

Ototoxicity in patients with invasive ductal breast cancer who were treated with docetaxel: report of two cases

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ABSTRACT

Docetaxel is an important anti-microtubule agent used to treat a variety of solid tumors, including breast cancer; notably, docetaxel-containing regimens improve outcomes for patients in metastatic, adjuvant, and neoadjuvant settings. However, the effectiveness of docetaxel in clinical practice can be compromised by suboptimal management of side effects. Here, we report two cases of docetaxel-based chemotherapy regimens in patients who exhibited invasive ductal breast cancer and underwent two different clinical treatment approaches. A 58-year-old postmenopausal female received salvage treatment with 8 cycles of docetaxel (67 mg/m²), and a 74-year-old female received 1 cycle of docetaxel (100 mg/m²). The two patients exhibited considerable hearing loss two days later. Of note, both patients had no hearing loss symptoms prior to docetaxel. Thus, ototoxicity may be a side effect of docetaxel that should be considered during treatment.

ARTICLE HISTORY

Received 14 January 2019
Revised 6 September 2020
Accepted 15 September 2020

KEYWORDS

Breast cancer; taxanes; docetaxel; ototoxicity; sensorineural hearing loss

1. Introduction

Ototoxicity constitutes a hearing disorder that results from temporary or permanent inner ear dysfunction after treatment with an ototoxic drug.^{1,2} Classic drugs with known ototoxic properties include aminoglycosides, loop diuretics, quinine, nonsteroidal anti-inflammatory drugs, and antineoplastic drugs. Cisplatin-based chemotherapeutic agents are the most common ototoxic antineoplastic drugs.^{3–5} As a result, docetaxel-induced ototoxicity has not been reported in the literature. Therefore, no warning is included regarding this side effect in the drug information sheets provided by drug companies.

Here, we report two cases of ototoxicity that occurred in patients with invasive ductal breast cancer who were treated with docetaxel. We will also speculate regarding the possible etiology of ototoxicity in the setting of a docetaxel agent.

2. Case reports

2.1. Case 1

A 58-year-old postmenopausal female was diagnosed with a low differentiated breast carcinoma in March 2013. She received 4 cycles of neoadjuvant chemotherapy (docetaxel and pirarubicin) and underwent a modified radical mastectomy on September 26, 2013. Postoperative pathology revealed invasive ductal carcinoma. Immunohistochemical staining of the resected specimen showed that the cancer tissue was positive for estrogen receptor (ER), but negative for progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2)/Neu (Figure 1a). The biomarkers of the postoperative path were consistent with previous. The excised breast

specimen showed a lesion with a mass of 1.0 cm × 1.0 cm × 0.5 cm. Left axillar lymphadenectomy was performed and nine lymph nodes were isolated; one showed presence of metastatic carcinoma (1/9). After the surgery, the patient received post-operative radiotherapy (50 Gy/25 f) to the left clavicular region and chest wall on November 26, 2013. During radiotherapy, she was treated with exemestane endocrine therapy. On February 10, 2017, she experienced pain in the left rib; PET-CT scanning showed abnormal 18 F-fluorodeoxyglucose uptake in the left humerus and 10th posterior rib metastases. Her disease-free survival time was 39 months. She exchanged exemestane for toremifene therapy on February 13, 2017. After two months of treatment with toremifene, her bone metastases progressed.

She then underwent salvage treatment with 8 cycles of intravenous docetaxel (67 mg/m² on day 1 of a 3-week cycle), beginning on April 21, 2017. On December 9, 2017, after the second day of the eighth cycle of docetaxel, she experienced buzzing and whistling in both ears, as well as reduced hearing perception. She then underwent an otolaryngologic examination due to worsening of these symptoms. She was diagnosed with sensorineural hearing loss, inner ear microcirculation obstruction, and peripheral neuritis. Cerebral magnetic resonance imaging and otomicroscopic examination showed no abnormal findings. Pure tone audiometry⁶ showed bilateral sensorineural hearing loss. Symptoms of deafness showed partial improvement after the otolaryngologist prescribed neurotrophic drug treatment. Subsequently, the patient completed several additional pure tone audiometry tests (Figure 2), which showed no significant improvement in her symptoms of deafness. Meanwhile, careful collection of medical history revealed

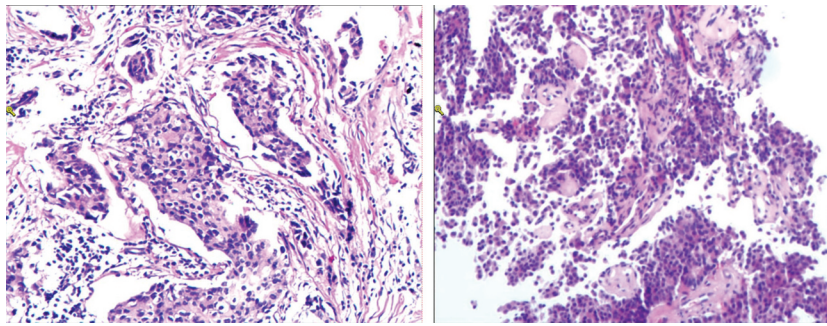


Figure 1. (a) Postoperative pathology revealed invasive ductal carcinoma (HE, 100× magnification). (b) Immunohistochemical staining of the resected specimen showed ER (1+), PR (-), HER-2 (2+), fish (-), Ki-67(20%~30%). Postoperative pathology revealed invasive ductal carcinoma (HE, 100× magnification). Immunohistochemistry showed ER (-), PR (-), HER-2 (-), Ki-67(50%).

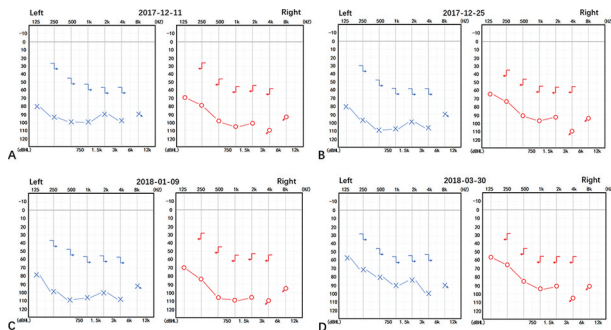


Figure 2. Pure tone audiometry showed bilateral sensorineural hearing loss. Figure A, B, C and D showed the pure tone audiometry performed by the patient on December 11, 2017, December 25, 2017, January 9, 2018 and March 30, 2018 respectively. Blue for left ear and red for right ear. The range of pure-tone in normal people is between 0 dB and 25 dB. The patient's bilateral ears had pure-tone averages of greater than 70 dB for air conduction (125 to 8000 Hz), which was classified as severe hearing loss according to the WHO classification criteria.

that the patient's hearing was normal before docetaxel treatment.

2.2. Case 2

A 74-year-old female patient was admitted with a tumor of the left breast in July 2013 and immediately underwent a modified radical mastectomy. Postoperative pathology revealed invasive ductal carcinoma. Immunohistochemistry analysis was negative for PR, ER, and HER-2/Neu (Figure 1b). The patient received 4 cycles of postoperative adjuvant chemotherapy, comprising pirarubicin combined with cyclophosphamide between September 30, 2013 and December 2, 2013. Then on December 30, 2013, she received 1 cycle of intravenous docetaxel (75 mg/m² on day 1 of a 3-week cycle) chemotherapy. Two days later, she experienced significant hearing loss in both ears. Notably, the patient had no hearing loss symptoms prior to docetaxel. In addition, during docetaxel treatment, the patient had not received other ototoxic drugs such as a platinum agent or suffered ear injuries. Therefore, we have reason to consider that the hearing loss was caused by the infusion of docetaxel. Otolaryngology consultation revealed bilateral sensorineural hearing loss with perforation of the left eardrum. Subsequently, the patient discontinued treatment

with docetaxel, and hearing loss symptoms improved slightly. However, she did not receive standard deafness treatment, and the symptom of binaural hearing loss increased in severity.

3. Discussion

As one of the most widely used taxane antineoplastic drugs, docetaxel has impressive curative efficacy in a variety of solid tumors, including breast cancer, non-small-cell lung cancer, and ovarian and cervical cancers, as well as many head and neck neoplasms.⁷ Docetaxel has an antineoplastic function in that it interferes with the microtubule network necessary for the cellular functions of mitosis and intercellular division. However, its antineoplastic curative efficacy is often accompanied by a variety of acute and long-term side effects; some are common, such as myelosuppression, allergic reactions, gastrointestinal reaction, fatigue, alopecia, and peripheral nerve damage.⁸⁻¹⁰

Few studies regarding ototoxicity associated with docetaxel have been published in the literature and textbook references. Atas et al.¹¹ reported that paclitaxel caused mild to moderate sensorineural hearing loss in mice. Importantly, paclitaxel and docetaxel share similar structures, and exert similar preclinical and clinical effects. Docetaxel has both a higher intracellular concentration and longer intracellular retention time than paclitaxel; therefore, it exhibits increased antineoplastic activity, relative to that of paclitaxel. Atas et al. showed that paclitaxel-induced ototoxicity in mice might cause histopathologic changes in the cochlea, which appear as vacuolization in the epithelial cells of the spiral limbus and stria vascularis, as well as vacuolization of fibroblasts and reduction in the number of fibroblasts in the spiral limbus. Notably, the mice showed no sensory cell loss. Hearing loss began with doses of ≤20 mg/kg and was not dose-dependent thereafter. That study was performed in mice; therefore, it requires confirmation with a longitudinal clinical trial approach.

Another prospective analytical study¹² was performed on 103 known cases of breast and ovarian cancer, during a period from 2004 to 2006 (20 months). All patients were treated with taxanes (paclitaxel or docetaxel). Patients underwent three pure tone audiometry tests for the evaluation of hearing (before treatment, during the treatment period, and after treatment). Notably, only two patients (1.9%) showed sensorineural

hearing loss. Nausea and vomiting were the most common side effects of the drugs in that study.

It is reported in the literature that patients who used docetaxel chemotherapy develop hearing loss, all of which are combined with cisplatin-based chemotherapy regimens.^{13,14} Potential mechanisms underlying cisplatin-induced ototoxicity include apoptosis and autophagy. These are primarily attributed to increased levels of reactive oxygen species, which cause a deficiency of intracochlear antioxidants, calcium inflow into hair cells, and induction of cell death.^{15,16} A potential ototoxic mechanism associated with docetaxel administration has not yet been reported. However, because of its similarity to paclitaxel, some studies of paclitaxel-induced ototoxicity may provide insight. Dong et al.¹⁷ demonstrated that paclitaxel can cause hearing loss at concentrations that are achieved in vivo. Paclitaxel exhibits greater toxicity to auditory nerve fibers and spiral ganglion neurons (SGNs), compared with hair cells. Damage to SGNs and auditory nerve fibers is concentration-dependent. Paclitaxel-induced SGN cell death is mediated by caspase activity, while hair cell death in organs of Corti is independent of caspase activity. Paclitaxel is a microtubule-stabilizing agent, which can inhibit depolymerization and maintain tubulin stability by promoting polymerization of tubulin. This shifts equilibrium toward excessive microtubule assembly, which inhibits dynamic reorganization of the microtubule network.¹⁸ Notably, microtubules are important in axonal transport; paclitaxel may severely disrupt axon transport, resulting in degeneration of nerve fibers, which leads to sensorineural hearing loss. Hirose et al.¹⁹ noted that paclitaxel did not promote hair cell degeneration, as it induces tubulin polymerization; thus, it may cause a “hidden hearing loss” by primarily damaging auditory nerve fibers, rather than affecting outer hair cell viability. In addition, the potential ototoxic mechanism of paclitaxel may be additive with that of other antineoplastic agents known to induce hearing loss.

In both cases, other possible causes of hearing loss were excluded, including trauma and the intake of other ototoxic drugs. The hearing loss was binaural and sensorineural in these two patients. In case 1, the patient reported a sensation of buzzing and whistling after the eighth cycle of docetaxel. Because damage to the sensorineural structure of the inner ear is irreversible, symptoms of hearing loss did not recede, although chemotherapy discontinued. In case 2, the patient experienced hearing loss and tinnitus after 1 cycle of docetaxel. As noted above, damage to SGNs and auditory nerve fibers by docetaxel is likely to be concentration-dependent. The second patient was older than the first patient, and received a higher dose of docetaxel. These factors may have contributed to her earlier presentation of hearing loss.

In conclusion, clinicians should note that ototoxicity is a possible adverse effect during docetaxel treatment.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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