Evaluating the Burden of Survival of Platinum-induced Hearing Loss in Pediatric Solid Tumor Patients: A Systematic Literature Review

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Introduction & Objective

Advances in chemotherapy (CXT)-based treatment approaches for pediatric solid tumors result in improved survival; platinum-based CXT is widely associated with irreversible, bilateral, progressive hearing loss; occurring as early as the 1st cycle of cisplatin.[1,2] This is concerning for pediatric patients, due to vulnerable auditory structures and neural pathways, which can increase severity of hearing loss[3] and affect child and adolescent critical learning, language, and social development. There are no current interventions to prevent CXT-induced ototoxicity (CIO). Current management strategies do not replace normal hearing. Enhancements such as FM systems and hearing aids help patients cope with hearing loss, but are not curative, resulting in lifelong and sometimes disabling burden for affected patients. A thorough understanding of lifetime burden of hearing loss in pediatric CXT patients would better inform the total cost of management and intervention for pediatric patients living with CIO. The purpose of this systematic literature review (SLR) was to assess current data on burden of survival for pediatric CXT patients receiving platinum-based regimens in terms of hearing loss, specifically related to costs and quality of life (QoL)-based metrics.

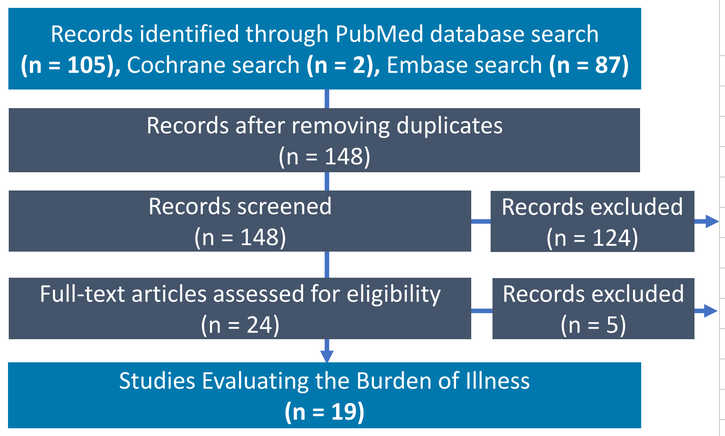
Methods

- The search strategy was designed in PubMed, and adapted to Cochrane and Embase; it was confined to 2009-2019 and included search terms shown in Table 1
- An additional search was conducted for SLRs and network meta-analyses (NMAs) in PubMed excluding "Chemotherapy Terms" in Table 1
- Abstract and full-text article reviews adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, shown in in Figure 1
- Principal summary measures included prevalence of hearing loss among the studied patient group, QoL metric, and results of QoL measurement

Table 1. Search Terms Utilized

Patient Type Term	Pediatric
Chemotherapy Terms	*AND* Chemotherapy; Cisplatin; Platinum; Carboplatin
Hearing Loss Terms	*AND* "Hearing loss"; Ototoxicity; "Hearing aid"; "Cochlear implant"
QoL Terms	*AND* "Burden of illness"; Cost; Economic; "Quality of life"; QOL; Outcomes; Burden; "Unmet need"; Psychosocial; "Developmental delay"; Professional; Employment; Social; Education; School

Figure 1. Study Selection Process, n=19 articles included in the final results



Exclusion criteria	Number of excluded records
Not ototoxicity focused	30
Focus on Genetic Mechanisms	14
Non-platinum chemotherapy	14
Clinical Data	13
Non-oncology	12
Clinical Practice Reviews / Guidelines	10
Case Reports	7
Focus on otoprotection	7
Animal/Lab Research	5
Focus on otomonitoring	4
Non-pediatric	3
Other	10
Total	***129***

Results

Literature findings

- The search yielded 19 full text articles, including observational studies (n=16) and literature reviews (n=3); overall, there were a limited number of secondary studies examining the implications of CIO in pediatric patients

Epidemiology

- Reporting varies due to: 1) differences in definition of hearing loss and scale, 2) differences in underlying patient populations, 3) timeframe in which hearing loss is captured
- Prevalence estimates for individual cohorts were reported across n=15 studies (Figure 3)
- Severe hearing loss was common, particularly given that a typical comparator group (in n= 5) was no, mild, or moderate hearing loss[5-9]; severity was reported as a function of risk factors (e.g., age, cumulative cisplatin dose, and concomitant cranial irradiation)[7,10-15]
- CIO can occur as soon as the first cycle and can also deteriorate over time; one study reported 33% of patients with initial hearing loss, worsened on long term follow-up[17]
- Children with ≤ Grade 1 hearing loss are monitored for change, whereas those with higher grades require active management, and have a greater negative impact to quality of life[19]

Developmental/Neurocognitive

- Developmental and neurocognitive outcomes were commonly reported topics; a negative impact on neurocognitive development was a consistent finding, though there is a lack of standardization in the metrics utilized to assess such outcomes
- It is clear there are considerable implications of pediatric CIO on language development, intellectual development and educational achievement

Economic/Heal care resource utilization (HCRU)/QoL

- No studies have prospectively evaluated costs associated with hearing loss in CXT patients
- One paper estimated costs based on cost inputs that were modelled over the relevant populations. Estimates of total present value lifetime costs related to hearing loss (including productivity losses and direct HCRU) were estimated to be $256 - $1020 per patient, for minimal hearing loss (captured ≤ 18 years of age) and $445,446 - $562,198 for Grade 3-4 hearing loss, per patient (≤ 65 years), with variability by tumor type. However, details on direct HCRU were limited as select cost inputs were based on estimates in British Colombia, Canada from a single treater[19]
- Hearing aid use was reported in 8 studies, resulting in a range of estimates from 11%-45% of all patients exposed to ototoxic chemotherapy[8-10,12,15-18]
- There is no standardized, well-documented economic or QoL scale measuring the impact of hearing loss due to platinum CXT among pediatric patients, and no established scales that measure impact over time, following CXT completion. One study noted 60% of children with irreversible ototoxicity report a devastating, life-long impact on QoL[1]
- Standardized QoL metrics were reported in one study, using the PedsQL scale; this study showed no difference between none, mild, and severe hearing loss groups[6]
- One study described social attainment, and noted a negative impact from pediatric ototoxicity on achieving social milestones (e.g. marriage, independent living) in pediatric cancer survivors[7] and is consistent with non-CXT SLRs[20]; lifetime milestone are visualized in Figure 3
- Other considerations include underemployment and lost earnings, delayed development and behavioral impact, learning impairment and loss of education[19,20]

Figure 2. Reported Prevalence Among Key Studies

	Study	Patient Type	Severity Measure	Time Horizon following end of therapy	Prevalence Among Study Cohort
Any	**Schreiber et al., 2014**	Pediatric medulloblastoma patients multimodal oncology treatment regimen	Not specified	5 years	**22%**
Any	**Al-Khatib, et al. 2010**	Pediatric patients who received platinum therapy	ASHA	Up to 6.6 years post diagnosis	**42%**
Any	**Kolinsky et al., 2010**	Pediatric patients following the end of cisplatin therapy	Late onset hearing loss	6 months	**51%**
Any	**Knight, et al. 2018**	Pediatric patients that received cisplatin treatment	SIOP	Mean follow-up 9 years	**73%**
Moderate/Severe	**Yancey et al., 2012**	Pediatric patients with a variety of tumor types	Brock score ≥ 2	Up to 2.8 years	**28%**
Moderate/Severe	**Castelan-Martinez, et al. 2014**	Pediatric patients that received ototoxic therapy	≥ CTCAE, grade 1	Not Specified	**52%**
Moderate/Severe	**Dionne, et al. 2012**	Pediatric patients recruited for genetic test evaluation	CTCAE, grades 2-4	Not Specified	**65%**
Severe	**Wei et al., 2018**	Pediatric neuro- or hepatoblastoma patients who received cisplatin	Chang ≥ 2a	Not Specified	**24%**
Severe	**Olivier et al., 2019**	Embryonal tumor patients treated with multimodal oncology treatments	Chang ≥ 2b	Up to 5 years post diagnosis	**25%**
Severe	**Waissbluth et al., 2018**	Pediatric patients after cisplatin and/or carboplatin treatment	Chang ≥ 2b	Mean follow-up 1.8 years	**28%**
Severe	**Peleva et al., 2014**	Patients that received platinum-based therapy	Chang ≥ 2b	Mean follow-up 3 years	**30%**
Severe	**Brinkman et al., 2015**	Adult survivors of pediatric CNS and non CNS tumors	Chang ≥ 2b	Up to 40+ years following diagnosis	**38%**
Severe	**Orgel et al., 2016**	Pediatric brain tumor patients treated with multimodal oncology treatments	Chang ≥ 2b	Up to 5+ years post diagnosis	**55%**

Figure 3. Reported Prevalence Among Key Studies

Conclusions

- Although platinum-based therapies result in close to 80% survival rates for pediatric localized solid tumors, CIO is a known, irreversible, toxicity, with no available therapies for prevention; currently available management strategies are not able to replace normal hearing
- The literature for pediatric CIO is underdeveloped, and lacks research across prevalence, HCRU, QoL, and evaluation of the burden of survival for patients across their lifetime
- Despite limited literature, it is clear that pediatric CIO is a large burden on patients and their families, and presents unique challenges to pediatric cancer survivors; this has been documented through the high incidence, significant lifetime costs (HCRU and productivity) of hearing loss, high risk of missed social milestones, and the resulting neurocognitive deficits that follow a pediatric cancer survivor through their life, however the total costs associated with these aspects are not readily measurable
- A characterization of the differentiated experience of a pediatric cancer survivor with hearing loss is a critical gap that prevents a complete picture of the burden of survival[21]
- Lack of standardization in clinical care and patient management is preventing a clear understanding of the hearing loss burden. Patients may not be adequately monitored as current monitoring is hindered by different hearing loss definitions, recommendations for surveillance modalities, frequency, duration and remediation[22]
- A heightened clinical focus on pediatric platinum-induced chemotherapy could encourage standardized monitoring, prevention and patient management strategies

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