Acute Reversible Life-Threatening Encephalopathy Following Conventional Doses Of Paclitaxel Infusion
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Citation

Abstract
Paclitaxel is widely used anti-neoplastic agent. Although peripheral neurotoxicity is a well-known side effect, CNS toxicity related to standard dose paclitaxel is extremely uncommon; probably because paclitaxel does not cross the blood brain barrier. We present a patient with advanced stage ovarian carcinoma who developed acute and spontaneous resolving encephalopathy after standard dose of paclitaxel. The patient did not have brain metastasis, or prior whole brain irradiation, or any type of neurosurgery. Radiological imaging studies showed no abnormalities. Other causes of encephalopathy were rule out. Paclitaxel at standard doses may cause CNS toxicity even in the absence of brain metastasis or disrupted blood brain barrier.

INTRODUCTION
Paclitaxel is an antimicrotubule interfering agent with activity against a variety of solid tumors including head and neck, lung, breast, and ovarian cancers (1). It is derived from the bark and needles of the pacific Yew (Taxus brevifolia). The main adverse effects of paclitaxel include myelosuppression and peripheral neurotoxicity (1). Probably because of the inability to cross blood brain barrier, central neurologic side effects are very rare.

We report the case of a patient with advanced stage ovarian carcinoma, who developed self-limiting acute onset encephalopathy after an infusion of a conventional dose of paclitaxel and carboplatin.

CASE REPORT
A 62 year-old woman who had no history of chronic illness or medication underwent surgery because of a pelvic mass. She was diagnosed with stage IIIa ovarian cancer. After the initial debulking surgery, adjuvant chemotherapy with six cycles of paclitaxel and carboplatin were planned.

The first cycle of paclitaxel (175 mg/m², over 3 hour) and carboplatin (AUC=5, over 1 hour) was administrated after the standard premedications (20 mg dexamethasone p.o. 12 hour and 1 hour before paclitaxel, 300 mg ranitidine i.v. 1 hour before paclitaxel and 8 mg ondansetron i.v. 30 minute before paclitaxel). She tolerated the chemotherapy infusion well, but approximately 6 hour after the administration, she became progressively confused. Neurological examination revealed no focal signs. Her blood pressure was within normal limits. Routine laboratory values including electrolytes, liver, and kidney functions were normal. A computer tomography (CT scan) and magnetic resonance imaging (MRI) of the brain showed no abnormalities. The symptom persisted for 4-5 hour and then resolved spontaneously. Examination of the cerebrospinal fluid (CSF) and an electroencephalogram were not done because of the rapid resolution of symptoms. The patient and her family refused further chemotherapy. She progressed 11 months after surgery.

DISCUSSION
Although peripheral neurotoxicity is a well recognized side effect, CNS toxicity is a rare observation in association with paclitaxel administration (1). In the medical literature, there are few publications reporting both acute and delayed (1-3 weeks) encephalopathy related to either high dose or standard dose of paclitaxel treatment (2,3,4,5,6). Most of the reported cases also had brain metastases or a history of prior whole brain irradiation and neurosurgery. To our knowledge, it is the second case of acute encephalopathy related to standard dose paclitaxel occurring in a patient who had an intact blood brain barrier.

Mc Guire et al (2) and Brown et al (3) reported two patients who experienced grand mal seizures after a standard dose of paclitaxel. However, one patient had brain metastases and sub-total therapeutic blood level of phenytoin. Perry et al (4)
reported two women with breast cancer, treated with standard dose of paclitaxel, who developed confusion, word finding difficulty, and behavioral changes. This clinical condition was transient, had a late onset starting one week after the administration of paclitaxel, and resolved spontaneously. Brain metastases or any other cause for encephalopathy were ruled out. Subsequent infusions were associated with similar self-resolving encephalopathy in one patient and recurrent headache and ataxia in the other.

Nieto et al. reported delayed encephalopathies related to high dose paclitaxel with stem cell support. In their study, a total of 114 patients received paclitaxel at doses of ≥600 mg/m² and 6 patients experienced delayed encephalopathy (3 patients died of irreversible coma, 3 patients recovered after 8-15 days either spontaneously or after high dose steroid). Two of these patients had a history of prior whole brain irradiation. Ziske et al. reported 3 patients who presented acute encephalopathy occurring after conventional doses of paclitaxel. One of these cases is similar to ours; including the dose of paclitaxel and the absence of whole brain irradiation or neurosurgery, the onset and duration of symptoms, and the spontaneous recovery. The two other patients had whole brain irradiation and one of them had neurosurgery because of a brain metastasis.

Paclitaxel does not cross the blood brain barrier and is not detectable in the CSF in humans after i.v. administration. In some of the reported cases the blood brain barrier of the patients had been disrupted by metastases, whole brain irradiation, or neurosurgery. In our case, paclitaxel should not have been detectable in the CSF.

The concurrent medications, carboplatin, the antiemetics, and the steroid, may also cause encephalopathy. In addition, Cremophor EL, in which paclitaxel is dissolved, is in itself known to be a neurotoxic agent and could also be a cause of encephalopathy in patients treated with paclitaxel. Cremophor EL and the other concurrent medications could have contributed to the CNS toxicity. However, parenchymal brain metastases, leptomeningeal carcinomatosis, electrolyte imbalances, and other metabolic disturbance were ruled out in our case. It is therefore possible that paclitaxel could cause a clinical condition characterized by CNS symptoms including encephalopathy or seizures, and this must be kept in mind when using this drug in cancer therapy.

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