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Case report

Profound sensorineural hearing loss after one cycle of intraperitoneal cisplatin in treatment of advanced ovarian cancer

Megan E. McDonald [a,*], Jordan Mattson [b], Emily Hill [a]

[a] Division of Gynecologic Oncology, The University of Iowa Hospitals and Clinics, Iowa City, IA, United States
[b] Department of Obstetrics and Gynecology, The University of Iowa Hospitals and Clinics, Iowa City, IA, United States

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ABSTRACT

Few advances in the treatment of advanced epithelial ovarian cancer have improved patient overall survival. However, the incorporation of intraperitoneal administration of platinum based chemotherapy to standard treatment was one such advancement. It is understood that the intraperitoneal regimen is associated with increased toxicity when compared to intravenous administration alone; however, information regarding the specific risk of ototoxicity is lacking in the literature. We report a case of almost complete sensorineural hearing loss after one cycle of intraperitoneal cisplatin. Three days after receiving an intravenous 24 h paclitaxel at 135 mg/m^2 and subsequent intraperitoneal infusion of cisplatin at 75 mg/m^2, the patient presented with profound bilateral sensorineural hearing loss. The patient experienced no recovery of hearing despite an aggressive systemic steroid taper and change in chemotherapy regimen to alternative agents. She is currently under consideration for cochlear device implantation. Generally, cisplatin related ototoxicity during treatment of epithelial ovarian cancer is gradual, limited to high-frequency ranges and dose-related; however, the toxicity with only one standard dose can be profound and irreversible. This risk should be addressed when counseling patients prior to initiation of treatment.

1. Case report

The patient is a 57-year-old G4P3 female who presented with abdominal pain. She initially underwent a transvaginal ultrasound with suboptimal visualization of gynecologic organs due to abdominal ascites. A subsequent CT scan demonstrated omental caking and large volume ascites. Serum Ca-125 was elevated at 1196. The patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo oophorectomy, infracolic and infragastric omentectomy, optimal cytoreductive surgery, and intraperitoneal port placement with a final diagnosis of stage IIIC high grade serous adenocarcinoma of the ovary. Her post-operative course was uncomplicated other than an ileus and she was discharged to home on post-operative day 9. Prior to discharge, the patient was noted to have an erythematous patch over the sacrum with vesicular lesions in multiple stages of healing. Herpes Simplex Virus 2 (HSV2) PCR returned positive. The patient was started on Valacyclovir 1 g three times a day for a one week course. Additionally, the patient was prescribed a 1 g daily suppressive dose of Valacyclovir to be continued throughout chemotherapy. Unfortunately, the suppressive Valacyclovir was not taken as recommended due to miscommunication.

On post-operative day 30, the patient was admitted to the hospital for cycle 1 of intravenous paclitaxel and intraperitoneal cisplatin chemotherapy. The patient received a 24 h infusion of paclitaxel at a dose of 135 mg/m^2 on cycle day 1. On cycle day 2, the patient received 25 g of mannitol intravenously, followed by cisplatin 75 mg/m^2. Per institutional protocol, the cisplatin was diluted in 1 L normal saline and infused as rapidly as possible via the intraperitoneal port. The patient tolerated the infusions well and there were no immediate complications.

On cycle day 6, the patient presented to clinic after calling with complaints of bilateral hearing loss. Audiogram with the Otolaryngologist confirmed profound sensorineural hearing loss bilaterally with a word discrimination score of 0% in both ears (ototoxicity grade 4). The same day, she was started on a 60 mg prednisone taper over the next 18 days. Day 8 intraperitoneal paclitaxel was held. On cycle day 9, the patient was admitted to the hospital with neutropenic fever of unknown origin and acute kidney injury, both of which resolved after antibiotics and hydration. Following discharge, the patient underwent an MRI of the brain to evaluate for metastatic lesions as a potential cause of hearing loss, which was normal. Repeat audiogram after completion of the steroid taper revealed no recovery in hearing. Chemotherapy treatment was switched to Docetaxel 60 mg/m^2 and Carboplatin AUC 5 for cycle 2. The Carboplatin dose was escalated to an AUC 6 for cycles 3–6, as this regimen was well tolerated with no grade 3–4 toxicities or readmissions. Six months after the initiation of chemotherapy, the

* Corresponding author at: Division of Gynecologic Oncology, The University of Iowa, 200 Hawkins Dr., Iowa City, IA 52242, United States.
E-mail address: megan-e-mcdonald@uiowa.edu (M.E. McDonald).

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patient has had minimal recovery from her profound hearing loss and is currently undergoing implantation of a cochlear device.

2. Discussion

Ototoxicity related to cisplatin can be attributed to the inhibition of adenylate cyclase and subsequent damage within the organ of Corti due to severe destruction of outer hair cells in the basal turn of the cochlea (Bagger-Sjoback et al., 1980; Guarino et al., 1979). Whereas the half-life of cisplatin in the serums is <1 h, an increase in cisplatin concentration over 24 h is seen within the organ or Cori (Nakai et al., 1982). This explains its particular sensitivity to the adverse effects of the drug. Cisplatin related ototoxicity is generally thought to be dose dependent, with development of clinically detectable high frequency hearing loss occurring only after high accumulated doses of >500 mg/m^2 (Chiuten et al., 1983). However, a wide variation in individual ototoxicity among patients has been reported and is thought to be multifactorial in etiology, with factors including the presence of genetic polymorphisms in the cisplatin metabolism pathway, method of cisplatin administration, presence of baseline hearing loss and dose per treatment (Riedemann et al., 2008; Peters et al., 2000; Pussegoda et al., 2013; Brock et al., 2012). Another possibly related co-existent medical condition in our patient was a recent infection with HSV, as there is data that viral infection, particularly with herpes zoster or simplex 1, can be implicated in idiopathic sudden sensorineural hearing loss (Awad et al., 2012; Stokroos et al., 1998). Despite the known risk of ototoxicity, there is insufficient data to recommend concomitant use of otoprotective agents with cisplatin, such as amifostine, vitamin E, or intratympanic dexamethasone. The mainstay in treatment of cisplatin related ototoxicity is early recognition and, if possible, treatment modification.

A series of phase III randomized controlled trials have demonstrated an overall survival benefit with intraperitoneal chemotherapy in the treatment of optimally debulked epithelial ovarian cancer, which led to an NCI Clinical Announcement in 2006 (Alberts et al., 1996; Markman et al., 2001; Armstrong et al., 2006). As such, intraperitoneal chemotherapy has become the standard of care in this patient population. The use of cisplatin in this group is often hindered by its dose-limiting adverse effects on kidney function, myelosuppression, gastrointestinal toxicity, and peripheral neurotoxicity; however, the specific risks of ototoxicity are poorly defined. While the rates of overall neurotoxicity are higher in the intraperitoneal arm of GOG 114 and 172, this more frequently reflects peripheral sensorial neuropathy (Markman et al., 2001; Armstrong et al., 2006). Only GOG 104 specifically comments on the frequency of tinnitus and hearing loss. Within this trial, the frequency of ≥grade 2 ototoxicity was actually found to be less in the intraperitoneal arm than the intravenous arm; tinnitus 7% vs 14% ($p = 0.01$) and hearing loss 5% vs 15% ($p < 0.0001$) (Alberts et al., 1996).

Although the precise rate of ototoxicity with the currently used intraperitoneal chemotherapy regimens remains somewhat unclear, there are available reports of patients developing severe hearing loss during this treatment. A 2011 phase II trial attempted to limit the toxicity of the intraperitoneal chemotherapy through modification of the GOG 172 treatment regimen. In this study, paclitaxel 135 mg/m^2 was infused over 3 h on day 1 and cisplatin 50 mg/m^2 was given intraperitoneally on day 1 and day 8. Despite the split dosing of cisplatin, of the 21 patients receiving this modified regimen, two were unable to complete the recommended treatment due to grade 3–4 hearing loss (Landrum et al., 2011). Additionally, there has been one other case report demonstrating profound hearing loss after one dose of intraperitoneal cisplatin for treatment of ovarian cancer (Nieves et al., 2007). Our case differs in that she received a lower dose of cisplatin (75 mg/m^2 rather than 100 mg/m^2) and at a longer interval from surgery (4 vs. 2 weeks). Our report further corroborates the finding that ototoxicity after minimal amounts of cisplatin can be significant and despite prompt management with systemic steroids, most likely permanent. This has considerable potential to negatively affect patient quality of life, which is an important consideration in a cancer where upfront treatment is rarely curative. The possibility of profound ototoxicity should be included in patient counseling about adverse effects associated with intraperitoneal cisplatin chemotherapy and consideration given to auditory testing before and during treatment.

Disclosures

The authors have no conflicts to disclose.

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