Case Reports in Oncology

Case Rep Oncol 2014;7:29–32

DOI: 10.1159/000357912
Published online: January 10, 2014

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1662–6575/14/0071–0029$39.50/0
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Unilateral Optic Disc Papilloedema following Administration of Carboplatin Chemotherapy for Ovarian Carcinoma

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Key Words
Unilateral optic disc oedema · Carboplatin · Ovarian carcinoma

Abstract
A 48-year-old woman with a positive BRCA1 gene mutation was diagnosed with stage 3b high-grade ovarian endometrioid carcinoma. She was treated with adjuvant carboplatin at a dose of 740 mg (AUC 6) in 3-weekly cycles. Five days after her fifth cycle of carboplatin, she awoke with new-onset blurred vision in her left eye. An ophthalmology review showed left-sided disc oedema with normal optic nerve function tests and 6/24 visual acuity. A CT scan of the head and orbits was performed which showed no evidence of metastasis or raised intracranial pressure. An autoimmune screen was performed which did not reveal any explanation for her visual symptoms. Fundus fluorescein angiography showed bilateral intense late disc leakage with no evidence of vasculitis. Her chemotherapy was stopped in view of a radiological and biochemical remission and her visual symptoms were monitored. She was also started on a tapering dose of prednisolone 40 mg daily. Five months after the initial review, she has developed left optic disc atrophy with 6/18 visual acuity, while the right eye remains asymptomatic. The diagnosis was felt to be that of carboplatin-induced unilateral disc oedema, a very rare side effect of this chemotherapy.

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Case Report

A 48-year-old woman with a positive BRCA1 gene mutation was referred with a pelvic mass. Ca-125 was >4,000 and a CT scan confirmed the presence of large bilateral ovarian

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tumours. She underwent debulking surgery, and histology revealed completely resected stage 3b high-grade endometrioid ovarian carcinoma. She was therefore referred to Oncology for consideration of adjuvant chemotherapy. She was well, with a performance status of 0 and no medical history of note. EDTA glomerular filtration rate was measured to be 98 ml/min.

She was prescribed the regime of weekly paclitaxel 80 mg/m^2 (total dose 150 mg) with concurrent 3-weekly carboplatin AUC 6 (total dose 740 mg) [1]. During the first cycle of paclitaxel, she suffered an immediate allergic reaction; therefore, subsequently her regime was switched to single-agent carboplatin at the previously calculated dose. She received 2 cycles without incident, but her third cycle was delayed by 1 week owing to thrombocytopaenia (platelet count 77 × 10^9/l), and her fourth was delayed by a further week due to neutropaenia (neutrophil count 0.9 × 10^9/l). At review prior to her fourth cycle, she mentioned an incidental finding of a blot haemorrhage at a routine optometrist visit, which was asymptomatic. Diabetic screening was performed at this stage in view of a strong family history, but was negative.

Five days after her fifth cycle of carboplatin, she awoke with new-onset blurred vision in her left eye. An ophthalmology review showed left-sided disc oedema (fig. 1) with normal optic nerve function tests and 6/24 visual acuity. No abnormality was seen in the right eye with 6/6 visual acuity. A CT scan of the head and orbits was performed which showed no evidence of metastases or raised intracranial pressure. An autoimmune screen was performed which did not reveal any explanation for her visual symptoms. Fundus fluorescein angiography showed bilateral intense late disc leakage with no evidence of vasculitis (fig. 2). In view of her low platelet count and no clinically evident disc oedema in the right eye, a lumbar puncture was not performed.

The diagnosis was felt to be that of carboplatin-induced unilateral disc oedema. At this point, her chemotherapy was stopped in view of a radiological and biochemical remission and her visual symptoms were monitored. She was also started on prednisolone 40 mg daily. Her symptoms did not improve with steroids, however, and the dose was gradually tapered down. Five months after the initial review, she has developed left optic disc atrophy with 6/18 visual acuity, while the right eye remains asymptomatic.

Discussion

Carboplatin is a commonly used chemotherapeutic agent for ovarian, lung and other cancers. Its cytotoxicity results from alkylation of nucleic acids, which causes cross linking and double-strand breaks in DNA. The resulting fragmentation of DNA and failure of DNA replication and RNA transcription lead to cell death. The most frequently reported side effect of carboplatin is bone marrow suppression, causing anaemia, thrombocytopaenia and neutropaenia. The British National Formulary reports that it is generally far better tolerated than the related platinum-based chemotherapeutic agent cisplatin, with a much lower incidence of nonhaematological toxicity [2]. Platinum-derived chemotherapeutic agents are known to have neurotoxic side effects, but these most commonly take the form of peripheral neuropathy and ototoxicity. Ophthalmic toxicity is rare but has been described, particularly in relation to cisplatin.

In 2006, a major review of the ocular side effects of systemic chemotherapy reported a range of visual problems related to both high-dose and cumulative-dose intravenous cisplatin therapy [3]. These ranged from blurred vision and papilloedema, reported as single cases and found to be reversible, to transient cortical blindness and macular pigmentary

changes. Intracarotid cisplatin administration was also implicated in cases of severe ocular toxicity, particularly ipsilateral retrobulbar neuritis [4].

Carboplatin has rarely been implicated as a causative agent in visual disturbance and optic nerve toxicity. In 1992, 2 cases of sudden bilateral visual loss were described in women being treated with carboplatin for ovarian carcinoma [5]. They were both receiving high-dose intravenous carboplatin (AUC 12, total doses 720 and 900 mg, respectively), and had impaired renal function (glomerular filtration rate 45 and 50 ml/min, respectively). The postulated mechanism was neurotoxicity from the agent crossing the blood-brain barrier in the context of poor renal excretion and high dose. A further report, in 1993, suggested an association between intravenous carboplatin and both maculopathy and optic neuropathy [6]. Both patients described in that report received standard-dose carboplatin intravenously. One patient was found to have bilateral maculopathy after 5 cycles of treatment, whilst the other suffered permanent visual disturbance which did not respond to steroids, leaving her with bilateral optic neuropathy and a coexistent right-sided maculopathy. This latter patient was found to have papilloedema on fundoscopy. The report recommended the discontinuation of treatment in patients complaining of visual disturbance.

In 2009, Fischer et al. [7] described a case of bilateral papilloedema in the context of treatment for stage 3c ovarian carcinoma with carboplatin (AUC 5, total dose not given). There was a loss of visual acuity in both eyes with visual field defects more prominent on the left side, along with a left-sided relative afferent pupillary defect. Intracranial pressure was normal and autoantibodies negative, leading the authors to suspect a diagnosis of carboplatin-induced papilloedema. In that case, high-dose steroids were given empirically and tapered over 10 weeks. The patient's vision gradually improved over the course of 2 years, although there were residual signs of bilateral optic nerve atrophy, which was worse on the left side.

No cases of unilateral papilloedema associated with intravenous carboplatin treatment were found in the literature. The review of ocular complications of chemotherapy in 2006 concluded that cases of optic neuropathy, cortical blindness, sore eyes, blurred vision, choroidoretinitis and optic neuritis associated with carboplatin administration were rare, and reversible [3].

Conclusion

We present a patient with normal renal function who was treated with standard-dose carboplatin, which produced irreversible unilateral papilloedema with resultant persistent visual disturbance. Fundus fluorescein angiography indicated right eye disc oedema and leakage, although these remained clinically nonevident.

This case, along with those described in 1992 [5] and 2009 [3], suggests that ocular toxicity, including papilloedema, may be a rare side effect of carboplatin treatment that can result in permanent visual damage. Any visual signs or symptoms therefore need to be taken seriously, and chemotherapy should be stopped until there has been a full ophthalmological review. Close liaison between ophthalmologists and oncologists is essential to achieve this.

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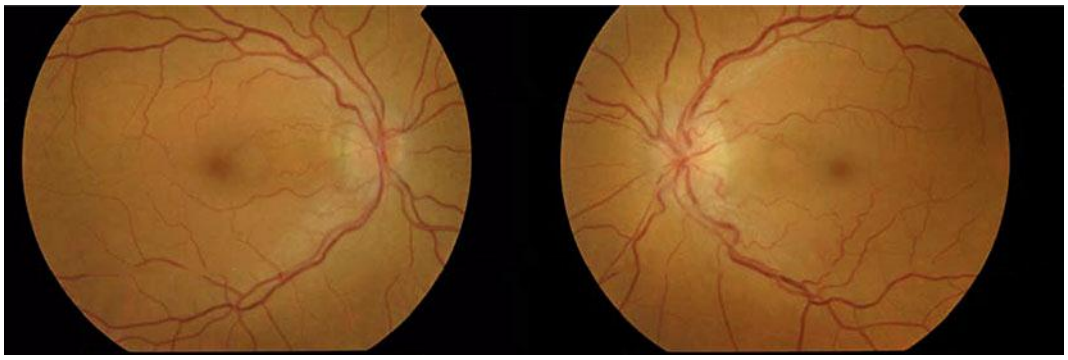

Fig. 1. Fundus photography shows left optic disc swelling.

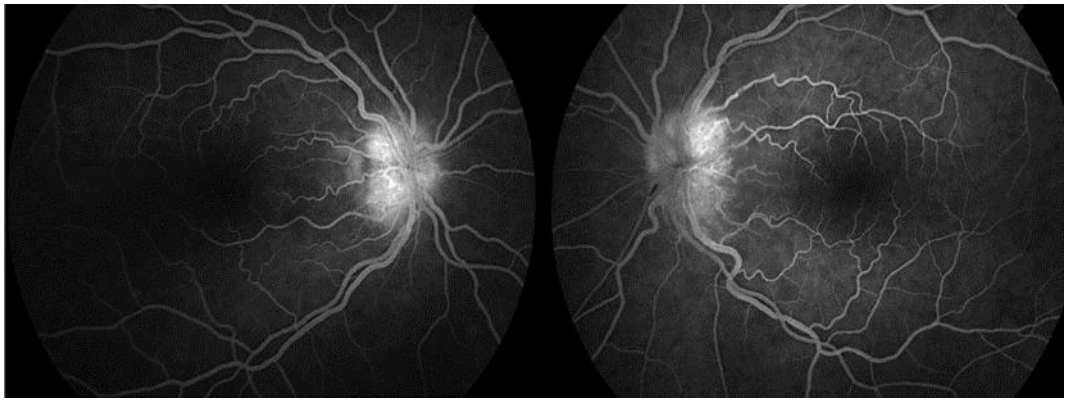

Fig. 2. Fundus fluorescein angiography demonstrates bilateral late optic disc hyperfluorescence.