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Auditory Late Effects of Childhood Cancer Therapy: a report from the Children's Oncology Group

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Abstract

Children treated for childhood malignancies may be at risk for early or delayed onset hearing loss that can impact learning, communication, school performance, social interaction, and overall quality of life (QOL). Survivors at particular risk include those treated with platinum compounds (cis-and/or carboplatin) for neuroblastoma, hepatoblastoma, osteosarcoma, or germ cell tumors and/or those treated with radiation impacting the ear at doses greater than 30 Gray (Gy) for pediatric head and neck tumors. The aims of the Auditory/Hearing Late Effects Task Force of Children's Oncology Group in this report were: 1) to review ototoxicity resulting from childhood cancer therapy including platinum compounds (cisplatin and carboplatin) and radiation; 2) to describe briefly cochlear pathophysiology and genetics of cisplatin-related hearing loss; 3) to explain the impact of hearing loss resulting from chemotherapy and radiation; and 4) to offer recommendations regarding evaluation and management of pediatric patients at risk for treatment-related hearing loss. A questionnaire is included as a tool to assist pediatricians in assessment.

Keywords

Ototoxicity; Carboplatin; Cisplatin; Radiation; Hearing loss

INTRODUCTION

With multimodality therapy, 80% of patients diagnosed with cancer in childhood or adolescence are expected to become survivors (<http://seer.cancer.gov/faststats>). Among functional impairments that result from cancer treatment, hearing loss may be detrimental to

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speech and language development, educational achievement, communication, social interaction, integration and overall quality of life (QOL), particularly in very young children.

Hearing loss as a late effect of therapy can occur following exposure to cancer therapeutic agents such as platinum compounds and cranial irradiation. Platinum agents (cisplatin and carboplatin) have improved cure rates of many childhood cancers, but their use may result in irreversible high frequency sensori-neural hearing loss.^{1–15} The deficit is progressive with increasing cumulative dosage of cisplatin. In general, approximately 50% of children treated with cisplatin-based regimens reportedly develop some degree of permanent hearing loss.^{2,3,11–13} With cumulative doses in excess of 400 mg/m², up to 90% of young children may suffer moderate to severe deficits, with severe hearing loss seen in up to 25%.^{2,6–8,11–13}

Cranial radiation therapy, when used as a single modality, typically results in ototoxicity only when cochlear dosage exceeds 32 Gray (Gy).¹⁴ Young patient age and presence of a brain tumor and/or hydrocephalus can increase susceptibility to hearing loss. The onset of radiation-associated hearing loss may be gradual, manifesting months to years after exposure. However, when used concomitantly with cisplatin, radiation therapy can substantially exacerbate the hearing loss associated with platinum chemotherapy.^{2,14,16–20}

The objectives of this manuscript are to increase awareness of auditory toxicity as a late effect of therapy for cancer in children and young adults, and to disseminate recommendations for risk-based screening of auditory complications from the Children's Oncology Group Long-Term Follow-Up Guidelines.^{21,22} A questionnaire for screening pediatric patients at risk for hearing loss is provided in Appendix 1.

BRIEF OVERVIEW OF CHILDREN'S ONCOLOGY GROUP (COG) GUIDELINES

The Children's Oncology Group Long-Term Follow-Up Guidelines^{21,22} are risk-based, exposure-related recommendations designed to direct follow up care for survivors of pediatric malignancies. The COG Guidelines are appropriate for the follow up of survivors who are two or more years following completion of therapy. Recommendations within the Guidelines are intended for screening of asymptomatic individuals. The Guidelines are reviewed and monitored by multidisciplinary Task Forces whose members are professionals and patient advocates with interest and expertise in specific late effects.

"Health Links" are patient education materials accompanying the COG Long-Term Follow-Up Guidelines that provide information about complications and provide an emphasis on healthy lifestyle.²³ These instructional materials, as well as the Guidelines, may be downloaded from www.survivorshipguidelines.org.²²

METHODS

Literature review methodology: The Auditory/Hearing Task Force performed three systematic reviews of 31 articles in the literature via MEDLINE (National Library of Medicine, Bethesda, Maryland) in 2004, 2006, and 2008. Key search words included "childhood cancer therapy", "complications", "late effects" "hearing loss", "ototoxicity", "otoprotection", "ear", "radiation therapy", "cisplatin", "platinum", "osteosarcoma", "germ cell tumors", "neuroblastoma", "bone marrow transplant". References from selected articles were used to expand the list. The development of COG Guidelines for monitoring of ototoxicity also included consideration of recommendations from the American Academy of Pediatrics Clinical Report, "Hearing Assessment in Infants and Children: Recommendations Beyond National Screening."²⁴

The evidence for the Guidelines was scored by a panel of experts in the late effects of pediatric malignancies using a modified version of the National Comprehensive Cancer Center Network “Categories of Consensus” system http://www.nccn.org/professionals/physician_gls/categories_of_consensus.asp.²⁵

Interpretation of the literature on ototoxicity requires knowledge of grading systems used to evaluate this complication. Knight et al suggest that the main criteria for detection of ototoxicity are those of the American Speech and Hearing Association (ASHA).¹¹ Two other grading systems, those of Brock et al³ and the Common Toxicity for Adverse Events, version 3 are also in use today.²⁶ Variability in reporting hearing loss via different criteria affects reported incidence and each grading system has limitations that may minimize the significance of hearing loss.¹¹ ASHA criteria may fail to detect communicatively significant hearing loss since these standards assess absolute change in hearing thresholds over time. The Brock system³, although developed specifically to evaluate cisplatin- related hearing loss, does not account for change in hearing over time. The National Cancer Institute Cancer Therapy Evaluation Program’s Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) lack agreement with those of ASHA and have similar potential risk of underestimation of ototoxicity.

GENETICS AND PATHOPHYSIOLOGY

Individual susceptibility to cisplatin ototoxicity is variable.^{27–31} Dolan et al²⁷ demonstrated that 38–47% of human variation in susceptibility to cisplatin-induced ototoxicity is due to genetic variables. Huang et al²⁸ identified 17 variations among 26 genes in cell lines derived from individuals in two large populations. Among these genes, DDIT4 is a mediator of reactive-oxygen species generation³²; NEK2 is required for proper execution of mitosis³¹, and MYC plays a role in cell-cycle progression, apoptosis, and cellular transformation.³⁰

The mechanism of platinum cochlear toxicity is through interference with signal transduction from the Organ of Corti in the cochlea. Three sites of damage occur: the outer hair cells (effector cells), the spiral ganglion (main nerve supply to the cochlea), and the stria vascularis (primary blood supply).^{33,34} Also, magnesium, a cation required to maintain hair cell permeability³⁵ and cochlear blood flow³⁶, may become depleted after cisplatin because of renal wasting or decreased intestinal absorption. Magnesium deficiency also affects the ionic composition of endolymph³⁷ and perilymph³⁸ in the stria vascularis, and lowers the threshold for stimulating a cochlear action potential.³⁵

Cochlear hair cells are arranged such that each hair cell is sensitive to a limited frequency range. Chemotherapy-related damage begins in the first row of outer hair cells at the base of the cochlea^{29,39,40} where high frequency sounds are processed. Hence, use of platinum compounds can result in bilateral sensorineural hearing loss, which initially involves the higher frequencies (4000–8000 Hz).^{2,41} With increasing cumulative doses of chemotherapy, or when compounded by other ototoxic factors such as pre-chemotherapy irradiation, loss of hair cells can progress apically in the cochlea to involve the speech frequencies.^{2,9,41} High frequency hearing sensitivity is critical for the understanding of speech. The speech frequencies are considered to be 500 Hz through 2000 Hz.⁴² However, fifty percent of English consonants contain energy through 8000 Hz. Many of the voiceless consonant and fricative sounds (such as, “th”, “f”, “k”, and “s”) lie in this range (Figure 1). The /s/ sound spoken by women and children are indistinguishable from the /f/ and /th/ when there is a significant hearing loss above 4000 Hz. As the English language relies heavily on consonants to convey the meaning of words, high-frequency hearing loss can give the feeling of “hearing but not understanding”.

CHEMOTHERAPY-ASSOCIATED HEARING LOSS

Chemotherapy-associated hearing loss can be caused by platinum agents, specifically, cisplatin and high-dose carboplatin.^{1–15} Cisplatin and carboplatin are active against a variety of childhood malignancies, including neuroblastoma, osteosarcoma, hepatoblastoma, germ cell tumors, and certain brain tumors.^{43,44} High-dose carboplatin may be part of myeloablative regimens for stem cell transplantation in children with solid tumors.^{6,12,44} Ototoxicity is a relatively common and well-studied side effect of these drugs.

Children are more susceptible to ototoxicity from platinum agents than adults.^{1,8} Cisplatin and carboplatin are not equivalent in terms of dosing. Whereas cisplatin is typically dosed on a milligram per meters squared basis, carboplatin may be administered based on glomerular filtration rate⁴⁵ or by body surface area.¹² For cisplatin, the risk of significant hearing loss involving the speech frequencies (500–2000 Hz) usually occurs with cumulative doses exceeding 400 mg/m² in pediatric patients.^{2,12} While in adult patients 600 mg/m² is considered to be the threshold for significant hearing loss involving the speech frequencies⁴⁶, in children 400 mg/m² is generally considered the maximum dose to avoid unacceptable speech frequency hearing deficits.¹¹ For carboplatin⁸, ototoxicity has been reported to occur at similar cumulative doses in excess of 400 mg/m². Transplant protocols for neuroblastoma may utilize doses nearly four times this amount.⁴⁷

Incidence and risk factors

Several factors determine risk of hearing loss with use of platinum agents. The major risk factors are younger age, higher cumulative dose of chemotherapy, central nervous system (CNS) tumors, and concomitant CNS radiation. Hence, patients with neuroblastoma and CNS tumors form a particularly high risk group for hearing loss.

Children with high-risk neuroblastoma are typically under 5 years at diagnosis, receive aggressive cisplatin-based chemotherapy, and may receive high-dose carboplatin-containing myeloablative preparative regimens for stem cell transplantation.^{6,11–13} Due to the high intensity of therapy, these children may also need supportive care with aminoglycosides and loop diuretics. Kushner et al¹² observed severe hearing loss in at least 50% of their under 5 year-old neuroblastoma patients, with moderate to severe deficit seen in up to 90%. Laverdiere et al¹³ reported hearing loss in 62% of 63 long-term survivors of neuroblastoma. Thirty-eight of 39 patients had received cisplatin (median dose 502 mg/m²). Nearly 50 percent of these survivors needed hearing aids.¹³

Young children with CNS tumors, such as medulloblastoma, comprise another high risk group for ototoxicity.^{2,4,16,20,48–50} These children undergo cranial surgery, often with ventriculoperitoneal shunt placement, and may require platinum-based chemotherapy as well as cranial radiation. In the report by Schell et al² the presence of a brain tumor alone was associated with a 12 dB worse hearing threshold in children who had received one to three courses of cisplatin. Packer et al⁵⁰ reported a 48% incidence of grade 3–4 toxicity in 63 patients and Kortman et al⁵ observed ototoxicity in 34% of 65 children. Other reports with smaller sample size have observed ototoxicity rates of up to 80–100%.^{19,51,52}

For patients with germ cell tumors (GCT) who receive cisplatin, two important determinants of ototoxicity are age at exposure and cumulative dose.^{9,10,49} As most pediatric GCT occur in older children, this group may be at lower risk for cisplatin-associated hearing loss.^{8–10,49} In a Pediatric Intergroup Study for patients with GCT, high dose (800 mg/m²) platinum was compared with low dose (400 mg/m²) administration.⁹ The overall incidence of grade 3–4 hearing loss was 14% versus 0%, respectively. In an analysis of data from children with GCT from the Intergroup Study, Li et al⁴⁹ observed a moderate to severe risk of hearing

loss in 40% of those <5 years of age exposed to 400 mg/m² of cisplatin compared with 5% among children over 15 years of age exposed to the same amount. These data suggest that older age at exposure and lower cumulative chemotherapy dosage are associated with lower risk for hearing loss.

Other factors may contribute to hearing loss associated with platinum agents. Medications such as aminoglycoside antibiotics and loop diuretics, used as supportive care, can also contribute to ototoxicity.^{53,54} Impaired renal function may delay excretion of the ototoxic platinum agents. Presence of co-existing ear pathology such as chronic otitis, middle ear effusions, or cerumen impaction can further worsen auditory impairment.

Onset and Duration

Clinically detectable hearing loss may require more than one cycle of a platinum agent to provide a threshold cumulative dose (Figure 2A) ². In a report of Knight et al ¹¹ which included children receiving platinum compounds for a variety of oncologic diagnoses, the median time to observation of ototoxicity as evaluated by the ASHA criteria was 135 days (Figure 2B). No patient in that series showed improvement in hearing. Most other reviews also suggest that hearing loss is permanent and stable after completion of therapy.^{2,6,12} However, one series by Bertolini et al ⁸ did observe progressive hearing loss as long as 136 months from the end of therapy with platinum compounds in a cohort of 120 survivors of pediatric solid tumors.

Carboplatin used in conventional (non-myeloablative) dosing is typically not ototoxic.^{6,8,55–58} A single recent report⁵⁹ observed ototoxicity following use of non-stem cell transplant dosing of carboplatin for retinoblastoma. Among 175 children exposed, eight developed hearing loss. Of note, in 7 of these the onset of ototoxicity was delayed with a median of 3.7 years.

As myelosuppression rather than nephrotoxicity is the dose limiting toxicity, carboplatin has evolved as part of a conditioning regimen for stem cell transplantation.^{6,12,44} With myeloablative dosing, carboplatin may cause significant ototoxicity. In children with neuroblastoma, Parsons et al ⁶ showed that children with existing ototoxicity (from prior cisplatin chemotherapy) before receiving high dose carboplatin conditioning were at high risk for further deterioration in hearing (Figure 3).

RADIATION-ASSOCIATED HEARING LOSS

Radiation-induced ear pathology can affect all parts of the auditory system. Approximately one third of problems have been reported to occur in the outer, middle, and inner ear, respectively.⁶⁰ Outer ear lesions may consist of chronic otitis externa, deep ulceration, osteoradionecrosis of the external auditory canal, atrophy, and ear canal stenosis.⁶⁰ Middle ear damage may include tympanic membrane perforation, chronic otitis media with effusion, dysfunction of the chorda tympani branch of cranial nerve VII (which carries taste sensation to the anterior part of the tongue), middle ear fibrosis, and mastoiditis. Inner ear symptoms may include hearing loss, tinnitus, vertigo, and other balance problems.

Sensori-neural hearing loss is determined by the radiation dose to the cochlea.^{14,16,18,60} This observation is based upon the fact that the cochlea is more sensitive to the effects of radiation than the brain or auditory nerves.^{61–65} The basal turn, which encodes high frequencies, is preferentially more sensitive to the effects of radiation than the apical region.⁶¹ Both outer and inner hair cell damage can occur.⁶⁶ The cochlea is extra-cranial, and therefore unlikely to be in the primary tumor field in a patient with a CNS tumor. At the same time, it may lie within the planning target volume or the gradient of highest doses.¹⁴

Treatment for infra-temporal and nasopharyngeal tumors is also likely to result in cochlear irradiation.

The “threshold dose” for auditory toxicity following radiation is in the range of 35–45 Gy for children.^{14,16} Merchant et al¹⁴ report that high frequency sensori-neural hearing loss is uncommon at cumulative doses of radiation less than 35 Gy given over 6 weeks. The exception is in patients with supratentorial tumors and ventriculoperitoneal shunts, in whom doses less than 30 Gy may be associated with intermediate frequency (1000–2000 Hz) hearing loss. Consequently, the recommendation is that the average cochlear dose should not exceed 30–35 Gy delivered over 6 weeks.^{14,16}

In patients with brain tumors, combined modality therapy (chemotherapy and radiation) has contributed to worse ototoxicity than either one alone.^{2,5,19,20} Administration of radiation prior to chemotherapy exacerbates risk.^{2,5,19,20} Kortmann et al⁵ reported ototoxicity in 34% of patients with medulloblastoma treated with radiation followed by cisplatin-containing chemotherapy, compared with 10 percent in those who received neoadjuvant chemotherapy prior to radiation. Grade 3 or 4 ototoxicity was reported in 9 percent of patients who were irradiated first, in contrast to 2 percent in the group initially treated with chemotherapy. In a study by Schell et al² approximately 50 percent of children with a variety of solid tumors treated at St. Jude Children’s Research Hospital with cumulative doses of cisplatin of > 450 mg/m² had significant high frequency hearing loss. Worsening involvement extending into the speech frequencies became apparent in a dose-dependent manner. However, the probability of substantial hearing loss in patients who also received cranial radiation increased to 40–60% at cisplatin doses of 270 mg/m² and 80–100% with doses of 450 mg/m² (Figure 4).

Conformal techniques, including intensity modulated radiation therapy, deliver radiation to target tissue with limited doses to surrounding normal tissue. Accordingly, the dose to the cochlea and eighth cranial nerve may be decreased.^{14,48} At a follow up of 10 years in a group of pediatric patients with low grade gliomas treated with conformal techniques, the cumulative incidence of hearing loss involving any frequency was only 5.7 +−3.3%.⁶⁷ Proton beam irradiation (PBI), a technique that concentrates radiation in the target tissue without the scattering effects of an “exit dose” may reduce the dose to the cochlea to nearly zero.^{18,68} Among 40 patients with brain tumors (10 each with optic pathway glioma, medulloblastoma, craniopharyngioma, and posterior fossa ependymoma) treated with PBI, dose distributions to the cochlea were below the threshold for radiation-induced hearing loss in all cases. The implications were most meaningful for patients with medulloblastoma, who also receive ototoxic chemotherapy.¹⁸

IMPACT OF HEARING LOSS IN CHILDREN

Hearing loss may impact QOL^{11,12,24,69}, socio-emotional development^{69,70} and academic performance.^{70–73} However, there is limited data in the cancer survivor population on actual impact. Gurney et al⁷⁰ studied parent-reported QOL in 137 survivors of neuroblastoma aged 8–17 years. These investigators noted twice the risk of problems with reading, math, general learning disability, and special educational needs in the 43 hearing-impaired survivors compared with the group without hearing loss. High concordance was found between poorer self- (patient) reported QOL and that of the parents in areas of school and psychosocial functioning.

Although data on hearing loss in the general population do not directly extrapolate to children and adolescents with treatment-related hearing loss, hearing impairment may affect speech and language acquisition, academic achievement, and psychosocial development

among affected children.^{71–77} In a report describing school performance of hearing impaired students without cancer in public school, 37% of children with minimal hearing loss were required to repeat a grade, in contrast to only 3% of other students.⁷¹ Even mild bilateral losses on the order of 15 to 26 dB have resulted in a delay of one grade level between expected and achieved academic performance.^{78,79} Bess and colleagues⁷¹ recorded less energy and more tiredness in junior high school students with mild hearing loss compared with a control group the same age. Ninth grade students in that series reported more stress, lack of social support, and lower self esteem that matched controls.

Thus, early identification of hearing deficits is important in order to facilitate normal or near normal acquisition of language, academic, and coping skills particularly in young children.^{71,74,75,80} Gifford et al provide an excellent review of hearing loss in children with emphasis on early intervention from the perspective of the American Academy of Pediatrics.⁸¹

OTOPROTECTANTS

Several otoprotectants are in clinical and preclinical trials, although their efficacy is unclear at present. Because cisplatin ototoxicity alters the antioxidant system of the outer hair cells^{33,34,82–84}, several agents that reduce oxidative stress in the cochlea have been tested.³³ Sodium thiosulfate^{69,85} is currently being tested by COG in an intervention trial in pediatric patients treated with cisplatin. Pre-clinical data indicate that this anti-oxidant confers otoprotection without affecting cytotoxicity.⁸⁴ Other antioxidant agents showing promise in the animal model include Vitamin E⁸⁶ and D-methionine.⁸⁷ After encouraging initial results in adult patients with ovarian cancer⁸⁸, amifostine as an otoprotectant was studied in children with high-risk germ cell tumors⁸⁹ and osteosarcoma⁹⁰ who received platinum-based regimens. Amifostine did not lessen the risk of unacceptable hearing loss in either group of pediatric patients, and was limited by emesis in patients with osteosarcoma.⁹⁰

RECOMMENDATIONS

Screening

All childhood cancer survivors should undergo yearly evaluation with appropriate risk-based screening for potential cancer-related complications.^{21–23} Specific screening for survivors exposed to potential ototoxic therapy is provided in Figures 5 and 6. A complete audiological evaluation consisting of air conduction, bone conduction, speech audiometry, and tympanometry should occur in survivors at risk for hearing loss upon entry into long term follow up, and more frequently if any change is noted⁹¹. Infants and survivors of any age who are difficult to test may require electrophysiological assessment such as auditory brainstem response measurement. Otoacoustic emissions provide objective information about outer hair cell function in patients treated with cisplatin. Patients who receive cranial irradiation are at risk for delayed onset hearing loss that may progress over a period of years, and thus need longer follow-up. Change in hearing sensitivity following ototoxic therapy should be evaluated relative to pre-treatment measures, when available, or according to the earliest known assessment.⁹²

Management of hearing loss

The general principles of management of hearing loss include awareness on the part of parents and providers, appropriate referrals to audiologists and otolaryngologists, and implementation of amplification and other adaptive strategies when indicated. Otolaryngology consultation may be considered for patients with chronic otitis media or externa, tympanic membrane abnormalities such as perforations, refractory cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss.⁶⁰ In

children with documented hearing loss, evaluation by a speech and language pathologist should also be obtained, since both articulation disorders and receptive and expressive language deficits may occur in hearing impaired children.

Amplification requires consideration of the severity and configuration of the hearing loss and age of the survivor. Hearing aids have been recommended in 30–40% of survivors of childhood cancers who experience hearing loss.^{12,13} In the report of Laverdiere et al¹³ the most frequent diagnosis for which hearing aids were prescribed was neuroblastoma, although osteosarcoma, germ cell tumors, and medulloblastomas were also represented. Further adaptations to enhance learning in the school setting include FM systems, reduction of background noise, preferential seating and mechanisms to increase face-to-face contact. Cochlear implants have been used rarely in childhood cancer survivors, such as medulloblastoma.^{93–95}

Health counseling

An explanation of hearing loss and its manifestations, as well as recommendations for health counseling for survivors with auditory toxicity are found in the Children's Oncology Group "Hearing Problems after Treatment for Childhood Cancer" Health Link. The "Educational Issues" Health Link is also applicable.

Children are being exposed to excessive amounts of hazardous levels of noise. It is estimated that 12.5% of US children 6 to 19 years old have a noise induced threshold shift in one or both ears.⁹⁶ Because noise induced hearing loss also affects outer hair cells in the basal turn of the cochlea^{96,97}, noise trauma is particularly important to avoid for survivors who already have ototoxicity from treatment. Survivors with and those at risk for hearing loss should avoid exposure to loud noise, which may exacerbate high frequency deficits. Activities that may cause noise-induced hearing loss include use of power saws, vacuum cleaners, lawn mowers, yard trimmers, leaf blowers, hair dryers, hand held music devices, stereo headphones or loud amplifiers. The American Academy of Pediatrics website includes a link entitled, "Impact of Headphones on Hearing" that cautions teenagers about use of headphones while engaging in other activities, such as cycling or jogging when outside noise requires turning up the volume on the headset. Using headphones at such times may not only worsen hearing loss, but may impair concentration and predispose to accidents (www.AAP.org).

Recreational exposures associated with hearing loss include hunting, boating or water skiing, and cycling with motorized vehicles. Recommendations for noise conservation can be obtained through various educational websites such as www.lhh.org/noise/children/references.html and www.AAP.org

CONCLUSION

Pediatric cancer survivors who develop ototoxicity from platinum compounds and/or radiation are at risk for late effects that may affect the entire auditory apparatus. They may experience impairments in learning, communication, school performance, social interaction and overall health-related QOL, and survivors exposed to potentially ototoxic agents require careful monitoring and adaptations. Screening of survivors at risk for hearing loss should be implemented in accordance with the Guidelines from the Children's Oncology Group (www.survivorshipguidelines.org).²² Whereas no confirmed benefit has yet been established for pharmacologic agents developed to prevent or reduce ototoxicity in children, avoidance of excessively loud noise and ototoxic medications, such as aminoglycoside antibiotics and diuretics, is recommended.

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Abbreviations in alphabetical order

ABR	Auditory Brainstem Response
ASHA	American Speech-Language-Hearing Association
BAER	Brainstem Auditory Evoked Response
CNS	Central Nervous System
DPOAE	Distortion Product Otoacoustic Emissions
GCT	Germ Cell Tumors
HCT	Hematopoietic Stem Cell Transplant
HL	Hearing Level
IMRT	Intensity Modulated Radiation Therapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OAEs	Otoacoustic Emissions
PBI	Proton Beam Irradiation
QOL	Quality of Life

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Appendix 1: Hearing Loss Screening Questionnaire

Instructions: This questionnaire is to be used in primary care settings to facilitate identification of children at risk for hearing loss following therapy when treatment records are unavailable or incomplete. If the answer to any question is “yes” the patient should be referred to an audiologist

Question	Response
Did the patient have any of the following tumor types: neuroblastoma, brain tumor, germ cell tumor, osteosarcoma, hepatoblastoma?	☐ Yes ☐ No
Did the patient receive cisplatin chemotherapy?	☐ Yes ☐ No
Did the patient receive cranial radiation or ear radiation?	☐ Yes ☐ No
Did the patient have a bone marrow transplant?	☐ Yes ☐ No
Has the patient had any type of surgery involving the brain or ear?	☐ Yes ☐ No
Does the patient have a VP shunt?	☐ Yes ☐ No
Has the patient received aminoglycoside antibiotics?	☐ Yes ☐ No
Has the patient received loop diuretics?	☐ Yes ☐ No
Was the patient less than 4 years old at diagnosis?	☐ Yes ☐ No
Was the patient's birth weight <2500g (5 pounds, 8 ounces)?	☐ Yes ☐ No
Does the patient experience ringing or noise in his/her ears?	☐ Yes ☐ No
Does the patient receive any speech therapy or accommodation in school?	☐ Yes ☐ No
Does the patient appear to have difficulty hearing in noisy situations?	☐ Yes ☐ No
Does the parent have any concerns about the child's speech or hearing?	☐ Yes ☐ No
Has the survivor had any kind of hearing assessment in the past?	☐ Yes ☐ No

Figure 1. Frequency composition (spectra) and approximate intensity ranges, within conversational speech, for different categories of speech sounds. From Hall JW, Mueller HG (eds) *Audiologist's Desk Reference*, with permission.⁴²

Figure 2.

Figure 2A. Progressive hearing loss with increasing cycles of cisplatin chemotherapy with threshold effect [with permission from Schell et. al²]

Figure 2B. Median time to hearing loss [with permission from Knight KR et. al¹¹]

Figure 3.

Sequential audiometry in a 4 year-old diagnosed with neuroblastoma: pre-chemotherapy (A); after completing treatment including 400 mg/m² of cisplatin (B); and following full therapy with cisplatin 400 mg/m² along with carboplatin 1,700 mg/m² (C). [Modified from Knight KR et. al with permission ¹¹]

Figure 4. Probability of hearing loss at various frequencies related to cumulative dose of cisplatin. A=group that did not receive cranial irradiation, B=group that received cranial irradiation [with permission from Schell et al ²]

CHEMOTHERAPY					HEAVY METALS	
Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
14	HEAVY METALS Carboplatin (in myelosuppressive doses only) Cisplatin Info Link: Patients who received carboplatin in non-myelosuppressive doses do not appear to be at risk for clinically significant ototoxicity based on results of currently available studies.	Ototoxicity Sensorineural hearing loss Tinnitus Vertigo	Host Factors Age < 4 years at treatment Treatment Factors Combined with: - Cranial/ear radiation - Ototoxic drugs (e.g., aminoglycosides, loop diuretics) Medical Conditions Chronic otitis Cerumen impaction Renal dysfunction	Host Factors CNS neoplasm Treatment Factors Cumulative cisplatin dose ≥ 360 mg/m ² High dose cisplatin (i.e., 40 mg/m ² per day x 5 days per course) Cisplatin administered after cranial/ear radiation Carboplatin conditioning for HCT Radiation involving ear ≥ 30 Gy	HISTORY Hearing difficulties (with/without background noise) Tinnitus Vertigo Yearly PHYSICAL Otoscope exam Yearly SCREENING Complete audiological evaluation Baseline at entry into long-term follow-up. If hearing loss is detected, test at least yearly or as recommended by audiologist. If clinical suspicion of hearing loss at any time, test as clinically indicated. If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs]. Info Link: A "complete audiological evaluation" includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. Frequency-specific auditory brainstem response (ABR) can be performed if the above is inconclusive.	Health Links Hearing Loss Educational Issues Considerations for Further Testing and Intervention Audiology consultation for amplification in patients with progressive hearing loss. Speech and language therapy for children with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. SYSTEM = Auditory SCORE = 1

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Figure 5.

RADIATION					POTENTIAL IMPACT TO EAR	
Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
58	≥ 30 Gy to: Cerebral Ear/Intracranial Nasopharyngeal Waldenstrom's Ring TBI*	Orbitotoxicity -Tympanosclerosis -Osteosclerosis -Eustachian tube dysfunction -Conductive hearing loss Sensorineural hearing loss -Tinnitus	Host Factors -Younger age at treatment Treatment Factors -Higher radiation dose Medical Conditions -Chronic otitis -Chronic cerumen impaction	Treatment Factors Dose ≥ 30 Gy Host Factors -Younger age at treatment -OHS tumor -CSP shunting Treatment Factors -Higher radiation dose; -Conventional (non-conformal) radiation	HEARING Hearing difficulties (with/without background noise) Tinnitus Vertigo Yearly ENTSCN Otoscopy exam Yearly SCREENING Complete audiological evaluation Yearly after completion of therapy for 5 years for patients <10 years old, continue yearly until age 10, then every 5 years; if hearing loss is detected, test at least yearly or as recommended by audiologist. If clinical suspicion of hearing loss at any time, test as clinically indicated. If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions (OAEs). Info Link: A "complete audiological evaluation" includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. Frequency-specific auditory brainstem response (ABR) can be performed if the above is inconclusive.	Health Links Hearing Loss Educational Issues Considerations for Further Testing and Intervention Audiology consultation for patients with progressive hearing loss. Otolaryngology consultation for patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for children with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologic, social worker, school counselor) to facilitate provision of educational resources. Consider specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. SYSTEM - Auditory SCORE = 1
<div><div>• This section is only applicable to patients who: 1) Received radiation to any of the specified fields at ≥ 30 Gy OR 2) Received a combination of radiation to any of the specified fields and TBI, the sum of which is ≥ 30 Gy • See dose calculation rules on page 48 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field. • See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.</div></div>						

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Figure 6.