



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

Kalin Hennegan¹, MPH; Abigail Silber¹, MPH; Sumudu Dehipawala¹, MPH; Kevin Chithran¹, MPH; Donna Lockhart², MD, MBBS, MBA

¹Trinity Life Sciences, Waltham, MA, USA; ²Fennec Pharmaceuticals, Research Triangle Park, NC, USA

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 loss³ 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.

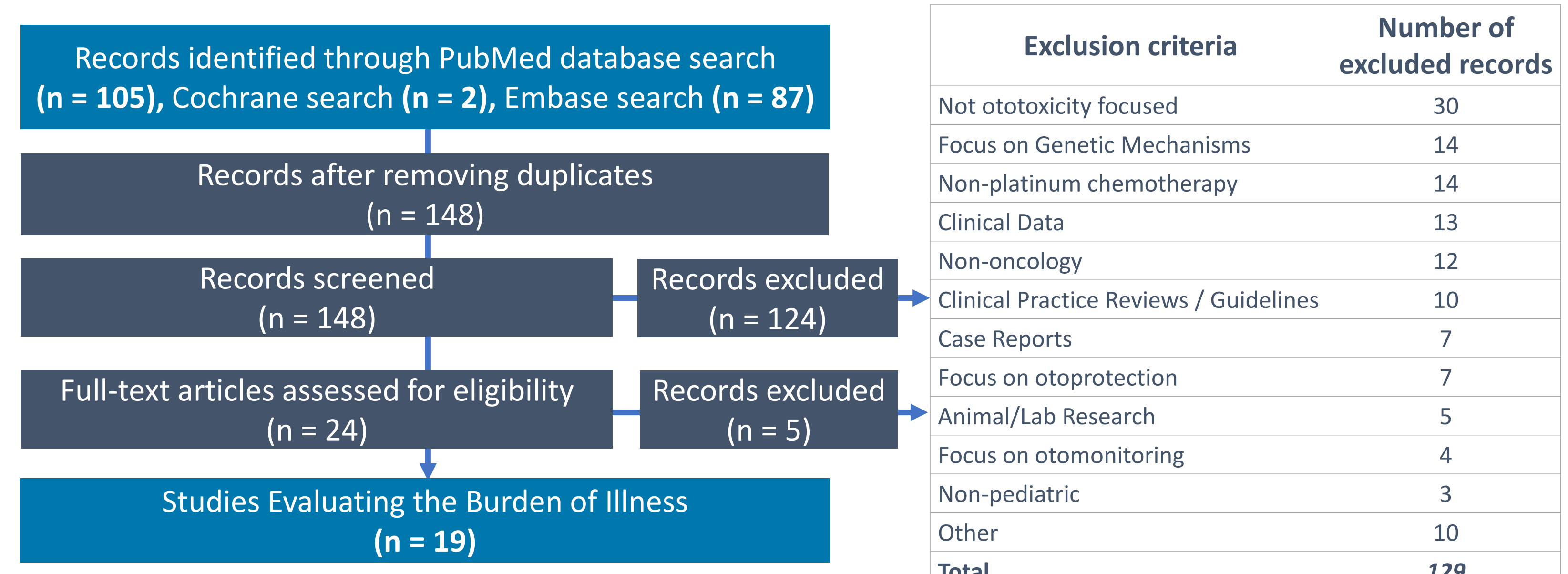
Methods

- 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



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 loss⁵⁻⁹; 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-up¹⁷
- 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 life¹⁹

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

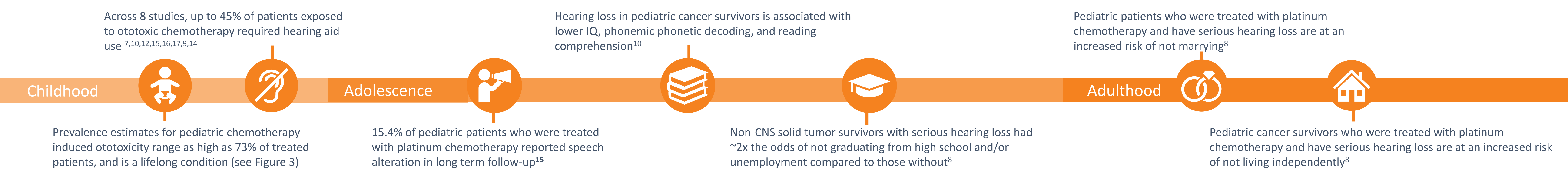
Economic/Health care resource utilization (HCRU)/QoL

- 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 Columbia, Canada from a single treater¹⁹
- 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 QoL¹
- Standardized QoL metrics were reported in one study, using the PedsQL scale; this study showed no difference between none, mild, and severe hearing loss groups⁶
- 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 survivors⁷ and is consistent with non-CXT SLRs²⁰; 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
Schreiber et al., 2014	Pediatric medulloblastoma patients multimodal oncology treatment regimen	Not specified	5 years	22%
Al-Khatib, et al. 2010	Pediatric patients who received platinum therapy	ASHA	Up to 6.6 years post diagnosis	42%
Kolinsky et al., 2010	Pediatric patients following the end of cisplatin therapy	Late onset hearing loss	6 months	51%
Knight, et al. 2018	Pediatric patients that received cisplatin treatment	SIOP	Mean follow-up 9 years	73%
Yancey et al., 2012	Pediatric patients with a variety of tumor types	Brock score ≥ 2	Up to 2.8 years	28%
Castelan-Martinez, et al. 2014	Pediatric patients that received ototoxic therapy	≥ CTCAE, grade 1	Not Specified	52%
Dionne, et al. 2012	Pediatric patients recruited for genetic test evaluation	CTCAE, grades 2-4	Not Specified	65%
Wei et al., 2018	Pediatric neuro- or hepatoblastoma patients who received cisplatin	Change ≥ 2a	Not Specified	24%
Olivier et al., 2019	Embryonal tumor patients treated with multimodal oncology treatments	Change ≥ 2b	Up to 5 years post diagnosis	25%
Waissbluth et al., 2018	Pediatric patients after cisplatin and/or carboplatin treatment	Change ≥ 2b	Mean follow-up 1.8 years	28%
Peleva et al., 2014	Patients that received platinum-based therapy	Change ≥ 2b	Mean follow-up 3 years	30%
Brinkman et al., 2015	Adult survivors of pediatric CNS and non CNS tumors	Change ≥ 2b	Up to 40+ years following diagnosis	38%
Orgel et al., 2016	Pediatric brain tumor patients treated with multimodal oncology treatments	Change ≥ 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 survival²¹
- 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 remediation²²
- A heightened clinical focus on pediatric platinum-induced chemotherapy could encourage standardized monitoring, prevention and patient management strategies

REFERENCES

1. Langer T, van Zeehoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends in Pharmacological Sciences*. 2013;34(8):458-469. 2. Chiries F, Albu S. Prevention and restoration of hearing loss associated with the use of cisplatin. *Biomed Res Int*. 2014;2014:925485. 3. Landler W. Ototoxicity and cancer therapy. *Cancer*. 2016;122(11):1647-1658. 4. Ellis LR, Oich AJ, Orgel E, Wong K. Reduction in Ototoxicity Using IMRT for Patients with Medulloblastoma/PNET. *International Journal of Radiation Oncology • Biology • Physics*. 2019;105(1):624. 5. Schreiber JE, Gurney JG, Palmer SL, et al. Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. *Neuro Oncol*. 2014;16(8):1129-1136. 6. Knight K FR, Doolittle N, Cahana D, Huddleston A. Quality of life in long-term survivors of pediatric cancer: The impact of hearing loss. *Neuro-Oncology*. 2018;20(suppl_6):NP-107. 7. Brinkman TM, Bass JK, Li Z, et al. Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the SEER Lifetime Cohort Study. *Cancer*. 2015;122(4):603-608. 8. Olivier TW, Bass JK, Ashford JM, et al. Cognitive Implications of Ototoxicity in Pediatric Patients With Embryonal Brain Tumors. *J Clin Oncol*. 2019;37(18):1566-1575. 9. Orgel E, O'Neill SH, Kayser K, et al. Effect of Sensorimotor Hearing Loss on Neurocognitive Functioning in Pediatric Brain Tumor Survivors. *Pediatr Blood Cancer*. 2016;63(3):527-534. 10. Castelan-Martinez OD, Jimenez-Mendez R, Rodriguez-Silva F, et al. Hearing loss in Mexican children treated with cisplatin. *International Journal of Pediatric Otorhinolaryngology*. 2014;78(3):1456-1460. 11. Robertson MS, Hayashi SS, Carrel ML, Tinkhaus K, Henry J, Hayashi BJ. Asymmetric sensorimotor hearing loss is a risk factor for late-onset hearing loss in pediatric cancer survivors following treatment. *Pediatr Blood & Cancer*. 2019;66(1):e2784. 12. Waissbluth S, Chang A, Del Valle A, Cordova M. Long-term platinum-induced ototoxicity in pediatric patients. *Int J Pediatr Otorhinolaryngol*. 2018;107:75-79. 13. Wei M, Yuan K. Cisplatin-induced Ototoxicity in Children With Solid Tumor. *Journal of Pediatric Hematology/Oncology*. 2019;41(2):97-100. 14. Whelan K, Stratton K, Kawashima T, et al. Auditory complications in childhood cancer survivors: a report from the childhood cancer survivor study. *Pediatr Blood & Cancer*. 2011;57(1):126-134. 15. Yancey A, Harris MS, Egebalakia A, Gilbert J, Pisoni DB, Benbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. *Pediatr Blood & Cancer*. 2012;59(1):144-148. 16. Al-Khatib T, Cohen N, Carret A-S, Daniel S. Cisplatin ototoxicity in children: long-term follow-up. *International Journal of Pediatric Otorhinolaryngology*. 2010;74(8):1319-1319. 17. Kolinsky DC, Hayashi SS, Karzon R, Mao J, Hayashi RJ. Late Onset Hearing Loss: A Significant Complication of Cancer Survivors Treated With Cisplatin-Containing Chemotherapy Regimens. *Journal of Pediatric Hematology/Oncology*. 2020;32(2):119-123. 18. Peleva E, Enami N, Alsharrah M, et al. Incidence of platinum-induced ototoxicity in pediatric patients in Quebec. *Pediatr Blood & Cancer*. 2014;61(11):2012-2017. 19. Diwan F, Mittal C, Razaiah K, et al. Economic impact of a genetic test for cisplatin-induced ototoxicity. *Pharmacogenomics J*. 2012;12(3):205-213. 20. Grewal S, Merchant T, Reynolds R, McInerney M, Hodge C, Shearer P. Auditory late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Pediatrics*. 2010;125(4):e938-950. 21. Roland L, Fischer C, Tran K, Radhakonda T, Kalligottig D, Lieu JE. Quality of Life in Children with Hearing Impairment: Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2016;155(2):208-219. 22. Purcell PL, Shin J, Davis GE, Sie KCY. Children with unilateral hearing loss may have lower intelligence quotient scores: A meta-analysis. *The Laryngoscope*. 2016;126(3):746-754. 23. Khan A, Mubdi N, Budnick A, et al. The experience of hearing loss in adult survivors of childhood and young adult cancer: A qualitative study. *Cancer*. 2020;n/a(n/a). 24. Clemens E, de Vries ACH, van Zeehoff-Dinnesen A, et al. Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors. *Pediatr Hematol Oncol*. 2017;34(2):120-129.