Ototoxicity in a Randomized Phase III Trial of Intra-Arterial Compared With Intravenous Cisplatin Chemoradiation in Patients With Locally Advanced Head and Neck Cancer


ABSTRACT

Purpose
Cisplatin concomitantly administered with radiotherapy is increasingly used in locally advanced head and neck squamous cell carcinoma. We aimed to compare the incidence of hearing loss between patients treated with intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate (CRT-IA) and intravenous high-dose cisplatin chemoradiation without sodium thiosulfate (CRT-IV).

Patients and Methods
We conducted a prospective analysis of hearing thresholds at low and (ultra-) high frequencies obtained before, during, and after treatment in 158 patients. Patients were randomly assigned for either CRT-IA (150 mg/m², four courses) with sodium thiosulfate cisplatin neutralization or CRT-IV (100 mg/m², three courses) without rescue. All patients received concomitant radiation therapy (RT; 70 Gy).

Results
CRT-IA resulted in approximately 10% less hearing loss at frequencies vital for speech perception, compared with CRT-IV (P < .001). In CRT-IA, fewer ears qualified for hearing aids (36% v 49%; P = .03). However, in both treatment arms, the incidence expressed in National Cancer Institute Common Terminology Criteria of Adverse Events (version 3) did not deviate (P > .14). Age, cumulative cisplatin dose, cumulative RT dose, and the considered frequency area determine the degree of hearing loss (P < .001). Cisplatin induced increasing hearing loss of 24% to 60% with increasing frequencies. RT induced hearing loss at speech frequencies of 9% to 12%.

Conclusion
Depending on the criteria used to assess hearing loss due to treatment, differences in ototoxicity between CRT-IA and CRT-IV were found in favor of CRT-IA. It is desirable to specify hearing loss criteria toward frequencies vital for speech perception, and to refine grading scales to reveal subtle and clinically relevant dissimilarities in ototoxicity between different treatment protocols.

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INTRODUCTION
Chemoradiotherapy has become increasingly important for treatment of head and neck squamous cell carcinoma. In the past, high-dose cisplatin chemotherapy schemes induced a 58% to 81% incidence of hearing loss at frequencies from 0.250 to 8 kHz. Others reported an incidence up to 46% of notable hearing loss. In addition, radiation-induced sensorineural hearing loss has been observed to an incidence of 49% immediately after treatment and to an incidence of 53% at 2 to 8 years after therapy of patients treated with cranial irradiation that exposed the inner ear. In studies of the combined-modality treatment of intra-arterially applied high-dose cisplatin and radiotherapy, a 53% incidence of sensorineural hearing loss more than 30 dB at 4 and 8 kHz and a 14% incidence of ototoxicity interfering with the chemotherapy regimen were described. Other studies did not comment on ototoxicity.

To increase drug doses in the tumor with minimal systemic toxicity, a superselective administration of intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate (CRT-IA) was designed. In this treatment model, cisplatin was infused directly in the nutrient artery of the tumor with concurrent intravenously administered sodium thiosulfate (STS) for cisplatin neutralization. Favorable results have been reported. Nevertheless, in this treatment modality, incidence rates up to 60% of hearing loss ≥ 10 dB at frequencies vital for...
speech perception also have been described,24 and in individual patients hearing loss was the cause for treatment interruption.25 Other reports on CRT-IA did not comment on hearing loss.26-30

The objective of this study was to compare the incidence of hearing loss in a phase III randomized trial comparing CRT-IA and intravenous high-dose cisplatin chemoradiation without sodium thiosulfate (CRT-IV).31

**Patients and Methods**

Patients and Treatment Characteristics

From 1999 to 2004, 162 patients with locally advanced head and neck squamous cell carcinoma participated in a randomized phase III trial in our center. Patients were assigned to either targeted intra-arterial cisplatin infusions (150 mg/m², cisplatin 1 mg/mL in saline, automatic pump 1 to 2 mL/sec, four courses on days 1, 8, 15, and 22) with simultaneous intravenously administered STS (9 g/m²/30 minutes, followed by 12 g/m²/2 hours) for cisplatin neutralization (CRT-IA), or to intravenously administered cisplatin infusions (100 mg/m² in 500 mL saline during 30 minutes, three courses on days 1, 22, 43) without rescue (CRT-IV). All patients received concurrent radiation therapy (RT). One hundred fifty-eight patients were included in our study (78 CRT-IA and 80 CRT-IV). Four patients were excluded from analysis; three patients did not receive high-dose cisplatin CRT and in one patient audiometry was not performed.

**RT and the Inner Ear Radiation Dose**

All patients received 70 Gy fractionated RT in 35 daily fractions of 2 Gy (Table 1).

The inner ear radiation dose was determined by measuring the distance of the inner ear to the boundary of the radiation field. Thereafter, we converted these distances into Grays according to a computed tomography (CT) –simulated patient model with cochleas located at several distances from the field and the RT dose computed digitally. In patients treated in a conventional way (two lateral radiation portals and one anterior-posterior adjacent supraclavicular field with customized shielding) the planning x-rays were reviewed to measure the distance of the center of the bony external auditory canal to the boundary of the field. By repeating this measurement twice we found a median uncertainty of 3.2 mm. In later years, radiation portals were planned at the time of a CT scan. By revision of these images, we computed the distance from cochlea to the radiation field digitally. By repeating the procedure twice, we found a median variation of 1.0 mm.

In most recent years, patients received intensity-modulated radiation therapy (IMRT; based on digital planning of radiation portals in CT scans). The cochlea radiation dose was calculated directly.

| Table 1. Patient, Tumor, and Treatment Characteristics for CRT-IA and CRT-IV |
|-----------------|-----------------|-----------------|
| Characteristic | CRT-IA | CRT-IV |
| No. of patients | 78 | 80 |
| Median age, years | 55 | 56 |
| Sex | | |
| Male | 78 | 75 |
| Female | 22 | 25 |
| T classification | | |
| 2 | 3 | 0 |
| 3 | 28 | 25 |
| 4 | 47 | 43 |
| N classification | | |
| 0 | 11 | 14 |
| 1 | 15 | 19 |
| 2 | 39 | 43 |
| 3 | 12 | 14 |
| Unknown | 1 | 0 |
| Tumor site | | |
| Oral cavity | 9 | 12 |
| Oropharynx | 50 | 64 |
| Hypopharynx | 19 | 24 |
| Radiation therapy dose to inner ear, median | 10.8 | 16.3* |
| Radiation protocol and inner ear dose, median | | |
| Conventional | 14.3 | 14.0 |
| CT-guided scan | 10.8 | 19.2* |
| IMRT | 8.4 | 12.7 |
| Cisplatin, median dose per infusion, mg | 267 | 180* |
| Cisplatin dose-intensity, mg/m²/wk | 86† | 43† |
| Side of CRT-IA infusion with regard to measured ear | | |
| Ipsilateral or contralateral | 43 | 57 |

Abbreviations: CRT-IA, intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate; CRT-IV, intravenous high-dose cisplatin chemoradiation without sodium thiosulfate; CT, computed tomography; IMRT, intensity-modulated radiation therapy. *Difference between CRT-IA and CRT-IV, Mann-Whitney U test, P < .05. †600 mg/m²/in 7 weeks administered intra-arterially (CRT-IA). ‡300 mg/m²/in 7 weeks administered intravenously (CRT-IV).
Audiometry was performed before therapy, 1 to 6 days after each cisplatin infusion, and a median 8 weeks after termination of therapy. In two CRT-IA patients the post-treatment audiogram was performed 10 days before and 1.8 years after the end of treatment, respectively. Air-conduction (AC) thresholds were measured at frequencies 0.125 to 16 kHz, and bone-conduction (BC) thresholds were measured at 0.5 to 4 kHz. We calculated mean thresholds at three pure tone averages (PTAs): 0.5, 1, and 2 kHz (BC and AC); 1, 2, and 4 kHz (BC and AC); and 8, 10, and 12.5 kHz (AC), representing speech perception in quiet, in noise, and perception of high-pitched sounds (eg, music), respectively. Air-bone gaps (ABGs) were calculated by the difference between AC and BC at 0.5, 1, and 2 kHz. Audiometric data are presented in decibels hearing level (HL) 0.125 to 8 kHz and decibels sound pressure level 8 to 16 kHz. All analyses were conducted per ear.

In the audiograms up to 8 kHz, 69% to 96% of the AC thresholds were measured. At ultrahigh frequencies (8 to 16 kHz), and particularly as the treatment progressed, many thresholds could not be measured because the patient was not able to complete the audiometry session. At 8, 10, and 12.5 kHz, the number of ears measured in CRT-IA and CRT-IV patients were 67% and 71%, 54% and 64%, and 27% and 29%, respectively. Excluding these patients may lead to an underestimation of hearing thresholds and to exclusion of patients with potentially the highest hearing threshold (shift) during CRT. Therefore, we reconstructed missing thresholds by extrapolating with the same slope as was found on average in the audiograms of our patients who were actually measured at all (ultra-) high frequencies.

Common Terminology Criteria of Adverse Events

The incidence of ototoxicity due to CRT-IA or CRT-IV was expressed in National Cancer Institute Common Terminology Criteria of Adverse Events (version 3; CTCAE; for patients enrolled onto a monitoring program).32 Grade 1 was defined as threshold shift 15 to 25 dB averaged at ≥ two contiguous frequencies at least in one ear, or subjective change in hearing. Grade 2 was defined as threshold shift more than 25 to 90 dB, averaged at two contiguous frequencies at least in one ear. Grade 3 was defined as threshold shift more than 25 to 90 dB, averaged at three contiguous frequencies at least in one ear. Grade 4 was defined as threshold shift more than 90 dB.

Statistics

Of 158 patients, nine were excluded for the multivariate analysis, leaving 76 in the CRT-IA and 73 in the CRT-IV arm. In six patients, no follow-up audiometry was performed, whereas in three patients no baseline audiogram was available.

Two statistical analyses were performed, in which hearing loss was defined as a percentage change in decibels of pretreatment hearing level: a comparison of hearing loss between CRT-IA and CRT-IV, and an explanatory analysis to determine the separate effects of patients and treatment variables. Repeated-measurement analysis of covariance was performed using all PTAs per patient. A logarithmic transformation was applied to the audiometric (measurements + 10 dB) to improve normality and constancy of variation. No structure was imposed on the variances and correlations of the 10 measurements per time point; based on Akaike’s information criterion, the (co)variances of the same PTA at the same ear were assumed to be constant over time (compound symmetry). PROC MIXED of SAS version 8.2 for Windows (SAS Institute, Cary, NC) was used.

In the first analysis, the development over time of the PTAs was modeled by a second-order polynomial during treatment and a separate difference between pretreatment and post-treatment value. The slopes during treatment were assumed to vary between patients according to a multivariate normal distribution. The coefficients of the polynomial and the pretreatment versus post-treatment difference were allowed to vary between thresholds as well as arms. To simplify interpretation, we tested whether the quadratic components could be removed from the model. The analysis was adjusted for baseline measurement, the effect of which was allowed to vary over the PTAs.

In the second analysis, relations between quantitative variables (cisplatin and RT dose, time, and age) and transformed PTA values were assumed to be linear. Other effects considered were ear at the side of infusion (no, yes, or intravenous), ipsilateral or contralateral to cisplatin infusion side in case of CRT-IA, and sex. The effect of cumulative cisplatin dose was allowed to vary with ear at the side of infusion, age, and sex. All effects were allowed to vary with type of PTA. The slopes against cumulative cisplatin dose were assumed to vary between patients in accordance with a multivariate normal distribution. In view of the large number of effects evaluated, P < .001 was considered statistically significant. Hierarchical backward elimination (P > .10) was applied to facilitate interpretation.

RESULTS

Patient and Treatment Characteristics

Patient and treatment characteristics are summarized in Table 1. Eleven CRT-IA patients received one to three infusions. Seven CRT-IV patients received zero to two infusions. In 70 CRT-IA patients and in 67 CRT-IV patients we were able to review sufficient RT data to calculate the amount of Gray received in the inner ear. The median RT dose of the inner ear was higher in CRT-IV, due to skewness in distribution of RT doses within the CT scan–guided patients (CRT-IV, 19.2 Gy; CRT-IA, 10.8 Gy).

Overall Hearing Loss

Figure 1 shows mean AC hearing thresholds at all frequencies before, during, and after therapy. In CRT-IV patients, a larger threshold shift after the first infusion of cisplatin at frequencies more than 4 kHz is visible, compared with CRT-IA patients.

Both treatment schemes induced increasing hearing loss with increasing frequency. Table 2 lists (sensorineural) hearing loss after the individual cisplatin infusions. Pretreatment hearing capability at all PTAs was similar between the two patient groups (P = .053 to .97, univariate analysis), as expected after the randomization procedure. Mean total threshold shifts at PTA BC 1, 2, and 4 kHz were 5.3 and 8.9 dB for CRT-IA and CRT-IV, respectively, whereas mean total threshold shifts at PTA 8, 10, and 12.5 kHz were 20.4 and 19.6 dB for CRT-IA and CRT-IV, respectively.

Comparison of Hearing Loss During and After Treatment Between the Two Treatment Arms

In both CRT schemes, hearing thresholds deteriorated during treatment at low frequencies (0.4%/day), high frequencies (0.7%/day), and ultrahigh frequencies (1%/day; all P < .0005). No evidence was found for a difference between the two arms during treatment (P ≥ .34).

After treatment, differences between the two arms were found to be approximately 10% in favor of CRT-IA for low and high frequencies (P < .001;Table 3). No difference was found at ultrahigh frequencies.

The comparison of hearing loss during therapy took place at 4 weeks and therefore included in CRT-IA four doses of 150 mg/m² cisplatin, and included in CRT-IV two doses of 100 mg/m² cisplatin. It seems likely that after that period, hearing loss increased more in the CRT-IV arm, given that an additional cisplatin dose was administered at 7 weeks.

Eligibility for Hearing Aids

An AC threshold more than 35 dB HL at speech frequencies (PTA 1, 2, and 4 kHz) is considered the criterion for reimbursement of hearing aids (HAs) in the Netherlands. Fewer ears qualified for HAs after CRT-IA treatment (51 of 143 measured ears; 36%) compared with those treated with CRT-IV (72 of 148 measured patients; 49%
In 2007, 55% of all ears that qualified for HAs (of the 25% of patients that were still alive and in our follow up), actually received (or planned to receive) a hearing aid, given that they suffered dysfunctional hearing capability after treatment.

**CTCAE**

Between both treatment arms, the incidence of CTCAE grades was similar (P = .72, linear-by-linear association trend test; Table 4).

In total, 76 CRT-IA patients and 73 CRT-IV patients were assessed. Seven CRT-IA patients (9%) and nine CRT-IV patients (12%) had threshold shifts less than 15 dB in both ears and no subjective changes in hearing due to treatment.

When we left out ultrahigh frequencies (> 8 kHz), a redistribution of ototoxicity grades was observed (Table 4). Eighteen CRT-IA patients (24%) and 15 CRT-IV patients (21%) had threshold shifts less

![Fig 1. Mean hearing thresholds of (A, C) intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate (CRT-IA) and (B, D) intravenous high-dose cisplatin chemoradiation without sodium thiosulfate (CRT-IV). Hearing at ultrahigh frequencies was expressed in decibels sound pressure level (dB SPL). Pretreatment (●), after first, second and third cisplatin infusions (▲, ■, ▼), and fourth cisplatin infusion in CRT-IA (●), after therapy (CRT-IA: ●; CRT-IV, ▲).](image-url)
than 15 dB in both ears and no subjective changes in hearing due to
treatment. Again, in both treatment schemes the incidence of hearing
loss was equal ($P \geq .36$).

**ABG**

Overall, 20 ears developed an ABG more than 10 dB during or
after therapy; results were equally distributed between CRT-IA and
CRT-IV patients.

**Explanatory Analysis**

For all patients (CRT-IA and CRT-IV together), age, cumulative
cisplatin dose, cumulative RT dose, and the type of hearing loss con-
sidered (the five PTAs) determine the extent of hearing loss due to
cisplatin chemoradiotherapy ($P < .0001$), whereas age also modifies
the effect of cumulative cisplatin dose ($P < .0001$). The younger the
patient, the more vulnerable he or she was to hearing loss due to
high-dose cisplatin chemoradiotherapy. A cumulative cisplatin dose
of 1,050 mg induces increasing (sensorineural) hearing loss with in-
creasing frequencies (at low, high, and ultrahigh frequencies from
24% to 60%), and a cumulative dose of 15 Gy RT is associated with an
increase in hearing loss at low and high frequencies at PTA 0.5, 1, and
2 kHz of 9% (BC) and 12% (AC), and hearing loss at PTA 1, 2, and 4
kHz of 9% (BC) and 9% (AC).

Averaged over all frequencies and patients, the degree of hearing
loss was not influenced by the treatment arm (whether intra-arterial
cisplatin injection with STS was administered; $P = .11$) Nevertheless,
the effect of cumulative cisplatin dose was found to be higher in
CRT-IV (63%) than in CRT-IA (24%).

**DISCUSSION**

Recently, it was found that the benefit in survival of chemotherapy
added to the locoregional treatment is accompanied by an increase
of 37% to 43% of acute adverse effects (CTCAE grade $\geq 3$) for cisplatin
added to RT.17,18 The current study reports on a prospective
analysis of ototoxicity within a randomized phase III trial comparing
CRT-IA versus CRT-IV. The first clinical evaluation of this trial
showed no significant difference between CRT-IA and CRT-IV in
locoregional control (62% and 68%, respectively) or overall survival
(61% and 63%, respectively) at 2 years of follow-up.31 Whether dif-
fences in ototoxicity between CRT-IA and CRT-IV were revealed
depended on the criteria used to assess the incidence and/or degree of
hearing loss due to treatment.

When we expressed hearing loss in a percentage change of base-
line hearing (in decibels), differences in hearing loss after treatment
between CRT-IA and CRT-IV were approximately 10% in favor of
CRT-IA at frequencies vital for speech perception ($P < .001$). No
difference of hearing loss after therapy was found at ultrahigh frequen-
cies. In correspondence, CRT-IA resulted in fewer ears that qualified
for HAs after therapy (36%) compared with CRT-IV (49%). These
results are in agreement with the report on DNA-adduct formation
from our group, which observed less DNA damage in healthy tissue in
CRT-IA patients compared with CRT-IV patients,19 assuming that a
higher cisplatin dose leads to increased adduct formation. Given that
we did not measure serum cisplatin concentrations in our patients, the
potential effect of the mode of cisplatin application on its serum level
cannot be identified. However, from our previous study, it became
evident that hearing loss correlated better with cisplatin dose than with
serum level.42

In our explanatory analysis, the effect of an equal dose of
cisplatin was found to be larger in the CRT-IV arm than in the
CRT-IA arm. A protective effect of CRT-IA may be explained by a
first-pass extraction of the tumor area in intra-arterial infusion
of cisplatin,35 and/or the infusion of STS. In previous studies,
the otoprotective capacity of thiols was tested in animal
models.36-38 The chemoproductant and chemotherapy treatment

### Table 4. Common Terminology Criteria for Adverse Events, Version 3.0

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<th>Audiogram Type and Group</th>
<th>Grade</th>
<th>No. of Patients</th>
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Abbreviations: CRT-IA, intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate; CRT-IV, intravenous high-dose cisplatin chemoradiation without sodium thiosulfate.
were separated in time and space to avoid a potential reduction of the tumoricidal effect of cisplatin: in a rat model, vertebral arteries were perfused with cisplatin whereas STS was applied intravenously. Depending on the timing of thiol administration, full ototoxicity was observed. In the guinea pig model, intracochlear application of STS was found to protect the organ of corti when cisplatin was infused intravenously. In the future, it may be desirable to examine additional possibilities for two-route administration schemes for chemotherapy and otoprotective drugs in humans.

We could not find a major confounding effect of RT imbalance in our conclusion of cisplatin-induced ototoxicity, given that the different RT doses in CRT-IV subgroups (13.4 Gy in IMRT/conventional therapy versus 19.5 Gy in CT-guided therapy; \( P < .002 \), Mann Whitney U test) were related to equal hearing losses at PTA BC 1, 2, and 4 kHz (10.0 vs 9.2 dB; \( P = .840 \)). Moreover, between treatment schemes, a similar discrepancy in hearing deterioration was found in patients with CT-guided therapy with RT imbalance (9.2 dB in CRT-IV therapy and 3.3 dB in CRT-IA therapy; discrepancy, 5.9 dB) versus IMRT/conventional therapy without RT imbalance (10.0 dB in CRT-IV therapy and 3.3 dB in CRT-IA therapy; discrepancy, 6.7 dB).

The incidence of hearing loss expressed in CTCAE criteria was equal in both treatment arms. When we applied these criteria to frequencies up to 8 kHz (not to 16 kHz), a decrease in the total incidence of 91% to 76% in CRT-IA and 88% to 79% in CRT-IV was found, and a redistribution of patients toward lower CTCAE grades was observed. This was expected, given that the mean ultrahigh frequency hearing loss (at PTA 8, 10, and 12.5 kHz) was larger than the mean high frequency hearing loss (at PTA 1, 2, and 4 kHz). Evidently, CTCAE grades 2 and 3 are too coarsely defined and do not allow for subtle differences in hearing loss between both treatment arms. Nevertheless, the incidence of CTCAE grade 2 to 3 ototoxicity up to 8 kHz (50% and 59% in CRT-IA and CRT-IV, respectively) is in accordance with previous studies of high-dose cisplatin CRT, which report up to 60% of \( \geq 10 \) dB hearing loss at speech frequencies and 62% \( > 10 \) dB hearing loss at 4 to 8 kHz.15,24,39

To evaluate the effect of treatment on hearing function in future studies, we suggest that hearing loss per ear be reported at frequencies of ultrahigh sounds (PTA AC 8, 10, and 12.5 Hz) for the early detection of ototoxicity; at PTA AC 1, 2, and 4 kHz for hearing loss at frequencies vital for speech perception in noise; and at PTA 0.5, 1, and 2 kHz for analysis of conductive hearing impairment. Furthermore, hearing loss criteria should be defined as threshold shifts relative to the pretreatment audiogram, and may be graded as 0 to 10, 15 to 25, 30 to 50, and more than 50 dB. A pretreatment and post-treatment audiogram is indispensable. In addition, the impact of hearing loss on daily life performance may be reflected as whether a patient will qualify for an HA after treatment (PTA AC 1, 2, and 4 kHz \( > 35 \) dB HL). To improve future study methodology, we suggest that researchers focus on IMRT to obtain the most accurate assessment of the inner ear and retrocochlear RT dose.40-44

**REFERENCES**

Hearing Loss in Cisplatin Chemoradiation


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