Korean J Gastroenterol Vol. 76 No. 5, 261-264
https://doi.org/10.4166/kjg.2020.121
pISSN 1598-9992 eISSN 2233-6869

CASE REPORT

췌장암 환자에서 Oxaliplatin 사용 후 발생한 돌발성 난청 1예

김승범, 김소영, 김국현, 김태년
영남대학교 의과대학 내과학교실

Oxaliplatin-induced Sudden Hearing Loss in a Patient with Pancreatic Cancer

Sung Bum Kim, So Yeong Kim, Kook Hyun Kim and Tae Nyeun Kim
Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Oxaliplatin is a new generation of platinum derivatives used frequently to treat solid organ malignancies, including colorectal and ovarian cancer. Recently, an oxaliplatin-based chemotherapeutic regimen was adopted for advanced pancreatic cancer. Although oxaliplatin has extensive therapeutic potential, its use can be limited by significant adverse effects, particularly ototoxicity. This paper reports a rare case of irreversible unilateral hearing loss in a 48-year-old female that developed after the intravenous infusion of oxaliplatin during pancreatic cancer treatment. To the best of the authors' knowledge, this is the second reported case of oxaliplatin-related ototoxicity in pancreatic cancer. **(Korean J Gastroenterol 2020;76:261-264)**

Key Words: Ototoxicity; Oxaliplatin; Chemotherapy; Pancreatic neoplasms

INTRODUCTION

Oxaliplatin is a third-generation platinum derivative used commonly to treat various solid organ malignancies, including colorectal, ovarian, and pancreatic cancer.[1-4] Recently, oxaliplatin-based chemotherapeutic regimens have played an important role in the treatment of advanced pancreatic cancer. The most frequent adverse effects of oxaliplatin are peripheral neuropathy characterized by acute reversible paresthesia. Although the ototoxic effects of cisplatin are well recognized, there are few reports on oxaliplatin. This paper reports the second case report of oxaliplatin-related ototoxicity in pancreatic cancer. A rare case of irreversible unilateral hearing loss occurred in a 48-year-old female after the intravenous infusion of oxaliplatin for the treatment of pancreatic cancer.

CASE REPORT

A 48-year-old woman presented with jaundice and an itching sense with a 3-week duration. Her prior medical history was unremarkable. An abdominal CT scan revealed a 2.5 cm sized mass in the pancreatic head, causing diffuse bile duct and pancreatic duct dilation. MRI confirmed a 2.5 cm sized mass in the pancreatic head with diffuse pancreatic duct dilatation. CT and MRI images showed the tumor abutting the superior mesenteric vein, suggesting a borderline resectable cancer. Endoscopic ultrasonography-guided fine-needle aspiration confirmed an adenocarcinoma. Endoscopic retrograde cholangiopancreatography was performed, and a plastic stent was placed into the bile duct for biliary decompression. With no evidence of a distant metastasis by

Received August 14, 2020. **Revised** September 10, 2020. **Accepted** September 11, 2020.

교신저자: 김국현, 42415, 대구시 남구 현충로 170, 영남대학교 의과대학 내과학교실
Correspondence to: Kook Hyun Kim, Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea.
Tel: +82-53-620-3576, Fax: +82-53-623-8001, E-mail: kimkh@yu.ac.kr, **ORCID:** https://orcid.org/0000-0001-7786-7882

Financial support: None. Conflict of interest: None.

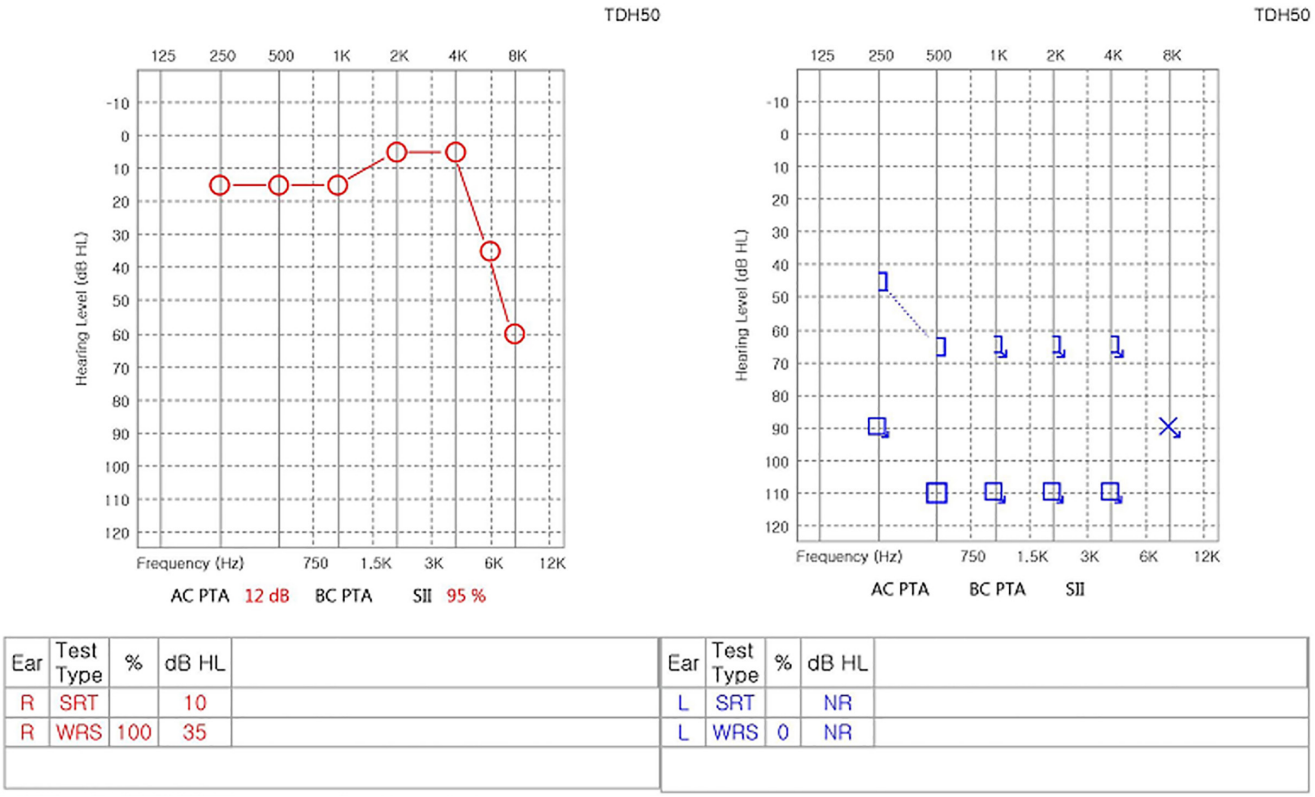
PET, neoadjuvant chemotherapy was planned using a FOLFIRINOX regimen (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, fluorouracil 400 mg/m^2 bolus infusion, followed by fluorouracil 2,400 mg/m^2 as a 48-hours continuous infusion), which was repeated every 14 days.

A follow-up CT scan after the 4th cycle of chemotherapy confirmed stable disease, and chemotherapy was continued. One week after the 6th cycle of chemotherapy, however, she visited the emergency room because of febrile sense, nausea, and vomiting.

Thirteen days after the 6th cycle of chemotherapy, she complained of tinnitus, dizziness, fullness, and hearing impairment of her left ear. She was referred to the otolaryngology section for an auditory evaluation. Neither the vestibular function test nor brain MRI revealed the cause of the hearing damage. Pure tone audiometry showed severe sensorineural hearing loss of the left ear (Fig. 1). With no other obvious cause of the hearing damage, oxaliplatin was suspected to be the source of the sudden hearing loss; the cumulative dose of oxaliplatin was 510 mg/m^2. Although high dose intravenous steroid therapy is the treatment of choice for sensorineural hearing injury, she received intratympanic steroid injection therapy due to the possibility of exacerbating the infection. The follow-up PET scan showed a decreased FDG uptake of pancreatic head cancer without evidence of distant metastasis. She underwent pylorus-preserving pancreatoduodenectomy for pancreatic cancer. A R0 resection was done for pancreatic cancer and the final TNM stage of pancreatic cancer was III (T2N2M0). Follow-up pure tone audiometry 1 month later showed no interval change. Gemcitabine-based adjuvant chemotherapy was performed for nine months. The follow-up PET scan performed after 11 months from surgery revealed FDG hot uptakes at the operation site and left supraclavicular station, indicating tumor recurrence. Fine needle aspiration of the left supraclavicular lymph node confirmed a metastasis. At this point, there was no significant clinical improvement of unilateral hearing loss.

DISCUSSION

Oxaliplatin is a new generation of platinum-containing derivatives that derives their activity by forming covalent bonds with DNA, thereby inhibiting DNA synthesis.[5] Platinum-based chemotherapeutic agents, such as cisplatin, carboplatin, and



Ear	Test Type	%	dB HL
R	SRT		10
R	WRS	100	35

Ear	Test Type	%	dB HL
L	SRT		NR
L	WRS	0	NR

Fig. 1. After 13 days from 6th cycle of a FOLFIRINOX regimen, audiometry revealed severe to profound hearing loss of the left ear.

oxaliplatin, are widely advocated for the treatment of a variety of malignancies, including colorectal and pancreatic cancer.[1,3,4] Although oxaliplatin has extensive therapeutic potential, its use can be limited by its significant adverse effects, especially neurotoxicity.[6] Oxaliplatin has often been associated with transient peripheral neuropathy and persistent neurosensory loss. Acute neurotoxicity with oxaliplatin, which frequently manifests as oral paresthesia or a tingling sensation of the extremities immediately after infusion, usually resolves spontaneously.[3] On the other hand, persistent neurotoxicity can occur when platinum drugs accumulate in the dorsal root ganglia.[7,8]

Persistent hearing loss and tinnitus can occur in cases of platinum-based chemotherapy-induced inner ear toxicity. Platinum-based agents often damage the outer hair cells in the organ of Corti and the vascularized epithelium in the lateral wall of the cochlea and stria vascularis.[9,10] The organ of Corti of the inner ear has a blood-labyrinth barrier that blocks the transport of platinum drugs to the perilymphatic space.[10] A previous animal study by Hellberg et al.[10] reported that the difference in the cochlear pharmacokinetics might result in substantially different ototoxic profiles. A remarkable difference in the uptake of antitumor agent into scala tympani perilymph fluid and total platinum concentration in cochlear cells have also been reported.[10] The difference in cochlear kinetic and cellular uptake in the hearing end organs can explain the different ototoxicities of the platinum-derivatives.[11] Therefore, the lower cochlear uptake of oxaliplatin than cisplatin may be a reasonable explanation for the lower ototoxic potential of oxaliplatin.[10,11]

This paper provides a summary of the five published case reports of oxaliplatin-related ototoxicity (Table 1). Malhotra et al.[3] reported the first case of ototoxicity, which occurred after a single intravenous infusion of oxaliplatin for a colorectal malignancy. Of the five cases reported, hearing loss developed in four cases,[1,4,3,12] and three cases, unfortunately, resulted in irreversible hearing damage, as in the present case.[3,4,12] In one case of hearing loss, the patient continued chemotherapy with oxaliplatin even after developing hearing loss, and the hearing loss was irreversible.[4] In the other three cases of hearing loss, chemotherapy with oxaliplatin was discontinued, and slight improvement of hearing loss was noted only in one case.[1,3,12] Even after discontinuing oxaliplatin after the development of hearing loss, recovery from hearing loss was not observed in current case. A decision about whether to switch or discontinue chemotherapy after ototoxicity should be made using a multidisciplinary approach. Interestingly, four out of the five cases involved female patients, as with current case, but no plausible explanation for this gender difference has been proposed.[3,4,12,13] Furthermore, these reports showed that oxaliplatin-related ototoxicity could occur at any age and any stage of treatment. Nevertheless, the rise in cumulative dose increases the risk of hearing damage. In the present case, the sensorineural hearing loss occurred after the 6th cycle of the FOLFINOX schedule.

Physicians should consider that oxaliplatin can be ototoxic, even though the risk is comparatively low. Patients treated with an oxaliplatin-based regimen should be monitored closely during treatment for the early diagnosis of potential hearing loss. Further study is warranted to elucidate the risk factors,

Table 1. Summary of Case Reports of Oxaliplatin-related Ototoxicity

Author	Age/sex	Malignancy	Affected ear	Regimen	Onset (cycle)	Cumulative dose (mg/m^2) at the onset	Reversibility
Malhotra et al. (2010)[3]	70/F	Rectum	Left	Oxaliplatin +capecitabine	After 1st	85	Irreversible
Vietor and George (2012)[13]	46/F	Sigmoid colon	NA	mFOLFOX	After 2nd	170	Reversible
Oh et al. (2013)[4]	85/F	Pancreas	Right	Oxaliplatin +gemcitabine	After 3rd	255	Irreversible
Hijri et al. (2014)[1]	70/M	Colon	Both	Oxaliplatin +capecitabine	After 8th	1,040	Reversible
Güvenç et al. (2016)[12]	64/F	Sigmnoid colon	Right	Oxaliplatin+5-FU +cetuximab	After 3rd	255	Irreversible
Present case (2020)	48/F	Pancreas	Left	FOLFIRINOX	After 6th	510	Irreversible

NA, not available; F, female; M, male.

temporal relationship, and dose-dependency for oxaliplatin-induced ototoxicity.

REFERENCES

1. Hijri FZ, Arifi S, Ouattassi N, Mellas N, El Mesbahi O. Oxaliplatin-induced ototoxicity in adjuvant setting for colorectal cancer: unusual side effect. J Gastrointest Cancer 2014;45:106-108.
2. Piccart MJ, Lamb H, Vermorken JB. Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. Ann Oncol 2001;12:1195-1203.
3. Malhotra NK, Aslam R, Lipman SP, Bilski VJ. Acute ototoxicity from a single infusion of oxaliplatin. Ear Nose Throat J 2010; 89:258-261.
4. Oh SY, Wasif N, Garcon MC, Rodriguez G, Saif MW. Ototoxicity associated with oxaliplatin in a patient with pancreatic cancer. JOP 2013;14:676-679.
5. Ibrahim A, Hirschfeld S, Cohen MH, Griebel DJ, Williams GA, Pazdur R. FDA drug approval summaries: oxaliplatin. Oncologist 2004;9:8-12.
6. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol 1998;9: 1053-1071.
7. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs 2003;63:1549-1563.
8. Hoff PM, Saad ED, Costa F, et al. Literature review and practical aspects on the management of oxaliplatin-associated toxicity. Clin Colorectal Cancer 2012;11:93-100.
9. Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevention. Hear Res 2007; 226:157-167.
10. Hellberg V, Wallin I, Eriksson S, et al. Cisplatin and oxaliplatin toxicity: importance of cochlear kinetics as a determinant for ototoxicity. J Natl Cancer Inst 2009;101:37-47.
11. Ding D, Allman BL, Salvi R. Review: ototoxic characteristics of platinum antitumor drugs. Anat Rec (Hoboken) 2012;295: 1851-1867.
12. Güvenç MG, Dizdar D, Dizdar SK, Okutur SK, Demir G. Sudden hearing loss due to oxaliplatin use in a patient with colon cancer. J Chemother 2016;28:341-342.
13. Vietor NO, George BJ. Oxaliplatin-induced hepatocellular injury and ototoxicity: a review of the literature and report of unusual side effects of a commonly used chemotherapeutic agent. J Oncol Pharm Pract 2012;18:355-359.