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Causes and long-term course of ototoxicity in pediatric medulloblastoma and ependymoma patients – cumulative platinum and cochlear irradiation dose matter

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Abstract

Purpose

This study aimed to define dose-dependent risk factors and thresholds for ototoxicity after cisplatin chemotherapy and radiotherapy (RT).

Methods

Patients from the HIT2000 trial receiving first-line treatment for medulloblastoma (MB) or ependymoma (EP) were eligible. Treatment details (incl. cochlear irradiation dose [CID]) and audiological outcome were analyzed. Ototoxicity was graded using the HIT ototoxicity grading system (HIT).

Results

Courses of 101 patients were analyzed. Median audiology follow-up was 6 years [range: 1.0–18.1 years]. Ototoxicity grade ≥ 1 was diagnosed for n = 66 patients (65.4%). Univariable analyses revealed differing distributions of ototoxicity regarding histology (classical medulloblastoma [CMB]: 50/65, large-cell/anaplastic medulloblastoma [LCAMB]: 3/3, desmoplastic medulloblastoma [DMB]/medulloblastoma with extensive nodularity [MBEN]: 8/12, EP: 5/21; $p < 0.001$), tumor localization (supratentorial: 3/9, infratentorial: 63/92; $p < 0.001$), metastatic status (non-metastatic disease [M0]: 46/77, metastatic disease [M+]: 20/24; $p = 0.003$), radiation field (craniospinal irradiation [CSI]: 59/75, local RT: 6/21, no RT: 1/5; $p < 0.001$), CID ($p < 0.001$) and cumulative cisplatinum dose ($p = 0.02$). Multivariable analyses confirmed the impact of cumulative cisplatinum dose ($p = 0.004$) and CID ($p = 0.046$). Receiver operating characteristic analyses defined cut-offs for high risk of ototoxicity grade ≥ 1 (cisplatinum: 70 mg/m2 body surface area [BSA], CID: 37.5 Gy): each 1 mg/m2 BSA increase in cisplatinum dose raised risk by 4%, and each 1 Gy increase in CID raised risk by 4.6%.

Conclusions

Ototoxicity affects a majority of children receiving adjuvant treatment for MB and EP. To avoid disabilities and negative effect on quality of life, dosage of cisplatinum and radiotherapy should be scrutinized and reduced whenever possible.

Key Points

● 65% of pediatric MB and EP patients have grade ≥ 1 ototoxicity.

● Cumulative cisplatin ≥ 70 mg/m² BSA and cochlear irradiation ≥ 37.5 Gy constitute a high risk of ototoxicity, increasing by 4% with each 1 mg/m² BSA and 4.6% with each Gy above these limits.

Introduction

Ototoxicity is a well-recognized side effect of platinum-based chemotherapeutics and radiotherapy (RT) used to treat childhood cancers [1–3]. It typically presents as bilateral, symmetric sensorineural hearing loss with tinnitus and vertigo, affecting higher frequencies (≥ 4 kHz) first and eventually extending to speech frequencies (< 4 kHz) [4]. High-frequency loss can render consonants inaudible, affecting speech recognition and the perception of music and environmental sounds [5], and even mild bilateral hearing loss impairs reading, spelling, phonological memory and discrimination [6]. Hearing loss may progress after platinum therapy ends, possibly because platinum is retained in the body for up to two decades [7], and because hearing is critical for language development, affected children are vulnerable to neurocognitive and psychosocial setbacks [8]. About 50% of children treated with cisplatin experience permanent hearing loss [1, 9, 10] and up to 40% require hearing aids [11].

Pediatric patients with medulloblastoma (MB) and ependymoma (EP) are particularly vulnerable, because their treatment combines platinum-containing chemotherapy with cranial or craniospinal irradiation, they are often very young, and late effects substantially affect quality of life [11]. MB is the most common high-grade malignant central nervous system (CNS) tumor in childhood, peaking between 6 and 8 years [12], with metastatic spread along the cerebrospinal fluid (CSF) pathways in around 30% of patients at diagnosis [13]; surgery, craniospinal radiotherapy and platinum-containing chemotherapy achieve 10-year survival of up to 90% in low-risk disease [14]. EP is the third most common high-grade pediatric brain tumor and may be supratentorial or infratentorial [15]; local radiotherapy is the mainstay of adjuvant treatment [16, 17], with additional platinum-containing chemotherapy in young or high-risk patients, achieving a 10-year progression-free survival (PFS) of approximately 58% and overall survival (OS) of approximately 73% [18].

While platinum- and radiation-induced hearing loss has been studied broadly in pediatric oncology, few studies have focused exclusively on CNS tumors or addressed the long-term course and complex dose-toxicity relationships in this population. This study therefore aimed to characterize the long-term incidence, course and dose-dependent risk factors of ototoxicity in a well-characterized cohort of pediatric MB and EP patients treated within the HIT2000 trial, and to define clinically applicable dose thresholds to inform risk-adapted treatment.

Methods

Patient selection and data collection

This retrospective cohort study included patients aged 0–21 years with newly diagnosed MB or EP enrolled in the HIT2000 trial (NCT00303810, registered March 15, 2006), treated per protocol at participating institutions between 2001 and 2011 and alive at last follow-up; data retrieval was performed in June 2023. The protocol recommended central review of histology, neuroradiology and CSF cytology. The trial was conducted in line with the Declaration of Helsinki and approved by the responsible

ethics committees; informed consent was obtained from the legal representatives of all patients after institutional review board approval.

Patient characteristics and follow-up data were reviewed by the authors, and missing audiograms were requested from participating centers. Ototoxicity was assessed from audiograms obtained during follow-up; cohort assembly is shown in Fig. 1a.

Standard procedures and treatment within the HIT2000 trial

The HIT2000 trial was a primary treatment protocol for children and young adults with intracranially localized primitive neuroectodermal tumors (PNET/medulloblastoma), ependymoma and pineoblastoma [19], aiming to optimize outcomes while minimizing treatment-related side effects, with long-term follow-up as an integral part. A risk-adapted approach stratified patients by age, histology and extent of resection, supported by central neuropathological and neuroradiological review, and adjuvant treatment was initiated after maximal safe resection and staging. Detailed treatment strategies have been published previously [20–24]; those applied in the present cohort are summarized in Online Resource 1. The protocol also predefined audiometric thresholds at which cisplatin was to be dose-reduced, replaced by carboplatin or discontinued (Online Resource 2).

Audiological assessment

The study protocol required an audiological examination at the time of initial diagnosis and, for children in the HIT2000-AB4 randomized arm, once during the first year after completion of therapy and when clinically indicated. For this study, pure-tone audiograms were analyzed retrospectively, using baseline and last available measurements.

Four classification systems were initially applied to grade ototoxicity: HIT, Brock, St. Jude and WHO [25, 26]; a comparison is provided in Online Resource 3 and the resulting grade distributions in Fig. 1b. The Brock and St. Jude systems miss mild ototoxicity by not considering threshold changes below 20 dBHL, and the WHO classification was not designed to address the subtleties of ototoxicity [25]. The HIT classification, which captures early ototoxicity by recording hearing loss below 2 kHz, was therefore used for the final analyses, with grade 1 as the threshold for manifest ototoxicity because of its clinical relevance.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 29), with descriptive statistics summarizing cohort characteristics. Pearson's chi-squared test assessed associations between categorical variables and ototoxicity (Fisher's exact test when expected cell frequencies were < 5). Ordinal regression analyzed the relationship between metric variables (radiation and chemotherapy

doses) and the risk of ototoxicity, and receiver operating characteristic (ROC) analysis identified optimal cut-off values for cisplatin and irradiation dose.

Univariately significant factors were assessed for interrelationships using a correlation matrix, and multivariable logistic regression with backward elimination explored the combined effects of uncorrelated or weakly correlated variables. Model 1 (n = 101) included cumulative cisplatin dose [mg/m² body surface area (BSA)], metastatic status (M0 vs. M+) and CSI dose [Gy]; model 2 (n = 84) additionally included cochlear irradiation dose, available for a subset of patients. Kaplan-Meier statistics estimated PFS probabilities according to treatment modification. All analyses were exploratory, and the local significance level was set to 0.05 without adjustment for multiple testing.

Results

Clinical characteristics of the study population

The final study cohort consisted of 101 patients with complete clinical data and both baseline and post-treatment audiograms (Fig. 1a); cohort characteristics are shown in Table 1. Most patients had medulloblastoma (79.2%), the most common subtype being classical medulloblastoma (CMB, 64.4%). The majority of medulloblastoma (56.2%) and ependymoma cases (95.2%) had neither relevant residual tumor nor meningeosis at diagnosis (R0/M0). The most common treatment strategy was HIT2000-AB4 (47.5%), followed by MET-HIT2000-AB4-M2-M4 (15.8%).

Table 1
Patient, tumor, and treatment characteristics of the HIT2000 cohort

Characteristic	HIT2000 cohort (n = 101)	Characteristic	HIT2000 cohort (n = 101)
Age at diagnosis		**Radiotherapy**	
< 4 years	23 (22.8%)	yes	95 (94.1%)
≥ 4 years	78 (77.2%)	CSI	75 (74.3%)
median age, years	6.77	median CSI dose	36 Gy
Sex		median cochlear radiation dose (CSI)	45 Gy
Male	65 (64.4%)	tumor bed only	21 (20.8%)
Female	36 (35.6%)	median cochlear radiation dose (tumor bed only)	24.5 Gy
Initial staging		hyperfractionated RT	47 (49.5%)
Medulloblastoma		Medulloblastoma	33 (34.7%)
R0/M0	45 (56.2%)	Ependymoma	14 (14.7%)
R ≥ 1.5 cm²/M0	11 (13.8%)	conventional fractionated RT	48 (50.5%)
M+	24 (30.0%)	VCR i.v.	78 (82.1%)
Ependymoma		no concomitant chemotherapy	17 (17.9%)
R0/M0	20 (95.2%)	no radiotherapy	5 (5.0%)
R ≥ 0.5 cm²/M0	1 (4.8%)	**Ototoxicity according to HIT**	
M+	0 (0%)	yes	66 (65.4%)
Histology, centrally reviewed		no	35 (34.6%)
CMB	65 (64.4%)	**Treatment modification due to toxicity**	
DMB	10 (9.9%)	yes	33 (32.7%)
LCAMB	3 (3.0%)	no	68 (67.3%)
MBEN	2 (2.0%)	**Dose of cisplatin**	
Grade II ependymoma	4 (4.0%)	per protocol	89 (89.1%)

[a]As documented per medical reports. CSI craniospinal irradiation, RT radiotherapy, VCR vincristine, CMB classical medulloblastoma, DMB desmoplastic medulloblastoma, LCAMB large-cell/anaplastic medulloblastoma, MBEN medulloblastoma with extensive nodularity

Characteristic	HIT2000 cohort (n = 101)	Characteristic	HIT2000 cohort (n = 101)
Age at diagnosis		**Radiotherapy**	
Grade III ependymoma	17 (16.8%)	reduced	11 (10.9%)
Localization		**Switch to carboplatin**	
Cerebrum	9 (8.9%)	yes	22 (21.8%)
Infratentorial, central	70 (69.3%)	no	79 (78.2%)
Cerebellar hemisphere / infratentorial, lateral	5 (5.0%)	**Relapse**	
Infratentorial, central and lateral	17 (16.8%)	yes	11 (10.9%)
Therapy as applied		CMB	7 (63.6%)
HIT2000 AB4	48 (47.5%)	DMB	1 (9.1%)
HIT2000 BIS4	7 (6.9%)	Grade II ependymoma	1 (9.1%)
MET-HIT2000 AB4-M1	3 (3.0%)	Grade III ependymoma	2 (18.2%)
MET-HIT2000 AB4-M2-M4	16 (15.8%)	no	90 (89.1%)
MET-HIT2000 BIS4	6 (5.9%)	**Posterior fossa syndrome**[a]	
E-HIT2000 AB4	12 (11.9%)	yes	9 (8.9%)
E-HIT2000 BIS4	9 (8.9%)	no	92 (91.1%)
Further surgery			
prior to adjuvant treatment	2 (2.0%)		
during adjuvant treatment	5 (5.0%)		
after relapse	8 (7.9%)		
no	86 (85.1%)		

[a]As documented per medical reports. CSI craniospinal irradiation, RT radiotherapy, VCR vincristine, CMB classical medulloblastoma, DMB desmoplastic medulloblastoma, LCAMB large-cell/anaplastic medulloblastoma, MBEN medulloblastoma with extensive nodularity

Most patients (94.1%) received radiotherapy, with 75 (74.3%) receiving craniospinal irradiation (CSI) and 47 (49.5%) receiving hyperfractionated radiotherapy. Additional surgery was performed in 2 patients (2%) before adjuvant treatment, 5 (5%) during adjuvant treatment and 8 (7.9%) after relapse, and posterior fossa syndrome was documented in 8.9%. Eleven patients relapsed, leading to tailored interventions in 6,

comprising local or craniospinal re-irradiation with posterior fossa boost, temozolomide (TMZ), and in one case response-integrated sparing therapy (RIST) [27] combined with stereotactic radiotherapy to a posterior fossa nodule.

Most patients (89.1%) received the prescribed cisplatin dose, while 11 (10.9%) received a reduced dose and 22 (21.8%) were switched to carboplatin. According to the HIT classification, 66 patients (65.4%) experienced ototoxicity of grade ≥ 1, and 33 (32.7%) required treatment adaptation because of toxicity.

Ototoxicity – incidence, course and treatment modification

The median follow-up since the end of treatment was 6 years (range 1–18 years). Of the 101 patients, 66 (65.4%) experienced ototoxicity (Fig. 1b): grade 1 in 9, grade 2 in 40, grade 3 in 13 and grade 4 in 4 patients.

The HIT2000 protocol allowed dose adjustments for treatment-related toxicities. Ototoxicity accounted for 26 (78.8%) of the 33 treatment modifications, while infection, nephrotoxicity and neurotoxicity contributed less frequently (Table 2). Figure 2a and 2b display the course of ototoxicity in patients whose treatment was adapted due to toxicity compared with those receiving the complete protocol treatment, and Fig. 2c summarizes outcomes according to the reason for adaptation.

Table 2
Causes for cisplatin dose reduction or switch to carboplatin in the HIT2000 cohort

Cause	**HIT2000 cohort** **n = 33**
Ototoxicity	26 (78.8%)
Infection	3 (9.1%)
Nephrotoxicity	2 (6.1%)
Neurotoxicity	1 (3%)
Carboplatin primary[a]	1 (3%)

[a]In one therapy center, carboplatin was primarily administered as standard

The course after adaptation for ototoxicity was variable: among patients with first-degree ototoxicity, hearing was unchanged in 1, improved in 1 and deteriorated in 5; among those with second-degree ototoxicity, 1 improved, 1 deteriorated and 8 were unchanged; among those with third-degree ototoxicity, 4 improved and 4 remained stable. When adaptation was based on non-ototoxic factors, ototoxicity generally remained stable, except for one patient who later developed third-degree ototoxicity after an adjustment for infection.

Of the 68 patients without treatment adaptation, 46 had audiograms available during treatment; 25 maintained normal hearing during follow-up while 21 developed audiometric changes, including progression from a normal baseline to first-degree (3), second-degree (5) and third-degree (1) ototoxicity, and further progression in patients with pre-existing first- or second-degree ototoxicity. Kaplan-Meier analysis comparing patients with and without treatment adaptation due to toxicity suggests that such adaptations do not negatively affect progression-free survival ($p = 0.09$, Fig. 2d).

Tumor localization, histology, meningeosis and the resulting treatment strategy are associated with ototoxicity

Tumor location was associated with ototoxicity of HIT grade ≥ 1 ($p = 0.02$). Ototoxicity was most common in tumors involving both central and lateral infratentorial compartments (15/17, 88.2%) and in central infratentorial tumors (46/70, 65.7%), and less frequent in cerebellar hemispheric or lateral infratentorial tumors (2/5) and cerebral tumors (3/9) (Fig. 3a). Dichotomized by compartment, ototoxicity affected 3/9 supratentorial versus 63/92 infratentorial patients ($p < 0.001$).

Ototoxicity grade distribution varied between histological subtypes (Fig. 3b, $p < 0.001$) and was more common in medulloblastoma (61/80) than ependymoma (5/21).

Relevant postoperative residual tumor and exact tumor size were not associated with ototoxicity grade ($p = 0.3$ and $p = 0.103$, respectively), whereas meningeosis at initial diagnosis was ($p = 0.0341$): patients with meningeosis more often had grade 2 ototoxicity (54.2% vs. 35.1%), while higher-grade ototoxicity was similarly distributed.

Ototoxicity prevalence also varied between treatment arms, reflecting the underlying histology and staging: the highest incidence occurred in the MET-HIT2000-AB4-M2-M4 arm for non-infant medulloblastoma with meningeosis, in which only 6.3% remained unaffected (Fig. 3c), while the E-HIT2000-AB4 and E-HIT2000-BIS4 ependymoma arms showed markedly lower rates ($p < 0.001$).

Precise effect of cumulative cisplatin dose on ototoxicity

Figure 3d compares cumulative cisplatin doses in patients with and without ototoxicity. Of the cohort, 70 patients received cisplatin and 31 did not; of the latter, 28 were treated in the HIT2000-BIS4, E-HIT2000-AB4 and E-HIT2000-BIS4 arms and 3 had individual reasons for omission. Patients with normal audiograms received 210–560 mg/m² (median 210), whereas patients with ototoxicity received 140–630 mg/m² (median 280).

Cumulative cisplatin dose was associated with ototoxicity of any grade ($p = 0.02$; OR 1.035, 95% CI 1.005–1.067 per 10 mg/m² BSA). Multivariable models supported this association: model 1 ($n = 101$) OR 1.077 (95% CI 1.043–1.112; $p < 0.001$) and model 2 ($n = 84$) OR 1.054 (95% CI 1.017–1.093; $p = 0.004$), demonstrating that higher cumulative cisplatin doses correlate with an increased risk of ototoxicity. The

corresponding ROC analysis (Fig. 3e) showed an AUC of 0.832 (95% CI 0.746–0.919) and identified a threshold of 70 mg/m² BSA for detecting ototoxicity of grade ≥ 1 at last follow-up, with a sensitivity of 0.894 and a specificity of 0.686.

Precise effect of irradiation on ototoxicity

Of the 101 patients, 96 received radiotherapy: 75 craniospinal irradiation and 21 local irradiation only. Of the five patients without radiotherapy, four remained free of ototoxicity and one experienced second-degree ototoxicity. Among patients receiving local radiotherapy, 15 of 21 had no ototoxicity, whereas among those receiving craniospinal radiotherapy 21.3% had no ototoxicity, 8% first-degree, 50.7% second-degree, 17.3% third-degree and 2.7% fourth-degree ototoxicity. Radiotherapy and radiation field were associated with ototoxicity ($p < 0.001$; Fig. 3f).

CSI dose was also analyzed (Fig. 3g): patients without ototoxicity (n = 35) received 23.4–40 Gy (median 23.4 Gy) and those with grade ≥ 1 ototoxicity (n = 66) a similar range (median 36 Gy), with no significant association on ordinal regression ($p = 0.78$).

Cochlear radiation doses were available for 84 patients: in the 24 without ototoxicity doses ranged from 1 to 68 Gy with a median of 23.4 Gy, whereas in the 60 with grade ≥ 1 ototoxicity they ranged from 2 to 68 Gy with a median of 47 Gy (Fig. 3h). Ordinal regression showed an association with ototoxicity of grade ≥ 1 at last follow-up (OR 1.047, 95% CI 1.018–1.077; $p < 0.001$), corresponding to a 47% increase in the odds of ototoxicity per 10 Gy. Multivariable analysis confirmed this association (OR 1.044, 95% CI 1.001–1.089; $p = 0.046$), corresponding to a 44% increase in odds per 10 Gy and in close agreement with the univariate result.

ROC analysis for cochlear irradiation dose yielded an AUC of 0.730 (95% CI 0.596–0.864) and a cut-off of 37.5 Gy, with a sensitivity of 0.721 and a specificity of 0.739 (Fig. 3i).

Of the 96 patients who received radiotherapy, 47 received hyperfractionated and 49 conventional radiotherapy; fractionation schedule was not associated with ototoxicity ($p = 0.719$).

Potential interaction and potentiation of risk factors

In the multivariable model including all 101 patients, cumulative cisplatin dose was significantly associated with the outcome (OR 1.077, 95% CI 1.043–1.112; $p < 0.001$), while meningeosis conferred an increased but non-significant risk (OR 3.020, 95% CI 0.837–10.900; $p = 0.092$).

In the subgroup of 84 patients with available cochlear irradiation data, cumulative cisplatin dose (OR 1.054, 95% CI 1.017–1.093; $p = 0.004$) and cochlear irradiation dose (OR 1.044, 95% CI 1.001–1.089; $p = 0.046$) remained significantly associated with the outcome, whereas CSI dose (OR 1.003, 95% CI 0.955–1.054; $p = 0.894$) and meningeosis (OR 5.441, 95% CI 0.596–49.684; $p = 0.133$) did not.

Discussion

In our study, 66 of 101 patients (65.4%) experienced grade ≥ 1 ototoxicity. The literature reports a wide range for cisplatin-related hearing loss in children, from 13% to 96%, reflecting differences in cisplatin regimens, cumulative doses, grading systems and timing of assessments [1, 8–10]. The grading system used strongly influences reported incidence. We applied the HIT scale, a modified WHO-based system focusing on the main speech frequencies (500–2000 Hz), which provides a clinically relevant assessment of functional hearing loss and, through its simplicity and high sensitivity for moderate to severe ototoxicity, is well suited to multicenter use. By excluding frequencies above 2000 Hz, however, it may miss early cisplatin-induced damage, and differences between classification systems complicate cross-study comparison.

Our analysis shows a higher incidence of ototoxicity in the cisplatin-containing treatment arms, suggesting a dose-dependent relationship, consistent with large cohort studies associating higher cumulative cisplatin doses with an increased risk of ototoxicity, particularly moderate to severe hearing loss [28–31]; each 100 mg/m² increase in cumulative dose raises this risk [30, 31].

Radiotherapy was also a significant contributor. Bass et al. demonstrated in survivors treated with radiation alone, at a median follow-up of nine years, that hearing loss can progress over time [32], emphasizing the need for longitudinal monitoring with annual audiograms. Murphy et al. developed a dose–response model showing that the risk of hearing loss was below 5% for mean cochlear doses up to 35 Gy but rose to around 30% at 50 Gy, depended strongly on age (25–40% in children under five vs. around 10% in older children), and predominantly affected high frequencies, with an average onset of 3.6 years after radiotherapy [33]. Conklin et al. reported treatment-related hearing loss in 67% of very young children treated for CNS malignancies, with 79% affected by six months and 90% by one year, associated with reductions in IQ, attention and adaptive functioning [34].

Keilty et al. quantified the additive risk of combined treatment, showing that 300 mg/m² of cisplatin equates to approximately 7.2 Gy of cochlear radiation, that the dose–response curve for severe hearing loss shifts towards higher doses in children over three years, and that cisplatin and carboplatin contribute additively rather than synergistically [31]. Our findings are also consistent with the International Late Effects of Childhood Cancer Guideline Harmonization Group and the PanCare Consortium, which identify high cumulative cisplatin doses and moderate-to-high cranial radiotherapy doses as significant risk factors for hearing loss [35].

This evidence underlines the critical role of accurate dose delivery, and the differences between treatment arms emphasize the need for personalized planning balancing efficacy against hearing complications. Clinically, our findings highlight the importance of cochlear dose constraints in radiotherapy planning, particularly in non-metastatic medulloblastoma and ependymoma where cochlear sparing is often feasible, whereas high-risk medulloblastoma frequently requires doses exceeding 30–36 Gy to the entire posterior fossa and cochlear region. The Kaplan-Meier curves further suggest that treatment adjustments due to toxicity, including cisplatin dose reductions, do not negatively impact

progression-free survival, consistent with previous reports [30], although survival bias cannot be excluded.

Several strategies may reduce ototoxicity without compromising efficacy. Replacing cisplatin with less ototoxic platinum compounds, as implemented in the HIT2000 trial, may be effective depending on tumor type and regimen [36]. Recent data also identified vincristine as an independent risk factor for chemotherapy-induced hearing loss, increasing this risk more than fourfold in patients with CNS tumors receiving radiotherapy and more than twofold without radiation exposure, suggesting a previously unrecognized ototoxic potential and supporting further investigation of treatment sequencing [30].

Otoprotective agents that neutralize cisplatin-induced reactive oxygen species are a further strategy [3, 4]. Amifostine has shown inconsistent trial results and remains controversial [37, 38]. Sodium thiosulfate (STS) reduced ototoxicity in hepatoblastoma in SIOPEL 6 without compromising survival, and an ACCL0431 subgroup analysis showed benefit in non-metastatic tumors including medulloblastoma (hearing loss 29% vs. 56%) with no survival difference; in metastatic disease STS was associated with worse survival (45% vs. 84%), prompting a cautious recommendation against routine use in this group, with STS given six hours after cisplatin and infusions limited to ≤ 6 hours [39]. STS has since been approved by the European Medicines Agency for children with non-metastatic solid tumors receiving cisplatin-based chemotherapy [40]. Local delivery is another option: transtympanic 10% N-acetylcysteine significantly reduced the incidence and severity of hearing loss in a phase I/II study, although it caused transient acute pain [41].

Our study has several limitations inherent to its retrospective, multi-institutional design, including variation in data quality, documentation practices and audiogram results. The relatively small sample size limits statistical power to detect subtle associations, and the focus on patients treated according to the HIT2000 protocol may introduce selection bias and limit external validity. Follow-up may not have captured the full course of ototoxicity in all patients, so longer-term observations are warranted, and other ototoxic concomitant treatments as well as the use of protective agents were not documented in a standardized manner.

Despite these limitations, our study contributes substantially to the understanding of ototoxicity in pediatric medulloblastoma and ependymoma patients undergoing radiochemotherapy. Ototoxicity affects a majority of these children, and to avoid disability and adverse effects on quality of life, cisplatin and radiotherapy doses should be scrutinized and reduced whenever oncologically feasible, guided by the thresholds identified here.

Declarations

Competing Interests

Andre O. von Bueren has received consulting fees from Alexion and Novartis. Non-financial interests: Gudrun Fleischhack has served on advisory boards for Novartis Pharma GmbH, Bayer Vital GmbH, and

Oncoscience GmbH.

Ethics approval

The trial was in line with the declaration of Helsinki and approved by the responsible ethical committees.

Consent to participate

Informed consent was obtained from the legal representatives of all patients after institutional review board approval.

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Author Contribution

D.O.-S. and S.R. conceived and designed the study. E.B., A.H., R.-D.K., R.S., B.T., B.B., M.W.-M., K.v.H., A.O.v.B., N.U.G., G.F., S.T., T.P., C.H., S.M.P., D.S. and M.M. collected the data. E.B., H.O.P., D.O.-S. and S.R. analyzed and interpreted the data. E.B. and H.O.P. performed the statistical analysis. E.B. wrote the first draft of the manuscript. D.O.-S. and S.R. supervised the study. All authors reviewed previous versions of the manuscript and read and approved the final manuscript.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

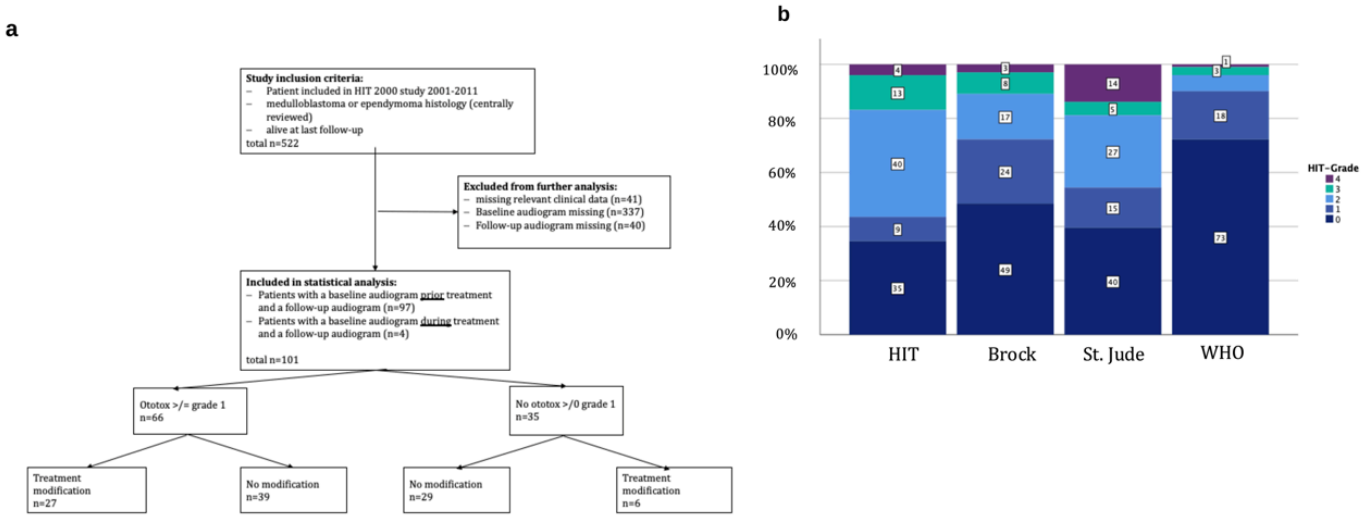


Figure 1

Cohort description and distribution of ototoxicity. a Consort diagram of cohort assembly. b Distribution of ototoxicity grades across the study cohort according to the HIT, Brock, St. Jude and WHO grading systems; numbers within the bars indicate patient counts

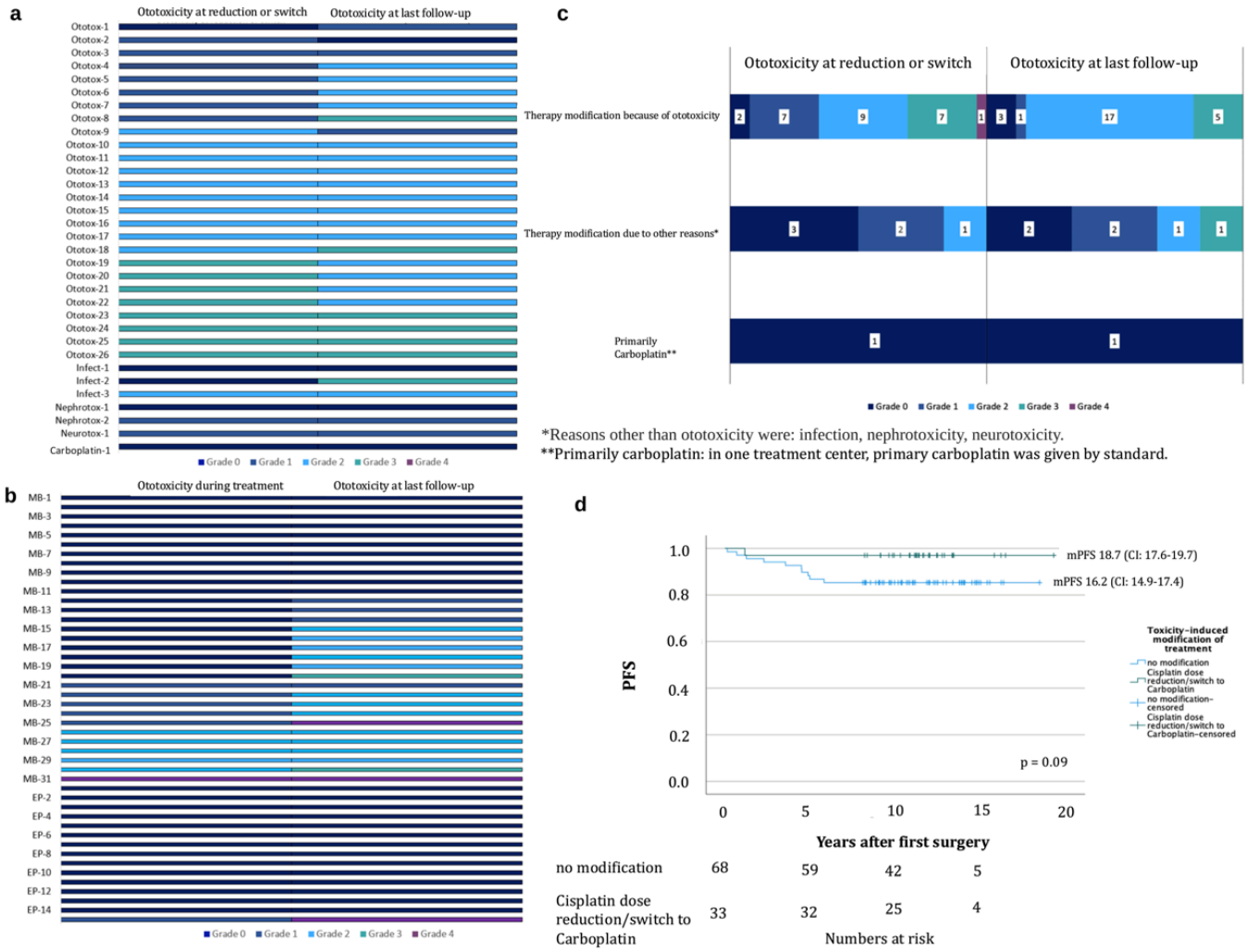


Figure 2

Course and outcome of ototoxicity. a Individual course of ototoxicity in patients with treatment modification, from the time of dose reduction or switch to last follow-up. b Individual course of ototoxicity in patients without treatment modification, from during treatment to last follow-up. c Distribution of ototoxicity grades at treatment modification and at last follow-up, grouped by reason for modification; numbers within the bars indicate patient counts. d Kaplan-Meier estimates of progression-free survival (PFS) for patients with versus without toxicity-induced treatment modification; mPFS denotes mean PFS, crosses denote censored observations

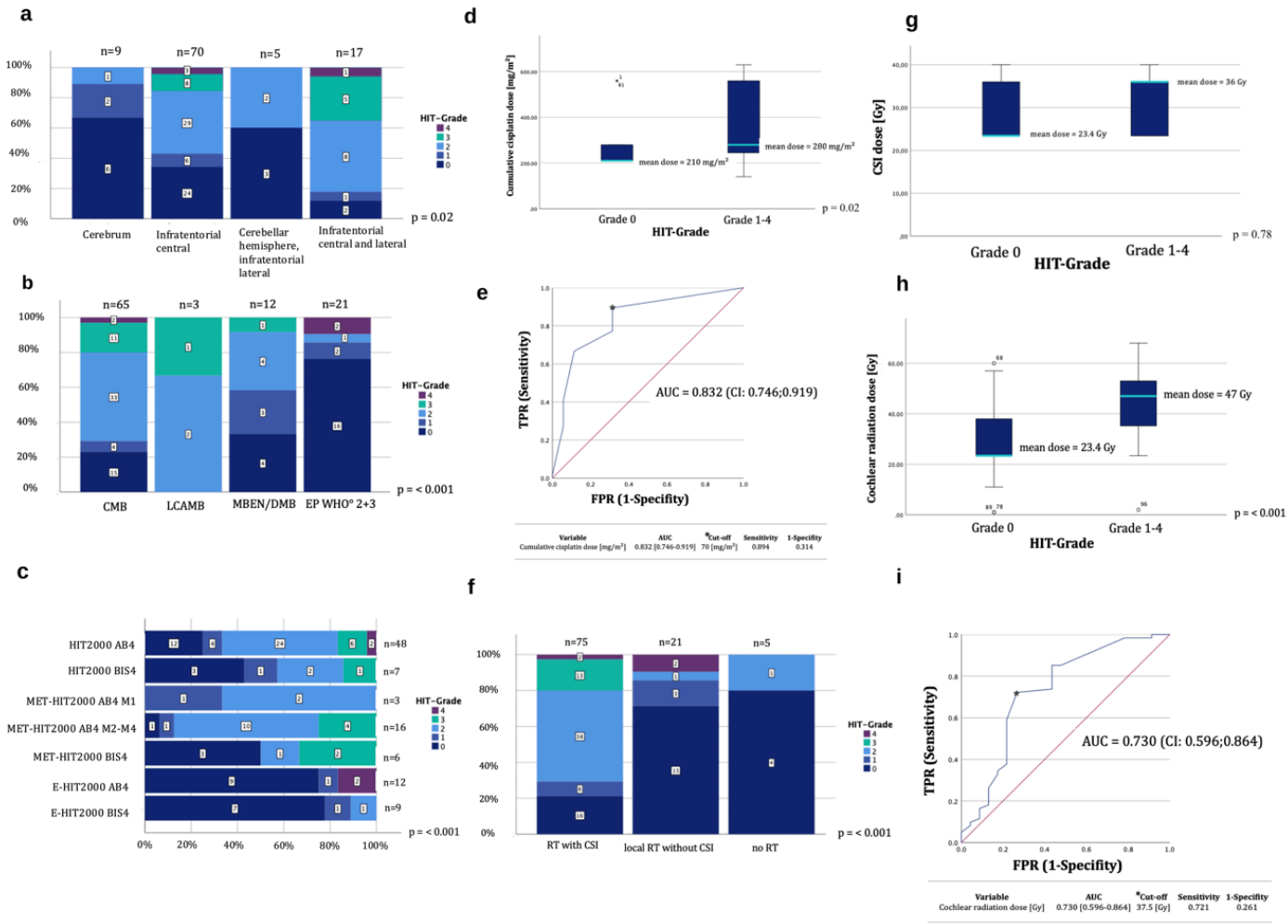


Figure 3

Factors associated with ototoxicity. a Tumor localization. b Histological subtype. c Treatment arm. d Cumulative cisplatin dose, shown as box plots with the median indicated. e Receiver operating characteristic (ROC) analysis of cumulative cisplatin dose; the asterisk marks the identified cut-off. f Radiation field. g CSI dose, shown as box plots with the median indicated. h Cochlear radiation dose, shown as box plots with the median indicated. i ROC analysis of cochlear radiation dose; the asterisk marks the identified cut-off. Numbers within the bars indicate patient counts; AUC area under the curve, TPR true positive rate, FPR false positive rate

Supplementary Files

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