

Oxaliplatin and ototoxicity: is it really safe for hearing?

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Background/aim: Oxaliplatin is an effective and widely used chemotherapeutic agent in the treatment of many solid tumors. The most common side effects are peripheral neuropathy, gastrointestinal toxicity, and neutropenia. There have been some case reports about ototoxicity with oxaliplatin, but no clinical trials. In this trial, we explored whether or not oxaliplatin has ototoxic effects.

Materials and methods: A total of 18 patients, 14 with colorectal cancer and 4 with pancreatic cancer, were included in this study. Four patients (22%) were treated with a capecitabine and oxaliplatin (CapeOx) regimen, and 14 patients (78%) were treated with fluorouracil, leucovorin, and oxaliplatin (FOLFOX-6). Patients' pretreatment and posttreatment hearing levels were assessed with high-frequency audiometry and otoacoustic emission tests.

Results: The median time between the first and the last oxaliplatin doses was 3.2 months (range: 2–7 months). There was no hearing loss in tests conducted for both ears of patients at frequencies of 500, 1000, 2000, 4000, 6000, 8000, 12,000, and 16,000 Hz. There was no difference between the pretreatment and posttreatment otoacoustic emission tests.

Conclusion: Oxaliplatin is a reliable agent in terms of ototoxicity.

Key words: Cancer, ototoxicity, oxaliplatin

1. Introduction

Oxaliplatin is a new platinum compound agent used in the treatment of many cancers, especially colorectal cancer (CRC). It gained European approval in 1996 and Food and Drug Administration approval in 2002. As a single agent, oxaliplatin shows modest activity in CRC, but when combined with fluorouracil and leucovorin, it has disease-free survival (DFS) benefits in stage II and III CRC patients. In a study by Andre et al., DFS rates were 78.2% in patients treated with fluorouracil plus leucovorin and oxaliplatin and 72.9% with fluorouracil and leucovorin alone ($P = 0.002$) (1). The DFS difference was statistically significant only in the stage III group. The National Surgical Adjuvant Breast and Bowel Project's C-07 trial further strengthened the role of oxaliplatin in the adjuvant setting. Its role in the metastatic setting has also been demonstrated in many trials, with both fluorouracil and capecitabine (2).

Oxaliplatin is also used (unlabeled) in the treatment of esophageal, gastric, advanced hepatobiliary, advanced ovarian, pancreatic, and refractory testicular cancers and refractory non-Hodgkin lymphoma (3).

Unfortunately, although oxaliplatin has a wide therapeutic range, it may cause serious side effects, the most common of which are fatigue, nausea, vomiting, diarrhea, constipation, and neuropathy (4). Neuropathy may be acute and persistent, and it may be dose-limiting (5). Oxaliplatin-induced neuropathy is generally seen in the peripheral nervous system. Although there are a few relevant case reports, there has not yet been a clinical trial on oxaliplatin-related ototoxicity (ORO), which is what we have aimed to provide here.

2. Materials and methods

The patients included in this study were diagnosed and treated with oxaliplatin-based chemotherapy regimens at the Cumhuriyet University Faculty of Medicine's Medical Oncology Department. Institutional review board approval was obtained for the study.

The patients' ages, sex, primary tumor types, tumor stages, chemotherapy regimens, tumor markers, hematological parameters, and liver and kidney function tests were recorded. Before and after 6 cycles of

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chemotherapy application, all patients' hearing evaluations were completed using pure-tone and high-frequency audiometry. Otoacoustic emission tests were also given to all patients.

The patients were treated with oxaliplatin-based regimens, either fluorouracil/leucovorin/oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (CapeOx).

Tympanograms were done with the Impedance Audiometer AZ 26. Pure-tone audiometry was conducted with the Clinical Audiometer AC 40 and TDH-39P Telephonic HB-7 earphones, and high-frequency audiometry analysis was completed with the AC 40 Interacoustic Clinical Audiometer and Koss digital earphones R/80. Hearing evaluations were done in accordance with the American National Standard S3-1. Hearing levels above 26 dB were accepted as pathological.

Data from the study were loaded into SPSS 14.5 and evaluated using the Mann-Whitney U test, analysis of variance, Bonferroni test, and chi-square test. The level of statistical significance was set at 0.05.

3. Results

A total of 18 patients (9 males, 9 females) were included in this study. Fourteen (77.7%) of them had CRC and 4 (22.2%) had pancreatic cancer (PC). Eleven of the 14 CRC patients received oxaliplatin in the adjuvant setting. The other 3 CRC patients and all of the PC patients were metastatic (Table 1). Fourteen (77.7%) patients received the FOLFOX treatment, and 4 patients (22.2%) received CapeOx.

Table 1. Patients' characteristics.

Age, years			58 (25–76)
Sex			
Male	(n)		9 (50%)
Female	(n)		9 (50%)
Primary cancer			
Colorectal cancer	(n)		14 (77.7%)
Pancreatic cancer	(n)		4 (22.2%)
Chemotherapy regimen			
FOLFOX	(n)		14 (77.7%)
CapeOx	(n)		4 (22.2%)
Median oxaliplatin dosage (mg)			672 (290–1200)

The median time between the first and last oxaliplatin administration was 105 days (range: 56–212 days). The hearing levels of all patients were assessed with hearing tests at 500, 1000, 2000, 4000, 6000, 8000, 12,000, and 16,000 Hz before and after chemotherapy (Table 2). There was no statistically significant difference between pretreatment and posttreatment hearing levels. Pretreatment and posttreatment otoacoustic emission testing was given to all patients and no pathologies were detected.

Table 2. Hearing levels before and after chemotherapy.

Frequency (Hz)	Right ear		P	Left ear		P
	BC (dB)	AC (dB)		BC (dB)	AC (dB)	
500	19.7 ± 10.7	19.1 ± 11.7		17.2 ± 10.6	18.8 ± 12.1	
1000	15.5 ± 9.5	16.1 ± 10.3		15.2 ± 9.4	18.3 ± 13.3	
2000	16.6 ± 13.1	17.7 ± 14.2		18.8 ± 12.5	21.9 ± 18.8	
4000	26.9 ± 16.8	29.1 ± 17.7		33.0 ± 19.2	36.3 ± 22.6	
6000	33.2 ± 24.5	36.1 ± 24.6	>0.05	38.6 ± 25.8	41.3 ± 26.2	>0.05
8000	39.7 ± 25.8	43.0 ± 24.7		41.9 ± 27.2	45.5 ± 25.7	
12,000	51.9 ± 26.3	53.3 ± 27.9		54.1 ± 23.4	55.2 ± 25.2	
16,000	51.3 ± 19.3	51.3 ± 21.2		51.9 ± 17.4	51.3 ± 18.3	

BC: Before chemotherapy, AC: after chemotherapy.

4. Discussion

This study assessed and analyzed the audiological functions of 18 patients undergoing chemotherapy with oxaliplatin. Ototoxicity due to platinum-containing agents, especially cisplatin and carboplatin, has been reported in many publications. These agents may damage the cochleae and may cause vertigo, tinnitus, and hearing loss. Ototoxicity due to cisplatin has been reported in 10%–70% of adults (6,7). In a study by Reddel et al. (8), ototoxicity was detected in 72% of adult patients treated with cisplatin. Cisplatin ototoxicity in adults and children may lead to hearing loss, starting as sensorineural tinnitus. Hearing loss begins at high frequencies and then progresses towards lower frequencies, which are crucial for hearing speech (9).

Dutta et al. investigated the audiological functions of patients who had been treated with cisplatin-based regimens. They found that bilateral sensorineural hearing loss had developed in 15% of patients. This hearing loss was especially prominent at 4000 Hz and higher frequencies (10).

Carboplatin is an ototoxic platinum analog. Although carboplatin has been found to be ototoxic, its toxicity is significant, especially in myeloablative doses. Kennedy et al. concluded that carboplatin is not ototoxic at standard doses and that routine audiometric surveillance need not be recommended (11).

Ototoxicity due to platinum compounds has also been reported in pediatric patients. The incidence of ototoxicity in this population is 50%–80% with cisplatin and 1%–35% with carboplatin (12,13).

The XELOX regimen was associated with a higher frequency and severity of diarrhea, thrombocytopenia, and hand-foot syndrome, whereas FOLFOX-4 was associated with more grade 3–4 neutropenia. However, since the efficacies of the different treatment regimens are equivalent in metastatic gastrointestinal tumors (14,15), the use of oral chemotherapeutic regimens is certainly more comfortable for outpatients and thus positively influences patient compliance.

In a study by Hellberg et al., oxaliplatin was found to have minimal ototoxicity, and they attributed this to limited cochlear uptake of oxaliplatin (16).

In our study, we did not find ototoxicity with oxaliplatin in either high-frequency audiometry or otoacoustic emission testing. The cochlear uptake of oxaliplatin is not as high as with cisplatin and carboplatin. Thus, ototoxicity is rare with oxaliplatin usage.

Oxaliplatin is one of the most-used agents for colorectal, pancreatic, and gastric cancers, and studies have also shown that oxaliplatin is active in many tumors. Its most common side effects are nausea, diarrhea, myelotoxicity, and peripheral neuropathy. As far as we know, this is the biggest trial of ORO in the literature, and we can say that oxaliplatin is a safe agent in terms of ototoxicity.

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