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Hearing loss after exposure to vincristine and platinum-based chemotherapy among childhood cancer survivors

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ABSTRACT

Background: The role of vincristine as a contributing risk factor for hearing loss among childhood cancer survivors (CCS) treated with platinum-based chemotherapy has not been fully elucidated. We examined the association of vincristine with hearing loss in a national cohort of CCS.

Methods: We included CCS registered in the Swiss Childhood Cancer Registry diagnosed at age ≤ 18 years and treated with platinum-based chemotherapy between 1990 and 2014. Audiogram and treatment data were extracted from medical records for all participants in our retrospective cohort study. We identified CCS exposed to vincristine and calculated the total cumulative dose. We defined clinically relevant hearing loss as grade ≥ 2 using the International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Scale at latest follow-up.

Results: Our study population included 270 CCS (43% female; median age at cancer diagnosis 6.8 years; interquartile range [IQR]: 2.1–11.7 years) with median age at audiogram 13.5 years (IQR: 9.3–17.0 years). Vincristine exposure was associated with an increased risk of hearing loss in the multivariable logistic regression analysis (odds ratio [OR] 4.8; 95% confidence interval [CI]: 1.8–12.9). We found no evidence of dose-response relationship (OR 1.0; 95% CI: 0.97–1.04) or effect modification from vincristine from other ototoxic treatments, such as type of platinum agent, cranial radiotherapy, and hematopoietic stem cell transplantation.

Conclusion: Vincristine is associated with a higher risk of hearing loss in CCS treated with platinum-based chemotherapy. We suggest future studies investigate the underlying mechanism and causality among CCS without exposure to other ototoxic cancer treatments.

1. Introduction

Hearing loss is a side effect of platinum-based chemotherapy among children [1]. It is usually irreversible and impairs neurocognitive functioning of childhood cancer survivors (CCS) [2,3]. Several studies identified risk factors for platinum-induced hearing loss such as age at cancer diagnosis, type of platinum agent, total cumulative dose of platinum, concomitant cranial radiotherapy (CRT), and hematopoietic stem cell transplantation (HSCT) [4–7]. However, such factors insufficiently explain interindividual variation of platinum-induced hearing loss, possibly involving additional factors, such as vincristine [4,8,9]. Vincristine is known as neurotoxic and reported to cause

central neuropathy with paralysis of the auditory nerve (cranial nerve VIII) [10,11]. In addition, vincristine-induced toxicity possibly affects the medial olivocochlear bundle and—to a lesser extent—the outer hair cells [12].

Only two studies were published that have examined the role of vincristine in platinum-induced hearing loss, highlighting the need for further evidence [4,9]. Both included vincristine as a co-variable in their analysis but did not further investigate the effect of the total cumulative dose of vincristine and whether there was effect modification between vincristine and other ototoxic cancer treatments. Therefore, we analyzed data from a nationwide cohort of CCS with treatment and audiogram data from medical records to 1) quantify the effect of

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Table 1
Demographic and clinical characteristics of study population.

	Total cohort		No Vincristine		Vincristine		P-value ^a
	N = 270		n = 125		n = 145		
Demographic characteristics	n	(%)	n	(%)	n	(%)	
Sex							0.192
Male	154	(57)	66	(53)	88	(61)	
Female	116	(43)	59	(47)	57	(39)	
Age at most recent audiogram							0.066
< 10 years	81	(30)	32	(26)	49	(34)	
10–15 years	108	(40)	47	(38)	61	(42)	
> 15 years	81	(30)	46	(37)	35	(24)	
Clinical characteristics	n	(%)	n	(%)	n	(%)	
Age at cancer diagnosis							< 0.001
< 5 years	112	(41)	42	(34)	70	(48)	
5–9 years	67	(25)	24	(19)	43	(30)	
10–18 years	91	(34)	59	(47)	32	(22)	
Period of cancer diagnosis							0.454
1990–1995	48	(18)	24	(19)	24	(17)	
1996–2001	75	(28)	36	(29)	39	(27)	
2002–2007	82	(30)	32	(26)	50	(34)	
2008–2014	65	(24)	33	(26)	32	(22)	
Diagnosis (ICCC-3)							< 0.001
III CNS and miscellaneous intracranial and intraspinal neoplasms	104	(39)	3	(2)	101	(70)	
IV Neuroblastoma and other peripheral nervous cell tumors	39	(14)	13	(10)	26	(18)	
V Retinoblastoma	5	(2)	2	(2)	3	(2)	
VI Renal tumors	6	(2)	3	(2)	3	(2)	
VII Hepatic tumors	15	(6)	14	(11)	1	(1)	
VIII Malignant Bone tumors	62	(23)	62	(50)	0	(0)	
IX Soft tissue and other extraosseous sarcoma	12	(4)	1	(1)	11	(8)	
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	27	(10)	27	(22)	0	(0)	
Treatments ^b							
Platinum agent							< 0.001
Cisplatin	151	(56)	98	(78)	53	(37)	
Carboplatin	62	(23)	17	(14)	45	(31)	
Cisplatin and Carboplatin	57	(21)	10	(8)	47	(32)	
Cumulative cisplatin dose categories							< 0.001
No cisplatin	62	(23)	17	(14)	45	(31)	
≤ 300 mg/m ²	51	(19)	11	(9)	40	(28)	
301–450 mg/m ²	71	(26)	38	(30)	33	(23)	
> 450 mg/m ²	86	(32)	59	(47)	27	(19)	
Cumulative carboplatin dose categories							< 0.001
No carboplatin	151	(56)	98	(78)	53	(37)	
< 1500 mg/m ²	29	(11)	3	(2)	26	(18)	
1500–3000 mg/m ²	53	(20)	14	(11)	39	(27)	
> 3000 mg/m ²	32	(12)	6	(5)	26	(18)	
Missing	5	(2)	4	(3)	1	(1)	
Cranial radiation							< 0.001
No	172	(64)	115	(92)	57	(39)	
Yes	98	(36)	10	(8)	88	(61)	
HSCT							0.004
No	244	(90)	120	(96)	124	(86)	
Yes	26	(10)	5	(4)	21	(14)	

Abbreviations: CNS, central nervous system; ICC-3, International Classification of Childhood Cancer–Third Edition; HSCT, hematopoietic stem cell transplantation.

^a P-values calculated from chi-square statistics comparing childhood cancer survivors with and without vincristine exposure.

^b Each subject could have had more than one treatment modality.

vincristine on platinum-induced hearing loss; 2) test for interactions between vincristine and other ototoxic cancer treatments; and 3) determine a possible dose-response relationship of vincristine-induced ototoxicity.

2. Methods

2.1. Study population

We analyzed data from CCS treated with platinum-based chemotherapy between 1990 and 2014 in the nine specialized pediatric oncology clinics in Switzerland [6]. We included CCS 1) registered in the national and population-based Swiss Childhood Cancer Registry (SCCR) [13], 2) diagnosed with cancer at age ≤ 18 years, 3) with no

evidence of hearing loss before start of cancer treatment in their medical records, and 4) available audiogram after completing platinum-based chemotherapy [6]. Further details about identifying eligible CCS and data collection are published elsewhere [6,14]. The Ethics Committee of the Canton of Bern approved the SCCR and the Swiss Childhood Cancer Survivor Study (KEK-BE: 166/2014; 2021–01462) [15].

2.2. Study procedure

We collected clinical information on cancer diagnosis and treatment from medical records and the SCCR in 2015 [6,14]. We extracted clinical variables, including sex (female, male); cancer diagnosis according to the International Classification of Childhood Cancer (3rd edition);[16] age at cancer diagnosis (< 5, 5–9, and 10–18 years);

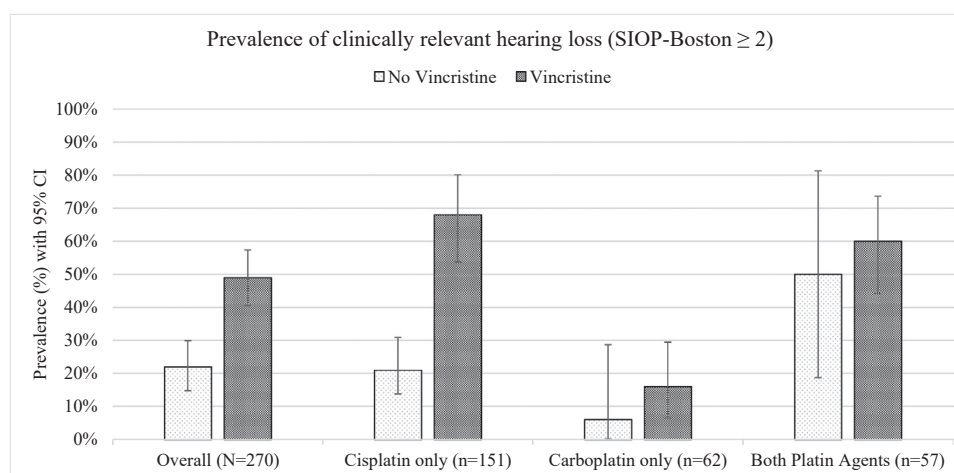


Fig. 1. Comparison of prevalence of clinically relevant hearing loss between childhood cancer survivors with and without vincristine exposure (N = 270). Prevalence is shown for the overall cohort and stratified by type of platinum-based chemotherapy.

period of cancer diagnosis (1990–1995, 1996–2001, 2002–2007, and 2008–2014); type and total cumulative dose (mg/m^2) of platinum agents (cisplatin, carboplatin); CRT (yes, no); and HSCT (yes, no). During initial data collection in 2015, no treatment information about vincristine exposure was collected. We went through all medical records and treatment protocols again in 2022 and calculated vincristine exposure and total cumulative vincristine dose (mg/m^2) as treated or—when unavailable—based on treatment protocol.

2.3. Measurement of hearing loss

We determined hearing loss at latest follow-up after completion of platinum-based chemotherapy. All audiograms were centrally reviewed using the classification system of the International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Scale [17]. Further details on the evaluation of the audiograms were previously published [6]. Based on the approach of previous studies, we defined clinically relevant hearing loss (yes, no) as SIOP-Boston grade ≥ 2 [4,6]. In cases of asymmetric hearing, we took the most affected ear as the reference for grading.

2.4. Statistical analysis

First, we compared the prevalence of clinically relevant hearing loss overall and stratified by type of platinum-based chemotherapy between CCS with and without vincristine exposure. We fitted univariable logistic regression models including sex, age at audiogram, age at cancer diagnosis, period of cancer diagnosis, type of platinum-based chemotherapy, exposure to vincristine, concomitant CRT, and HSCT as exposures and clinically relevant hearing loss (yes, no) as outcome [6]. The multivariable regressions included a priori sex, age at most recent audiogram, age at cancer diagnosis, and all other clinical characteristics previously associated with hearing loss at $P < 0.05$ in the univariable models. To examine effect modification of other ototoxic treatments, we included interaction terms between vincristine exposure and type of platinum-based chemotherapy, CRT, and HSCT [4,18,19]. We also included the total cumulative dose of cisplatin, carboplatin, and vincristine as a continuous variable in a sub-analysis, which included only CCS who received vincristine, to determine a possible dose-response relationship. We excluded survivors with missing values for the cumulative dose of vincristine or platinum-based chemotherapy from the regression analysis. We calculated global P -values using likelihood-ratio tests (LRT).

We performed a sensitivity analysis to control for additional ototoxic factors, such as brain surgeries or cerebrospinal fluid shunts, associated with central nervous system (CNS) tumors diagnosis [1,20].

We included CNS tumor diagnosis (yes, no) as a co-variable in our multivariable regression model.

We used Stata version 16.1 (StataCorp LP, Austin, TX, USA) for all analyses.

3. Results

3.1. Characteristics of study population

We included 270 CCS with a median age at cancer diagnosis of 6.8 years (interquartile range [IQR]: 2.1–11.7 years) in our analysis (Table 1). A detailed flow-diagram of the study population was published elsewhere [6]. Median time from cancer diagnosis to most recent audiogram was 5 years (IQR 2.5–8.1 years). The most common cancer diagnoses were CNS tumors ($n = 104$; 39%). Over half ($n = 145$; 54%) received vincristine with a median total cumulative dose of $23 \text{ mg}/\text{m}^2$ (IQR 10.1–40.9 mg/m^2) (Supplement Figure A.1). For $n = 140$ (97%) CCS, we had total cumulative vincristine dose information available. We extracted vincristine doses directly from medical records for $n = 57$ (41%) CCS, and for $n = 83$ (59%) CCS, we estimated the dose based on the treatment protocol and treatment arm. CCS previously treated with vincristine were younger at cancer diagnosis, more likely survivors of CNS tumors or neuroblastoma, and received more often carboplatin, CRT, and HSCT than CCS without vincristine exposure. Of those CCS who did not receive vincristine, the majority had been diagnosed with a malignant bone tumor ($n = 62$; 50%) or a germ cell tumor ($n = 27$; 22%).

3.2. Role of vincristine in platinum-induced hearing loss

Of the included CCS treated with vincristine, 49% (95% CI: 41–57) had hearing loss compared with 22% (95% CI: 15–30) of CCS not treated with vincristine ($p < 0.001$) (Fig. 1). Stratified by type of platinum-based chemotherapy, we saw the largest difference in prevalence of hearing loss between CCS with and without vincristine exposure among those treated with only cisplatin (68% vs. 21%).

Exposure to vincristine was associated with a higher risk for hearing loss in the univariable (odds ratio [OR] 3.5, 95% CI: 2.0–6.0) and multivariable (OR 4.8, 95% CI: 1.8–12.9) logistic regression analyses (Table 2). Using interaction terms, we found no evidence for effect modification between exposure to vincristine and type of platinum-based chemotherapy, CRT, and HSCT (all $P > 0.05$) (Table 3). In a sub-analysis including only CCS with vincristine exposure, we found no evidence for a linear effect of total cumulative vincristine dose on the risk of hearing loss (OR 1.0, 95% CI: 0.97–1.04) (Table 2) (Supplement

Table 2
Results from univariable and multivariable^a logistic regression analyses.

	SIOP-Boston grade ≤1 n = 172		SIOP-Boston grade ≥2 n = 98		Univariable n = 270		Multivariable ^b n = 270		Multivariable ^c n = 139	
	n	(%)	n	(%)	OR ^d (95%-CI)	P-value ^e	OR ^d (95%-CI)	P-value ^e	OR ^d (95%-CI)	P-value ^e
Sex										
Female	75	(44)	41	(42)	Reference	0.778	Reference	0.726	Reference	0.791
Male	97	(56)	57	(58)	1.1 (0.7–1.8)		1.1 (0.6–2.2)		1.1 (0.4–2.9)	
Age at audiogram										
< 10 years	63	(37)	18	(18)	Reference	0.006	Reference		Reference	0.034
10–15 years	62	(36)	46	(47)	2.6 (1.4–5.0)		7.8 (2.7–22.7)		7.6 (1.4–40.0)	
> 15 years	47	(27)	34	(35)	2.5 (1.3–5.0)		8.0 (2.3–27.2)		4.5 (0.8–25.5)	
Age at cancer diagnosis										
< 5 years	61	(35)	51	(52)	3.0 (1.6–5.5)	0.001	9.0 (3.0–27.2)	< 0.001	10.1 (1.8–57.2)	0.014
5–9 years	40	(23)	27	(28)	2.4 (1.2–4.8)		2.4 (0.9–6.1)		1.4 (0.4–5.0)	
10–18 years	71	(41)	20	(20)	Reference		Reference	0.011	Reference	0.037
Period of cancer diagnosis										
1990–1995	18	(10)	30	(31)	7.4 (3.1–17.3)	< 0.001	5.4 (1.8–16.1)		7.9 (1.6–39.3)	
1996–2001	46	(27)	29	(30)	2.8 (1.3–6.1)		1.7 (0.6–4.7)		1.3 (0.3–5.4)	
2002–2007	55	(32)	27	(28)	2.2 (1.0–4.7)		1.4 (0.6–3.7)		2.5 (0.7–8.7)	
2008–2014	53	(31)	12	(12)	Reference		Reference		Reference	
Treatments										
Platinum-based chemotherapy										
Carboplatin only	54	(31)	8	(8)	Reference	< 0.001	Reference	< 0.001	n.a.	
Cisplatin only	94	(55)	57	(58)	4.1 (1.8–9.2)		15.2 (5.0–45.8)		n.a.	
Both platinum agents	24	(14)	33	(34)	9.3 (3.7–23.1)		8.8 (2.8–27.4)		n.a.	
Cumulative cisplatin dose										
Per 100 mg/m ² increase	n.a.	n.a.	n.a.	n.a.	n.a.		n.a.		1.6 (1.1–2.3)	0.008
Cumulative carboplatin dose										
Per 500 mg/m ² increase	n.a.	n.a.	n.a.	n.a.	n.a.		n.a.		0.8 (0.7–1.0)	0.023
Vincristine										
No	98	(57)	27	(28)	Reference	< 0.001	Reference	0.002	n.a.	
Yes	74	(43)	71	(72)	3.5 (2.0–6.0)		4.8 (1.8–12.9)		n.a.	
Cumulative vincristine dose										
Per 1 mg/m ² increase	n.a.	n.a.	n.a.	n.a.	n.a.		n.a.		1.0 (0.97–1.04)	0.871
Cranial radiation										
No	122	(71)	50	(51)	Reference	0.001	Reference	0.286	Reference	0.790
Yes	50	(29)	48	(49)	2.3 (1.4–3.9)		1.7 (0.6–4.4)		1.2 (0.3–4.7)	
HSCT										
No	166	(97)	78	(80)	Reference	< 0.001	Reference	0.013	Reference	0.006
Yes	6	(3)	20	(20)	7.1 (2.7–18.4)		5.2 (1.4–19.4)		12.1 (1.7–83.6)	

Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplantation; n.a., not applicable; OR, odds ratio; SIOP, International Society of Pediatric Oncology.

^a Factors associated with hearing loss at $P < 0.05$ were included in the multivariable analyses. Sex, age at audiogram, and age at cancer diagnosis were included in the multivariable model independent of the strength of the association in the respective univariable model.

^b Main analysis including vincristine (yes, no) and exposure to platinum-based chemotherapy (cisplatin, carboplatin, both platinum agents) as categorical variables ($N = 270$).

^c Sub-analysis including only childhood cancer survivors (CCS) exposed to vincristine with total cumulative doses of chemotherapy as continuous variables ($N = 139$). CCS with missing dose information ($n = 6$) were excluded from analysis.

^d Odds ratio from univariable and multivariable logistic regression models: OR < 1 indicates that SIOP-Boston grade ≤ 1 is more likely. OR > 1 indicates that SIOP-Boston grade ≥ 2 is more likely.

^e Global P -value calculated from likelihood-ratio test.

Table 3
Interactions between vincristine and other ototoxic cancer treatments.

	Multivariable ^a	
	OR ^b (95%-CI)	P-value ^c
Model 1		
Test for interaction between platinum-based chemotherapy and vincristine		0.274
Carboplatin	Reference	
Cisplatin × vincristine exposure	2.8 (0.2–35.2)	
Both platinum agents × vincristine exposure	0.5 (0.03–11.0)	
Model 2		
Test for interaction between CRT and vincristine		0.200
No CRT	Reference	
CRT × vincristine exposure	0.3 (0.04–2.0)	
Model 3		
Test for interaction between HSCT and vincristine		0.354
No HSCT	Reference	
HSCT × vincristine exposure	4.4 (0.18–105.8)	

Abbreviations: CI, confidence interval; CRT, cranial radiotherapy; HSCT, hematopoietic stem cell transplantation; OR, odds ratio.

^a Each interaction between vincristine and the variables platinum-based chemotherapy, CRT, or HSCT was analyzed in a separate multivariable model (Models 1–3) (N = 270). Each model was adjusted for sex, age at audiogram, age at diagnosis, period of diagnosis, other ototoxic cancer treatments (i.e. platinum-based chemotherapy, CRT, or HSCT).

^b Odds ratio from univariable and multivariable logistic regression models: OR < 1 indicates that SIOP-Boston grade ≤ 1 is more likely. OR > 1 indicates that SIOP-Boston grade ≥ 2 is more likely.

^c Global P-value calculated from likelihood-ratio test.

Figure A.1). We excluded CCS (n = 6; 2%) with missing dose information for platinum-based chemotherapy or vincristine from the sub-analysis.

In our sensitivity analysis, diagnosis with a CNS tumor (yes, no) was not associated with an increased risk for hearing loss in the multivariable regression (OR 0.8, 95% CI: 0.2–2.7) (Supplement Table A.1). The effect size of vincristine (yes, no) did not change compared with the model without adjustment for CNS tumor diagnosis (OR 5.3, 95% CI: 1.7–17.0 vs. OR 4.8, 95% CI: 1.8–12.9).

4. Discussion

In our nationwide cohort study of CCS treated with platinum-based chemotherapy, we found the prevalence of platinum-induced hearing loss higher among CCS with additional vincristine than of CCS without vincristine exposure. Vincristine exposure increased the risk of hearing loss fivefold when adjusting for clinical characteristics. However, we found no evidence of a dose-response relationship of cumulative vincristine dose and the risk for hearing loss, or evidence of effect modification by other ototoxic cancer treatments.

Our study is strengthened from analyzing the ototoxicity of vincristine in a large cohort of CCS in terms of overall exposure and considering the total cumulative vincristine dose and potential interactions with other ototoxic cancer treatments. Further strengths include the well-described cohort with clinical data on hearing function, cancer diagnosis, and platinum-based chemotherapy available. However, we cannot conclude whether vincristine is ototoxic independently or only in combination with platinum agents because all included CCS were treated with platinum-based chemotherapy. Furthermore, we had no data on brain surgery or cerebrospinal fluid shunts among survivors of

CNS tumors, which have been associated with an increased risk of hearing loss in other studies [1,20,21]. Because 70% of CCS in our cohort who received vincristine were diagnosed with CNS tumors and most patients with CNS tumors were exposed to vincristine (97%), we cannot exclude that part of the association of vincristine with hearing loss as possibly explained by other factors associated with the diagnosis of CNS tumors or other concomitant treatments. However, in our sensitivity analysis, CNS tumor diagnosis was not associated with an increased risk of hearing loss and the effect of vincristine remained unchanged after controlling for CNS tumor diagnosis. We also lack data on use of concomitant ototoxic drugs such as aminoglycoside antibiotics and on prophylactic administration of sodium thiosulfate [1,22]. However, sodium thiosulfate was only recently been approved in the United States for clinical use; it is not yet approved in Switzerland [23]. Other limitations are the retrospective study design, the use of non-standardized routine data from different clinics, and the restriction to patients who have survived their cancer, allowing for potential survival bias. Recent studies have indicated that in addition to the total cumulative dose of platinum-based chemotherapy, other dose parameters such as dose per cycle, dose per day, and infusion time may also contribute to the risk of hearing loss [4,24]. We did not include such detailed information on the dose regimen of platinum-based chemotherapy in our analysis and thus could not adjust for potential differences between CCS with and without vincristine exposure.

Ototoxicity of vincristine was reported mainly in case studies of adult patients with cancer and in two recent cohort studies involving CCS [4,9,11,25–28]. Moke and colleagues examined hearing loss in a large multi-center cohort of 1481 children, adolescents, and young adults treated with cisplatin [4]. They also collected data on vincristine exposure and reported that vincristine (yes, no) increased the risk for cisplatin-induced hearing loss by a factor of four (OR 3.6) at latest follow-up [4], which is consistent with our estimate (OR 4.8). In another cohort study of 368 pediatric patients with cancer, Meijer and colleagues demonstrated vincristine exposure (hazard ratio 2.9) was an important determinant for the cumulative incidence of cisplatin-induced hearing loss [9]. The results of both studies are consistent with our findings, supporting the emerging evidence for a potential ototoxic effect of vincristine. However, neither of the two cohort studies included data on the cumulative dose of vincristine [4,9].

We did not observe an effect from higher cumulative doses of vincristine on the risk of hearing loss, yet we had no data on administration method, timing of administration with other drugs (particularly platinum agents), pharmacokinetics, drug-drug interactions with azole antifungals, and genetic factors possibly affecting total exposure and toxicity of vincristine [29–32]. Two prospective studies with small sample sizes (N ≤ 23) examined ototoxicity of vincristine and included dose information [12,33]. Lugassy and colleagues enrolled adult patients with cancer (N = 23) in their study and did not observe any deleterious effects from vincristine on hearing among patients with moderate dose exposure (mean total dose of 12 mg) [33]. One patient on high-dose vincristine (total dose of 24 mg) developed sensorineural hearing loss during the observation period [33]. Riga and colleagues enrolled pediatric patients diagnosed with leukemia in their study (N = 15) who had been treated according to the Berlin-Frankfurt-Muenster-95 (BMF-95) protocol. In their study, exposure to low and moderate doses of vincristine (≤ 1.5 mg/m² per dose) did not result in any abnormal changes (≥ 15 dB) in mean hearing thresholds levels measured by pure tone audiometry at latest follow-up [12]. But they found abnormalities in transient evoked otoacoustic emissions (TEOAE) and a decrease in contralateral suppression after three cycles of vincristine administration, indicating a measurable neurotoxic effect of vincristine on outer hair cells and the medial olivocochlear bundle [12]. However, the study's short observation period of 22 days does not allow prediction of the reversibility of observed effects or subsequent detection of hearing loss [12].

5. Conclusion

Our results support emerging evidence for an increased risk of platinum-induced hearing loss with concomitant vincristine administration [4,9]. Interindividual variability in hearing loss after platinum-based chemotherapy is large and not yet fully understood [8], which emphasizes the importance of identifying additional risk factors for hearing loss among CCS, such as the neurotoxic treatment vincristine. However, we suggest to include TEOAE or distortion-product otoacoustic emissions (DPOAE) measurements in further studies to better understand the mechanism and clinical course of vincristine-induced neurotoxicity in the medial olivocochlear bundle and its influence on platinum-induced hearing loss. In addition, we suggest investigating causality of vincristine and hearing loss among CCS without platinum-based chemotherapy or CRT to determine whether vincristine causes permanent hearing loss even without established ototoxic cancer treatments and whether genetic factors possibly play a role. Also, preclinical studies should be performed to better understand the mechanism of vincristine ototoxicity and potential interaction with platinum-based chemotherapy at the cellular level.

Clinical trial registration

Not applicable.

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CRedit authorship contribution statement

Sven Strebel: Conceptualization, Methodology, Data preparation, Data curation, Statistical analysis, Writing – all stages, Visualization; **Luzius Mader:** Writing – review & editing, Statistical analysis; **Philippa Jörger:** Writing – review & editing; **Nicolas Waespe:** Writing – review & editing. **Seraina Uhlmann:** Data collection, Data preparation, Data curation, Writing – review & editing. **Nicolas von der Weid:** Supervision, Writing – review & editing; **Marc Ansari:** Supervision, Writing – review & editing; **Claudia E. Kuehni:** Supervision, Conceptualization, Methodology, Statistical analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejcped.2023.100017](https://doi.org/10.1016/j.ejcped.2023.100017).

References

- [1] W. Landier, Ototoxicity and cancer therapy, *Cancer* 122 (2016) 1647–1658.
- [2] J.K. Bass, W. Liu, P. Banerjee, T.M. Brinkman, D.A. Mulrooney, A. Gajjar, et al., Association of hearing impairment with neurocognitive functioning in survivors of childhood cancer, *JAMA Oncol.* 6 (2020) 1363–1371.
- [3] E. Orgel, S.H. O'Neil, K. Kayser, B. Smith, T.L. Softley, S. Sherman-Bien, et al., Effect of sensorineural hearing loss on neurocognitive functioning in pediatric brain tumor survivors, *Pediat. Blood Cancer* 63 (2016) 527–534.
- [4] D.J. Moke, C. Luo, J. Millstein, K.R. Knight, S.R. Rassekh, B. Brooks, et al., Prevalence and risk factors for cisplatin-induced hearing loss in children, adolescents, and young adults: a multi-institutional North American cohort study, *Lancet Child Adolesc. Health* 5 (2021) 274–283.
- [5] E. Clemens, A.C. de Vries, S.F. Pluijm, A. Am Zehnhoff-Dinnesen, W.J. Tissing, J.J. Loonen, et al., Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study, *Euro. J. Cancer* 69 (2016) 77–85.
- [6] S. Strebel, L. Mader, T. Sláma, N. Waespe, A. Weiss, R. Parfitt, et al., Severity of hearing loss after platinum chemotherapy in childhood cancer survivors, *Pediat. Cancer* 69 (2022) e29755.
- [7] Y. Li, R.B. Womer, J.H. Silber, Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose, *Eur. J. Cancer* 40 (2004) 2445–2451.
- [8] T. Langer, am Zehnhoff-Dinnesen A, Radtke S, Meiert J, Zolk O. Understanding platinum-induced ototoxicity, *Trends Pharmacol. Sci.* 34 (2013) 458–469.
- [9] A.J.M. Meijer, K.H. Li, B. Brooks, E. Clemens, C.J. Ross, S.R. Rassekh, et al., The cumulative incidence of cisplatin-induced hearing loss in young children is higher and develops at an early stage during therapy compared with older children based on 2052 audiological assessments, *Cancer* 128 (2022) 169–179.
- [10] M.L. Madsen, H. Due, N. Ejlskjær, P. Jensen, J. Madsen, K. Dybkær, Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review, *Cancer Chemother. Pharmacol.* 84 (2019) 471–485.
- [11] S.L. Mahajan, Y. Ikeda, T.J. Myers, M.G. Baldini, Acute acoustic nerve palsy associated with vincristine therapy, *Cancer* 47 (1981) 2404–2406.
- [12] M. Riga, I. Psarommatas, S. Korres, M. Varvutsi, I. Giotakis, N. Apostolopoulos, et al., Neurotoxicity of vincristine on the medial olivocochlear bundle, *Int. J. Pediatric Otorhinolaryngol.* 71 (2007) 63–69.
- [13] G. Michel, N.X. von der Weid, M. Zwahlen, S. Redmond, M.P. Strippoli, C.E. Kuehni, Incidence of childhood cancer in Switzerland: the Swiss childhood cancer registry, *Pediat. Blood Cancer* 50 (2008) 46–51.
- [14] A. Weiss, R. Kuonen, H. Brockmeier, M. Grotzer, C. Candrea, R. Maire, et al., Audiological monitoring in Swiss childhood cancer patients, *Pediat. Blood Cancer* (2018) 65.
- [15] C.E. Kuehni, C.S. Rueegg, G. Michel, C.E. Rebholz, M.P. Strippoli, F.K. Niggli, et al., Cohort profile: the Swiss childhood cancer survivor study, *Int. J. Epidemiol.* 41 (2012) 1553–1564.
- [16] E. Steliarova-Foucher, C. Stiller, B. Lacour, P. Kaatsch, International classification of childhood cancer, third edition, *Cancer* 103 (2005) 1457–1467.
- [17] P.R. Brock, K.R. Knight, D.R. Freyer, K.C. Campbell, P.S. Steyger, B.W. Blakley, et al., Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 30 (2012) 2408–2417.
- [18] K. Gertson, S.S. Hayashi, K. Trinkaus, F. Wan, R.J. Hayashi, Prevalence of ototoxicity following hematopoietic stem cell transplantation in pediatric patients, *Biol. Blood Marrow Transpl. J. Am. Soc. Blood Marrow Transpl.* 26 (2020) 107–113.
- [19] J.K. Bass, C.H. Hua, J. Huang, A. Onar-Thomas, K.K. Ness, S. Jones, et al., Hearing loss in patients who received cranial radiation therapy for childhood cancer, *J. Clin. Oncol. Official J. Am. Soc. Clin. Oncol.* 34 (2016) 1248–1255.
- [20] D.J. Guillaume, K. Knight, C. Marquez, D.F. Kraemer, D.M. Bardo, E.A. Neuwelt, Cerebrospinal fluid shunting and hearing loss in patients treated for medulloblastoma, *J. Neurosurg. Pediatr.* 9 (2012) 421–427.
- [21] A. Weiss, G. Sommer, R. Kasteler, K. Scheinmann, M. Grotzer, M. Kompis, et al., Long-term auditory complications after childhood cancer: a report from the Swiss Childhood Cancer Survivor Study, *Pediatric Blood Cancer* 64 (2017) 364–373.
- [22] P.R. Brock, R. Maibach, M. Childs, K. Rajput, D. Roebuck, M.J. Sullivan, et al., Sodium thiosulfate for protection from cisplatin-induced hearing loss, *New England J. Med.* 378 (2018) 2376–2385.
- [23] P. Brock, A. Meijer, P. Kogner, M. Ansari, M. Capra, J. Geller, et al., Sodium thiosulfate as cisplatin otoprotectant in children: the challenge of when to use it, *Pediatric Blood Cancer* (2023) e30248.
- [24] M.L. Camet, A. Spence, S.S. Hayashi, N. Wu, J. Henry, K. Sauerburger, et al., Cisplatin ototoxicity: examination of the impact of dosing, infusion times, and schedules in pediatric cancer patients, *Front. Oncol.* 11 (2021) 673080.
- [25] G. Lugassy, A. Shapira, Sensorineural hearing loss associated with vincristine treatment, *Blut* 61 (1990) 320–321.
- [26] I. Aydogdu, O. Ozturan, I. Kuku, E. Kaya, A. Sevinc, R. Yildiz, Bilateral transient hearing loss associated with vincristine therapy: case report, *J. Chemother.* 12 (2000) 530–532.

- [27] M.T. Kalcıoglu, I. Kuku, E. Kaya, S. Oncel, I. Aydogdu, Bilateral hearing loss during vincristine therapy: a case report, *J. Chemother.* 15 (2003) 290–292.
- [28] H. Yousif, S.G. Richardson, W.A. Saunders, Partially reversible nerve deafness due to vincristine, *Postgrad. Med. J.* 66 (1990) 688–689.
- [29] M.E. van de Velde, G.L. Kaspers, F.C.H. Abbink, A.J. Wilhelm, J.C.F. Ket, M.H. van den Berg, Vincristine-induced peripheral neuropathy in children with cancer: a systematic review, *Crit. Rev. Oncol./Hematol.* 114 (2017) 114–130.
- [30] M.E. van de Velde, A. Uittenboogaard, W. Yang, E. Bonten, C. Cheng, D. Pei, et al., Genetic polymorphisms associated with vincristine pharmacokinetics and vincristine-induced peripheral neuropathy in pediatric oncology patients, *Cancers* (2022) 14.
- [31] M.E. van de Velde, G.J.L. Kaspers, F.C.H. Abbink, J.W.R. Twisk, I.M. van der Sluis, C. van den Bos, et al., Vincristine-induced peripheral neuropathy in pediatric oncology: a randomized controlled trial comparing push injections with one-hour infusions (The VINCA Trial), *Cancers* (2020) 12.
- [32] M.E. van de Velde, J.C. Panetta, A.J. Wilhelm, M.H. van den Berg, I.M. van der Sluis, C. van den Bos, et al., Population pharmacokinetics of vincristine related to infusion duration and peripheral neuropathy in pediatric oncology patients, *Cancers* (2020) 12.
- [33] G. Lugassy, A. Shapira, A prospective cohort study of the effect of vincristine on audition, *Anti-Cancer Drugs* 7 (1996) 525–526.