Ototoxicity Monitoring in Children

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Outline

- About Ototoxicity Monitoring in Children
- Platinum-Based Chemotherapy
- Consequences of Adolescent Hearing Loss
- Schedule for Testing
- Types of Mechanical Testing
- Monitoring Protocol
- Challenges to Ototoxicity Monitoring in Children

About Ototoxicity Monitoring in Children

- Incidence of ototoxicity in children treated with platinum chemotherapy: 26% to over 90%
  - Differences in dose of drugs, time between courses, time of administration, cumulative dose
  - Differences in age
  - Definition of ototoxicity
  - Individual Variability
- Ototoxicity monitoring for children is inconsistently practiced due to:
  - Lack of age-specific regulations
  - Lack of studies to determine monitoring frequency

Characteristics of Platinum Ototoxicity

- Hearing loss in the high frequencies initially
- Hearing loss increases in severity and spreads to lower frequencies with continued treatment
- Platinum causes damage to stria vascularis, outer hair cells, and eventually inner hair cells

References:
Blakely et al., Otolaryngology Head & Neck Surgery, 1993; Breglio, Rusheen, Shide, Fernandez, Spielbauer, McLachlin, Hall, Amable, Cunningham (2017) Cisplatin is retained in the cochlea indefinitely following chemotherapy. Karasawa T & Steyger P. (2015). An integrated view of cisplatin-induced nephrotoxicity and ototoxicity, Toxicol Lett, 17,237 (3), 219-27. Sheth et al. (2017). Mechanisms of Cisplatin-induced Ototoxicity and Ototoprotection, Front Cell Neurosci, 11:388

Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium

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At what frequency and for how long should surveillance be done?

Risk of hearing loss in children, adolescent, and young adult cancer survivors	
Hearing function might deteriorate over time after platinum-based drugs (as a group); in some patients, hearing function improves or remains stable	Level C[32,33,51–55]
Hearing function might deteriorate over time after cranial radiotherapy (also in combination with platinum or CSF shunts); in some survivors hearing function improves or remains stable	Level C[5,10,55–57]
Predictors for change of hearing function over time unknown	No studies
Unknown likelihood of change of hearing loss over time after comedication, surgery involving the ear or cranial nerve VIII, or after noise exposure	No studies
Risk of tinnitus in children, adolescent, and young adult cancer survivors	
Unknown likelihood of change of tinnitus over time	No studies

Clemens E, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol*. 2019;20(1):e29-e41.

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

Childhood cancers commonly treated with platinum chemotherapy:

<u>Cisplatin:</u>
Brain and CNS cancers
Neuroblastoma
Hepatoblastoma
Osteosarcoma
Germ cell tumors

<u>Carboplatin:</u>
Brain and CNS cancers
Low-risk neuroblastoma
Retinoblastoma
Optic nerve glioma

Factors that increase a child's risk for platinum ototoxicity

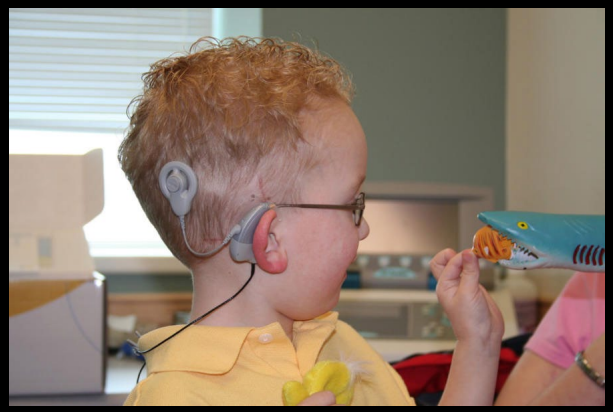
- Young age
- Cranial radiation before platinum chemotherapy exposure > 30 Gv
- Cumulative cisplatin does > 360 mg/m^2
- Treatment with more than one ototoxic medication
- Genetic predisposition

Li et al., Pediatric Blood and Cancer, 2004
Carleton et al., *Clin Pharmacol Ther*, 2014; 96(3):296-98
Lewis et al., *Pediatr Blood Cancer*, 2009; 52(3):387-91
Chang & Chinosornvatana, *J Clin Oncol*, 2010; 28:1788-95

Why Monitor and Manage Ototoxicity?

- Oncologist may be able to change treatment
  - decrease platinum dose or use a different treatment
- Recommend habilitation for hearing loss if needed
- Provide information to parents/ teachers

*children may not report difficulty hearing



Consequences of High Frequency Hearing Loss

- Difficulty hearing/discriminating high frequency speech sounds (s,f,th,k,p,h,sh,ch)
  - Consonants provide most of the information in the speech signal
  - HF consonants provide important morphological markers (plurals, tense)
- Difficulty hearing any speech over distance and in noise
- Even mild HL can delay speech and language development in young children and increase risk for difficulty in school

Stelmachowicz et al, Archives Otolaryngology Head & Neck Surgery, 2004

Schedule for Testing

- Cisplatin
  - Before first platinum treatment perform baseline
  - Monitoring evaluations before each dose
  - Final evaluation 4-6 week after final dose
- Carboplatin
  - Baseline exam
  - Final evaluation at the end of therapy
    - For infants, monitor during therapy
- Posterior Fossa Radiation
  - Baseline exam
  - Final evaluation at the end of therapy

* Long-term follow ups are suggested after therapy is complete

OAEs

- Middle ear fluid
  - Ear specific
- OAEs interpreted as present vs. absent in pediatric ototoxicity monitoring
  - Used in PEDIATRIC cancer drug trials for testing protocols
  - May not result in treatment change but provide insight that cochlear function is being impacted
- May identify ototoxic change before hearing loss is detected with pure tone audiometry

OAE Changes Greater than Normal Test-Retest Variability Can Indicate Ototoxicity

- Change criteria for DPOAEs depends on test-retest variability with OAE instrumentation, population, and duration of monitoring

Test-retest variability is greater:

- With increase time between measurements (>4 months)
- In the high frequencies >6000 Hz
- In children compared to adults

Konrad-Martin et al. (2017). Long-term Variability of Distortion-Product Otoacoustic Emissions in Infants and Children and its Relation to Pediatric Ototoxicity Monitoring. Ear Hear, doi: 10.1097/AUD.0000000000000536

ABR/ ASSR

- Estimates hearing thresholds when audiometry is not possible
- Usually requires sedation
- Click-evoked ABR will not sensitively identify ototoxicity
  - Tone-burst evoked measurements are necessary
  - Including 6000 or 8000 Hz threshold will increase sensitivity and allow for earlier detection of ototoxicity

Ototoxicity Monitoring Protocol

Baseline/ End of Therapy:

- Pure-tone audiometry 500-8000 Hz
- Otoscopy, tympanometry, wideband reflectance
- DPOAE
- AR
- Recommended test: speech recognition

Monitoring:

- Behavioral audiometry
- DPOAE, otoscopy, tympanometry
- Recommended test: EHF

Brooks & Knight. (2018). Ototoxicity monitoring in children treated with platinum chemotherapy. *Int J Audiol. 57* (sup4),S34-S40

Ototoxicity Monitoring Protocol

Baseline/ End of Therapy:

- Pure tone audiometry (500-8000 Hz, EHF thresholds)
- Speech recognition
- DPOAE, otoscopy and tympanometry
- AR
- Tinnitus

Monitoring:

- Pure tone audiometry (500-8000 Hz, EHF thresholds)
- DPOAE, otoscopy and tympanometry

*If hearing loss and or conductive middle ear pathology become present conduct bone conduction threshold testing

Brooks & Knight. (2018). Ototoxicity monitoring in children treated with platinum chemotherapy. *Int J Audiol. 57* (sup4),S34-S40

Challenges to Ototoxicity Monitoring Children

- Incomplete results
  - Age, development, health status, cooperation
  - Sound field testing (earphone refusal)
  - Conductive middle ear disease
  - Need for bedside testing
- Logistics/time/scheduling
  - Same-day/ urgent appointments
  - Coordinated with other sedated procedures (ABR)

Citation

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