or vague criteria for study subject entry, and the use of incomplete or ambiguous testing data leaves this field with many unanswered questions. This effort will utilize stringent inclusion criteria to ensure the population analyzed has unambiguous clinical data so that clear interpretations of the test results and definitive conclusions can be rendered. Preliminary data has suggested that patients with AHL are at increased risk for LOHL (Hayashi, et al., 2014). We wish to expand our understanding of AHL and LOHL by examining an expanded cohort of childhood cancer survivors treated with CDDP.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Washington University School of Medicine Human Research Protection Office. It was a retrospective chart review of medical record data existing at the initiation of our study. Audiology charts of pediatric oncology patients at St. Louis Children's Hospital treated from August 1, 1990 through March 31, 2015 were reviewed. There were 993 patients in the entire cohort. There were two arms to this study: 1.) Late onset hearing loss (LOHL) arm and 2.) Asymmetric hearing loss (AHL) arm. Eligibility criteria for both arms required prior CDDP treatment. Patients whose routine medical care did not include CDDP were excluded up front. These include the following diagnoses: retinoblastoma, sickle cell anemia, histiocytosis, acute lymphoblastic leukemia, acute myeloid leukemia, and juvenile myelomonocytic leukemia. The remaining patient charts were reviewed for eligibility, identifying those patients who had a history of CDDP exposure, resulting in 248 patients (Figure 1), none of which received oto-protectants any time during the course of their treatment. The medical record of these patients were then reviewed to extract the following variables of interest: gender, birthdate, date of diagnosis, race, ethnicity, diagnosis, cumulative CDDP dose, presence of carboplatin and the corresponding cumulative dose, radiation exposure, radiation treatment to head, radiation treatment to the posterior fossa, proton beam radiation involving the head, the location of any radiation boost, date when all therapy ended, date of last CDDP administration, living status, date of last audiogram, and audiometric thresholds.

Audiologic Methods

Audiometric evaluations were performed by licensed audiologists from St. Louis Children's Hospital. All evaluations were completed according to the department of audiology's clinical monitoring protocol for ototoxic induced hearing loss (Appendix A). Pure-tone

thresholds were measured in a sound treated booth using a Grason Stradler two-channel clinical audiometer equipped with TDH39 headphones and ER-3A insert earphones. Soundfield testing was used when headphones and insert earphones would not be tolerated. The age, physical status and cooperation of the patient determined whether VRA, CPA, or conventional audiometry was used. The time interval between audiologic evaluations as well as the number of evaluations varied between patients. Air conduction thresholds recorded included 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz.

Every effort to generate and adhere to stringent criteria was made to eliminate exams that were ambiguous or could not be clearly classified. Audiograms with predominantly conductive thresholds were not evaluable. Eligible baseline audiograms had to have thresholds $\leq$ 20 dB with at least two frequencies between 1 kHz - 4 kHz. A "no response" threshold was logged as the highest threshold tested and negative thresholds were recorded as such. Evaluable audiograms minimally had to have good to fair reliability.

The air-bone gap was evaluated to differentiate between a conductive hearing loss and a CDDP induced high frequency SNHL. A threshold was not accepted if the air-bone gap difference was $\geq$ 15 dBnHL. Air-bone gaps of interoctaves were assumed to be $\leq$ 10 dB and were evaluable if bone conduction was not tested as long as tympanometry indicated a normal middle ear status (a static admittance of $\geq$ 0.3 mmho), a large canal volume consistent with patent tubes, or a normal otologic exam per an otolaryngologist. A frequency specific threshold was not evaluable if there was a $\geq$ 15 dB decrease from the previous audiogram, no bone line, and a static admittance $\leq$ 0.2 mmho on tympanometry unless the audiograms on either side confirmed the sensorineural loss or there was a normal otologic exam by an examining otolaryngologist. Any 6 kHz - 8 kHz hearing loss was assumed to be sensorineural if

tympanometry was $\geq$ 0.3 mmho. An audiogram with no change that had an absent tympanogram or a static admittance $\leq$ 0.2 mmho was considered evaluable.

Excluded patients were codified as follows: (1) incomplete audiologic data, (2) conductive hearing loss, (3), incomplete medical data, (4) patient currently receiving treatment, and (5) abnormal hearing at baseline.

Criterion for assigning a patient for LOHL and/or AHL assessment

We defined arbitrarily LOHL as a change in hearing greater than six months after completion of CDDP, to confidently identify changes in hearing that occurred long after CDDP had cleared the body. Thus, to assess a patient for LOHL, they were required to meet the following criteria: Every patient had a normal baseline audiogram, and either two audiograms at least six months after the last CDDP administration or one earlier and one after the six month cut off with no change between the two, to fully classify the hearing state of the patient six months after CDDP therapy was complete.

To assess a patient for AHL, the criterion was simpler as we included all patients who developed AHL regardless as to when it occurred. Thus, only two audiograms were needed as we included patients where AHL could occur either during or after all therapy was completed. Thus, the eligibility criteria for AHL required that patients have at least a normal baseline with a subsequent ear specific audiogram conducted any time after the last CDDP administration or no baseline with a normal audiogram(s) conducted any time after the last CDDP administration. Soundfield audiograms were evaluable for the baseline audiogram as long as there was a subsequent ear specific audiogram.

Data from patient charts meeting the criteria above were evaluated through March 31, 2015 as long as CDDP treatment was completed by that date. A maximum of three audiograms was logged in the database for each patient. The audiograms logged were placed into one of four subcategories: (a) baseline audiogram prior to CDDP therapy, (b) first audiogram after the last CDDP treatment but less than six months after treatment, (c) audiogram at least six months after CDDP treatment and (d) most recent evaluable audiogram when an audiogram meeting criteria (c) also existed. The (b) audiogram was only logged when there were not at least two audiograms six months after the last CDDP and there was no change from the (b) to the (c) audiogram. Our study allowed the baseline audiogram to be absent/abnormal if a subsequent audiogram documented normal hearing.

In our study, a normal behavioral hearing test was defined as thresholds of $\leq$ 20 dB from 1 kHz - 4 kHz, and $\leq$ 30 dB at 6 kHz to 8 kHz to account for tympanostomy tubes. A normal ABR, at our institution was defined as thresholds of $\leq$ 30 dBnHL from .5 kHz to 1 kHz and $\leq$ 20 at 2 kHz to 8kHz. If any frequency was outside the defined normal range on the baseline audiogram, the audiogram for that ear was not evaluable. If there was a normal baseline audiogram and sufficient data for only one ear, thresholds were collected; such patients were only evaluable for LOHL and not AHL.

Each ear was assigned a SIOP classification relative to the bone conduction thresholds of the most recent audiogram. Audiograms with a normal 4 kHz threshold but an absent or not evaluable 6 and 8 kHz threshold were codified as “not gradable test”, meaning that it could not utilize the SIOP classification. For this study, SIOP grades 1 and 3 were based on at least one frequency referenced in the SIOP grade level. This was due to the retrospective nature of the

present study and the fact that not all desired frequencies are always obtained in each test session with pediatric oncology patients.

Classification for LOHL

LOHL is defined as a significant change in hearing six months after the last CDDP administration. The magnitude of the decrease was at least $\geq$ 15 dB in one frequency from 1 kHz to 8 kHz, or a $\geq$ 10 dB at two or more frequencies 1 kHz to 8 kHz in the same ear as compared with the previously entered audiogram. Change was only evaluable if there was a bone line (in the audiogram being examined or another audiogram before or after) to confirm loss $\leq$ 4 kHz. If the loss was at or above 6 kHz, documentation was needed of a normal middle ear state through static admittance $\geq$ .3 mmho, large canal volume consistent with patent tubes, and/or a normal otologic exam by an otolaryngologist. Bone conduction thresholds always superseded tympanometric measures in the current study. A decrease of $\leq$ 10 dB at one evaluable frequency was not considered a significant change. The patient's final audiograms were coded as evaluable for LOHL, not evaluable for LOHL, positive for LOHL, or negative for LOHL.

Classification for AHL

AHL was arbitrarily defined as a threshold difference between ears of $\geq$ 20 dB at any one frequency 1 kHz and above, or $\geq$ 15 dB at two or more frequencies 1 kHz and above. Each patient was coded as evaluable for AHL, not evaluable for AHL, positive for AHL (Figure 2), and negative for AHL.

Statistical Methods

Patients were divided into three overlapping subsets, one with those evaluable for AHL, one with those evaluable for LOHL, and one evaluable for both AHL and LOHL. In the first two subsets logistic regression was used to compare the odds of AHL or LOHL by diagnosis, radiation (any radiation, radiation to the head, radiation boost to the posterior fossa), gender of patient, age of patient at study baseline and at first CDDP exposure, concurrent exposure to carboplatin and cumulative CDDP dose. A test for trend over an ordinal scale (Jonckheere's test) was used to compare SIOP scores in the better or worst ears by presence of AHL or LOHL. In the third subset McNemar's test was used to test for co-occurrence of AHL and LOHL. All analyses were carried out using SAS/STAT v14.1 for Windows.

RESULTS

Of the 993 patients in the entire database, 248 patients received CDDP and their medical records were reviewed. One-hundred and thirty-six patients met the eligibility criteria for inclusion in the AHL study, while 112 patients met the eligibility criteria for inclusion in the LOHL study. Criterion for exclusion for the AHL study included: 1.) Incomplete audiologic data (n = 69), 2.) Incomplete medical data (n = 4), 3.) Conductive hearing loss (n = 4), 5.) Patient actively treated (n =7), 6.) Possessed an ear with an abnormal baseline (n = 27). Criterion for exclusion of the LOHL study included: 1.) Incomplete audiologic data (n = 108), 2.) Incomplete medical data (n = 4), 3.) Patient actively treated (n = 7), 4.) Possessed an ear with an abnormal baseline (n = 16).

Table 1 summarizes the patient characteristics for those included in each study. Each of the study populations are representative of the general cancer population treated at Saint Louis Children's Hospital – a predominantly Caucasian patient demographic with a slight male

predominance. The cancer diagnoses reflect populations typically treated with CDDP using standard treatment regimens. Some patients also received carboplatin and/or radiation therapy which are also known to be ototoxic.

LOHL

There were 64 males and 48 females included in the LOHL study. 87 (78%) patients had CDDP only, while 25 (22%) had a combination of CDDP and carboplatin. 50 (45%) patients had radiation treatment to the head as part of their treatment. Of the 112 patients that met the eligibility criteria, 47 (42%) exhibited LOHL.

The observed risk of LOHL differed by diagnosis ($p = .03$). The odds of LOHL were 70% - 80% lower in patients with osteosarcoma and patients with other solid tumors compared to those with a diagnosis of medulloblastoma. Odds ratios are osteosarcoma versus medulloblastoma 0.21 (0.056, 0.76) and other solid tumors versus medulloblastoma 0.30 (0.099, 0.93). At their most recent audiogram, patients with medulloblastoma had higher SIOP scores in both the better ear ($p = .0023$) and worse ear ($p = .021$) compared to the other tumors types in this arm of the study, further illustrating the vulnerability of patients with this cancer diagnosis.

The features of patients with and without LOHL are summarized in Table 2. Radiation is a major risk factor for LOHL with a nearly five fold increased risk compared to those who did not receive radiation as part of their therapy (odds ratio = 4.9 (2.0, 11.8), $p = .0004$). Having radiation to the head increased the odds of LOHL 2.5 times (odds ratio = 2.5 (1.1, 5.3), $p = .022$). Furthermore, radiation boost to the posterior fossa, which contains the cochlea in the field, also associated with an increased risk of LOHL (odds ratio = 2.5, $p = .037$). There is no evidence that gender, the addition of carboplatin, or the total cumulative exposure of CDDP are associated

with an increased risk of LOHL. There is also no evidence of a significant difference in SIOP scores between ears.

Older age appears to be protective against LOHL. The odds of LOHL decrease by 12% for each 1-year increase in the age at baseline hearing exam or age at diagnosis (odds ratio = .88 (0.82, 0.96) in each case, p-values are .0016 and .0014 for age at the baseline hearing exam and age at diagnosis, respectively).

Figure 3 plots patients with LOHL verses the time interval from the end of CDDP treatment to the last audiogram of the study and compares those patients without LOHL. Patients with LOHL were associated with a longer follow-up (median 55 months) compared to those without LOHL (median 30 months). This association was maintained even when the time interval from the completion of *all* therapy to the last audiogram of the study was plotted. Thus, patients with the longest follow-up were more likely to display findings consistent with LOHL.

AHL

Table 2 displays the features of the patients who fulfilled eligibility criterion to assess for AHL. There were 78 males and 58 females included in the AHL study. Ninety-eight (72%) patients had CDDP, while 38 (28%) had a combination of CDDP and carboplatin. Fifty-one (37.5%) patients had radiation treatment to the head in addition to CDDP. Of the 136 patients that met the eligibility criteria 35 (26%) exhibited AHL.

The odds of AHL are lower for all diagnoses relative to medulloblastoma (p = .003). For instance, the odds are about 90% lower among patients with ‘other solid tumors’ (including germ cell tumors and hepatoblastomas odds ratio = .071 (0.014, 0.35)), about 80% lower among patients with osteosarcoma (odds ratio = 0.20 (0.066, 0.63)) and non-medulloblastoma brain

tumors (odds ratio = 0.19 (0.045, 0.79)), and about 70% lower among neuroblastoma patients (odds ratio = .29 (0.098, 0.88)). Similar to the LOHL study, SIOP scores at the most recent audiogram are highest, in both better and worse ears, in medulloblastoma patients than in patients with other tumors (in the better ear p = .0003, in the worst ear p = .0067). There is no evidence that SIOP scores were preferentially worse in one ear (left versus right) even when factoring diagnoses.

AHL treatment characteristics are summarized in Table 3. Radiation is also associated with an increased risk of AHL. A history of radiation as part of the patient's treatment increased the odds of AHL by 2.5 times (1.1, 5.9), p = .034), while radiation to the head increased the odds by 2.6 times (1.2, 5.6, p = .019), and a radiation boost specifically to the posterior fossa increased the odds of AHL by 3.8 times (1.6, 9.1), p = .0025). There is no evidence that any other factor examined including gender, age at diagnosis, or the use of carboplatin with cisplatin is associated with greater odds of AHL (p = .98 for gender, p = .59 for carboplatin).

AHL as a Predictor of LOHL

Given the similarities in risk factors for developing AHL and LOHL, we examined whether there was a relationship between these two clinical entities. This required the generation of an additional dataset, ensuring that the criterion for both AHL and LOHL was present for the same patients, since there were some patients that were assessable for one and not the other. Ninety-six of the 248 were eligible for both AHL and LOHL studies, of which 35 were positive for AHL and 47 were positive for LOHL. Twenty-one of the 96 included in both studies were positive for both AHL and LOHL (Figure 4). The diagnoses of patients who were positive for both AHL and LOHL included: medulloblastoma (n = 10), neuroblastoma (n = 5), osteosarcoma

(n = 2), choroid plexus carcinoma (n =1), hepatoblastoma (n =1), germinoma (n =1), and nasopharyngeal carcinoma (n =1), which is representative of the original distribution of diagnoses in the AHL and LOHL studies.

AHL does appear to be strongly associated with LOHL. Seventy-five percent of patients with AHL also had LOHL. Similarly, those patients with no AHL also had a low incidence of LOHL (28%).

McNemar's test also concludes that AHL tends to occur with LOHL and no AHL was associated with the absence of LOHL ($p = .019$).

A logistic regression of LOHL was calculated, revealing that both radiation and AHL are independently significant as risk factors for LOHL. The odds of LOHL are about 6 times greater in patients with AHL than those without (odds ratio = 6.3 (2.2, 17.8), $p = .0005$), after taking into account the effect of radiation.

DISCUSSION

Serious developmental consequences stem from the presence of hearing loss in the pediatric population, namely its effects on speech, language, social skills, listening skills, and learning to read and write. Hearing loss also affects the structures in the brain associated with the auditory system; the brain needs to be able to hear sound in order to make sense of it. Without the incoming stimulation, the auditory centers of the brain are not being properly stimulated and developed (Merzenich, 2010).

This investigation demonstrates that individuals receiving CDDP therapy are at risk for developing both LOHL and AHL. LOHL and AHL are relatively under-appreciated complications in the current literature regarding pediatric cancer survivors, yet this report suggests that they affect a significant percent of those receiving platinum based therapy.

In this study, we characterized the prevalence and risk factors of LOHL and AHL with the longest follow-up consisting of 208 months (17 years). The data analysis revealed that LOHL is a frequent complication of patients receiving CDDP, with almost half of the patients developing LOHL, and that radiation and diagnosis are significant risk factors. A high prevalence was also observed in the AHL cohort, with almost one-third of the patients developing AHL. Further analysis revealed that those patients who either developed AHL and/or received radiation treatment were at an increased risk (Odds Ratio = 2.7) for LOHL. Physicians and audiologists should be aware of these findings in order to be able to identify affected patients early and recognize the critical need for vigilant, long term follow-up as many appear to have worsening hearing with time.

This study is unique due to the rigor of data included in the analysis. Patients were only included if they had a normal baseline audiogram, if bone conduction thresholds were recorded to confirm the sensorineural nature of the hearing loss, and if their audiograms had good to fair reliability. Patients were excluded if they had incomplete audiologic data (i.e., poor reliability, bone conduction not tested, insufficient number of audiograms for analysis), a conductive hearing loss, incomplete medical data, and if they were currently being treated at the time of the study. Previous studies have failed to use this level of criterion, for example, often mixing patients with conductive hearing losses into their study population. The stringent criteria utilized in this study allows for a more reliable estimate of the prevalence of LOHL and AHL and their associated risk factors.

The findings in the current study provide significant information to guide clinicians in the management of this patient population. The present study spans the full scope of ages and

diagnoses in the pediatric oncology population and indicates that both AHL and LOHL affect a significant fraction.

One of the reasons AHL may be under-appreciated in the literature is due to the assumption that ototoxicity from treatment with platinum compounds results in systemic exposure in which clinicians would expect a bilateral, symmetric hearing loss. The presence of AHL needs to be recognized and identified as a serious complication after chemotherapeutic treatment, given its potential impact on this population. Children with AHL may have difficulties in communicating, fail to achieve developmental milestones, understanding speech in noisy settings, learning in classroom settings, and locating sounds (Vila & Lieu, 2015). Behavioral issues have also been reported in children with AHL in addition to lower levels of self esteem and higher levels of exhaustion and stress due to the increased effort put in to simply trying to listen (Bess et al., 1998; Ross, Gaffney, Green, & Holstrum, 2008). Not specific to the AHL literature, but of significance, are the findings of Orgel et al. (2016); the group examined pediatric brain tumor survivors and found that those with SNHL were at an increased risk for noteworthy neurocognitive and intellectual deficits. In terms of hearing aid fitting in patients with AHL, it is important for the audiologist to recognize that there is not balanced hearing from both sides and that certain steps during hearing aid programming must be taken to give the patient the best unified incoming signal possible.

Given today's long term survival rates in pediatric cancer patients and the continued identification of LOHL with increased length of follow-up, continued monitoring of these patients is essential for the earliest intervention as hearing deteriorates. Close monitoring will also be critical in terms of the possible need to reprogram the patient's hearing aids, i.e., providing more amplification, especially with the known risk of progressive hearing loss in

certain populations. Additionally, it is important for the audiologist to counsel these patients on the effects of harmful levels of noise, (i.e., from concerts and other loud recreational activities) as high levels of noise have been reported to potentiate CDDP-induced hearing loss (Peleva, Aloy, Carret, & Daniel, 2014; Steyger, 2009). One study revealed that even a mild noise exposure during CDDP treatment significantly increases risk of permanent hearing loss. Even when the CDDP caused no ototoxicity, they found that the interaction of noise and non-ototoxic doses of CDDP could cause a significant hearing loss. The study advances the need for strict audiological monitoring and counseling for the possibility of increased susceptibility of permanent hearing loss from noise exposure both during and after treatment with CDDP (Boettcher, Henderson, Gratton, Danielson, & Byrne, 1987).

There were limitations of this study. It is a retrospective chart review, in which there was a lack of regimented serial monitoring as patients were tested in variable intervals. Patients who were lost to follow-up or had incomplete audiologic data could not be accounted for. Many patients were excluded from this study due to the exceptionally strict inclusion criteria that was implemented. Also, all ototoxic agents that could have an additional affect on the hearing levels of the patients examined were not taken into account; only carboplatin, CDDP, and radiotherapy information was collected. Despite these limitations, this study illustrates the importance of close monitoring of this patient population.

CONCLUSION

The clinical implications for the current study are that regular follow up is critical in patients treated with cisplatin and radiation therapy to identify patients with LOHL and AHL. Patients with certain diagnoses are at an even higher risk for developing AHL and LOHL, and

AHL was a risk factor for developing LOHL. The presence of AHL should be a red flag for clinicians that these patients' hearing loss may get progressively worse long after the completion of treatment. Future studies are needed to assess the impact of LOHL and AHL on the long term function and quality of life of our pediatric cancer survivors.

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TABLE 1

Demographics: All Eligible Patients

	Eligible LOHL	Eligible AHL
No. Patients	112	136
Gender		
Male	64	78
Female	48	58
Age range at diagnosis (mo)	2 - 249	2 - 226
Mean age at diagnosis (mo)	94	98
Race		
White	96	112
African American	12	17
Other	4	7
Ethnicity		
Hispanic or Latino	0	1
Not Hispanic or Latino	110	132
Participant Refused	2	3
Diagnosis		
Hepatoblastoma	9	8
Medulloblastoma	31	33
Neuroblastoma	18	28
Osteosarcoma	20	32
Non-medulloblastoma brain tumors	11	11
Other solid tumors	13	12
Germ cell tumors	10	14
Total	112	136
CDDP only	87	98
CDDP and carboplatin	25	38
Radiation		
Yes	68	80
No	44	56
Radiation to Head	50	51
Radiation boost to posterior fossa	29	29

LOHL indicates LOHL; AHL indicates asymmetric hearing loss; CDDP indicates cisplatin.

TABLE 2

LOHL Patient & Treatment Characteristics

	No LOHL	LOHL	Total
No. Patients	65 (58%)	47 (42%)	112
Gender			
Male	33 (52%)	31 (48%)	64
Female	32 (67%)	16 (33%)	48
Age range at diagnosis (mo)	3 - 249	2 - 199	2 - 249
Mean age at diagnosis (mo)	112	70	88.5
Race			
White	55 (57%)	41 (43%)	96
African American	8 (67%)	4 (33%)	12
Other	2 (50%	2 (50%)	4
Ethnicity			
Hispanic or Latino	0 (0%)	0 (0%)	0
Not Hispanic or Latino	64 (58%)	46 (42%)	110
Participant Refused	1 (50%)	1 (50%)	2
Diagnosis			
Hepatoblastoma	7 (78%)	2 (22%)	9
Medulloblastoma	14 (45%)	17 (55%)	31
Neuroblastoma	7 (39%)	11 (61%)	18
Osteosarcoma	16 (80%)	4 (20%)	20
Non-medulloblastoma brain tumors	6 (55%)	5 (45%)	11
Other solid tumors	7 (54%)	6 (46%)	13
Germ cell tumors	8 (80%)	2 (20%)	10
Total	65 (58%)	47 (42%)	112
CDDP only	52 (60%)	35 (40%)	87
CDDP and carboplatin	13 (52%)	12 (48%)	25
Radiation			
Yes	30 (44%)	38 (56%)	68
No	35 (88%)	9 (20%)	44
Radiation to Head	23 (46%)	27 (54%)	50
Radiation boost to posterior fossa	12 (41%)	17 (58%)	29

LOHL indicates late onset hearing loss. CDDP indicates cisplatin.

TABLE 3

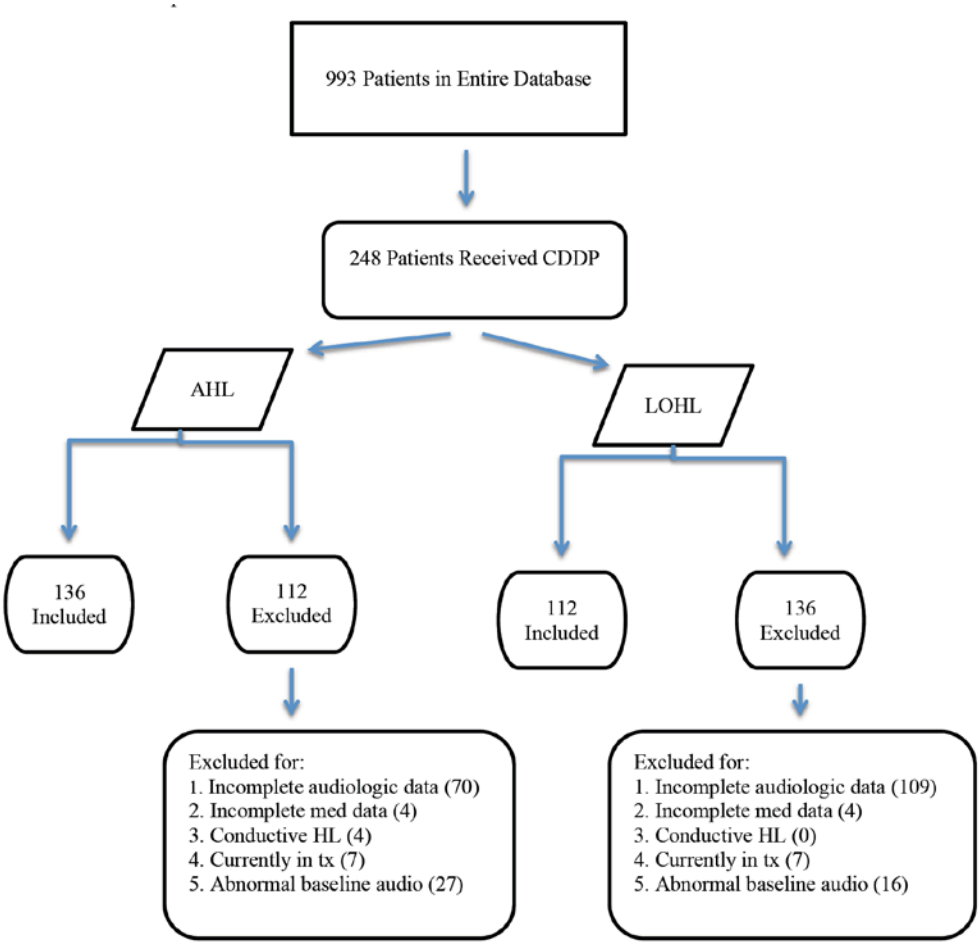
AHL Patient & Treatment Characteristics

	No AHL	AHL	Total
No. Patients	101 (74%)	35 (26%)	136
Gender			
Male	58 (74%)	20 (26%)	78
Female	43 (74%)	15 (26%)	58
Age range at diagnosis (mo)	2 - 226	4 - 218	2 - 226
Mean age at diagnosis (mo)	104	80	92
Race			
White	83 (74%)	29 (26%)	112
African American	12 (71%)	5 (29%)	17
Other	6 (86%)	1 (14%)	7
Ethnicity			
Hispanic or Latino	1 (100%)	0 (0%)	1
Not Hispanic or Latino	97 (73%)	35 (27%)	132
Participant Refused	3 (100%)	0 (0%)	3
Diagnosis			
Hepatoblastoma	7 (87.5%)	1 (12.5%)	8
Medulloblastoma	15 (47%)	17 (53%)	32
Neuroblastoma	21 (75%)	7 (25%)	28
Osteosarcoma	26 (81%)	6 (19%)	32
Non-medulloblastoma brain tumors	9 (82%)	2 (18%)	11
Other solid tumors	11 (92%)	1 (8%)	12
Germ cell tumors	12 (92%)	1 (8%)	13
Total	101 (74%)	35 (26%)	136
CDDP only	74 (76%)	24 (24%)	98
CDDP and carboplatin	27 (71%)	11 (29%)	38
Radiation			
Yes	54 (67.5%)	26 (32.5%)	80
No	47 (84%)	9 (16%)	56
Radiation to Head	32 (63%)	19 (37%)	51
Radiation boost to posterior fossa	15 (52%)	14 (48%)	29

AHL indicates asymmetric hearing loss. CDDP indicates cisplatin.

FIGURE 1

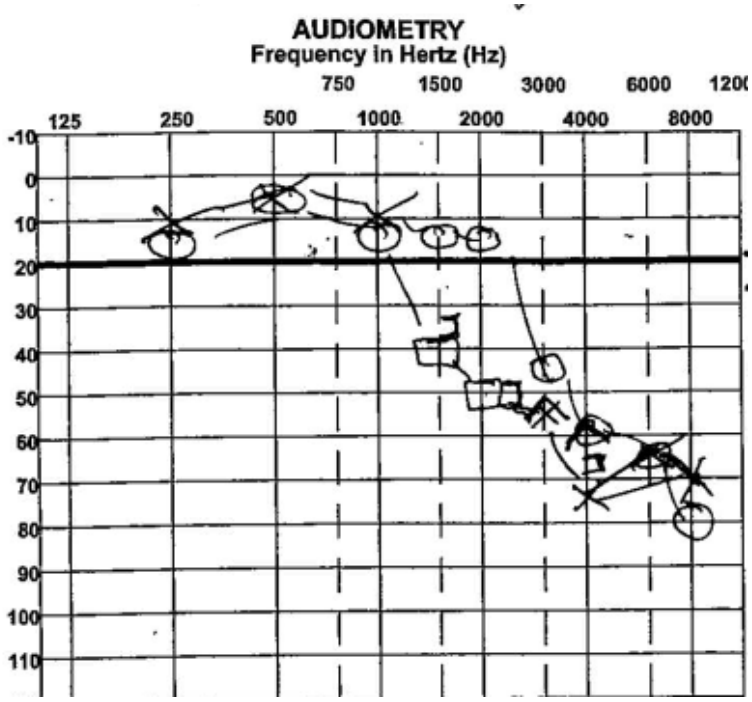
Overall Patient Population Selection



Reviewed charts of pediatric oncology patients at St. Louis Children's Hospital treated from August 1, 1990 through March 31, 2015. 993 patients in the entire cohort. 2 arms to this study: 1.) LOHL arm 2.) AHL arm. Patients must have been treated with cisplatin to be included. Reviewed patient charts, identifying those patients who had a history of cisplatin exposure, resulting in 248 patients.

FIGURE 2

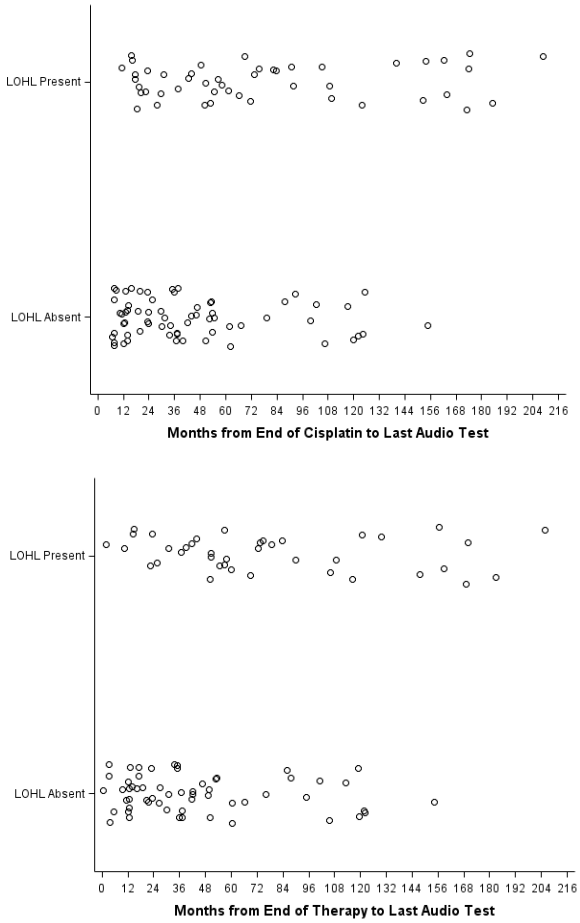
Example of Asymmetric Hearing Loss



Example audiogram of AHL. Defined in present study as a threshold difference between ears of ≥ 20 dB at any one frequency 1 kHz and above, or ≥ 15 dB at two or more frequencies 1 kHz and above.

FIGURE 3

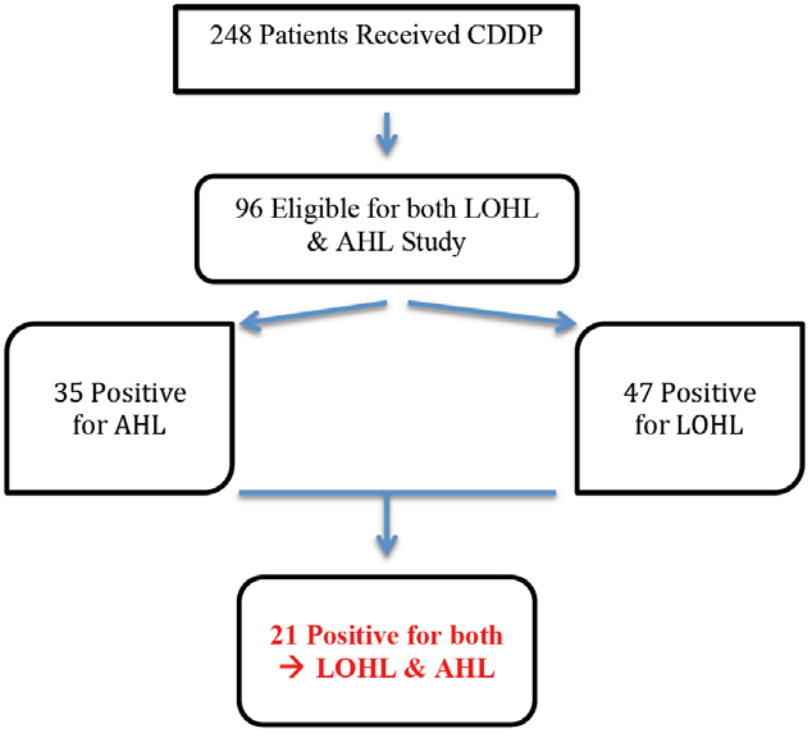
Plots of Time to LOHL



Patients with & without LOHL verses the time interval from the last cisplatin treatment to the most recent audiogram. Patients with LOHL were associated with a longer time interval versus those without LOHL. This association held true even when plotting the time period from the end of *all* therapy to the most recent audiogram.

FIGURE 4

Patient Population Selection: LOHL & AHL



96 of 248 were eligible for AHL & LOHL studies, 35 were positive for AHL; 47 were positive for LOHL. 21 of the 96 included were positive for both AHL and LOHL. Diagnoses of patients positive for both include: medulloblastoma (n = 10), neuroblastoma (n = 5), osteosarcoma (n = 2), choroid plexus carcinoma (n =1), hepatoblastoma (n =1), germinoma (n =1), and nasopharyngeal carcinoma (n =1).

APPENDIX A

St. Louis Children's Hospital

Audiologic Assessment/Monitoring of Hematology/Oncology Patients

Initial Behavioral Hearing Test Protocol

a) Pure tone thresholds 250 Hz-8KHz with bone if needed. Begin at 1 or 2KHz and above. Include 3K and 6KHz if possible. Use 3A inserts as long as ears are cleared of wax and if patient tolerates **wearing them**. Log the type of transducer used. Note on audiogram if IVAC is in sound suite.

b) Tympanometry

c) Speech recognition testing if possible. Standardized presentation if possible.

d) OAE's if a brain tumor patient has a sensorineural asymmetry.

NOTE: Ultrahigh frequencies are no longer tested as of 2010.

e) If consistent, reliable responses could not be obtained, recommend "sedated ABR if current thresholds are needed." The hem/onc medical team will schedule as appropriate.

Initial ABR Hearing Test Protocol

a) Click, 4KHz, 8KHz, 2KHz, 1KHz and 500 Hz if possible.

b) Include OAEs if possible, especially for brain tumors.

c) Tympanometry as needed if possible.

Follow-Up Protocols

a) Look for previous audiologist notes and meeting notes. Notes will be in Clin Desk>Notes>Progressnotes>Audiology progress notes. It is important to know where the patient is in their treatment course before making recommendations.

b) Follow-up protocols are the same as the initial protocols except for speech recognition, which is not tested unless a significant change is noted in hearing sensitivity. **Always test both ears, including B/C, even if one is profound.**

Follow-up Protocol Recommendations: (Still on chemotherapy)

1) **If no change from previous hearing test and normal tympanogram:**
    1) Follow-up per protocol or managing physician or sooner if change is noted or if tinnitus is experienced.
    2) Noise precautions (music, hunting, work, recreation)
2) **If no change from previous hearing test but abnormal tympanogram:**
    1) Follow up per protocol or managing physician or sooner if change is noted or if tinnitus is experienced
    2) Noise precautions (music, hunting, work, recreation)
    3) Otologic exam by managing physician.
3) **If conductive hearing loss (inpt/outpt):**
    1) Call 4-6018 and ask for patient's clinical nurse coordinator (CNC) or nurse practitioner, explain results and ask if they can be seen. If patient is going home or has no available time the rest of the day, after appointment, send a CNC group e-mail informing them of loss and recommendations. Include this information in patient's progress notes to be scanned.

2) Recommend otologic management **with managing hem/onc team** and follow up per protocol.

4) <u>If change in conventional frequencies (inpt/outpt):</u>

<u>ONE OF 3 SITUATIONS:</u>

1) If patient is receiving chemo that day,call 4-6018 **after the patient leaves** to speak with the patient's clinical nurse coordinator (CNC) or nurse practitioner. Explain results, write the disposition in patient's progress notes to be scanned.

2) If they are still receiving therapy, but not that day, send an e-mail by the end of the day to the CNC group e-mail. Write in patient's progress notes that an e-mail was sent to the CNC group e-mail for scanning.

3) If patient is post therapy, the significant change can just be noted on the audiogram (because there is no therapy to be changed). **Follow Post Treatment recommendations on next page as well as any additional standard audiologic recommendations.**

5) <u>If hearing loss impacts speech understanding:</u>

1) See if previous notes began the discussion with family or medical team. If hearing aids have been broached, chemotherapy treatment is complete and the medical team advised audiology to proceed, counsel/schedule appropriately.

2) If no previous discussions have occurred, send a group CNC e-mail to see if amplification is appropriate at this time both for the patient and the

family. Write a chart note and scan. It is important for the medical team to understand the intent of the recommendation and what is involved in the process. If this is not a good time, inform them that loaners and a pocket talker are available. Ask if it is an appropriate time to move forward with a speech/language evaluation as well.

Post Treatment Recommendations:

6) **When cranial irradiation only (without being combined with ototoxic drugs) has ended:**

   a) If hearing is normal 2 years post therapy, a hearing test is recommended only if hearing or school concerns arise.

7) **When cisplatin with or without carboplatin treatment has ended:**

   1) Hearing tests at 3,6,12 months and annually
   2) Noise precautions
   3) Speech /language evaluation as needed but especially for those with hearing loss.

8) **When Carboplatin with or without radiation has ended:**

   1) **Annually until they reach 10 years of age or 5th grade or are able to reliably self report.**
   2) **NF and Retinoblastoma patients will be tested annually.**

9) **Post Bone Marrow Transplants: (With no previous treatments)**

   1) **Hearing is tested at the 110 day marker (~3 months). If hearing is normal, a follow-up test is recommended at 1 year post transplant. If hearing is normal at the second year audiogram, further hearing test**

are recommended only if concerns arise. If a hearing loss exists at the 100 day marker, recommendations are the same as the cisplat follow up above.

2) **If patient has had previous chemo treatments, follow recommendations 7 or 8 above.**

Sickle Cell Patients (Chronically transfused and on chelation therapy (exjade/desferol) and monitoring of hearing is ongoing)

(1) Annual audiograms or sooner if hearing or school concerns arise.

(2) **Word recognition and speech-in-noise testing should be done at each annual hearing evaluation.**

Late Effects Patients (Some were treated at SLCH – some were not)

Follow the Post Treatment Recommendations (6/7/8/9) above.

Hearing aids if appropriate. If **families have** financial difficulties, **funding packets are available.** Center for Hearing and Speech has funding programs and scholarships as well. **For those patients whose hearing aids are managed at outside facilities, a hearing aid check will be recommended by the Late Effects team prior to receiving a Neuropsychological evaluation. This is to ensure that the aids are functioning and offering appropriate gain.**

Put a copy of all hem/onc patient audiograms in the envelope (outpts/inpts, h/a pts, CAP pts, ENT pts, sickle cell pts, late effects pts) in Sue Hayashi's mailbox. The patients will be reviewed, discussed at the hem/onc meetings and chart notes written on each patient. All faculty and staff are sent meeting notes as a reminder of our recommendations.

If the patient is an inpatient, place a copy of the results in the inpatient chart and remember to enter the test results into his/her KIDDOS chart.

Hearing test paperwork is scanned the same day. The Orange Hem/Onc Scan folder is currently behind the fee sheet bin at the Audiology Registrars' desk.

Written by/Effective Date: S. Hayashi 1/06

Reviewed by Date: S. Hayashi, P. Koprowski

Revised by Date: S. Hayashi, P. Koprowski 4/2015

Revised by Date: Audiology Hem/Onc Team 4/2015