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OTOLOGY

Hearing and tinnitus in head and neck cancer patients after chemoradiotherapy

Riina Niemensivu[1] · K. Saarilahti[2] · J. Ylikoski[3] · A. Aarnisalo[1] · A. A. Mäkitie[1,4]

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Abstract Head and neck cancer patients treated with high-dose cisplatin and radiotherapy will suffer from hearing deficits. The current low-dose regimen seldom causes hearing threshold decrease. Tinnitus in this patient population has not been investigated earlier. We aimed to evaluate the possible ototoxicity of low-dose (40 mg/m^2) weekly administered cisplatin with concomitant radiotherapy. Twenty-two patients with locally advanced head and neck cancer were prospectively recruited to participate the study after treatment recommendation for chemoradiotherapy with low-dose cisplatin and intensity-modulated radiotherapy. They filled in a Tinnitus Handicap Inventory and undertook audiologic evaluations before and after treatment. Ototoxicity was determined by >10 dB threshold shift at frequencies 4 and 8 kHz or in pure tone average. A historical cohort of nine patients treated with high-dose (100 mg/m^2) cisplatin and radiotherapy was used for comparison. After treatment, study patients demonstrated no significant changes in their hearing over frequencies 0.5–4 kHz, and the threshold shifts were minor at 4 and 8 kHz. More than 50 % of patients reported no tinnitus after treatment and the remainder only had slight to moderate tinnitus causing no interference with their daily activities. In contrast, five of the nine patients having received high-dose cisplatin reported disturbing tinnitus. Further, changes in pure tone averages were exhibited in three of these patients and six had significant threshold shifts at 4 and 8 kHz. Head and neck cancer patients treated with concomitant intensity-modulated radiotherapy and low-dose cisplatin seem to experience only minor audiological sequelae and therefore, these patients appear to require no routine audiological monitoring. Such evaluation could be performed only when needed.

Keywords Head and neck cancer · Chemoradiotherapy · Ototoxicity · Hearing · Tinnitus

Introduction

Concomitant chemoradiotherapy (CRT) with cisplatin and intensity-modulated radiotherapy (IMRT) is considered to be a standard treatment for head and neck cancer patients with locally advanced cancer (large tumor or regional lymph nodes), with inoperable cancer, or as postoperative treatment in patients with high risk of local recurrence. IMRT technique allows high and effective radiation doses to be targeted to the tumor area while minimizing the dose to vital surrounding tissues such as salivary glands, orbit, cochlea, and spinal cord. For head and neck cancer patients IMRT was first introduced in 1997 [1]. It has several advantages, but requires experienced and careful planning in the complicated anatomical sites of the head and neck area [2]. At the Helsinki University Hospital, IMRT has been used in the treatment on head and neck cancer patients since 2000 [3–5]. In the management of these patients, we have used mainly weekly given low-dose

✉ Riina Niemensivu
riina.niemensivu@hus.fi

1 Department of Otolaryngology, Head and Neck Surgery, University of Helsinki and Helsinki University Hospital (HUH), P.O.Box 220, 00029 Helsinki, Finland

2 Department of Oncology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

3 Helsinki Ear Institute, Helsinki, Finland

4 Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska Hospital, Stockholm, Sweden

cisplatin (40 mg/m^2) as our standard protocol treatment since the year 2000 to avoid the toxicity of high-dose cisplatin regimens.

Cisplatin is widely used as a chemotherapeutic agent for head and neck, and other cancers. Cisplatin-based chemotherapy, however, can potentially cause permanent, binaural, sensorineural, high-frequency hearing loss (HL), and tinnitus. In addition to its ototoxicity, cisplatin is also nephro- and neurotoxic. Underlying HL and age increase the risk of post-treatment HL [6]. Cisplatin-induced ototoxicity is also dose-dependent [7]. Severe outer hair cell loss, in particular in the basal and middle turns of the cochlea, is seen in animals treated with high doses of cisplatin [8].

Head and neck cancer patients receiving protocol treatment including high-dose (100 mg/m^2) cisplatin every 3 weeks will suffer HL [9–11]. This higher dose cisplatin is associated with significantly more acute toxicity, including ototoxicity, than, for example, the alternative lower dose, daily-administered two courses of cisplatin and 5-fluorourasil, with concurrent radiotherapy [12]. This HL is both subjective and objective [13]. High-dose cisplatin-based CRT also causes more sensorineural HL than radiotherapy alone [14]. Accelerated radiotherapy does not seem to damage the ear. In particular, radiation doses 40 Gy or less to the cochlea without chemotherapy fail to cause clinically significant HL [6, 11]. No previous reports exist on tinnitus caused by the standard treatment protocol using low-dose cisplatin (40 mg/m^2).

In this study, we compared hearing and tinnitus results in head and neck cancer patients treated with 6 weekly courses of low-dose cisplatin (40 mg/m^2) with a cohort of patients who had been treated with three courses of high-dose cisplatin (100 mg/m^2) every 3 weeks with concomitant IMRT. Based on our clinical experience, we hypothesized that the lower dose cisplatin-based CRT would cause less ototoxicity.

Patients and methods

The study was conducted at the Departments of Otolaryngology-Head and Neck Surgery and Oncology, Helsinki University Hospital (HUH), Helsinki, Finland between 2010 and 2013. The Research Ethics Board at the HUH approved the study protocol. All patients were prospectively recruited to participate after evaluation and treatment recommendation by a multidisciplinary tumor board. Patients signed an informed consent before participation. Twenty-nine patients with locally advanced head and neck cancer and treatment recommendation for CRT participated the prospective part of the study. They received low dose weekly cisplatin 40 mg/m^2 and concurrent IMRT. Patients completed the Tinnitus Handicap Inventory (THI) [15] and underwent hearing and emission examinations before and after CRT. The post-treatment audiogram was performed in median 8 months after CRT treatment (range, 3–19). Seven patients had only baseline audiologic tests: five died and two were lost during the follow-up. Therefore, 22 patients with a mean age of 61 years (range, 40–74) were able to complete the study. For comparison, retrospective data were gathered for nine head and neck cancer patients who had been treated with 100 mg/m^2 cisplatin-based CRT. Their mean age was 58 years (range, 41–81).

Most of the study patients received a total dose of 70 Gy (mean 68.5; range, 60–70) IMRT. There were 10 patients who were able to complete all the intended six courses of weekly 40 mg/m^2 cisplatin treatment, 8 patients received 5 courses, 2 patients 4, one patient received 3 courses, and 1 patient 2 cisplatin treatments (Table 1). In the comparison group with 9 patients, a mean total radiation dose was 66 Gy (range, 50–72). Of these patients, six were treated with IMRT and only three with conventional 3-D radiotherapy. In addition, for these three patients CT-based treatment planning was used and their cochlear dose did not exceed 40 Gy. Four (44 %) of these patients could complete the intended chemotherapy. The primary site of the tumor in the study group was either in hypopharynx ($n = 3$), larynx (3), tonsil (5), tongue (1), base of tongue (6), nasopharynx (1), or nasal cavity (1), and 2 patients had an unknown primary site. The tumor was staged T3-4 in 7 patients, T2 in 10, and T1 or T0 with regional pathological lymph nodes in 5 patients.

All patients underwent pretreatment audiometry as a baseline study. Pure tone audiometry was performed in a sound booth using Aurical Plus Audiometry (Otometrics, Denmark). Thresholds over frequencies from 125 Hz to 8 kHz were measured. Mean thresholds over the frequencies 0.5–4 kHz (pure tone average, PTA) and thresholds at 4 and 8 kHz were calculated. Transient otoacoustic emissions (TEOAE, ILOV6) were performed before and after treatment. They were analyzed for emission levels signal to noise ratio (S/N) and reproducibility for the whole wave response and for frequency bands at 1.0, 1.4, 2.0, 2.8, and 4.0 kHz. All hearing testing measurements were performed by the same licensed audiologist. The audiograms were analyzed before and after treatment for sensorineural changes at 0.5–4 kHz (PTA) and at 4 and 8 kHz. A significant hearing loss change (criteria for ototoxicity) was defined as a decrease of $\geq$10 dB at 4 and 8 kHz or in PTA.

For tinnitus measurement, we used tinnitus handicap inventory (THI), which is a self-administered questionnaire to help determine the degree of distress experienced by the patient. The severity of tinnitus is classified from slight to catastrophic and the grading from 1 to 5 accordingly. The

Table 1 Patient and treatment characteristics, post-treatment hearing and tinnitus results, and status at the last follow-up in 22 patients treated with low-dose cisplatin CRT

Patient/gender	Radiation dose/cisplatin courses	PTA change post-treatment	Threshold shift (at 4 or 8 kHz)	Tinnitus and THI score	Patient status	Change in score and significance
1/M	70/6	No	10 dB (8)	Mild (18)	NED	**18**
2/M	70/6	No	10 dB (8)	Slight (0)	NED	0
3/M	70/6	No	No	No (0)	DOD	0
4/M	70/6	No	15 dB (4)	No (0)	NED	0
5/M	70/2	No	no	Mild (20)	NED	**20**
6/M	70/6	No	20 dB (8)	No (0)	NED	0
7/F	70/5	No	No	No (0)	AWD	0
8/F	70/5	No	10 dB (8)	No (0)	NED	0
9/F	60/6	No	No	No (0)	AWD	0
10/M	70/4	No	10 dB (4)	No (0)	NED	0
11/M	66/6	No	No	No (0)	NED	0
12/M	60/6	No	No	Slight (2)[a]	NED	−6
13/M	70/6	No	No	Slight (14)	DOD	**14**
14/M	70/6	No	No	Slight (16)[a]	NED	**−32**
15/M	70/5	No	20 dB (8)	Slight (2)	NED	2
16/M	70/4	No	10 dB (8)	No (0)	NED	0
17/M	70/5	No	10 dB (4)	No (0)	NED	0
18/M	60/5	No	No	Slight (0)	NED	0
19/M	70/5	No	No	No (0)	NED	0
20/F	70/5	No	No	Moderate (44)	NED	**44**
21/M	70/5	No	10 dB (8)	No (0)	DOD	0
22/F	70/3	No	No	No (0)	NED	0

M male, *F* female, Radiation dose in Gy, *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease

[a] Less disturbing tinnitus after treatment than at the baseline and the meaningful responses are marked with bold text

scores vary between 0 and 100. Patients were asked to fill in the questionnaire before and after CRT treatment [15]. A minimum clinically significant change in the THI score can be defined by a difference of 7 points either up- or downwards [16].

Results

Twenty-two patients (17 males) completed the prospective study. Their mean age was 61 years (range 40–74). Low-dose cisplatin with concurrent IMRT was well tolerated. Eighty percent of the study patients were able to receive 5–6 courses of low-dose cisplatin treatment.

The study patients' hearing results are presented in the Table 1. None of them had significant post-treatment threshold shifts in PTA over frequencies from 500 to 4 kHz. Minor changes were seen at the higher frequencies at 4 and 8 kHz and the maximum (20 dB) threshold shift at 8 kHz. Median audiologic follow-up time between the baseline audiogram and post-treatment audiogram was 8 months (range 3–19).

We tested the statistical significance of the differences between the tinnitus results in these two groups with Fisher's Exact Test (2-sided) and found a p value of 0.001 when comparing one out of the 22 patients having moderate tinnitus in the low-dose cisplatin group and six out of the nine patients in the high-dose cisplatin group reporting disturbing tinnitus. After CRT, eight (36 %) study patients had slight or mild tinnitus, one patient had moderate tinnitus, and all the other 13 (59 %) did not report either having tinnitus or suffering from a tinnitus experience. One person with earlier onset occupational noise exposure induced tinnitus scored less in the THI, i.e. his tinnitus was less disturbing after CRT. Another patient experienced tinnitus (score 48) before treatment, but post-treatment tinnitus was only of slight level (score 16). Tinnitus did not predict change in hearing levels. The post-treatment tinnitus results are presented in the Table 1 and it demonstrates changes in THI scores before and after treatment. Kidneys of these patients tolerated the low dose treatment well. There were two study patients who received 5 courses of cisplatin instead of six because of signs of nephrotoxicity.

The historical high-dose cisplatin group comprised nine head and neck cancer patients who had been treated with 100 mg/m^2 cisplatin with concurrent radiotherapy. Toxicity-related symptoms led to cessation of treatment in over 50 % of these patients. Seven out the nine patients in this group developed HL in the higher frequencies and four of them had significant changes in their PTA. Six out of the nine patients reported onset of disturbing tinnitus after CRT.

Discussion

In the present prospective cohort study, head and neck cancer patients treated with weekly low-dose cisplatin (40 mg/m^2) and concomitant IMRT had only minor HL and tinnitus. Whereas most head and neck cancer patients treated with high-dose cisplatin (100 mg/m^2) had hearing threshold shifts in the higher frequencies and four had also changes in their PTA. Earlier reports have shown that CRT with high-dose cisplatin (100 mg/m^2) is a significant risk factor for high-frequency HL [9, 11–13, 17]. Use of lower dose cisplatin-based CRT has decreased the risk of clinically significant HL [11, 12]. In addition, long-term minor progression in hearing impairment after treatment of high-dose cisplatin has been reported [9]. Our results are in line with earlier reports and suggest that the cisplatin ototoxic effects are dose-dependent. More importantly, the present study is the first to evaluate tinnitus experience in this patient population receiving the current protocol treatment using weekly administered low-dose cisplatin.

In earlier reports, the use of radiotherapy alone in head and neck cancer patients has not been deteriorating to the inner ear [6]. In particular, radiation doses of 40 Gy or less to the cochlea have not resulted in clinically significant HL. Hitchcock et al. have recommended the use of low-dose weekly administered cisplatin when possible. Further, IMRT is favored in order to avoid excess cochlear radiation in the treatment of head and neck cancer patients [11]. In this study, all the patients were treated with IMRT technique up to the total dose of 70 Gy.

Cisplatin-induced post-treatment tinnitus in head and neck cancer patients has been scarcely studied and the mechanism remains unknown. In animal studies, loss of outer hair cells (OHC) function has been suggested to be an important factor and maybe a trigger of tinnitus-related hyperactivity in the dorsal cochlear nucleus (DCN). The nucleus activity can also be caused by direct toxic effect of cisplatin on the DCN, independent of the effect on OHCs [18, 19]. Both OHC and inner hair cells were damaged after topical injection of cisplatin to the round window [20].

The present post-treatment THI results varied from no tinnitus to moderate, i.e., the patients experienced no tinnitus as a problem after low-dose cisplatin treatment. During the treatment, only one of the study patients failed to complete the planned 6th cisplatin dose because of severe tinnitus, but by the time of filling in the THI questionnaire, his tinnitus was only slight. Four of the study patients had significantly higher scores in THI after treatment, nonetheless, three patients' self-perceived tinnitus handicap was mild in severity and one patient experienced moderate tinnitus. She had nasopharyngeal carcinoma and her Eustachian tubes were obstructed post-treatment, probably causing a more disturbing tinnitus experience. After CRT, two patients had decreased THI scores, of which one was clinically significant (Table 1).

There is no consensus definition for ototoxicity in the literature, and this fact makes comparison of various study results difficult [21]. American Speech-Language-Hearing Association criteria refer to a threshold shift of $\geq$20 dB at one frequency or a shift $\geq$10 dB at two or consecutive frequencies [22]. Simpson et al. found multiple frequencies averaging above 8000 Hz, and also multiple frequency averages between 3000 and 8000 Hz, useful in monitoring the ototoxic effects of cisplatin. This method takes normal variability in hearing threshold levels into account [23]. A criterion of $\geq$10 dB threshold shift at $\geq$2 adjacent frequencies tested in (1/6)-octave steps was useful in monitoring ototoxicity. If tested 1/2-octave step size, the best results in monitoring were achieved for shifts $\geq$15 dB at one or more frequencies. Thus, the smaller frequency steps improved test performance [24].

Hitchcock et al. defined clinically significant HL as a $\geq$10 dB loss [11]. Ototoxicity can be determined by comparing the audiologic baseline evaluations with post-treatment results. Significant clinical change occurs when the threshold shifts between reliable measurements exceed normal variability [25]. In our study, a significant HL change and therefore criteria for ototoxicity, was defined as a decrease of $\geq$10 dB at 4 and 8 kHz or in PTA. These criteria are quite strict and confirm that low-dose cisplatin is well tolerated and causes only minimal if any HL that could be measured with existing clinical equipment.

In the present study, TEOAE failed to prove to be a useful tool in monitoring ototoxicity. One reason for this could be that TEOAE fails to measure high frequencies, but is able to calculate more frequencies between 1 and 4 kHz. Our emission results showed no deterioration after treatment. This might be explained by the fact that the ears tolerate low-dose cisplatin well, as was seen in audiograms PTA (0.5–4 kHz). Therefore, the TEOAE findings, without deterioration of emission levels signal to noise ratio (S/N) and reproducibility, could also confirm the present audiogram results. We decided to use the TEOAE instead of distortion-product otoacoustic emissions (DPOAE) because TEOAE is in frequent clinical use at our institution and thus we feel confident in interpreting the results. Other

studies have proved that DPOAE could be a better tool for monitoring ototoxicity [7, 26]. It has proved to be extremely sensitive and superior to TEOAE [26]. In addition, ultra-high-frequency audiometry technique could identify ototoxic damage earlier than conventional audiometry [25]. Monitoring and early detection of ototoxicity is considered beneficial in order to minimize or prevent communication impairment. If HL changes are seen, alternative treatment dosages or medications can be considered, or the patient can be prepared to cope with hearing impairment. If no HL is identified, the planned aggressive cancer treatment can be continued [25].

The present findings are novel and promising, but they must be interpreted cautiously. The number of study patients was limited and the historical group even smaller. We used strict ototoxicity criteria, which led to the identification of even small changes in audiograms. In the detection of minimal ototoxic effects, extended high-frequency audiometry and DPOAE could have been more sensitive. Additional audiological testing could have confirmed our results, but these patients are experiencing treatment related side effects and therefore are unsuitable for repeated examinations. The strengths of the study are the prospective setting and unambiguous finding with no significant PTA shift in the study population. Therefore, we do not recommend routine screening of hearing after low-dose cisplatin treatment and concurrent IMRT. Audiologic testing could be performed if the patients have symptoms, such as subjective HL or tinnitus.

Conclusion

Low-dose (40 mg/m^2) cisplatin-based CRT was well tolerated with only mild toxic side effects and most of the study patients completed the CRT as planned. In PTA, there were no significant threshold shifts and only minor changes at frequencies of 4 and 8 kHz. TEOAE failed to help in ototoxicity monitoring. After low-dose weekly administered cisplatin with IMRT, over 50 % of the study patients had no tinnitus and all the rest only had slight tinnitus that caused no interference in their daily activities. Therefore, the number of study patients with clinically significant ototoxicity was minimal, suggesting that audiologic evaluation is likely not necessary in patients treated with low-dose cisplatin-based CRT. High-dose cisplatin with concomitant RT demonstrated significantly more toxicity, including hearing loss and tinnitus. It is important to be aware of the risk of ototoxicity in cisplatin treated patients. More importantly, audiological monitoring and rehabilitation should be started without delay, to minimize progression of communication problems in the head and neck cancer patients managed with chemotherapy.

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Compliance with ethical standards

Conflict of interest No conflict of interest.

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