

Long-term hearing outcomes and quality of life in childhood cancer survivors treated with cisplatin

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Hospital



Disclosures

I have no relevant financial relationships or conflicts of interest to disclose



Objectives

- Review cancer therapies that can cause hearing loss and the mechanisms of ototoxicity
- Summarize the prevalence of hearing loss related to cancer treatment in children and review the impact of hearing loss and long-term outcomes
- Review ototoxicity monitoring protocols for infants and children
- Discuss current and future strategies for mitigating and managing hearing loss

For additional information:

International Journal of Audiology, 2018: Vol 7 supplement 4:
Ototoxicity: Special Topics in Clinical Monitoring



Ototoxicity

- Certain medications or chemicals can cause damage to the inner ear that results permanent hearing loss, tinnitus, and/or balance disorders.

Potentially ototoxic cancer treatment:

- Platinum chemotherapy: cisplatin, carboplatin
- Cranial radiotherapy involving the inner ear

Platinum Chemotherapy

- 1/3 of children with cancer will receive a platinum analogue as first or second line treatment
- ~5000 children aged 1-15 years are treated with platinum annually in the U.S.¹

Childhood cancers commonly treated with platinum chemotherapy:

Brain and CNS cancers

Neuroblastoma

Hepatoblastoma

Osteosarcoma

Germ cell tumors

Retinoblastoma

¹Ward et al. CA Cancer J Clin, 2014; 64:83-103

Platinum chemotherapy

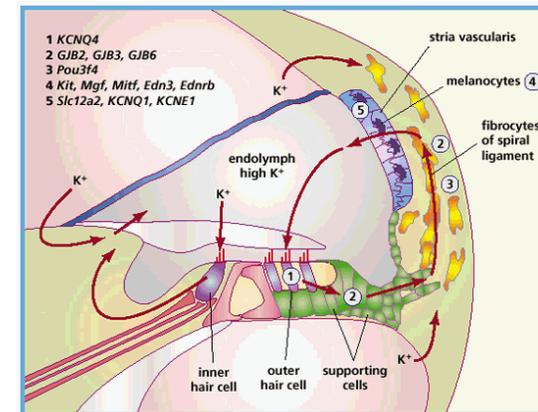
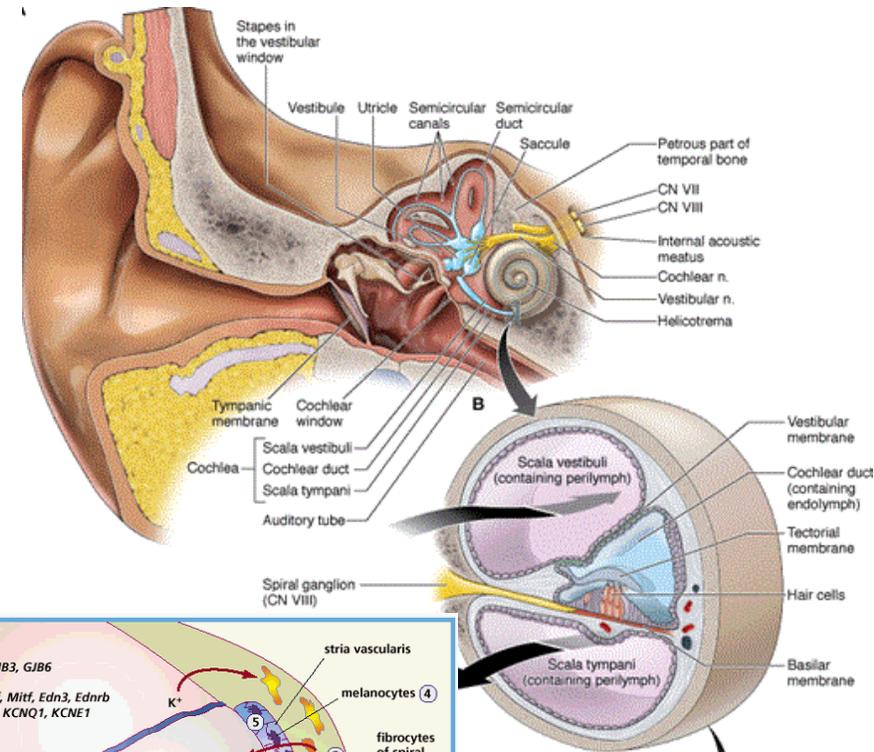
- iv administration, dose based on the child's body mass (mg/m^2) or weight (mg/kg) if under 3 years
- *Individual dose*: dose per course/cycle
 - Dose, duration of infusion (# hours), number of days administered
- *Cumulative dose*: total dose of platinum received at the completion of therapy
- Treatment protocol/plan depends on cancer diagnosis, disease risk (stage of disease) and age
 - Chemotherapy drugs
 - Dose and schedule
 - Total number of chemotherapy courses
 - Any modifications for ototoxicity
- “Dosing to toxicity”

Cranial radiation

- Daily for 4-8 weeks
- Often completed before platinum chemotherapy
- Avoided in children younger than 3 years
- Highest risk for ototoxicity with posterior fossa radiation >30 Gy
- 40% acute middle ear dysfunction, risk for long-term middle ear complications
- Typically late-onset of hearing loss
- IMRT (intensity modulated radiation therapy) and proton beam radiotherapy appear to have less risk for inner ear damage

Mechanisms of platinum ototoxicity

- Following iv injection, cisplatin and carboplatin cross the BLB and enter the cochlear fluids
- Several possible trafficking pathways and methods of entry into the cochlear HC's and supporting cells¹
- Cisplatin is retained in the cochlea for months to years²
- OHC's permanently damaged by the loss of EP, excessive generation of reactive oxygen species and depletion of antioxidant defense mechanisms¹⁻⁴



¹Karasawa T & Steyger P, *Toxicol Lett*; 2015, 17;237(3):219-27

²Breglio et al., *Nat Commun*; 2017, 8:1654

³Goncalves et al., *Laryngol Otol*, 2013; 127(6):536-41

⁴Sheth et al., *Front Cell Neurosci*, 2017; <https://doi.org/10.3389/fncel.2017.00338>

Mechanisms of platinum ototoxicity

- Oxidative damage activates apoptosis causing degeneration of the cochlear outer hair cells, and eventually inner hair cells
- Damage begins at the base of the cochlea and progresses toward the apex

Prevalence of ototoxicity in the literature

The rate of ototoxicity will vary depending on how hearing loss is defined

- Many ototoxicity classification systems have been used in clinical trials and research (CTCAE, Brock, Chang, SIOP)
- Purposes of ototoxicity classification systems:
 - Communicate audiologic results with medical team
 - Report hearing outcomes in groups of patients enrolled on cancer treatment studies or for clinical research
 - Compare toxicity of different treatment regimens, pool data
 - Efficacy of otoprotective drugs
 - Phenotypes for genomic studies

Ototoxicity prevalence in clinical trials

- Institutional reporting may under-estimate ototoxicity
 - 120 children treated for hepatoblastoma¹: CTCAE 3 or 4 ototoxicity
 - Institutional reporting 4%
 - Auditory specialist: 38%
 - 333 children treated for neuroblastoma²: CTCAE 3 or 4 ototoxicity
 - Institutional reporting: 6%³
 - Audiologist review: 71%²

¹Katzenstein et al. *Cancer*, 2009; 115(24), 5828-35

²Landier et al., *J Clin Oncol*, 2014; 32(6):527-34

³Kreissman et al., *J Clin Oncol*, 2007; 25(18S), 9505

NCI CTCAE Pediatric Ototoxicity Grades v3

- Grade 1: threshold shift of 15-25 dB, averaged at 2 or more contiguous frequencies in at least one ear.
- Grade 2: threshold shift >25-90 dB, averaged at 2 contiguous frequencies in at least one ear.
- Grade 3: hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g. ≥ 20 dB bilateral HL in the speech frequencies, ≥ 30 dB unilateral HL; and requiring additional speech-language related services)
- Grade 4: audiologic indication for cochlear implant and requiring additional speech-language related services

Brock Hearing Loss Grades

- Grade 0: Hearing thresholds <40 dB at all frequencies
- Grade 1: Thresholds \geq 40 dB at 8000 Hz
- Grade 2: Thresholds \geq 40 dB at 4000-8000 Hz
- Grade 3: Thresholds \geq 40 dB at 2000-8000 Hz
- Grade 4: Thresholds \geq 40 dB at 1000-8000 Hz

ASHA Ototoxicity Criteria

- ≥ 20 dB decrease in pure-tone threshold at one test frequency

OR

- ≥ 10 dB decrease at two adjacent test frequencies

OR

- Loss of response at 3 consecutive test frequencies where responses were previously attained

SIOB Boston Ototoxicity Scale:

International grading system developed to report ototoxicity outcomes in pediatric clinical trials

Grade 0: ≤ 20 dB HL at all frequencies

Grade 1: > 20 dB HL (i.e. 25 dB HL or greater) SNHL above 4000 Hz (i.e. 6 or 8 kHz)

Grade 2: > 20 dB HL SNHL at 4000 Hz and above

Grade 3: > 20 dB HL SNHL at 2000 Hz or 3000 Hz and above

Grade 4: > 40 dB HL (i.e. 45 dB HL or more) SNHL at 2000 Hz

Based on sensorineural hearing thresholds in dB HL (bone conduction or air conduction with a normal tympanogram)

Ototoxicity prevalence in clinical trials

By tradition only grade 3 or 4 toxicities are reported.

In a series of 222 patients treated with cisplatin (52 institutions, multiple cancer diagnoses), central audiology review:

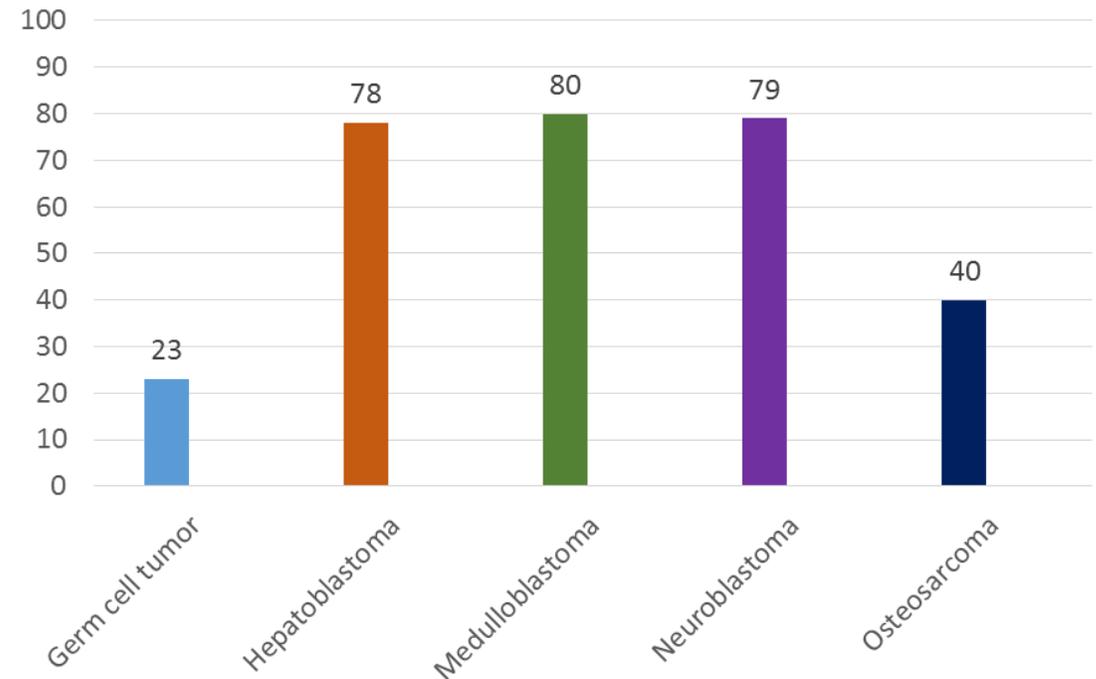
	ASHA	SIOP	Brock	CTCAE v3
Number of subjects evaluable for ototoxicity, n (%)	209 (94%)	215 (97%)	210 (95%)	215 (97%)
Subjects with ototoxicity at the end of treatment, n (%)	117 (56%)	118 (55%)	85 (40%)*	109 (51%)
Grade 3 or 4	NA	37 (18%)	14 (7%)*	25 (14%)

* P< .001

Prevalence of treatment-induced ototoxicity in pediatric cancer patients: (*standard test frequencies*)

- Cisplatin: 50-60%¹
- Carboplatin: 5-25%^{2,3}
- Cisplatin + myeloablative carboplatin: 90%⁴
- Cranial radiation: 10-14%⁵
- Cranial radiation + cisplatin: >80%¹

Incidence of ototoxicity conventional test range by diagnosis (n=314)



¹Knight et al., *J Clin Oncol*, 2017; 35(4):440-445

²Quaddoumi et al., *J Clin Oncol*, 2012; 30(10):1034-41

³Soliman et al., *Pediatr Blood Cancer*. 2018;65(5):e26931

⁴Landier et al., *J Clin Oncol*, 2014; 32(6):527-34

⁵Bass et al. *J Clin Oncol*, 2016; 34(11):1248-55

Risk factors for ototoxicity

1. Younger age

Children younger than 5 years at treatment are at 21 times the risk for hearing loss compared to adolescents

2. Higher platinum dose per course and total dose^{2,3}

Exposure >360 mg/m²

3. Cranial radiation before cisplatin therapy

Exposure >30 Gy

4. Use of more than one ototoxic medication²

5. Genetic differences⁴

6. Cerebrospinal fluid shunting⁵

¹Li et al., *European Journal of Cancer*, 2004; 40(16):2445-2451

²Chang & Chinosornvatana, *J Clin Oncol*, 2010; 28:1788-95

³Lewis et al., *Pediatr Blood Cancer*, 2009; 52(3):387-91

⁴Ross et al., *Nature Genetics*, 2009; 41(12):1335-1350

⁵Guillaume et al. *J Neurosurg Pediatr*, 2012; 9(4):421-7

Presentation of hearing loss

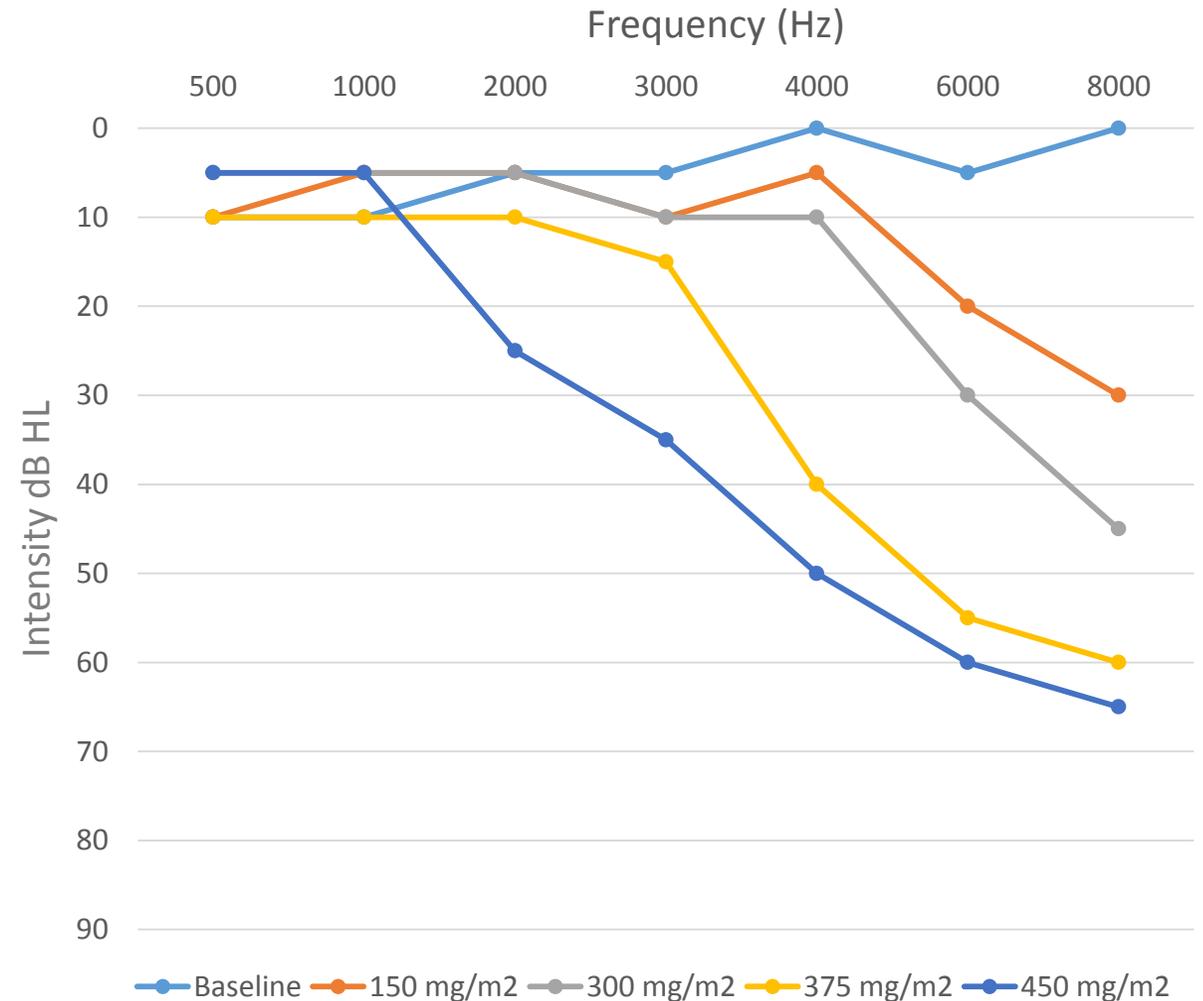
Time of onset is variable, but can occur as early as the first or second cycle of cisplatin

Typically permanent and bilateral

Progressing from high to low frequencies with continued treatment

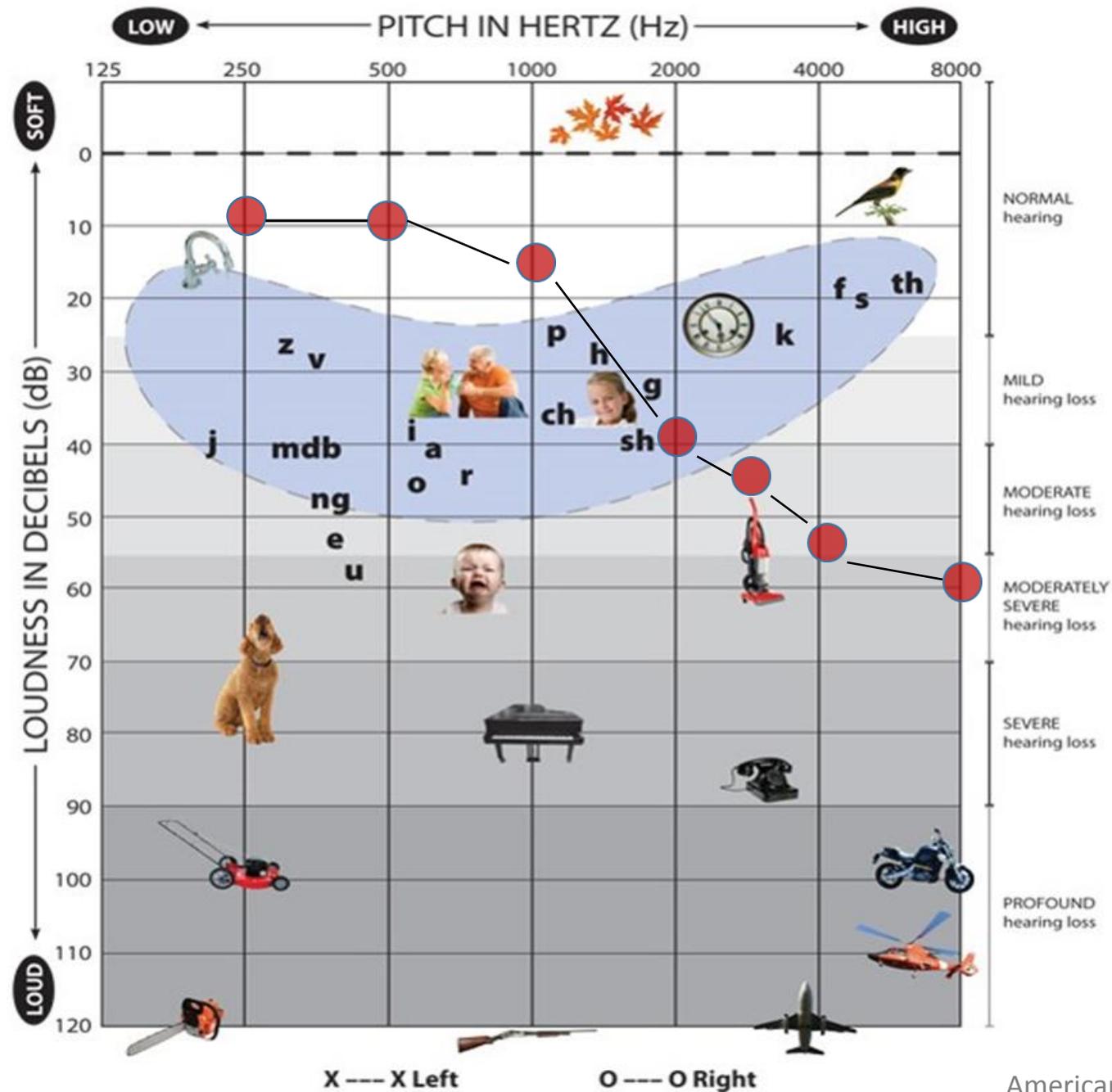
- Tinnitus, aural fullness, imbalance/dizziness

8 year old treated for medulloblastoma; cisplatin 75 mg/m²



Impact of ototoxicity:

- Communication
- Speech-language development
- Cognition
- Educational progress
- Social-emotional
- Socioeconomic



Current strategies for managing ototoxicity

- Continuing treatment in spite of worsening hearing (e.g. hepatoblastoma)
- Dose reduction or change in treatment once a certain amount of hearing loss is documented (e.g. medulloblastoma)

COG ACNS0331:

50% reduction in cisplatin dosage if:

≥ 30 decibel loss at 4,000 – 8,000 Hz

≥ 20 decibel loss at 500-3,000 Hz

Development of hearing loss in 42 children treated for MB

Treatment:

Cranial radiation + cisplatin 75 mg/m² * 6 cycles
(450 mg/m² total)

12F, 30M

Median age at treatment: 8.3 years

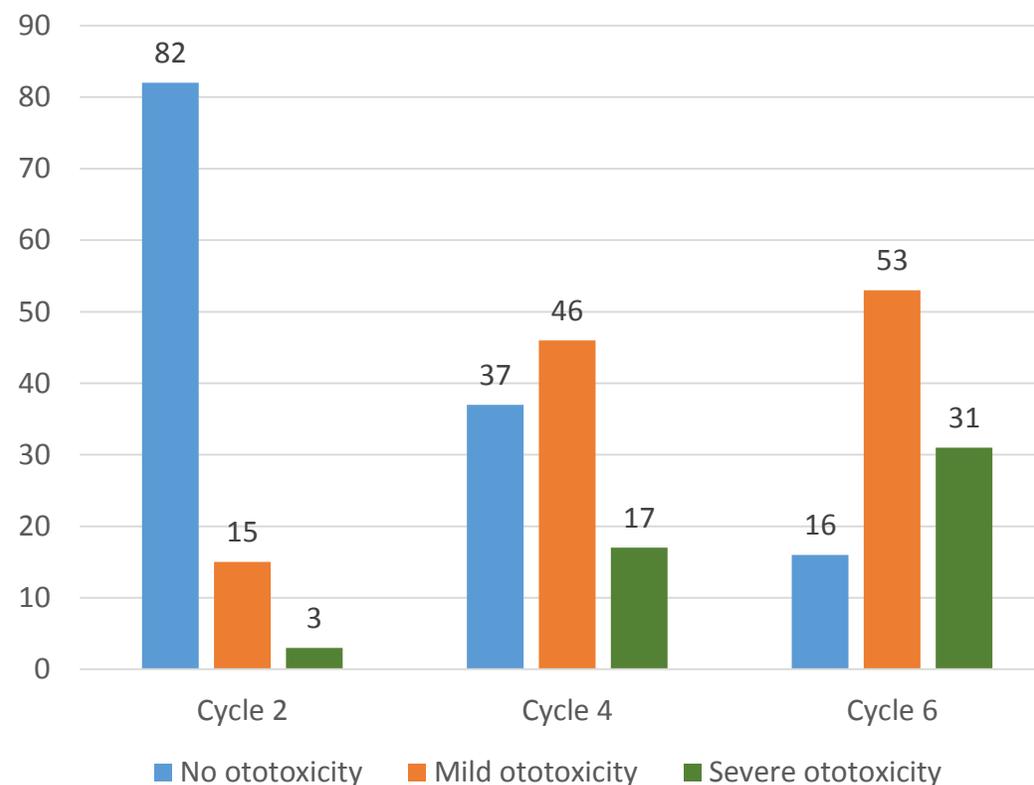
Dose reductions for ototoxicity: 27 (64%)

Ototoxicity: (SIOP)

all grades: 35 (83%)

severe (grades 3 and 4): 13 (31%)

Ototoxicity by cisplatin cycle



Purposes of ototoxicity monitoring

Early detection and early intervention of hearing loss

- Communicate information to the health care team
- May be possible to change treatment to avoid further hearing loss

Inform family and caregivers about changes in hearing

- Impact on understanding
- Strategies to maintain communication
- Initiate early intervention/management of hearing loss

Ototoxicity monitoring guidelines

Guidelines 1993 / II - 81



AMERICAN
SPEECH-LANGUAGE-
HEARING
ASSOCIATION

Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy

*Ad Hoc Committee on Audiologic Management of Individuals
Receiving Ototoxic and/or Vestibulotoxic Drug Therapy*

www.asha.org/policy/gl1994-00003/

American Academy of Audiology
Position Statement and
Clinical Practice Guidelines

Ototoxicity Monitoring

October 2009

www.audiology.org/publications-resources/document-library/ototoxicity-monitoring

Schedule for testing

- Cisplatin
 - Baseline before the first platinum treatment
 - Monitoring evaluations before each cisplatin cycle
 - End of treatment evaluation 4-6 weeks after the last cisplatin course
- Carboplatin
 - Baseline and end of therapy, monitor during therapy for infants
- Posterior fossa radiation
 - Baseline and end of therapy
- Long-term follow-up evaluations

Challenges in pediatric ototoxicity monitoring

- Logistics/time/scheduling
- Conductive middle ear disease
- Bedside testing may be necessary
- Age/development/health status/cooperation can limit results
- Valid/complete baseline evaluation is not always possible
- Sound field testing may limit the test frequency range
- Receiving referrals when patients are scheduled for ototoxic therapy

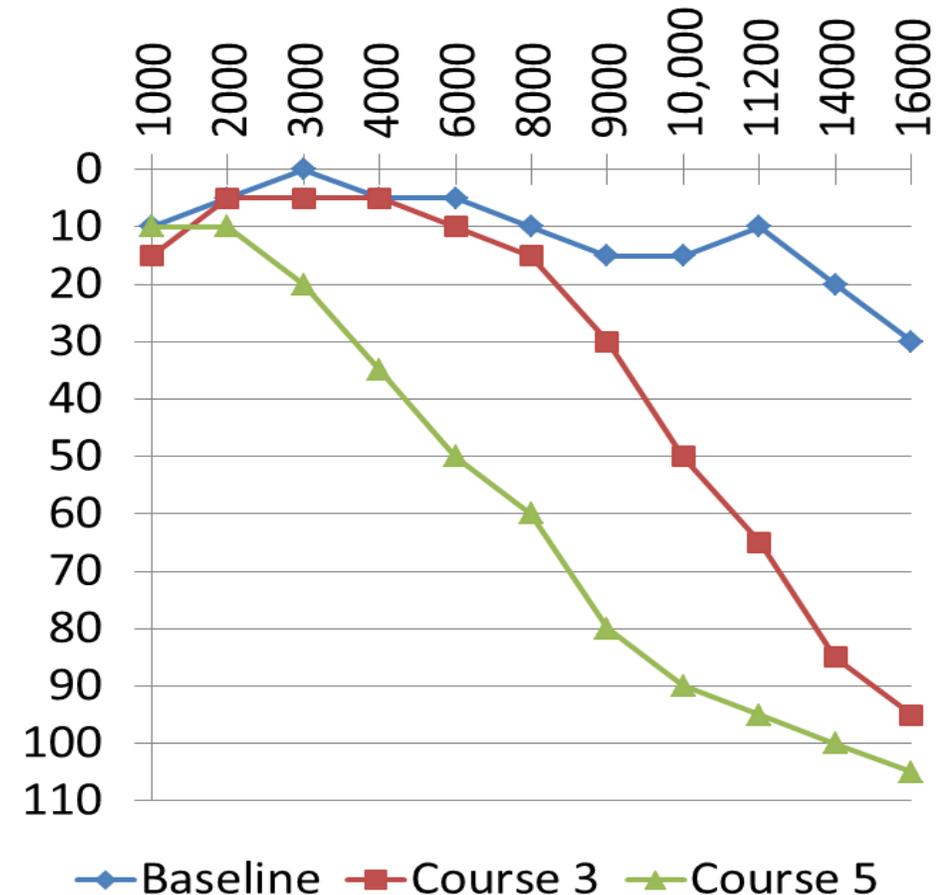
Ototoxicity monitoring methods

- Behavioral audiometry
(.5, 1, 2, 3, 4, 6, 8 kHz)
standard, play, VRA
- Speech Audiometry
- Otoscopy/tympanometry
- DPOAEs
- Extended high frequency audiometry (>8000 Hz)
- Acoustic reflexes
- ABR/ASSR
- Tinnitus questionnaire



Extended high frequency audiometry

- Can be used for monitoring in most children 4-5 years and older
- Earliest detection - provides a more sensitive signal for ototoxicity research, but at this time does not impact clinical care
- In young children, the speech frequency range (500-8000 Hz) should be measured first



High frequency audiometry

301 OHSU pediatric patients treated with cisplatin, 147 had EHF testing (49%):

133 (90%) ototoxicity in the EHF range

84 (63%) ototoxicity in the conventional test range

In all cases ototoxicity was detected in the EHF range before or at the same time as hearing loss in the conventional range.

Subset of 42 patients treated for MB: median cumulative dose to ototoxicity:

EHF range: 150 mg/m²

Standard range:

225 mg/m² severe ototoxicity

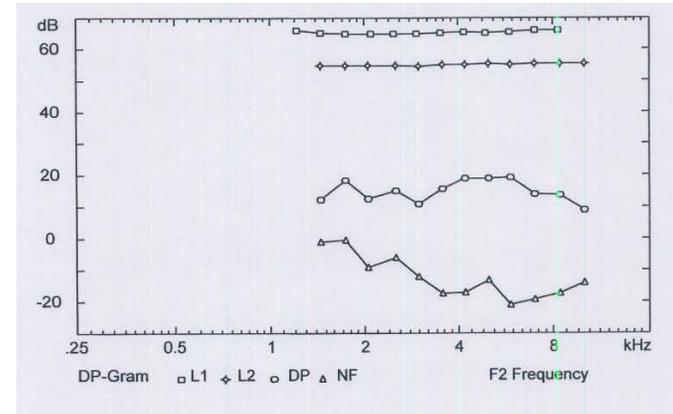
300 mg/m² mild ototoxicity

EHF ototoxicity did not predict risk for severe ototoxicity

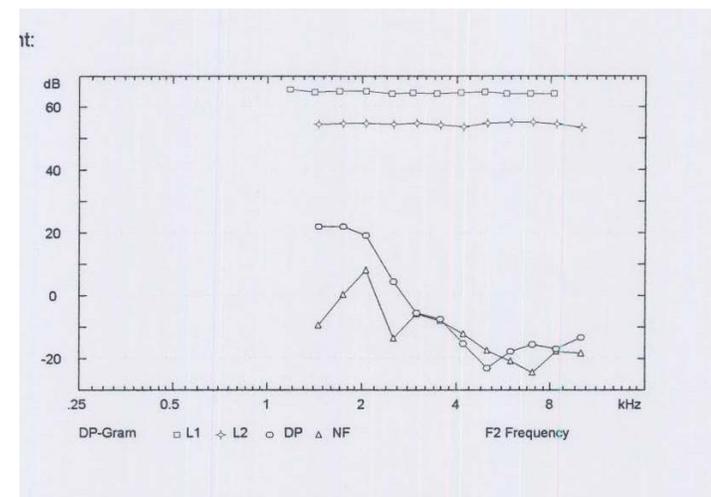
DPOAEs

- May identify ototoxic damage before pure tone audiometry
- Currently no ototoxic change criteria or grading system for DPOAEs
- Variables
 - Middle ear function
 - Cooperation/crying
 - Maturational changes in DPOAE level during first 12 months of life

Baseline



After 4th cisplatin course (400 mg/m²)



Coradini et al., *J Pediatr Hematol Oncol.* 2007;29(6):355-60

Knight et al., *J Clin Onc,* 2007;25(10):1190-5

Konrad-Martin et al., *Ear Hear,* 2017; doi: 10.1097/AUD.0000000000000536

Prieve et al., *J Acoust Soc Am;* 102:2871–2879

Acoustic reflex measurement or screening

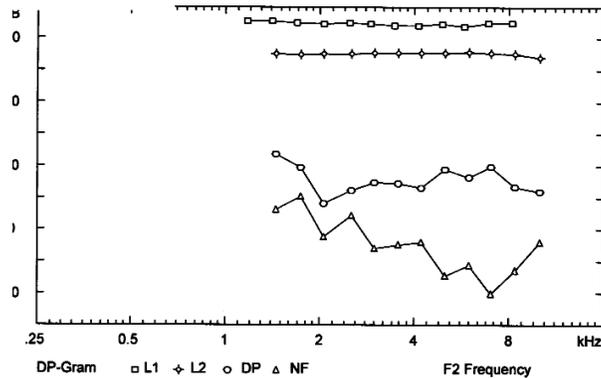
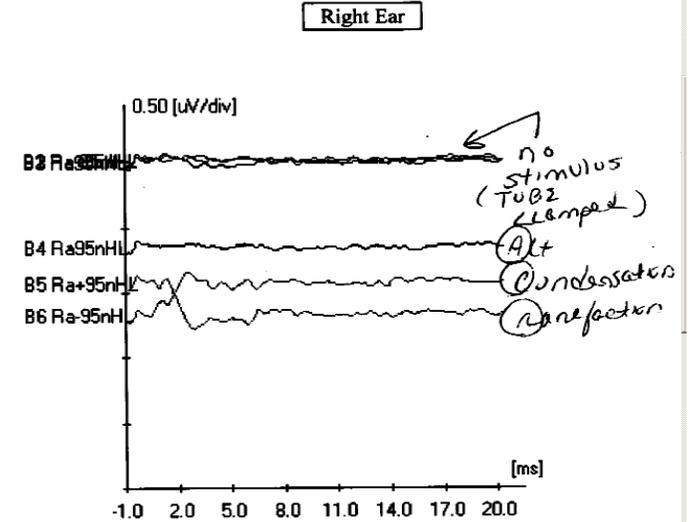
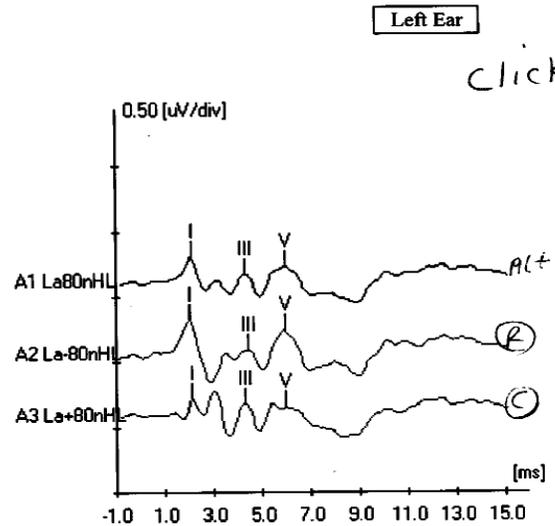
Screen ipsilateral reflexes:

1000 and 2000 Hz: 85–95 dB HL or
broad-band noise: 75–90 dB HL

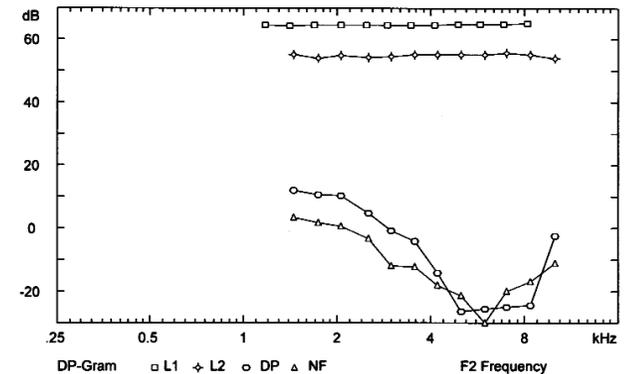
Additional diagnostic measurement if
reflexes are absent.

In 256 patients with brain tumors
followed at DCH, 10 were diagnosed
with neural/retrocochlear HL hearing
loss at baseline related to tumor or
resection

S2709



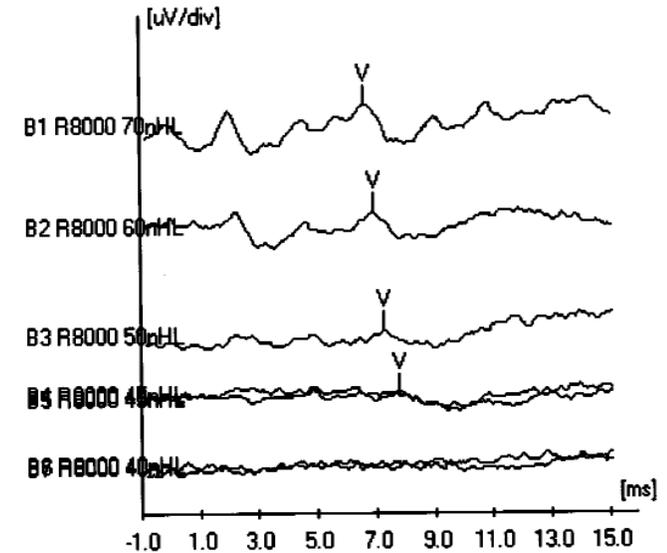
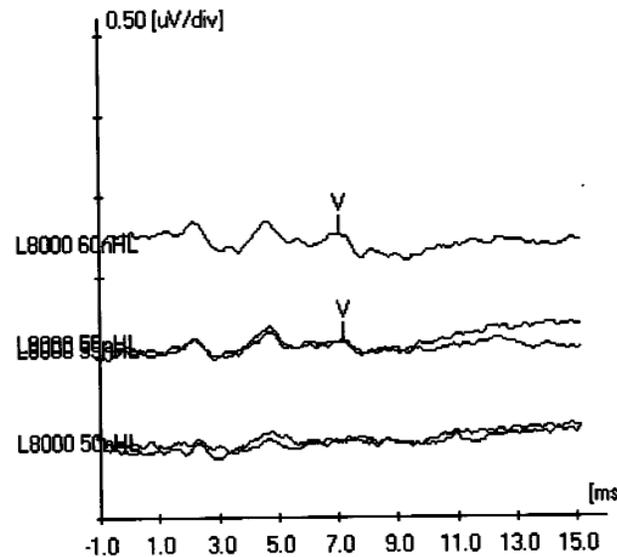
Baseline DPOAEs



End of treatment DPOAEs

ABR

- May be combined with other sedated procedures
- Click-evoked ABR will not identify ototoxicity
 - Tone-burst evoked threshold measurement is necessary
 - Including 6000 or 8000 Hz thresholds will increase sensitivity and allow for earlier detection of ototoxicity



Speech audiometry

- Important for assessing the functional impact of ototoxicity
- Average vs soft speech, quiet vs noise
- Options:
 - Ling sounds + /k/ and /t/
 - UWO Plurals
 - High frequency word lists
 - BKB SIN
 - QuickSIN

Suggested monitoring protocols

5 years +

Baseline and end of therapy:

Pure tone audiometry + >8000 Hz

Speech recognition

DPOAE, otoscopy,
tympanometry, AR

Tinnitus

Monitoring:

Pure tone audiometry+ >8000 Hz

DPOAE, otoscopy, tympanometry

7 months – 5 years

Baseline and end of therapy:

Pure tone audiometry+ >8000 Hz
if possible

DPOAE, otoscopy,
tympanometry, AR

Speech recognition if possible

Monitoring:

Behavioral audiometry

EHF if possible

DPOAE, otoscopy, tympanometry

Infant or patient with limited responsiveness

Baseline and end of therapy:

ABR, DPOAE, otoscopy and
tympanometry

Monitoring:

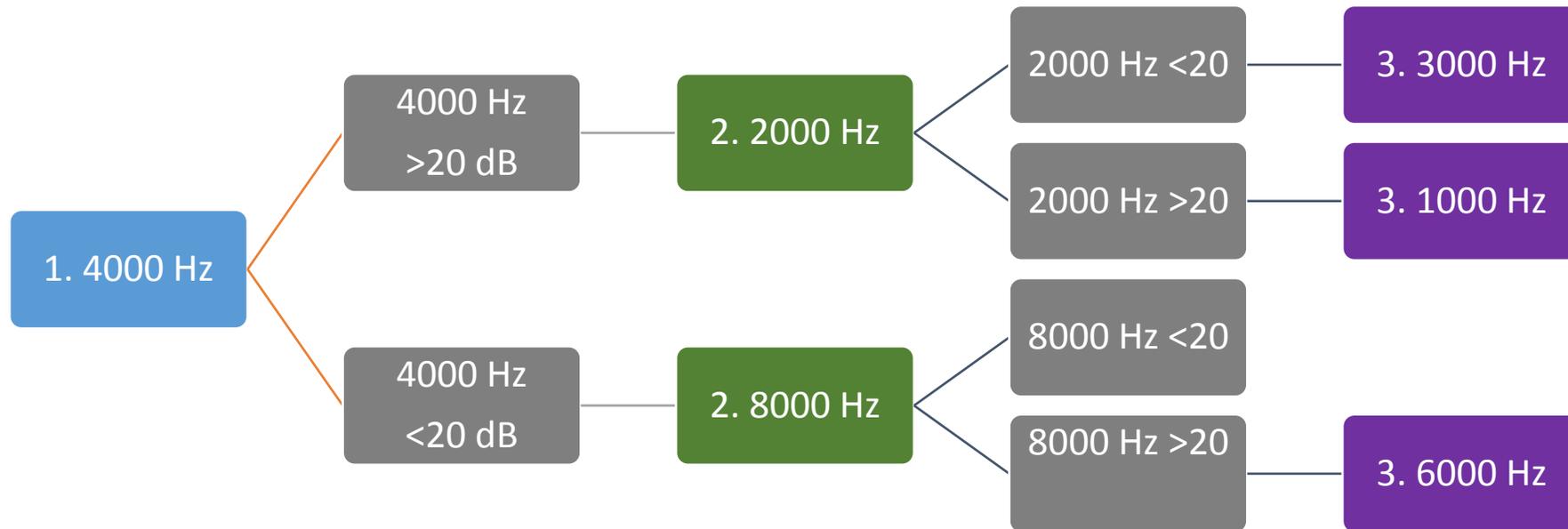
DPOAE, otoscopy and
tympanometry.

Repeat ABR if DPOAEs indicate
hearing loss at frequencies that
inform treatment or indicate
intervention

*Audiometry as soon as able.

Minimal test battery sequence

Goal: obtain most essential information first



Improving patient access to ototoxicity monitoring

- Portable equipment for testing at bedside or in the oncology clinic area
 - DPOAEs, tympanometry, portable audiometer, ABR
- Available to see patients on short-notice, same-day
 - Urgent/blocked appointment times
 - Easy scheduling – point person
- Coordinate follow-up visits with admissions for chemotherapy
- Audiology included in pediatric survivorship program

Engaging the healthcare team

- Ask the team how they would like to receive communication about results
- Assist families and survivors with resources and care coordination

Children's Oncology Group Long-term Follow-up Guidelines

- Patients with history of exposure to cisplatin or carboplatin (myeloablative doses or any dose if age at exposure was <1 year)
 - Hearing evaluation at entry into long-term follow-up program
 - If hearing loss is detected, test at least yearly or as recommended by the audiologist

Children's Oncology Group Long-term Follow-up Guidelines

- Patients with history of cranial radiation (>30 Gy)
 - 10 years and older: annual hearing evaluation for 5 years after completion of therapy
 - Younger than 10 years: continue annual hearing evaluations until age 10, then every 5 years.

If hearing loss is detected, test at least yearly or as recommended by the audiologist.

Long-term outcomes: hearing

Hearing loss can worsen years after treatment

- 97/204 (48%) had further deterioration in hearing from 6-125 months post-treatment¹

Incidence higher in patients with a longer follow-up period (70% >60 months)

- 30/59 (51%) worsening hearing loss from 12-91 months post-treatment²

Posterior fossa radiation (P=0.02) and the use of hearing aids (P=0.01) were significantly associated with progressive hearing loss

¹Peleva et al., *Pediatr Blood Cancer*, 2014; 61(11):2012-7

²Kolinsky et al., *J Pediatr Hematol Oncol*, 2010; 32(2):119-23

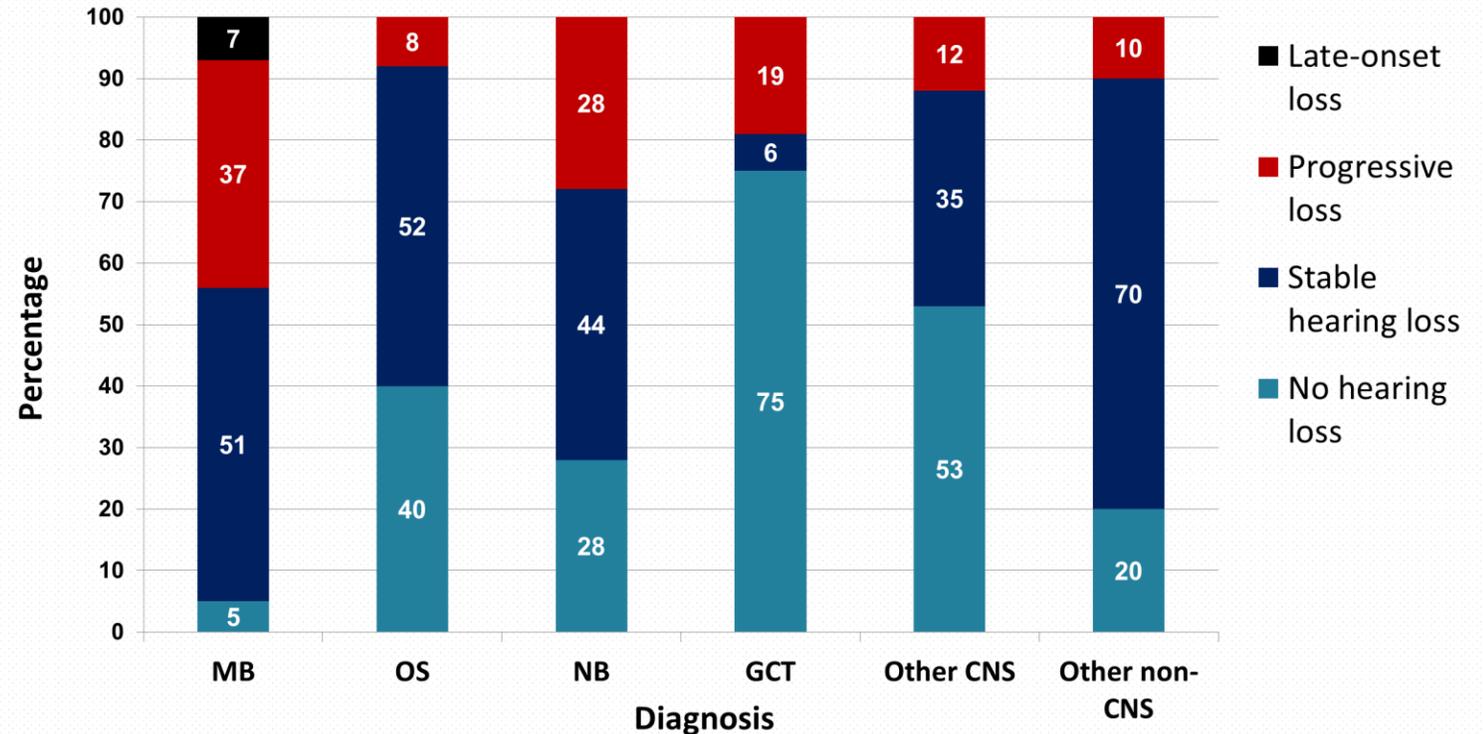
Long-term hearing outcomes

Progressive hearing loss 28/127 (22%) childhood cancer survivors followed at DCH.

Mean time to identification of hearing loss progression: 3.6 years after end of treatment

Risk factors:

- Cranial radiation + cisplatin (P=0.03)
- Younger age at treatment (P=0.03)
- Greater length of follow-up (P=0.04)



Long-term outcomes: Learning and cognition

137 neuroblastoma survivors, 11 years after diagnosis¹

- Survivors with hearing loss had twice the rate of parent-reported problems with reading, math, attention, learning disability, and/or special education needs
- Children with hearing loss reported poorer QOL and school functioning

165 medulloblastoma survivors, 5 years after diagnosis²

- Severe hearing loss was independently associated with declines in cognition (-2.07 points/y; P<.01) and reading ability (-1.69 points/y; P<.01)

¹Gurney et al., *Pediatrics*, 2007; 120(5):1229-36

²Schreiber et al., *Neuro Oncol*, 2014; 16(8):1129-36

Long-term outcomes: socioeconomic

226 childhood cancer survivors who received cisplatin for treatment of non-CNS pediatric solid tumors

Mean age: 31 years (19-53 years)

Average 22 years since cancer diagnosis

89 (39%) had severe hearing loss

Survivors with severe hearing loss were at twice the risk for non-independent living, not graduating from high school or being unemployed

Long-term outcomes: Quality of Life

HRQOL prospectively assessed with the Pediatric Quality of Life Inventory (Peds QL) + cancer module

Eligibility

- ≥ 200 mg/m² cisplatin
- 18 years or younger at the time of cisplatin therapy
- ≥ 1 year between completion of treatment and enrollment

Parent proxy versions for participants ≤ 18 years

Hearing questionnaire and used to obtain information about school services, history of hearing device use, and perceived communication difficulties.

Hearing status was obtained from end-of-treatment and current audiologic evaluations.

Results:

Data has been analyzed for 66 participants (36M, 30F)

- Median age 17.7 years (3.6-35.11)
- Mean time since completion of platinum therapy: 9 years (1.5-22.0)
- Hearing status at the end of therapy:
 - No hearing loss: 18 (27%)
 - Mild hearing loss: 25 (38%)
 - Severe hearing loss: 23 (35%), 7 reported current hearing aid use

Results:

- No differences in HRQOL as measured by the Peds QL among survivors based on hearing loss.
- Severe hearing loss was associated with:
 - Speech language delay ($P < .01$)
 - Learning disability ($P = .03$)
 - Limited participation in activities due to hearing loss ($P < .0001$)
 - Need for educational accommodations or special education services ($P < .01$)
- Survivors with severe hearing loss reported greater difficulties with communication: background noise, in a group, on the phone, listening to audio

Pediatric otoprotection trials

In 2005: Two phase III randomized clinical trials were developed to study sodium thiosulfate (STS) for protection against cisplatin induced hearing loss in children

- Children's Oncology Group (COG): ACCL0431
- International Society of Pediatric Oncology Liver Tumours Strategy Group (SIOPEL): SIOPEL 6
- First cooperative group trials developed to study otoprotection

Methods: audiologic evaluations

- Pure tone audiometry
 - 500-8000 Hz
 - >8000 Hz for children 5+ years, and where available
- Otoacoustic emissions
- Otoscopy and tympanometry
- Frequency specific ABR when audiometry was not possible

Baseline, before each cisplatin course and 4 weeks after completion of therapy

Study audiologists: independent central review of all audiologic results

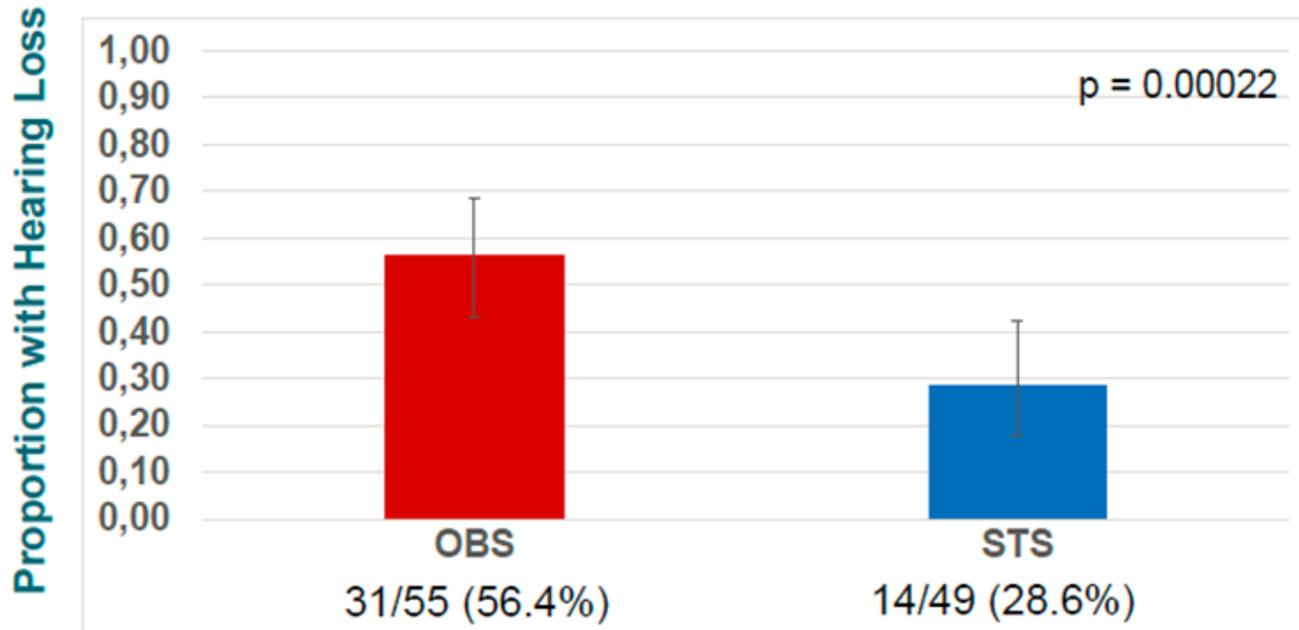
Primary endpoint:

ACCL0431: Hearing status 4 weeks after the last cisplatin dose

SIOPEL 6: Hearing status measured by pure tone audiometry at age 3.5 years

Results: COG ACCL0431

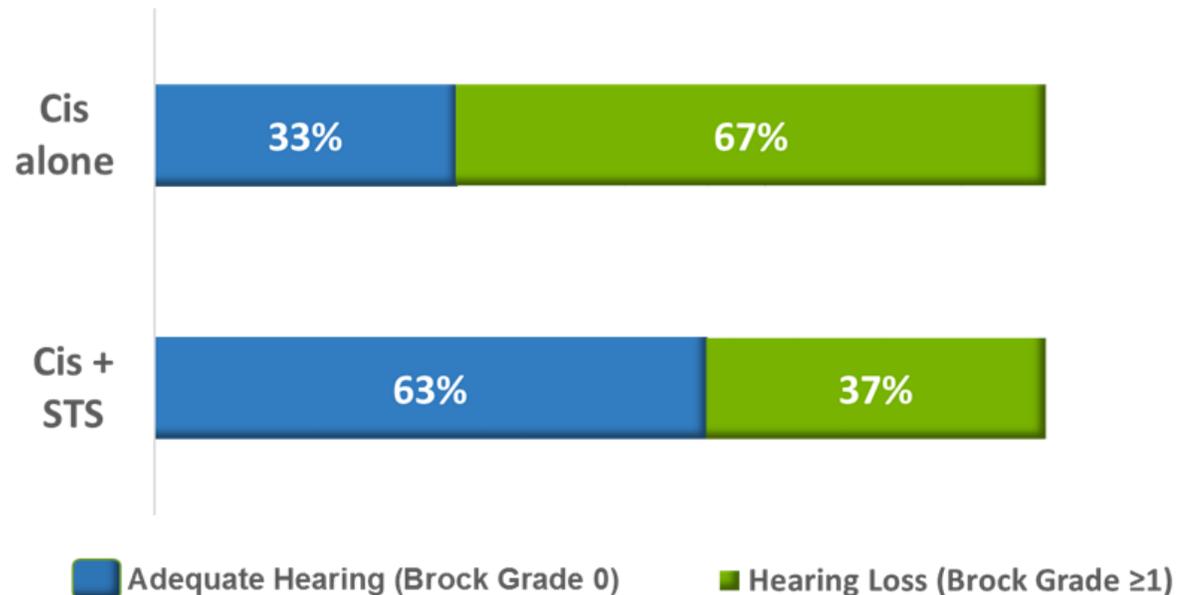
Hearing loss by randomized group n=104



- 32 COG sites in US and Canada
- Various cancer diagnoses, stages, treatment regimens
- STS iv 16 g/m² 6 hours after each cisplatin cycle
- Ototoxicity: ASHA, audiologist central review

Results: SIOPEL 6

Hearing loss by randomized group n=99



- 51 SIOP centers in Europe, Japan, S America, Australia Children with standard-risk hepatoblastoma, cisplatin monotherapy
- STS iv 20g/m² 6 hours after each cisplatin cycle
- Ototoxicity: ≥ Brock 1, audiologist central review

Other agents that show promise for platinum otoprotection

- D-Methionine (D-MET)
- Ebselen
- Intra-tympanic steroids
- N-Acetylcysteine (NAC)
- Neuroprotectin (AP-001)
- SENS-401

Audiologists will have an important role in clinical trials designed to study efficacy.

Summary

- Ototoxicity is common following cisplatin chemotherapy.
- Children treated with ototoxic therapy require audiologic monitoring during and after treatment.
- Audiology is an essential component of care and audiologists are an important member of the clinical team.
- Ototoxicity monitoring improves long-term outcomes and quality of life in children who require ototoxic therapy.

Summary

- The acceptance of hearing loss in children treated with cisplatin has changed.
- Central audiology review is feasible and is essential for clinical trials of ototoxicity or otoprotectants.
- There is an expectation and obligation for continued research into methods that can reduce or prevent treatment-induced hearing loss.