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ABSTRACT

Introduction: Head and neck squamous cell carcinoma (HNSCC) patients treated with cisplatin-based chemoradiation often suffer from cisplatin-induced hearing loss (CIHL). To prevent toxicities, patients receive hydration before and after cisplatin infusions. This study evaluated cisplatin-induced hearing loss between a long and short duration of infusion and volume of hydration schedule (DIVHS).

Methods: Between 2019 and 2023, 161 patients were included in two Dutch hospitals. Patients received either weekly cisplatin (Cis40qw, n = 77) or triweekly cisplatin (Cis1003q3w, n = 88). Two different short and long DIVHS were used in each cisplatin regimen. Pure tone audiometry was performed at baseline and three months after chemoradiation. Pure tone averages (PTA) were calculated for PTA 1–2–4 kHz and PTA 8–10–12.5 kHz. CIHL was assessed using mean threshold shift.

Results: In the Cis40qw group, the mean threshold shift at PTA 1–2–4 kHz was 3.1 dB in the short and 4.7 dB in the long DIVHS ($p = 0.37$). In the Cis100q3w cohort, the mean threshold shift was 5.3 dB in the short and 7.1 dB in the long DIVHS ($p = 0.36$). At PTA 8–10–12.5 kHz, the mean threshold shifts of the Cis40qw groups were 11.8 dB in the short versus 15.4 dB in the long DIVHS ($p = 0.30$). In the Cis100q3w cohort, the mean threshold shift was 19.9 dB in the short compared to 19.4 dB in the long DIVHS ($p = 0.85$).

Conclusion: This study found no significant difference in CIHL between different DIVHS during cisplatin-based chemoradiation in HNSCC patients.

Introduction

Curative therapy for locally advanced Head and neck squamous cell carcinoma (HNSCC) often consists of radiotherapy (RT) with concurrent cisplatin-based chemotherapy. Cisplatin is administered either in a triweekly dose of 100 mg/m^2 (Cis100q3w) in three cycles or a weekly dose of 40 mg/m^2 (Cis40qw) in seven cycles [1,2]. Compared to RT alone, adding cisplatin improves locoregional control and disease-free survival [3–6]. Despite its beneficial effects, cisplatin causes severe short-term side effects such as nausea, stomatitis, and myelosuppression

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but may also cause long-term side effects, including nephrotoxicity, neurotoxicity, and ototoxicity [3,4,7].

Cisplatin may cause irreversible and symmetrical sensorineural hearing loss (SNHL) and tinnitus. Cisplatin-induced hearing loss (CIHL) begins at the extended high frequencies and gradually progresses to the lower frequencies with ongoing treatment and increased cumulative cisplatin dose [7–9]. The severity depends on the cumulative cisplatin dose [7–9]. Various cochlear structures are possibly damaged by cisplatin. These structures include the outer and inner hair cells, stria vascularis, and spiral ganglion [7,8,10–12]. Several biological processes are involved in the development of CIHL, such as the release of toxic reactive oxygen species and the depletion of protective antioxidants of the cochlea [7,8,10–12]. Patients with favorable pre-treatment hearing capacity or lower skeletal muscle mass are more prone to develop CIHL [13–16]. Also, treatment-specific factors may give a higher risk for CIHL, such as a concomitant mean cochlear radiation dose of 30 Gray (Gy) or more, or a Cis100q3w dose-intensity schedule [17–21]. Since hearing loss can cause problems in communication, isolation, and loneliness, adequate hearing is essential for maintaining a good quality of life. Additionally, hearing impairment is associated with disabilities, increased risk of falls, depression, and dementia [22].

In general, hydration before and after cisplatin infusion is used to prevent platinum-related toxicities. However, the effect of pre- and post-hydration on CIHL is unknown. A wide variety in the quantity, duration, and composition of these hydration schedules exists [23], even within countries. Earlier research in various types of cancer showed that a short duration of infusion and volume of hydration schedule (DIVHS) may be the most effective in preventing dose-limiting nephrotoxicity [24–27]. A short DIVHS may decrease hospital stay and consequently reduce healthcare costs [28]. One of the studies that found less nephrotoxicity in a short DIVHS observed more dose-limiting ototoxicity, based on clinical assessment, in the same group compared to longer DIVHS [27]. However, to our best knowledge, no data is available regarding the severity of CIHL measured with audiometry between different hydration schedules, including volume, duration, and infusion rate. This research primarily aims to evaluate CIHL between a long and short DIVHS in both the Cis40qw and the Cis100q3w chemoradiotherapy (CRT) in HNSCC patients.

Material and Methods

Patients and study design

This multicenter retrospective cohort study was performed at the University Medical Center Utrecht (UMCU) from 2021 to 2023 and at the Netherlands Cancer Institute (NKI) from 2019 to 2023. The study was approved by the NKI institutional review board (IRB) and the UMCU Medical Ethical Research Committee (METC) (IRBd22-217 and METC ID 22–946/DB).

Adult patients were included if diagnosed with HNSCC with an indication for curative primary or adjuvant cisplatin-based chemoradiotherapy (CRT). RT was delivered with a photon-based volumetric modulated arc treatment technique in 2 Gy fractions. Fractions were delivered five times per week for seven consecutive weeks, with a cumulative dose of 70 Gy in the primary setting or 66 Gy in the adjuvant setting, with concomitant intravenous cisplatin. Patients were treated with either 40 mg/m^2 cisplatin every week for seven cycles (Cis40qw, days 1, 8, 15, 22, 29, 36, and 43) or 100 mg/m^2 cisplatin per three weeks for three cycles (Cis100q3w, days 1, 22 and 43). Patients were not eligible for analysis when pre- or post-treatment audiograms were missing.

We recorded sex, age, CRT regimen, DIVHS, tumor localization, TNM stage (UICC, 8th edition) [29], treatment phase (primary or adjuvant setting), cumulative cisplatin dose (in mg/m^2), the occurrence of hypomagnesemia, cisplatin dose-limiting toxicities (CDLT), and the radiation dose on the cochlea (in Gy). Audiometry data was collected at baseline and post-treatment. Hypomagnesemia was defined as magnesium levels below 0.7 mmol/L measured during the CRT. For the Cis100q3w group, CDLT was defined as any toxicity resulting in a cisplatin dose reduction of $\geq$ 50 %, a postponement of treatment of $\geq$ 4 days, or a definite termination of cisplatin before all scheduled cycles of therapy are administered [30]. For the Cis40qw patients, CDLT was defined as definite termination or skipped cisplatin treatments [30]. A cumulative cisplatin dose of 200 mg/m^2 is considered the minimum dose needed to increase the anticancer effect in advanced HNSCC patients [31,32]. Therefore, CDLTs resulting in a cumulative dose of less than 200 mg/m^2 were also reported.

Hydration regimens

Table 1 shows the duration and composition of the hydration schemes of Cis40qw and Cis100q3w per hospital. The UMCU uses a short DIVHS, with a low total volume of 3.5 L in 6 h for Cis40qw and a total volume of 4.5 L in 8 h for Cis100q3w. The mean infusion rates in the short DIHVS were relatively higher, with 583 ml/h for the Cis40qw and 562 ml/h for the Cis100q3w. In contrast, the NKI uses a long DIVHS, with a high total volume of 4.5 L in 20 h for patients treated in a Cis40qw schedule and a total volume of 9.5 L in 59 h for the Cis100q3w. The mean infusion rates in the long DIVHS were lower, with 200 ml/h for the Cis40qw and 161 ml/h for the Cis100q3w.

Table 1
Detailed description of the different hydration schemes administered at the University Medical Center Utrecht (UMCU) and the Netherlands Cancer Institute (NKI) for cisplatin-based chemoradiotherapy (CRT).

	Short DIVHS Cis40qw	Long DIVHS Cis40qw	Short DIVHS Cis100q3w	Long DIVHS Cis100q3w
Hydration fluid	NaCl (0.9 %)	NaCl (0.9 %)	NaCl (0.9 %)	NaCl (0.9 %)
Prehydration				
Volume (L)	2	1	2	2
Infusion time (h)	2	2	2	13
Prehydration electrolytes	2.5 g $MgSO_4$	500 mg $MgSO_4$ 20 mmol KCl 300 mg $C_{12}H_{22}CaO_{14}$	2.5 g $MgSO_4$	–
Cisplatin				
Volume (L)	0.5	1	0.5	0.5
Infusion time (h)	2	4	2	4
Hydration during cisplatin				
Volume (L)		1		3
Infusion time (h)		2		18
Added electrolytes during cisplatin		500 mg $MgSO_4$ 20 mmol KCl 300 mg $C_{12}H_{22}CaO_{14}$		1500 mg $MgSO_4$ 60 mmol KCl 870 mg $C_{12}H_{22}CaO_{14}$
Post-hydration				
Volume (L)	1	1	2	4
Infusion time (h)	2	12	4	24
Post-hydration electrolytes	2.5 g $MgSO_4$ 20 mmol KCl	500 mg $MgSO_4$ 20 mmol KCl 300 mg $C_{12}H_{22}CaO_{14}$	2.5 g $MgSO_4$ 20 mmol KCl	–
Total hydration				
Volume (L)	3.5	4	4.5	9.5
Infusion time (h)	6	20	8	59
Mean infusion rate (ml/h)	583	200	562	161

Abbreviations: $C_{12}H_{22}CaO_{14}$: calcium gluconate, Cl: potassium chloride, DIVHS: duration infusion and volume of hydration schedule, $MgSO_4$: magnesium sulfate.

Audiometry assessment

Audiometry was performed at baseline and, on average, 13 weeks after CRT. Air conduction (AC) thresholds were measured for standard frequency pure tone audiometry (frequency range 0.125–8.0 kHz expressed in decibel (dB) Hearing Level (HL)), and extended high-frequency audiometry (frequency range 8.0–16.0 kHz expressed in dB Sound Pressure Level (SPL)). Bone conduction (BC) thresholds were measured for standard frequency pure tone audiometry at 0.5, 1.0, 2.0, and 4.0 kHz (in dB (HL)). If the difference between the AC and BC thresholds was $\geq$ 10 dB at 0.5, 1, 2, or 4 kHz, BC thresholds were used for analysis to ensure sensorineural hearing levels were used. The measurements were obtained in a sound-proof booth using the Decos Audiology Workstation in both centers. The Telephonics TDH-39P headphone was used for standard frequency AC, the RadioEar B71 bone conductor for BC, and the Sennheiser HDA 200 headphone was used to measure extended high-frequency audiometry.

A Pure Tone Average (PTA) was computed for the frequencies 1–2–4 kHz (in dB HL), which are relevant for speech perception. A PTA at frequencies 8–10–12.5 kHz (in dB SPL) was additionally calculated. These frequencies are pertinent to perceiving (ultra-)high sounds in music or nature and speech perception in noise [33,34].

CIHL definitions

Different ways to define CIHL are used, including the incidence of clinically relevant hearing loss at different PTAs, the different ototoxicity grading scales, and CDLT. PTA threshold shifts and single frequency threshold shifts were calculated as post-CRT PTA minus pre-CRT PTA for PTA 1–2–4 kHz and PTA 8–10–12 kHz, and post-CRT hearing threshold minus pre-CRT hearing threshold for single frequencies. Clinically relevant CIHL was defined as a threshold shift of $\geq$ 10 dB in at least one of the two PTAs in one or both ears. Hence, we also defined another outcome measure to represent the post-treatment hearing level, namely a de novo indication for rehabilitation with hearing aids after CRT as described in the Netherlands: a PTA 1–2–4 kHz of $<$ 35 dB before treatment and $\geq$ 35 dB after treatment (de novo hearing aid indication) [35,36]. Subsequently, we calculated the incidence of clinically relevant treatment-related CIHL at both 1–2–4 kHz and 8–10–12.5 kHz, as well as the occurrence of de novo hearing aid indication, for our four study groups separately. Additionally, the severity of CIHL was evaluated using three distinct ototoxicity grading scales. Specifically, the ASHA grading scale for hearing loss due to ototoxic drugs (0.125–16 kHz) [37], the CTCAE version 5.0 (0.125–8 kHz) [38], and the TUNE criteria (0.125–16 kHz) [39], as illustrated in Appendix A. It may be valued that all three grading scales use a combination of threshold shift and post-treatment hearing level to grade ototoxicity.

Missing data

If the AC threshold for 8.0 kHz was not available from extended high-frequency (expressed in dB (SPL)), the threshold was calculated by taking the threshold at 8 kHz from standard frequency pure tone audiometry (expressed in dB (HL)) and adding 13 dB (NKI) or 17.5 dB (UMCU), depending on the automated headphone settings, following the guidelines of ISO 389–1 [40]. Another correction was applied when patients' hearing threshold exceeded the maximum output capacity of the audiometer during the post-CRT measurement. This threshold was computed by adding 10 dB to the maximum measurable threshold of the audiometer, which depended on the audiometer's settings (e.g., 100 or 110 dB) (ISO 389–1) [40]. When extended high-frequency audiometry was completely missing, the PTA 8–10–12 kHz SPL value was calculated by taking the value of 8 kHz SPL and adding the mean difference between 8 kHz SPL and PTA 8–10–12 kHz SPL. This was done for the baseline and post-treatment values separately.

Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation (SD) if data was normally distributed or as median $\pm$ interquartile ranges (first (Q1) and third (Q3) percentile) in case of no normal distribution. Categorical variables are constructed as frequencies, including percentages. Differences in binary or categorical data were tested using Pearson's Chi-Square and Fisher exact tests, one-way ANOVA, or Kruskal Wallis tests for non-normally distributed continuous variables. All tests were performed as two-tailed statistical testing.

The mean difference in thresholds at PTA 1–2–4 kHz and PTA 8–10–12.5 kHz pre- and post-CRT between patient groups were compared using Linear mixed models (LMM). The incidence of clinically relevant hearing loss at PTA 1–2–4 kHz and PTA 8–10–12.5 kHz, and new indications for hearing aids de novo (threshold of $\geq$ 35 dB post-CRT) were compared between groups using a Chi-square test. The ototoxicity grading score outcomes (ASHA, CTCAE v5.0, and TUNE) were compared using a linear-by-linear test. LMM were applied to assess the association between ototoxicity and other covariates with hearing loss for CIHL on PTA 1–2–4 kHz and PTA 8–10–12.5 kHz. In all models, the intercept was estimated as a random parameter. Univariate models to test associations between hearing loss on both PTAs included the following variables: DIVHS, age, sex, cumulative cisplatin dose, CRT regimen (Cis40qw and Cis100q3w), baseline hearing at PTA 1–2–4 kHz, cochlear radiation dose, and hypomagnesemia. A p-value of < 0.1 was used to incorporate the variables in the multivariate LMM.

Data analysis was performed using IBM SPSS Statistics 29. A p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Patients were treated with cisplatin-based CRT, including 109 from the UMCU, and 175 patient records from the NKI. In total, 123 patients were not eligible for analysis. In the UMCU, 28 patients and in the NKI, 88 patients had incomplete audiometry data, and seven patients in the UMCU received an older and more prolonged DIVHS. This resulted in a total of 161 evaluable patients included for analysis. In the UMCU, 74 patients were treated with the short DIVHS; 22 were treated in the Cis40qw, and 52 in the Cis100q3w schedule. In the NKI, 87 were treated in the long DIVHS; 55 were treated in the Cis40qw and 32 in the Cis100q3w schedule.

Patient, tumor, and treatment characteristics of all four groups are presented in Table 2. The median age at baseline was 60 years, comparable for all groups ($p = 0.54$). In all four groups, the proportion of male and female patients was similar ($p = 0.52$). In the short hydration regimen of Cis40qw cisplatin, relatively many patients were treated in the adjuvant setting (71 %), compared to 29 % of all patients. There was a higher prevalence of stage IV/IVa disease in the long DIVHS Cis100q3w group (41 %) compared to the overall cohort (26 %). In comparison, the short DIVHS Cis100q3w group showed a lower proportion (15 %) of these advanced stages.

Audiometry results at speech-related frequencies

Audiometry data is presented in Fig. 1A–1D and Table 3. The mean threshold shift at PTA 1–2–4 kHz of patients treated in the Cis40qw regimen was 3.1 ($\pm$ 5.9) dB in the short DIVHS and 4.7 ($\pm$ 8.5) dB in the long DIVHS ($p = 0.37$). The incidence of clinically relevant CIHL was 23 % in the short DIVHS compared to 20 % in the long ($p = 0.99$). In the Cis100q3w cohort, the mean threshold shift at PTA 1–2–4 kHz was 5.3 ($\pm$ 9.3)dB in the short DIVHS and 7.1 ($\pm$ 9.6) dB in the long DIVHS ($p = 0.36$). The incidence of clinically relevant hearing loss was 27 % in the short DIVHS and 41 % in the long DIVHS ($p = 0.23$).

Table 2
Patient, tumor, and treatment characteristics of the study population categorized by the duration of infusion and volume of hydration schedules.

Variable	Total (n = 161)	Short DIVHS Cis40qw	Long DIVHS Cis40qw	Short DIVHS Cis100q3w	Long DIVHS Cis100q3w	*p*-Value
	N (%)	22	55	52	32	
Age at diagnosis (median [Q1-Q3])	60 [53–66]	61 [58–65]	60 [55–67]	59 [51–66]	60 [52–67]	0.543[a]
Gender						0.524[b]
Female	45 (28)	8 (36)	13 (24)	13 (25)	11 (34)	
Male	116 (72)	14 (64)	42 (76)	39 (75)	21 (66)	
Tumor localization						< 0.001[c]
Larynx	14 (9)	4 (18)	3 (6)	5 (10)	2 (6)	
Hypopharynx	9 (6)	0 (0)	7 (7)	1 (2)	4 (13)	
Oropharynx	89 (55)	4 (18)	34 (62)	40 (77)	11 (34)	
Oral cavity	27 (17)	11 (50)	9 (16)	3 (6)	4 (13)	
Nasopharynx	12 (7)	0 (0)	3 (6)	1 (2)	8 (25)	
Unknown primary	6 (4)	1 (5)	2 (6)	1 (2)	2 (6)	
Other	4 (2)	2 (9)	0 (0)	1 (2)	1 (3)	
UICC category						< 0.001[c]
I	19 (12)	3 (14)	2 (4)	13 (25)	1 (3)	
II	34 (21)	0 (0)	20 (36)	9 (17)	5 (16)	
III	31 (19)	2 (9)	15 (27)	10 (19)	4 (13)	
IVa/IV	42 (26)	7 (32)	14 (26)	8 (15)	13 (41)	
IVb	35 (22)	10 (46)	4 (7)	12 (23)	9 (28)	
Baseline hearing level at PTA 1–2–4 kHz (mean ± SD)	18 (12)	19 (11)	19 (14)	16 (10)	18 (12)	0.290[d]
Primary or adjuvant CRT (n (%))						<0.001[b]
Primary	115 (71)	6 (27)	43 (78)	46 (89)	20 (63)	
Adjuvant	46 (29)	16 (73)	12 (12)	6 (11)	12 (38)	
Cumulative cisplatin dose given (median [Q1-Q3])	280 [200–280]	280 [240–280]	280 [240—280]	263 [200–300]	243 [200–300]	n.a.
Radiotherapy dose on cochlea (median [Q1-Q3])	3.1 [1.5–9.7]	1.1 [0.7–2.1]	4.4 [2.6–12.5]	1.7 [1.2–3.6]	9.0 [3.2–23.9]	< 0.001[a]

[a] = tested with independent-sample Kruskal Wallis Test, [b] = tested with Chi Square Test, [c] = tested with Fisher-Freeman-Halton Exact Test, [d] = Linear Mixed Model. Abbreviations: DIVHS = duration infusion and volume of hydration schedule; Q1-Q3 = interquartile range of first and third percentile; kHz = kilohertz; UICC = Tumor Node Metastasis (TNM) stage based on the Union for International Cancer Control.

Audiometry results at the extended-high frequencies

At PTA 8–10–12.5 kHz, the mean threshold shifts of the Cis40qw groups were 11.8 (± 10.7) dB in the short DIVHS versus 15.4 (± 15.4) dB in the long DIVHS ($p = 0.30$). The incidence of clinically relevant CIHL of the Cis40qw cohort was 73 % in the short hydration group and 69 % in the long DIVHS ($p = 0.79$). In the Cis100q3w cohort, the mean threshold shift at PTA 8–10–12.5 kHz was 19.9 (± 18.3) dB in the short DIVHS compared to 19.4 (± 18.5) dB in the long DIVHS ($p = 0.85$). The incidence of clinically relevant hearing loss was 85 % in the short DIVHS versus 72 % in the long DIVHS ($p = 0.17$). In both the Cis40qw and Cis100q3w cohort, there was no significant difference in new indications for hearing aids ($p = 0.43$ and $p = 0.15$), ASHA criteria ($p = 0.33$ and $p = 0.87$), CTCAE criteria ($p = 0.44$ and $p = 0.52$) and, TUNE criteria ($p = 0.13$ and $p = 0.29$).

Ototoxicity as cisplatin dose-limiting toxicity

The CDLTs were analyzed separately for the Cis40qw and Cis100q3w cohorts, and the results are shown in Table 3. The proportions of CDLTs did not significantly differ between the groups in the Cis40qw schedule ($p = 0.80$) and the Cis100q3w schedule ($p = 0.11$). In the Cis40qw cohort, five patients (23 %) in the short DIVHS and none of the patients in the long DIVHS suffered from dose-limiting ototoxicity ($p < 0.01$). In the Cis100q3w cohort, only one patient in the short DIVHS did not reach a cisplatin dose of ≥ 200 mg/m^2 due to ototoxicity, compared to two patients in the long DIVHS ($p = 0.29$).

In the Cis100q3w regimen, 15 patients (29 %) in the short DIVHS compared to two patients (6 %) in the long DIVHS had dose-limiting ototoxicity ($p < 0.01$). Of these patients, seven in the short DIVHS and none in the long did not reach a dose of 200 mg/m^2 due to ototoxicity ($p = 0.04$). All other CDLTs were more often observed in the long DIVHS than in the short DIVHS in the Cis40qw and Cis100q3w cohort ($p = 0.03$ and $p < 0.01$, respectively). However, other CDLTs resulting in a dose limitation of < 200 mg/m^2 had comparable proportions in the groups in both the Cis40qw and Cis100q3w schedules ($p = 0.99$ and $p = 0.29$, respectively).

Multivariable analysis of cisplatin-induced hearing loss

The results of univariable and multivariable LMM are presented in Table 4. In univariable and multivariable LMM, no associations were found between the four different DIVHS and CIHL at PTA 1–2–4 kHz and CIHL at PTA 8–10–12.5 kHz. A positive association was found between CIHL at PTA 1–2–4 kHz and age at diagnosis ($p < 0.01$), and cochlear RT dose ($p = 0.03$), indicating that older patients and patients with higher cochlear RT doses had more CIHL. Negative associations were observed between CIHL at PTA 1–2–4 kHz and baseline hearing levels ($p < 0.01$), meaning that patients with better baseline hearing levels had more CIHL. Negative associations with CIHL at PTA 8–10–12.5 kHz were found for age at diagnosis ($p = 0.03$), and baseline hearing level ($p < 0.01$), implicating that younger patients and patients with better baseline hearing levels had more CIHL.

Discussion

This study evaluated the association between short and long DIVHS and CIHL in HNSCC patients treated with cisplatin-based CRT. No significant differences in the incidence of clinically relevant CIHL were found. Neither were there any significant differences in mean threshold shifts at both speech-related frequencies (PTA 1–2–4 kHz) and extended high-frequencies (PTA 8–10–12.5 kHz), essential for speech in noise, for both the Cis40qw and Cis100qw schedules [33,34]. Also, we found no differences between the DIVHS in indications for hearing aids and three different hearing loss criteria. Our multivariable analysis did not show an association between CIHL and short and long DIVHS. However, it identified cochlear radiation dose as a significant risk factor associated with CIHL at PTA 1–2–4 kHz, and associated baseline hearing level and

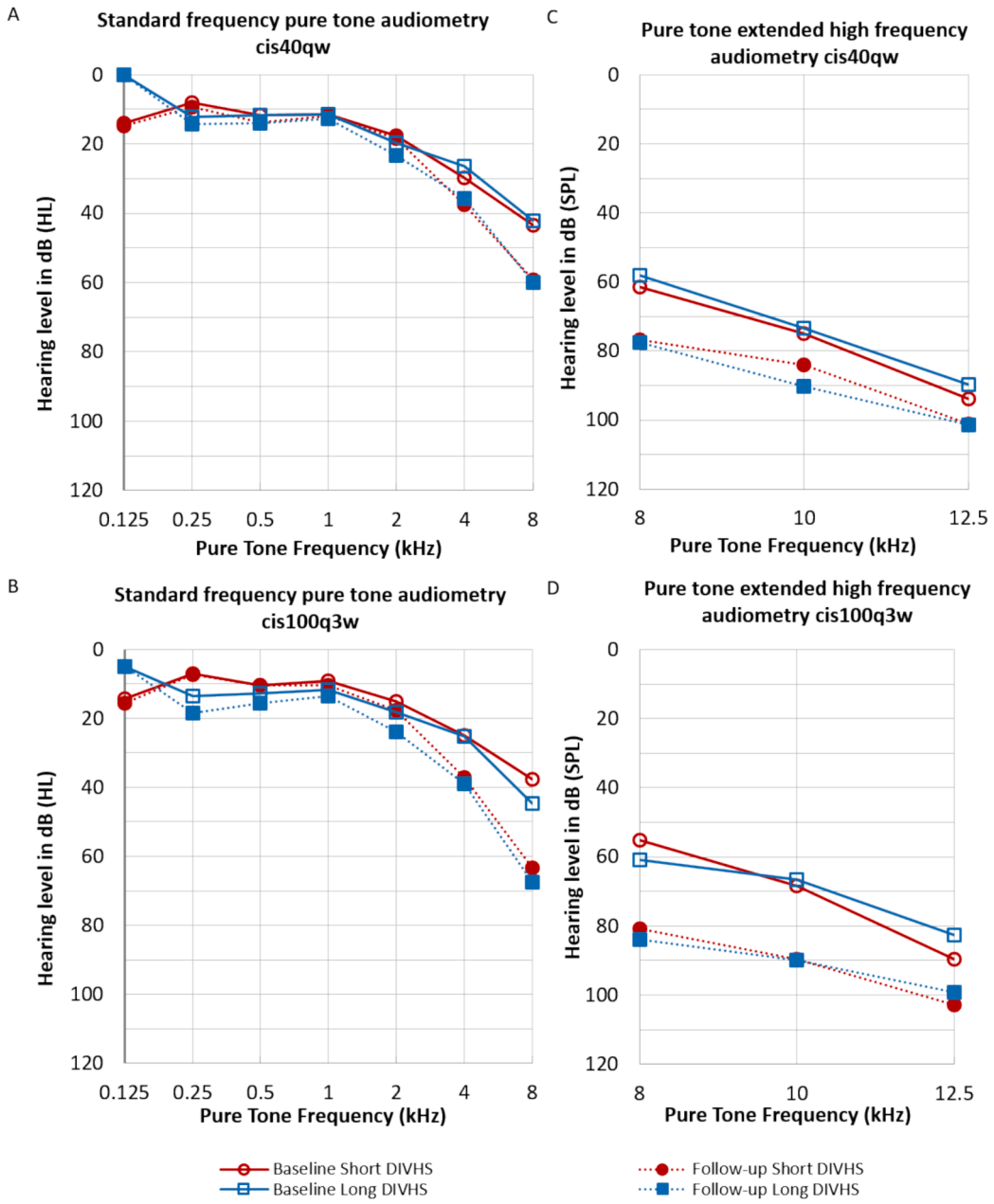

Fig. 1. Baseline and follow-up mean audiometry values for short DIVHS and long DIVHS. A = standard frequency audiometry of the Cis40qw regimen; B = standard frequency audiometry of the Cis100q3w regimen; C = extended high-frequency audiometry of the Cis40qw regimen; D = extended high-frequency audiometry of the Cis100q3w regimen. Abbreviations: DIVHS = duration infusion and volume of hydration schedule; HL = hearing level; kHz = kilohertz; SPL = sound pressure level.

age with CIHL at both PTAs.

Our study is the first to assess a potential association between various DIVHS and CIHL development in HNSCC patients based on audiometry. A cohort study in children and young adults treated with cisplatin for other types of cancers than HNSCC stated that a shorter duration of cisplatin infusion decreased the risk for CIHL but did not address the DIVHS [41]. A recent study on differences in CDLT between different hydration schedules reported less dose limiting ototoxicity in a short DIVHS, however this was based on clinical assessment only [27].

In accordance with this earlier research, our research observed an increased number of ototoxicity-related CDLTs in the short DIVHS [27]. However, in these specific patients, the average threshold shifts and incidence of clinically relevant CIHL did not differ significantly between the short and long DIVHS. When looking at statistically significant factors from our multivariate analysis, baseline age and baseline hearing levels at PTA 1–2–4 kHz were similar and cannot explain these results. The median RT dose on the cochlea was lower in patients treated in the short DIVHS compared to patients in the long DIVHS regimen, and therefore a contradictory relationship would have been expected. Consequently, the observed difference in clinically-assessed CDLT could result from individual differences or considerations in treating physicians, as patients from the long and short DIVHS were treated in two different tertiary hospitals. Dose-limiting ototoxicity can also be due to complaints of tinnitus, which is not always accompanied by a threshold shift on audiometry. Furthermore, the overall fitness of patients, logistics, and judgement of the health care professional on the choice of treatment adaptations were not evaluated.

Our multivariable analysis showed several factors associated with treatment-related CIHL. A significant association between cochlear RT dose and CIHL on PTA 1–2–4 kHz was found, which is in line with previous research [17–19]. In agreement with prior research, our model found that the more pre-existing SNHL at baseline, the less treatment-

Table 3
The incidence of clinically relevant cisplatin-induced hearing loss (≥ 10 dB threshold shift) at PTA 1–2–4 kHz (in dB [HL]) and PTA 8–10–12.5 kHz (in dB [SPL]) in the short and long DIVHS in the Cis40qw and Cis100q3w regimen, the incidence of an indication for hearing aids de novo (PTA ≥ 35 dB after CRT and < 35 dB at baseline), and scores on various grading scales (appendix A), cisplatin dose-limiting toxicities.

Variables	Short DIVHS Cis40qw	Long DIVHS Cis40qw	*p*-value	Short DIVHS Cis100q3w	Long DIVHS Cis100q3w	*p*-value
	22	55		*52*	*32*	
Hearing loss at PTA 1–2–4 kHz						
Incidence clinically relevant CIHL (%)	5 (23)	11 (20)	0.999[a]	14 (27)	13 (41)	0.232[a]
Hearing loss in dB per ear (mean ± SD)	3.1 (5.9)	4.7 (8.5)	0.374[b]	5.3 (9.3)	7.1 (9.6)	0.361[b]
Hearing loss at PTA 8–10–12.5 kHz						
Incidence clinically relevant CIHL (%)	16 (73)	38 (69)	0.791[a]	44 (85)	23 (72)	0.174[a]
Hearing loss in dB per ear (mean ± SD)	11.8 (10.7)	15.4 (15.4)	0.296[b]	19.9 (18.3)	19.4 (18.5)	0.846[b]
Hearing aids indicated	1 (5)	8 (15)	0.433[c]	7 (14)	9 (28)	0.151[a]
Grading scales						
ASHA (0.125–16 kHz)			0.325[d]			0.865[d]
no hearing loss (%)	6 (27)	10 (18)		5 (10)	3 (9)	
grade A (%)	2 (9)	3 (6)		1 (2)	1 (3)	
grade B (%)	13 (59)	38 (69)		45 (87)	26 (81)	
grade C (%)	1 (5)	4 (7)		1 (2)	2 (6)	
CTCAE v5.0 (0.125–8 kHz)			0.435[d]			0.516[d]
grade 0 (%)	16 (73)	40 (73)		29 (56)	17 (53)	
grade 1 (%)	3 (14)	2 (4)		7 (14)	5 (16)	
grade 2 (%)	2 (9)	3 (6)		9 (17)	1 (3)	
grade 3 (%)	1 (5)	10 (18)		7 (14)	9 (28)	
grade 4 (%)	0 (0)	0 (0)		0 (0)	0 (0)	
TUNE (0.125–16 kHz)			0.131[d]			0.286[d]
grade 0 (%)	5 (23)	10 (18)		6 (12)	4 (13)	
grade 1a (%)	8 (36)	15 (27)		10 (19)	3 (9)	
grade 1b (%)	1 (5)	0 (0)		2 (4)	3 (9)	
grade 2a (%)	7 (32)	19 (35)		25 (48)	12 (38)	
grade 2b (%)	0 (0)	1 (2)		2 (4)	1 (3)	
grade 3 (%)	1 (5)	10 (18)		7 (14)	9 (28)	
grade 4 (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Cisplatin dose-limiting toxicities						
All CDLT (%)	8 (36)	22 (40)	0.802[a]	26 (50)	22 (69)	0.114[a]
All CDLT resulting in < 200 mg/m^2 (%)	2 (9)	3 (6)	0.620[c]	8 (15)	3 (9)	0.520[c]
Ototoxicity (%)	5 (23)	0 (0)	**0.001[c]**	15 (29)	2 (6)	**0.013[c]**
Ototoxicity resulting in < 200 mg/m^2 (%)	1 (5)	0 (0)	0.286[c]	7 (14)	0 (0)	**0.041[c]**
Other toxicity (%)	3 (14)	22 (40)	**0.032[c]**	11 (21)	20 (63)	**< 0.001[a]**
Other toxicity resulting in < 200 mg/m^2 (%)	1 (5)	3 (6)	0.999[c]	1 (2)	3 (9)	0.293[c]

[a] = Chi-Square test; [b] = Linear mixed model; [c] = Fisher's exact test,) [d] = Linear-by-linear test. A p-value of < 0.05 is considered statistically significant. Abbreviations: ASHA = American Speech-Language-Hearing Association criteria; CIHL = cisplatin-induced hearing loss CTCAE = Common Terminology Criteria for Adverse Events; DIVHS = Duration infusion hand volume of hydration schedule; kHz = kilohertz; PTA = Pure Tone Average; SPL = Sound pressure level; TUNE = TUNE criteria.

related CIHL is expected [13]. Interestingly, a positive association between age and CIHL at PTA 1–2–4 kHz was found, indicating more CIHL in older patients. On the contrary, a negative association with CIHL at PTA 8–10–12.5 kHz was observed, indicating less CIHL in older patients. A possible explanation could be that hair cell loss is due to, for instance, presbyacusis, which also starts at higher frequencies, and the maximum SNHL is reached in an earlier stage of treatment at the extended high-frequencies. The negative association, indicating younger patients have more hearing loss, aligns with two studies by Zuur et al [42,43]. Whereas other authors stated that increasing age was associated with more CIHL [14].

The comparison in our retrospective cohort study included both differences in duration, volume and composition of the hydration between the groups (Table 1). Especially in the Cis100q3w cohorts a large difference in volume is observed between the short and long DIVHS, respectively 4.5 and 9.5 L. Despite the larger volume the mean infusion rate of the hydration was lower in the long DIVHS group (0.2 L/hour) compared to the short DIVHS (0.6 L/hour) in both the Cis40qw and Cis1003qw cohort. It is hypothesized that this higher infusion rate reduces cisplatin concentration by means of a higher clearance in and by the kidneys and therefore results in less nephrotoxicity.

While providing valuable insights and several strengths, this study has limitations. Due to the retrospective design of the research, the cohorts were not wholly similar, as the RT dose on the cochlea was lower in the short DIVHS in both the Cis40qw and Cis100q3w cohorts, and relatively more TNM stage IV patients were treated in the short DIVHS Cis40qw and long DIVHS Cis100q3w group. Furthermore, as the different DIVHS are administered in two different hospitals, our comparison is a combination of the duration of infusion and volume, but also hospital-specific differences may have influenced the results. However, a multivariable analysis was used to correct for confounding variables as much as possible. For example, the schedules differed in the amount and timing of magnesium supplementation, however the occurrence of hypomagnesemia showed no association with ototoxicity in our LMM. One of the strengths of this study is the availability of comprehensive and complete audiometry data from two large treatment centers, including extended high-frequency audiometry. Additionally, our research can be readily compared to future studies because of the application of various ototoxicity grading systems.

This study was initiated to provide missing literature on the association between DIVHS and ototoxicity for developing an (inter-)national hydration protocol. While it is standard protocol to administer pre- and post-hydration, various hydration regimens are utilized amongst healthcare facilities (inter)nationally and even within a single institution [23]. Several recent studies in various types of cancer revealed that short DIVHS are more sufficient in preventing nephrotoxicity than conventional long DIVHS protocols [24–27]. Earlier research showed that a short DIVHS is safe and feasible in the outpatient setting [44]. Hence, short regimens could decrease patients' hospital stay and healthcare costs [28]. As the results of our study do not show a difference in CIHL between the short and long DIVHS when objectified with audiometry, the (inter-)national guidelines can be based on the

Table 4
Linear mixed models for cisplatin-induced hearing loss at pure tone average 1–2–4 kHz (in decibel Hearing Level) and pure tone average at 8–10–12.5 kHz (in decibel Sound Pressure Level).

Variable	Univariable analysis				Multivariable analysis			
		95 % CI				95 % CI		
	Est.	Lower bound	Upper bound	*p*-value	Est.	Lower bound	Upper bound	*p*-value
Linear mixed model for cisplatin-induced hearing loss at PTA 1–2–4 kHz								
Hydration scheme								
Short DIVHS Cis40qw	−4.00	−8.38	0.38	0.073	−2.76	−7.20	1.67	0.220
Long DIVHS Cis40qw	−2.40	−5.91	1.75	0.180	−2.23	−5.75	1.28	0.212
Short DIVHS Cis100q3w	−1.80	−5.36	1.75	0.317	−0.89	−4.59	2.63	0.592
Long DIVHS Cis100q3w	Ref.				Ref.			
Age at diagnosis (years)	0.20	0.07	0.33	**0.003**	0.31	0.17	0.46	**<0.001**
Sex								
Male	Ref.							
Female	1.49	−1.47	4.44	0.321				
Cisplatin schedule								
Triweekly	1.74	−0.75	4.23	0.170				
Weekly	Ref.							
Cumulative cisplatin dose	−0.02	−0.04	0.00	0.058	−0.01	−0.03	0.01	0.194
Baseline hearing level at PTA 1–2–4 kHz	−0.12	−0.21	−0.03	**0.010**	−0.19	−0.28	−0.09	**<0.001**
Radiotherapy dose Cochlea	0.12	0.01	0.22	**0.026**	0.12	0.01	0.23	**0.028**
Linear mixed model for cisplatin-induced hearing loss at PTA 8–10–12.5 kHz								
Hydration scheme								
Short DIVHS Cis40qw	−7.35	−15.72	1.02	0.085	−6.65	−14.47	1.17	0.095
Long DIVHS Cis40qw	−3.85	−6.05	7.54	0.260	−2.23	−8.57	4.11	0.489
Short DIVHS Cis100q3w	0.74	−6.05	7.54	0.829	0.71	−5.66	7.09	0.826
Long DIVHS Cis100q3w	Ref.				Ref.			
Age at diagnosis (years)	−0.44	−0.69	−0.19	**<0.001**	−0.30	−0.56	−0.03	**0.027**
Sex								
Female	5.53	0.23	10.83	**0.041**	5.05	−0.07	10.18	0.053
Male	Ref.				Ref.			
Cisplatin schedule								
Triweekly	5.31	0.57	10.06	**0.028**	0.00			
Weekly	Ref.							
Cumulative cisplatin dose	0.01	−0.04	0.05	0.756				
Baseline hearing level at PTA 1–2–4 kHz	−0.39	−0.56	−0.22	**<0.001**	−0.28	−0.45	−0.10	**0.003**
Radiotherapy dose Cochlea	0.15	−0.04	0.35	0.121				
Hypomagnesemia	−2.76	−7.56	2.04	0.258				

Abbreviations: DIVHS = duration infusion and volume of hydration schedule; PTA = pure tone average; kHz = kilohertz.

differences in nephrotoxicity. Additionally, as the toxic effect of cisplatin causes CIHL, the results of this study might possibly be generalized to other tumor types with similar cisplatin chemoradiation regimens, such as cervix carcinoma [45].

In conclusion, although this study shows that CIHL stays a major side effect of cisplatin in general, this study revealed no significant association between CIHL development and different DIVHS in HNSCC patients in the weekly Cis40qw and triweekly Cis100q3w cisplatin dose-intensity schedule.

Trial registration numbers

IRBd22-217 and METC ID 22–946/DB..

CRediT authorship contribution statement

Anouk V.M. Burger: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Melissa A. Koot:** Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Dorieke E.M. van Balen:** Writing – review & editing, Supervision, Conceptualization. **Anouk W.M.A. Schaeffers:** Writing – review & editing, Data curation, Conceptualization. **Charlotte L. Zuur:** Writing – review & editing, Supervision. **Lot A. Devriese:** Writing – review & editing, Supervision, Methodology. **Micha de Ridder:** Writing – review & editing, Data curation. **Alex E. Hoetink:** Writing – review & editing, Supervision, Methodology. **Tim Schutte:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Mirjam Crul:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization.

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.

Appendix A

Table 5
Overview of the different implemented ototoxicity grading scales.

Grading scale	Definition of hearing loss
ASHA [37]	A) 20 dB decrease at any one tested frequency B) 10 dB decrease at any two adjacent test frequencies C) Loss of response at three consecutive test frequencies where responses were previously obtained
CTCAE v5.0 [38]	Based on the threshold shifts up to 8 kHz HL: – Grade 1: Threshold shift of 15–25 dB averaged at 2 contiguous test frequencies in at least one ear OR Subjective change in hearing in the absence of documented hearing loss; – Grade 2: Threshold shift of > 25 dB averaged at 2 contiguous test frequencies in at least one ear; – Grade 3: Threshold shift of > 25 dB averaged at 3 contiguous test frequencies in at least one ear OR hearing aid or intervention indicated – Grade 4: Decrease in hearing to profound bilateral loss (absolute threshold > 80 dB HL at 2 kHz and above); non-serviceable hearing
Tune [39]	Grade 0: No hearing loss Grade 1a: Threshold shift ≥ 10 dB at [8–10–12.5] OR subjective complaints in the absence of a threshold shift Grade 1b: Threshold shift ≥ 10 dB at [1–2–4] Grade 2a: Threshold shift ≥ 20 dB at [8–10–12.5] Grade 2b: Threshold shift ≥ 20 dB at [1–2–4] Grade 3: Hearing level ≥ 35 dB HL at [1–2–4] de novo Grade 4: Hearing level ≥ 70 dB HL at [1–2–4] de novo

Abbreviations: ASHA: American Speech-Language-Hearing Association; CTCAE: Common Terminology Criteria for Adverse Events (version 5.0), HL: hearing level.

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