Bilateral blindness with secondary retinitis pigmentosa following postoperative docetaxel and platinum combination chemotherapy in primary small-cell carcinoma of the endometrium: An unusual case report and review of the literature

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Abstract. Ocular toxicity is an uncommon complication of cytotoxic chemotherapy. Bilateral blindness with secondary retinitis pigmentosa (RP) following docetaxel and platinum combination chemotherapy at the recommended dose is extremely rare. The present study reports a case of advanced small-cell carcinoma (SCC) of the endometrium in a patient with diabetes mellitus type 2. The patient suffered from RP with a sharp decline in vision after the fourth course of postoperative docetaxel and platinum combination chemotherapy. Unfortunately, the patient developed bilateral blindness after another course of chemotherapy at a reduced dose. No tumor recurrence was observed during the 33 months of follow-up. A total of 35 cases of docetaxel- and/or platinum-induced retinal toxicity were found in the English literature and reviewed. The ischemic and electrophysiological hypotheses may have been implicated in the pathogenesis of ocular toxicity in the present case, particularly with the history of diabetes. Understanding the ocular side effects of this combination chemotherapy may assist gynecological oncologists and ophthalmologists with early recognition and timely intervention before blindness is established.

Introduction

Ocular toxicity induced by cancer chemotherapy includes a broad spectrum of disorders, such as cortical blindness, blurred vision and maculopathy, reflecting the unique anatomical, physiological and biochemical characteristics of the eye. The ocular side effects may be grouped into adnexal, anterior segment, posterior segment and neuro-ophthalmic. Posterior segment lesions are important due to the marked visual loss that may occur (1). Visual loss secondary to secondary retinitis pigmentosa (RP) is an uncommon complication of cytotoxic chemotherapy. Docetaxel and platinum have been frequently used in combination to treat various solid tumors, and are relatively rarely associated with severe side effects (2). Although secondary RP with bilateral blindness following docetaxel and platinum combination chemotherapy is extremely rare, this complication warrants attention due to its devastating impact on the quality of life of patients who receive various anticancer therapies. We herein report a case of a patient with small-cell carcinoma (SCC) of the endometrium who suffered from bilateral blindness during postoperative chemotherapy at the recommended dose, and review docetaxel- and/or platinum-induced retinal toxicity in terms of clinical manifestations, diagnostic and preventive strategies, with the aim of improving patient safety during anticancer therapy.

Case report

On 13th October 2013, a 48-year-old Chinese woman was admitted to the Department of Obstetrics and Gynecology of the First Affiliated Hospital of Jinan University (Guangzhou, China) complaining of irregular vaginal bleeding for 1 month. Magnetic resonance imaging (MRI) revealed a 5.0-cm mass in the endometrial cavity and cervical stromal invasion. Dilation and curettage and histological examination revealed SCC of the endometrium involving the cervix. Immunohistochemical examination showed positive staining for synaptophysin, chromogranin A and neuron-specific enolase in the tumor cells.
The patient also had a 1-year history of diabetes mellitus type 2, treated with 50 mg acarbose per day. The blood pressure and blood sugar levels were normal, there were no visual abnormalities, and other systemic investigations were also negative. After systemic metastasis of SCC was excluded, the patient underwent open extensive hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. Pathological evaluation revealed that ~90% of the tumor in the corpus uteri was SCC with myometrial invasion and cervical involvement, and 10% was endometrioid adenocarcinoma (Fig. 1). Metastatic SCC was also observed in the left external iliac and obturator lymph nodes. The patient was diagnosed with SCC of the endometrium, International Federation of Gynecology and Obstetrics stage IIIC1 (3). Docetaxel and platinum combination adjuvant chemotherapy was administered after the operation. After the first four courses of chemotherapy with docetaxel 120 mg (70 mg/m²) and cisplatin 90 mg (50 mg/m²) at 3-week intervals, the patient complained of visual impairment, particularly farsightedness. The visual acuities were 0.3 on the right and 0.5 on the left side, and MRI revealed no intracranial space-occupying lesion. Following exclusion of ophthalmological contraindications, the fifth
| Author(s)          | Age, years | No. of cases | Toxicity                                      | Drug                                    | Diagnosis                      | Ophthalmic evaluation | Occurrence after chemotherapy | Follow-up | (Refs.) |
|--------------------|------------|--------------|-----------------------------------------------|-----------------------------------------|---------------------------------|-----------------------|-----------------------------|------------|---------|
| Berman and Mann    | 30         | 1            | Cortical blindness                            | Cisplatin, vinblastine and bleomycin    | Embryonic cell carcinoma of the testicle | The patient could not perceive light; an optokinetic examination was positive for blindness | 1 cycle         | Reversible | (4)     |
| Wilding et al      | ND         | 11           | Blurred vision (n=8)/ altered color perception (n=3) | Cisplatin (high-dose cisplatin (200 mg/m² in five divided daily doses) | Ovarian carcinoma               | Retinal toxicity in the form of cone dysfunction was documented by ERG and color vision testing | 2-4 cycles     | Reversible | (5)     |
| Kupersmith et al   | ND         | 3            | Maculopathy (severe macular retinal pigment abnormality) | Cisplatin (intra-arterially administered), carmustine | Malignant gliomas               | Localized retinal pigment disturbance in the macula | ND             | ND        | (6)     |
| Khawly et al       | ND         | 8            | Cotton-wool spots, intraretinal hemorrhages and macular exudate | Cisplatin, cyclophosphamide, carmustine and autologous bone marrow transplantation | Breast cancer                     | ND                     | 1-5 months                  | Reversible | (7)     |
| Hilliard et al     | ND (pediatric patients) | 2 | Symptomatic retinopathy with abnormal ERG and VER (both patients had abnormal renal function) | Cisplatin, etoposide                  | Retinal toxicity documented by VER and ERG | ND                     | ND             | Irreversible | (8)     |
| Tan and Walsh      | 65/45      | 2            | Blurred vision with flashing lights; photopsia | Cisplatin, paclitaxel                 | Lung cancer                     | ND                     | 2 cycles/1 cycle            | Reversible | (9)     |
| Wang et al         | 47         | 1            | Bilateral blindness                           | Cisplatin, carmustine                  | Breast cancer                   | Histopathological examination of the eye and optic nerves at autopsy revealed nerve fiber layer infarction secondary to right inferior temporal retinal artery thrombosis | 1 cycle         | Irreversible | (10)    |
| Gonzalez et al     | ND         | 1            | Acute blindness in the left eye               | Cisplatin                              | Lung cancer                     | ND                     | Immediately after treatment | Irreversible | (11)    |
Table I. Continued.

| Author(s)          | Age, years | No. of cases | Toxicity                                                | Drug                                      | Diagnosis                                | Ophthalmic evaluation                                                                 | Occurrence after chemotherapy | Follow-up   | (Refs.) |
|--------------------|------------|--------------|--------------------------------------------------------|-------------------------------------------|------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|-------------|---------|
| Watanabe et al     | 58         | 1            | Visual disturbance, vision loss in left eye            | Carboplatin (intracarotid injection)     | Glioblastoma                             | Diffuse chorioretal atrophy with optic atrophy                                         | 30 h                          | Irreversible | (12)    |
| Katz et al         | 55         | 1            | Bilateral visual loss                                  | Four times the intended dose of intravenous cisplatin | Non-Hodgkin lymphoma                     | Visual fields showed central scotomas bilaterally; an ERG showed markedly reduced a-wave amplitudes and absent b-waves | Immediately after treatment | Irreversible | (13)    |
| Kwan et al         | 31         | 1            | Vision loss in left eye                                | Cisplatin, bleomycin, etoposide          | Non-seminomatous germ cell testicular tumor | Fluorescein angiography revealed bilateral retinal ischemia and left retinal neovascularization | 10 weeks                      | Irreversible | (14)    |
| Li et al           | 56         | 1            | Bilateral blindness                                    | Cisplatin, paclitaxel                    | Nasopharyngeal cancer                    | Abnormal visual-evoked potentials and transient, flash ERGs                             | 10 days                       | Irreversible | (2)     |
| Kord Valeshabad et al | 78     | 1            | Blurred vision                                         | Gemcitabine, docetaxel                   | Sarcoma                                  | Uveal effusion and outer retinal disruption                                               | 2 cycles                      | Reversible  | (15)    |
| Tang et al         | 48         | 1            | Bilateral blindness                                    | Platinum, docetaxel                      | Small-cell carcinoma of the endometrium  | Retinal current map examination showed the binocular dark optic rod b-wave response and dark optic mixed reaction b-waves; secondary retinitis pigmentosa was diagnosed | 4 cycles                      | Irreversible | Present study |

OCT, optical coherence tomography; ND, no data; VER, visual evoked response; ERG, electroretinogram.
course of chemotherapy consisted of docetaxel 120 mg (70 mg/m²) and reduced lobaplatin 45 mg (25 mg/m²) was administered. After 2 weeks, the patient was admitted to the hospital for worsening vision with light perception. Fundus fluorescence angiography revealed early-stage diffuse depigmentation of the retinal pigment epithelium and a window defect (hyperfluorescence) involving the macular area in both eyes. Electroretinography revealed loss of function of rod and cone cells bilaterally. Optical coherence tomography showed thinning of the macular retina (Fig. 2). Retinal current map examination showed that the binocular dark optic rod b-wave response and dark optic mixed reaction b-waves were not recorded, and absence of photopic a- and b-wave cone response. Fundus angiography showed secondary RP. Treatments aimed at improving fundus microcirculation were performed, including administration of enteric-coated aspirin and tanshinone. Unfortunately, the visual acuity of the patient did not improve following cessation of chemotherapy. There was no tumor recurrence during the 33-month follow-up, but the patient developed bilateral blindness.

The patient provided written informed consent to the publication of this case report and associated images.

Discussion

Although postoperative adjuvant chemotherapy with docetaxel and platinum is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer with lower toxicity and good tolerability (3), some of these toxicities are irreversible and may adversely affect the patient's quality of life, or even cause a permanent disability (2). To the best of our knowledge, RP with bilateral blindness following docetaxel and platinum combination chemotherapy has not yet been reported in the English literature.

Of note, paraneoplastic retinopathy-related bilateral blindness from SCC of the endometrium should be excluded. The initial symptoms of paraneoplastic retinopathy-related bilateral blindness were decreased visual acuity and narrowing of the visual field, or blindness on exposure to bright light and total achromatopsia. In the present case, the patient first presented with visual disturbances >2 months after the diagnosis of SCC of the endometrium. Visual disturbances associated with malignant neoplasms are more often caused by metastasis to the brain, meninges, optic nerve, orbit, choroid, or retina. MRI revealed no intracranial space-occupying lesion and metastatic brain tumor from SCC of the endometrium was also excluded.

A total of 35 cases involving docetaxel- and/or platinum-related retinal toxicity have been reported and are summarized in Table I. The mean age of the patients was 51.3 years. Vision loss developed immediately after treatment with paclitaxel, one possible theory is that Müller cell toxicity results from intracellular fluid accumulation and subclinical extracellular fluid leakage. Reversible uveal effusion and outer retinal disruption were reported following gemcitabine and docetaxel chemotherapy (15).

Bakbak et al (18) reported that systemic administration of cisplatin and paclitaxel affected the peripapillary retinal nerve fibre layer thickness and visual field index, as revealed by frequency-doubling technology (FDT) perimetry. Optical coherence tomography and FDT perimetry may be adjunctive tools for the screening of ocular toxicity in patients treated with these agents.

It has been reported that children and those patients with renal dysfunction or diabetes mellitus appear to be the highest risk groups for cisplatin-related neurotoxicity (19,20). Patients with diabetic complications may opt to avoid paclitaxel plus platinum combination therapies if there are alternative effective treatment options available (20). Unfortunately, our patient suffered from diabetes and developed an apparent accelerated decline in visual function during conventional adjuvant chemotherapy; an alternative regimen of adjuvant radiotherapy was not applied.

Due to its rarity, retinal toxicity may be under-recognized or considered as a minor complication when compared with other life-threatening complications. Understanding the ocular side effects of chemotherapy may assist ophthalmologists and oncologists with early identification and timely intervention, before blindness becomes established.

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