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

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Summary

Childhood, adolescent, and young adult (CAYA) cancer survivors treated with platinum compounds and/or head/brain radiation have an increased risk of ototoxicity (hearing loss and/or tinnitus). To ensure optimal care and reduce consequent problems with speech and language, social-emotional development, and learning difficulties for these CAYA cancer survivors, clinical practice guidelines for monitoring ototoxicity are essential. The implementation of surveillance across clinical settings is hindered by differences in definitions of hearing loss, recommendations for surveillance modalities and remediation. To address these deficiencies, the International Guideline Harmonization Group organized an international multidisciplinary panel including 32 experts from ten countries to evaluate the quality of evidence for ototoxicity following platinum chemotherapy and head/brain irradiation and formulate and harmonize ototoxicity surveillance recommendations for childhood, adolescent, and young adult cancer survivors.

Introduction

Advances in the treatment of childhood, adolescent, and young adult (CAYA) cancer over the past decades have greatly improved long-term survival, with 5-year overall survival now exceeding 80% in most resource-rich countries.[1-3] However, improvements in outcomes are compromised by the presence of long-term adverse effects of treatment. Ototoxicity is an adverse effect that has been reported by approximately 50% of CAYA cancer survivors following treatment with platinum compounds and/or head/brain radiation.[4,5] Treatment-induced ototoxicity manifests as high-frequency hearing loss, often accompanied by tinnitus.[6-9] Platinum compounds (cisplatin and carboplatin) have been shown to be highly effective for a variety of pediatric malignancies, such as osteosarcoma, neuroblastoma, hepatoblastoma, brain tumors, and malignant germ cell tumors. In addition, head/brain radiotherapy is a critical component of the treatment of several head and neck tumors, most brain tumors, and relapsed leukemia. Treatment with radiotherapy for such tumors may include the temporal bone and brain stem area, typically with relatively high doses ($\geq$30 Gray (Gy)). Hence, the middle ear, inner ear and brain stem are often exposed to significant radiation dose. Older radiotherapy techniques are more likely to cause serious ototoxic sequelae than currently available therapies that reduce exposure to critical aural structures due to their improved conformality in targeting tumors.[5,10] Ototoxicity can manifest in both children and adults treated with these modalities, but children are more vulnerable to treatment-induced hearing loss.[4,5,11] This is important because hearing deficits may adversely affect speech and language, social-emotional development, and academic performance in children.[12,13]

Recent population-based surveys suggest that despite recommendations, monitoring of hearing loss in survivors is insufficient at the population level, with only 72% of those at risk having hearing tests during follow-up, and only 43% having full audiological monitoring (before, during, and after treatment)[14]. Therefore, clinical practice guidelines are needed to facilitate timely identification of and intervention for ototoxicity among at-risk CAYA cancer patients and survivors after completion of therapy.

Clinical practice guidelines for CAYA cancer survivors have been developed by representatives from several pediatric cancer multinational, national, and institutional groups[15-21]. Definitions of at-risk populations, surveillance modality and frequency, as well as recommendations for interventions differ across the national clinical practice guidelines for CAYA cancer survivors, hindering the implementation of surveillance across international settings. In order to

establish a global consensus, an international effort was organized to harmonize existing surveillance recommendations for CAYA cancer survivors. We present here a summary of the evidence and recommendations for ototoxicity surveillance in CAYA cancer survivors, proposed by an expert panel within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) in collaboration with the European Union-funded PanCare consortium.[22]

Data collection

Detailed information about the IGHG methods has been previously described.[23] For this effort, a core group was assembled consisting of 32 representatives from the Children's Oncology Group (COG)[16], the Dutch Childhood Oncology Group (DCOG)[17], the UK Children's Cancer and Leukaemia Group (CCLG)[18], Australian and New Zealand Children's Hematology/Oncology Group (ANZCHOG)[24], PanCare[22], as well as experts in ototoxicity from a range of medical specialties (pediatric oncology and hematology, radiology, radiation oncology, otolaryngology, pharmaco-oncology, pediatric audiology, epidemiology, survivorship care providers, and guideline experts).

We evaluated concordances and discordances across the previously more widely published COG, DCOG, and the CCLG guidelines. Clinical questions were formulated to address discordance, covering the following standard key issues: 1) who needs surveillance?; 2) what surveillance modality should be used?; 3) how often and for how long should surveillance be performed?; and 4) what should be done when abnormalities are identified? (Appendix pp 1-3) For concordant guideline areas, the evidence cited by the guidelines was assessed to determine whether supporting evidence existed and whether it sufficiently supported these guidelines.

Search strategy and selection criteria

Systematic literature searches were performed of literature published between January 1980 and November 2017. We searched MEDLINE (through PubMed) using the search terms "childhood cancer", "hearing loss", "tinnitus", "ototoxicity", "platinum agents", "radiotherapy", "cerebrospinal fluid shunt", "cranial nerve", "surgery", "audiometry", "hearing aid". Detailed search strategies are provided in the Appendix (pp 5-11). We contacted experts in the field to determine if any additional evidence was available (expert opinion). Only reports published in the English language were reviewed. If not included initially, cross-references identified during the review procedure were also selected.

The inclusion criteria were based on study population, outcomes, type, and date of study. Eligible study populations were CAYA cancer survivors, in which 75% or more had been diagnosed with cancer before the age of 30 years. Eligible study outcome was ototoxicity, defined as damage to the ear (cochlea, middle ear, or auditory nerve), manifested as hearing loss, and/or tinnitus. Studies that used self-reported hearing loss were excluded. All study

designs were eligible. For studies focused on the risk of hearing loss and/or tinnitus, only those with a sample size of 20 patients or more using multivariable analysis were eligible.

Based on studies meeting the inclusion criteria (Figure 1 and Appendix p 4), evidence summaries were generated to answer the clinical questions. When evidence was lacking or only low-quality evidence was identified, relevant information was extrapolated from studies not meeting the eligibility criteria and we also searched for guidelines in other patient populations (Appendix pp 7-8, 10-13). Conclusions from this supplemental search were discussed, and when agreed upon, were described as reflecting expert opinion.

Definitions used

CAYA cancer survivors were defined as individuals diagnosed with cancer at age 30 years of age or younger, who had completed treatment, regardless of current age. Platinum agents consisted of cisplatin, carboplatin, and oxaliplatin. Radiotherapy potentially exposing the brain, middle ear or cochlea was included in our search strategy. Ototoxicity was defined as damage to the ear (cochlea, middle ear, or auditory nerve), manifested as hearing loss after administration of an ototoxic agent, determined by pure-tone audiometry, of more than 15 decibel (dB) loss at frequencies between 250-16000 Hz, and/or tinnitus.[25] Central nervous system and vestibular dysfunction were excluded. In clinical studies many classification systems are used to grade and describe hearing loss (Appendix pp 137-139). If the included studies used a classification system, the classification system was recorded.

Final recommendations

The guideline panel reached consensus on the final recommendations based on scientific data from the evidence summaries, combined with other considerations including clinical experience, potential harms from excessive surveillance, and the need to maintain flexibility across different healthcare systems. The quality of the evidence and the strength of the recommendations were graded according to published evidence-based methods developed by experts within Cochrane Childhood Cancer[26] and the IGHG (Table 1).[23,27,28] For randomized clinical trials (RCTs), separate criteria for grading and formulating overall conclusions were used. The harmonized ototoxicity surveillance recommendations were critically appraised by three independent experts in the field and two patient representatives.

Findings

The discordances and concordances between the available national recommendations are displayed in Table 2). Concordance was identified across guidelines for the following statements: survivors of childhood cancer treated with cisplatin have an increased risk of ototoxicity; surveillance using medical history, pure-tone audiometry and tympanometry should be used; referral to a specialist is generally warranted. Levels of evidence to support concordant areas are included in Table 1. There was discordance for the following guideline areas: 1) ototoxicity risk by cisplatin dose, carboplatin treatment, or head/brain radiation treatment; 2) use of otoscopic examination, speech audiometry, or auditory brainstem response for surveillance of ototoxicity; 3) frequency of surveillance in survivors treated with cisplatin, carboplatin, and/or head/brain radiotherapy; and 4) effect of speech and language therapy or hearing assistance in survivors with ototoxicity. The evidence summaries and conclusions of evidence tables for discordant guideline areas are presented in Appendix pp 15-132. The levels and conclusions of evidence, and the final recommendations are summarized in Table 3 and Figure 2.

Hearing loss

Who needs ototoxicity surveillance?

Evidence

There are two studies that compared survivors who received cisplatin with survivors who did not receive cisplatin[29,30], and one study that compared survivors treated with cisplatin with survivors treated with a combination of cisplatin and carboplatin.[7] There is *moderate* quality evidence that CAYA cancer survivors treated with cisplatin have an increased risk of developing hearing loss (level B evidence).[7,29,30] The risk of hearing loss is proportionately higher in survivors treated with higher cumulative cisplatin doses (cut-off dose cannot be determined from available literature) (level A evidence).[7,31-35] Evidence suggests that the risk of hearing loss is higher in platinum-treated survivors who were younger at diagnosis (level B evidence), although a cut-off age for an increased risk for ototoxicity cannot be defined.[5,7,30,32-37] There is no evidence of any effect of sex on the risk of hearing loss (level B evidence).[34,36,38-40] No studies were found that evaluated ototoxicity risk after treatment with only carboplatin or oxaliplatin by multivariable analysis. However, we identified several studies that did not fulfill the inclusion criteria (e.g. no multivariable analysis, sample size <20, or still on active

cancer treatment), but summarize expert opinion (Appendix pp 12-13). The guideline panel agreed that an increased risk of hearing loss may exist after treatment with myeloablative doses of carboplatin (>1500 mg/m^2), especially in combination with cisplatin (expert opinion).[41-47]

No studies were identified by the guideline panel that included multiple variable analyses that investigated the independent effect of head/brain radiotherapy on hearing loss. Although the evidence regarding the effect of head/brain radiotherapy versus no head/brain radiotherapy on the development of ototoxicity is currently insufficient, the guideline panel agreed that there is an increased risk of ototoxicity after head/brain radiotherapy (expert opinion, Appendix pp 12-13).[10,36,48] Furthermore, regarding the effect of dosage, there is *moderate* quality evidence that CAYA cancer survivors who received moderate to high-dose head/brain radiotherapy (≥30 Gy) have an increased risk of hearing loss (level B evidence).[5,10,30,48]

We found *low* quality evidence that CAYA cancer survivors who received doses ≥30 Gy to the cochlea have an additional increased risk of hearing loss when co-treated with ototoxic chemotherapy in the presence of a cerebrospinal fluid (CSF) shunt (level C evidence).[10] It should be noted that the cochlear radiation dose was calculated for each patient in this study, and such information is often not available to clinicians making decisions on the basis of the prescribed radiation dose to the head/brain, or adjacent structures.

There is *moderate* quality evidence that CAYA brain tumor survivors with CSF shunts are at increased risk of ototoxicity (level B evidence)[5,7,10,39,40] There is *low* quality evidence that survivors co-treated with cisplatin and ototoxic supportive care medication (e.g. aminoglycosides, furosemide) are at increased risk of hearing loss (level C evidence).[7,40]

It is unclear whether co-treatment with amifostine during active cancer treatment decreases the risk of hearing loss. *Low* quality evidence from one randomized controlled trial and one cohort study showed inconsistent otoprotective benefit in cisplatin-treated survivors co-treated with amifostine.[48-50] There is a moderate level of evidence from more recent randomized clinical trials that a second agent in this class, sodium thiosulfate (STS), significantly reduces the severity of hearing loss in CAYA cancer survivors[50-52]; nevertheless, a significant proportion of survivors continue to experience hearing loss; thus, there is insufficient evidence to support less frequent screening of survivors treated with amifostine or STS.

Recommendations

Based on the evidence and the panel's consensus, the guideline panel recommends that CAYA cancer survivors treated with cisplatin (level A and B evidence) (with or without high-dose carboplatin (>1500 mg/m^2), or head/brain radiotherapy ≥30 Gy (expert opinion), and their health care providers, should be made aware of the potential risk of hearing loss (strong recommendation). Surveillance for hearing loss is recommended for survivors treated with cisplatin (level A and B evidence) (with or without high-dose carboplatin (>1500 mg/m^2) or head/brain radiotherapy ≥30 Gy (expert opinion; strong recommendation). For survivors who had placement of a CSF shunt (level B evidence) the guideline panel agreed that surveillance may be reasonable (weak recommendation). The use of otoprotection with amifostine or sodium thiosulfate during childhood cancer treatment does not affect the surveillance recommendations.

How often and for how long should surveillance for hearing loss be performed?

Evidence

There is *low* quality evidence that hearing function in CAYA cancer survivors may deteriorate over time after treatment with platinum agents[34,35,53-56], head/brain radiotherapy, or a CSF shunt (level C evidence).[5,10,57-59] However, in some survivors hearing function remains stable or even improves over time.[34,35,53-56,60] The predictors for change of hearing function over time are unknown. From existing literature, it is difficult to define an appropriate surveillance interval indicating the length of time during which testing should be performed. There is a gap in evidence regarding how long ototoxicity surveillance should continue in survivors who have normal hearing at the end of treatment. Hearing improvement in cases with hearing loss has been reported, but may be temporary and in cases with an intracranial tumor, may be related to tumor location, with infra-tentorial tumors possibly showing more improvement.[10] Also, it is always important to check for cerumen impaction as this can also impair hearing.[61] Usually, survivors are tested at frequencies ≤8000 Hz and if no losses >15 dB are observed, hearing function is considered to be normal and surveillance is discontinued. However, damage to the cochlea may occur >8000 Hz, and whether and when it will deteriorate involving lower frequencies is unknown. Furthermore, hearing loss from head/brain irradiation may be delayed so surveillance should continue for at least 5 years.

Recommendations

Surveillance is usually mandatory for at risk patients during treatment. Although there was *low* quality evidence from the literature, there was consensus among the guideline panel that surveillance in survivors should start no later than the end of treatment and should be performed annually for children younger than 6 years of age, every other year for children 6-12 years of age, and every five years for adolescents and young adults over 12 years, as late-onset hearing loss is well-recognized by the expert panel. These recommendations were ranked as strong for survivors treated with cisplatin (level A and B evidence), and/or head/brain radiotherapy $\geq$30 Gy (expert opinion), and weak for survivors with CSF shunts (level B evidence). As young survivors are still acquiring language skills, the guideline panel recommends more frequent surveillance until language skills are well developed (typically at the age of 5 or 6 years).

What surveillance modality should be used?

Evidence

The existing guidelines for follow-up were concordant regarding the use of medical history, pure-tone audiometry, and tympanometry as components of screening for hearing loss. Ideally, surveillance should not be limited to one testing method. The gold standard for determining hearing status is complete audiological assessment performed with a test battery approach (Appendix pp 133-136) since a single metric is inadequate for determination of hearing loss in at-risk survivors treated with ototoxic treatment modalities. Multiple procedures should be used to cross-check findings. Similarly, data from multiple procedures, performed at each point in time, provides a more robust comparison from one time point to the next than a single metric. This is particularly valuable for patients who may be inconsistently able to complete behavioural threshold testing.

There is *moderate* quality evidence that there is agreement between pure-tone audiometry and distortion product otoacoustic emission (DPOAE) in detecting abnormalities, but there is also evidence that DPOAE detects abnormalities earlier than pure-tone audiometry (level B evidence) and is more sensitive for detecting subtle or sub-clinical abnormalities than audiometry.[47,62-64] There is *low* quality evidence that high-frequency audiometry detects more abnormalities than pure-tone audiometry (level C evidence)[62] and *low* quality evidence that pure-tone audiometry detects more abnormalities than auditory brainstem response (level C

evidence).[65] However, based on available published data, it is unclear whether high-frequency audiometry and frequency-specific auditory brainstem response are helpful in CAYA cancer survivors.

Recommendations

The guideline panel recommends that pure-tone audiometry at 1000-8000 Hz is the gold standard for routine surveillance of CAYA cancer survivors aged ≥6 years in order to avoid over-testing (evidence-based guidelines and expert opinion). Additional testing with high-frequency audiometry at >8000 Hz is recommended if equipment is available. For survivors younger than 6 years, referral to an audiologist for annual developmentally-appropriate, comprehensive testing is recommended (strong recommendations).

What should be done when abnormalities are identified?

Evidence

There is a paucity of evidence describing benefits of interventions to remediate hearing loss in CAYA cancer survivors with ototoxicity. One study assessed hearing aids in four CAYA solid tumor survivors and reported that difficulties with speech distortion were markedly reduced with the use of hearing aids (level C evidence).[66] A case report in a survivor of renal clear cell sarcoma treated with cisplatin reported that cochlear implants improved hearing function (level C evidence).[67] Evidence-based guidelines for children with hearing loss reported that education, amplification or hearing-assistive technology, cochlear implantation, hearing aids, tactile aid, FM system, communication approaches or intervention programs, such as early and consistent speech therapy, minimize the social and intellectual impact of hearing loss (Appendix pp 97-101). However, these recommendations about intervention methods are largely based on international guidelines in the general pediatric population and not in CAYA cancer survivors.[5,8,68-75] The guideline panel also recognized that many survivors suffer from comorbidities that may influence the applicability of guidelines for hearing loss interventions used in the general population (e.g. hearing loss interventions in a child with neurocognitive deficits from radiotherapy may be different from an otherwise healthy child).

The guideline panel endorsed the following interventions: referral to an audiologist, remote microphone technology for survivors with hearing loss at 6 kHz and above in one or both ears, personal hearing aids plus consideration of remote microphone technology for survivors with

high-frequency loss at 3 kHz and above in one or both ears, and electro-acoustic stimulation device (e.g., cochlear implant, including electroacoustic stimulation to give access to high-frequency sound spectrum) plus remote microphone technology for survivors with hearing loss adversely affecting speech understanding and not adequately remediated by hearing aids. In addition, general management for permanent hearing loss in adolescents and young children should be considered. These include: supportive counselling for the young person and their partner/family about the hearing loss and its implications for communication, learning, and in the work-place; teaching of compensatory communication strategies; speech therapy and language therapy as needed to ensure development of clear speech, comprehensive language use, and acquisition of appropriate social skills; and accommodations and instructional support at school/college or in the work-place. Behavioral interventions are important to preserve hearing among survivors with milder hearing loss (i.e. avoid loud noise exposure).

Recommendations

The guideline panel recommends that referral to an audiologist, auditory clinic or ear, nose, and throat (ENT) physician as appropriate for any survivor who has symptoms suggesting hearing loss and/or abnormal audiological test results showing a loss of more than 15 dB at 1000-8000 Hz (expert opinion) (strong recommendation).

Tinnitus

Evidence

We identified only one study that investigated the risk of tinnitus in CAYA cancer survivors. This study suggested that patients treated with platinum agents and/or moderate to high-dose head/brain radiotherapy ≥30 Gy have an increased risk of tinnitus (level C evidence).[76] It is unknown whether tinnitus in CAYA cancer survivors can diminish or worsen over time (no studies). Regarding potential interventions, an evidence-based guideline for patients with tinnitus reported that several intervention/management options can be offered to patients with tinnitus.[77] These can be divided into psychological/social interventions (such as cognitive behavioral therapy, counseling/education, and/or education about management strategies) and audiological interventions (such as hearing aids and/or sound therapy).

Recommendations

Based on the evidence and expert consensus, the guideline panel agreed that CAYA cancer survivors treated with cisplatin (with or without high-dose carboplatin (>1500 mg/m^2) (level C evidence), and/or head/brain radiotherapy ≥30 Gy (expert opinion), and their healthcare providers, should be aware of the potential risk of tinnitus. Referral to an audiologist is recommended for survivors who may suffer from tinnitus (strong recommendation).

Discussion

This paper presents the IGHG recommendations for ototoxicity surveillance designed specifically for CAYA cancer survivors. Evidence-based recommendations were formulated to facilitate consistent follow-up care for survivors, based on a critical review of the existing literature combined with expert consensus. In addition, we identified gaps in knowledge that require research to improve surveillance in CAYA cancer survivors (panel 1). The guideline panel would, however, like to highlight the need for audiological surveillance during follow-up, according to these guidelines, which are designed specifically for long-term follow-up of CAYA cancer survivors.

The systematic search identified evidence for a higher risk of ototoxicity after exposure to cisplatin (level B), especially after higher cumulative doses (level A), moderate- to high-dose head/brain radiotherapy (level B), concomitant treatment with aminoglycosides or furosemide (level C), and CSF shunts (level B), even in the absence of any other therapy. Multiple studies have demonstrated an association between cisplatin and ototoxicity[7,9,29,30], with higher cumulative dose exposure substantially increasing risk.[7,31-35] However, even lower cumulative doses of cisplatin can cause ototoxicity. Therefore, we concluded that any dose of cisplatin should be considered to confer a potential risk of hearing loss or tinnitus. Although no published studies regarding ototoxicity in CAYA cancer survivors treated with carboplatin alone met our inclusion criteria, myeloablative doses of carboplatin may impair hearing function, especially when used in combination with cisplatin.[44] Several investigations evaluated the combined effect of carboplatin with cisplatin in childhood cancer patients.[44,46,47,78] Landier et al. evaluated ototoxicity in the setting of young children treated for high-risk neuroblastoma (n=333) and demonstrated by multivariable analysis a >3-fold risk for severe hearing loss among children who had received cisplatin and myeloablative doses of carboplatin, as compared to those who received cisplatin alone.[44] Similar results were reported by Parsons et al.[46] and Punnett et al.[47] in neuroblastoma patients.

Moderate quality evidence showed that CAYA cancer survivors treated at a younger age (threshold not defined but <5 years typically used[51]) have an increased risk of hearing loss compared to older survivors. This may be related to the continued development of the auditory system after birth.[43,79] This group may also be impacted by hearing loss during critical periods of speech and language acquisition that starts at birth and continues up to adolescence.

Permanent/long-term CSF shunting also confers risk for hearing loss.[5,10,39] Bass et al. reported an association between CSF shunting and risk of hearing loss post radiotherapy in children.[5] They observed that patients with a CSF shunt were twice as likely to suffer from radiation-induced hearing loss compared to those without a shunt. As more posterior fossa brain tumor patients need CSF shunts, tumor location may be more relevant than shunting. Merchant et al. noted similar findings but the length of follow-up of the cohort may not have been sufficient to accurately assess the incidence of radiation-related hearing loss.[10] Guillaume et al. also demonstrated an independent association between CSF shunting and hearing loss in children receiving treatment for medulloblastoma.[39] This is not surprising as hearing loss is a well-known complication of shunt placement for hydrocephalus and other procedures resulting in loss of cerebrospinal fluid.[80,81] The etiology of hearing loss after shunt placement is not fully understood; however, it is conceivable that changes in cerebrospinal fluid pressure may alter cochlear physiology. Also, excessive cerebrospinal fluid drainage through the dilated cochlear aqueduct has been associated with hearing loss. Hence, children may be at greater physiological risk for hearing loss after shunt placement or other procedures that cause cerebrospinal fluid pressure change related to their developmentally dilated cochlear aqueduct.[81-85]

It is hypothesized that surgical injury may influence the occurrence of hearing loss for some patients, but it is not clear what role the extent of surgery or the degree of hydrocephalus at diagnosis may contribute to hearing loss and whether shunting and correction of increased intracranial pressure facilitates healing from surgical injury over time. Interestingly, the Merchant study showed a predominance of right-sided hearing loss that was attributed to preferential placement of shunts on the non-dominant right side. This study also observed that the greatest hearing deficit was found in patients with an infratentorial tumor requiring a CSF shunt. The study by Bass et al. did not find a significant association between hearing loss and infratentorial and supratentorial tumor locations in multivariable analysis.[5] Notably, in this study patients with infratentorial ependymoma were younger and the prescribed radiotherapy dose (54-59·4 Gy) was relatively higher for ependymoma. Hence, younger patients were more likely to have received higher cochlear radiation doses.

Moderate quality evidence showed that CAYA cancer survivors who received moderate to high dose head and brain radiotherapy have an increased risk of hearing loss. The highest quality data that address dose thresholds for hearing loss support 30 Gy as a level below which

impairment is unlikely. Although no published studies regarding radiotherapy defined a threshold dose, a cut-off dose of 30 Gy was chosen to define moderate to high dose radiotherapy based on longstanding clinical experience (i.e., expert opinion). After cranial radiotherapy alone (without chemotherapy or CSF shunting) the likelihood of impaired hearing is small at doses below 30 Gy. Several studies support the increased prevalence of hearing loss with large radiation doses to the head/brain (i.e., doses greater than 40-45 Gy).[5,10,48,57]A systematic review by van As et al. described two randomized controlled trials (RCTs) and one controlled clinical trial evaluating amifostine as a possible otoprotective intervention in childhood cancer patients.[50] Due to methodological limitations of these clinical trials, there currently is no evidence that otoprotection with amifostine benefits CAYA cancer survivors. A recently published RCT (ACCL0431) of a second otoprotective agent in the same class, sodium thiosulfate, showed significant evidence for protection from cisplatin-induced hearing loss in childhood cancer patients.[51] Furthermore, a second trial published in 2018 after our systematic literature review evaluated delayed treatment with sodium thiosulfate after cisplatin treatment in pediatric patients with standard-risk hepatoblastoma.[52] They observed a 48% reduction in prevalence of cisplatin-induced hearing loss after the addition of sodium thiosulfate. Based on the limited availability of studies evaluating ototoxicity in long-term CAYA survivors, the panel concluded that there is currently insufficient evidence to support less frequent screening of survivors treated with amifostine (level C evidence) or sodium thiosulfate (level B evidence).

There are important limitations that should be considered in the interpretation of our ototoxicity surveillance recommendations. The different ototoxicity classification systems used in the studies featured in this review hinder comparison of results between studies. In addition, variability in the classification systems used to grade hearing loss severity across studies may impact the reported prevalence of hearing loss in CAYA cancer survivors. Several previous studies have attempted to address the need to adopt a uniform classification system, which was beyond the scope of the current paper[44,86,87]. Differences in methods used to assess hearing function and mechanisms for collecting and reporting audiological data also pose challenges in comparing outcomes across studies. Finally, our systematic search identified only a few studies regarding medical devices, interventions or guidance for clinical management of hearing impairment or tinnitus in CAYA cancer survivors. Nevertheless, the guideline panel advises referral to an audiologist or auditory clinic for any survivor who has

symptoms suggesting hearing loss and/or abnormal audiological test results showing a loss of more than 15 dB for standard interventions that are generally used among non-cancer populations with hearing loss.

Based on the gaps in knowledge highlighted by our systematic review, future studies should focus on evaluation of otoprotectants and identification of optimal threshold doses for ototoxicity of both platinum compounds and head/brain radiotherapy in the design of clinical trials. It is important, however, that concern about ototoxicity does not lead to individual platinum or head/brain irradiation dose reduction that may compromise cure. Other risk factors, such as CSF shunts, age at exposure, additional ototoxicity contributed by co-treatment with aminoglycoside or furosemide, and genetic susceptibility should also be considered in future studies (panel 1).

This IGHG ototoxicity surveillance guideline aims to improve health outcomes by facilitating more consistent long-term follow-up care for current CAYA cancer survivors, to allow interventions which can benefit speech, socialization and education, and to promote strategically planned future research that will inform future guideline updates.

Author's contribution

EC, MMvdH-E, WL, RC, RLM, MMH, and LCMK contributed to the conception and design of the study. All authors contributed to the search strategy, data extractions, interpretation of the data, and formulation of the recommendations.

EC, MMvdH-E, WL, RC, RLM, RS, LCMK, MMH, JKB, AaZD, TL and CEK drafted, and LSC, EB, NXB, PB, BB, BC, EC, KWC, EvD, KJ, KN, PCN, EO, PKP, JR, KS, DT, ACHdV, TW and AW critically revised the report. All authors approved the final version.

Conflicts of interest

ECvD reports grants from Stichting Kinderen Kankervrij (KiKa), the Netherlands, during the conduct of the study. PRB reports personal fees from Fennec Pharmaceuticals, outside the submitted work. The other authors declared no conflicts of interest.

Declaration of interests

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