Acute transient encephalopathy after paclitaxel infusion: report of three cases

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Paclitaxel (Taxol®) is a diterpene plant product and antineoplastic agent that promotes the assembly of microtubules as well as stabilizing their formation by preventing depolymerization. Myelosuppression was found to be dose-limiting, but peripheral neurotoxicity is also a well known side-effect. Central nervous system toxicity is rare, probably because paclitaxel does not cross the blood–brain barrier. We observed three patients who presented with acute encephalopathy within 6 h after infusion of paclitaxel at normal doses. All patients had received prior whole brain irradiation (WBI) and one patient had prior brain metastasectomy. Computer tomography and magnetic resonance imaging showed no evidence of cerebral metastases. An effect from other organ toxicities was excluded in all patients. All recovered spontaneously within 4–6 h. From this we can conclude that paclitaxel can cause severe acute transient encephalopathy, which may occur more frequently after prior WBI and/or surgery due to alteration of small vessel function.

Key words: chemotherapy, encephalopathy, paclitaxel, transient

Introduction

Paclitaxel (Taxol®) is an antineoplastic agent derived from the needles and bark of the Pacific Yew (Taxus brevifolia). Unlike other antimicrotubule agents, such as colchicines or vincristine, which induce the disassembly of microtubules, paclitaxel has been shown to promote the assembly of microtubules as well as to stabilize their formation by preventing depolymerization in vitro [1, 2]. The main adverse effects of paclitaxel include myelosuppression and peripheral neurotoxicity. Optic neuropathy occurs rarely [3–7]. Central nervous system (CNS) toxicity, although also rare, has been described after high-dose paclitaxel treatment, probably reflecting negligible penetration of paclitaxel over an intact blood–brain barrier [4]. In our study, we report on three patients who developed self-limiting encephalopathy within 5 h after paclitaxel infusion. One patient had a recurrent episode after a second infusion.

Patients and methods

Standard medication accompanied paclitaxel treatment and supportive measures were the same in all patients: 20 mg dexamethasone p.o. 14 h and 1 h before paclitaxel, 300 mg ranitidine i.v. 1 h before paclitaxel, 2 mg clemastine i.v. 1 h before paclitaxel and ondansetrone 8 mg 30 min before the paclitaxel infusion.

Patient 1

A 53-year-old woman received paclitaxel for metastatic breast cancer. Her receptor-positive adenocarcinoma had been treated initially with radical mastectomy and recurred after 4 years with liver metastases. Six cycles of chemotherapy with epirubicine and cyclophosphamide resulted in a complete response. After 2 years of treatment with tamoxifen, however, cancer recurred with two brain and multiple liver metastases. Initially, she received whole brain irradiation (WBI) with 30 Gy over 10 fractions and a complete response could be obtained. Two weeks after completion of WBI, paclitaxel 220 mg (135 mg/m2) was administered as a 3-h infusion with standard premedication on an outpatient basis. This was tolerated well until 6 h later when she became progressively confused for 6 h and was admitted for investigation. Concurrent medications were haloperidol and diazepam for anxiety. Examination at admission revealed fluctuating attention, disorientation and difficulty recalling words. Her neurological state was otherwise normal. Mild pancytopenia was found. Other routine laboratory values including cerebrospinal fluid (CSF) were normal, and a computer tomography (CT) scan and magnetic resonance imaging (MRI) showed diffuse white matter atrophy. The symptoms persisted for 6 h and then resolved spontaneously. She remained afebrile with no evidence of an infectious disease. At last follow-up, 6 months after the episode, she had no evidence of recurrent brain disease, but had developed new lung and progressive liver metastases.
Patient 2
A 67-year-old woman had metastatic breast carcinoma with hepatic metastases at first presentation. She initially received six cycles of cyclophosphamide/epirubicin followed by tamoxifen and showed a partial response. Progressive liver disease recurred 6 months after she had completed therapy. Tumor progression was unresponsive to megestrolacetate. A cranial CT scan was performed because of persistent headaches and one focal lesion, highly suggestive of metastatic carcinoma was found. Because she did not want the brain lesion to be operated on, WBI was performed with 30 Gy over 10 fractions. The lesion had a complete response 3 weeks after completing WBI. Paclitaxel treatment was initiated with 230 mg (135 mg/m²) and was administered over a 3 h period after standard premedication. This was tolerated well until 6 h later when she became progressively confused for 5 h with a clinical picture resembling patient 1. High-dose steroids (250 mg prednisone i.v.) were given and the symptoms resolved within 2 h with no evidence of an accompanying disease that could explain the symptoms. Her CT scan showed no cerebral metastases. Concomitant psychotropic medication consisted of morphine hydrochloride (20 mg bd). A naloxone test was not performed. The patient died 6 months later from hepatic metastases. No further clinical symptoms were noted for recurrent CNS metastases. Permission for autopsy was not granted.

Patient 3
A 62-year-old man underwent surgery for two lesions in the brain and was diagnosed with adenocarcinoma of the lung, with brain and liver metastases. He received WBI, with 30 Gy in 10 fractions, and achieved a complete response. After completing WBI he received 600 mg carboplatin (300 mg/m²) and 300 mg paclitaxel (150 mg/m²); within 5 h a state of confusion similar to the ones described above was seen. CSF examination as well as brain imaging with CT scan and MRI were normal despite scars after resection of two brain metastases. Plasma alcohol level was determined in patient 3 due to a prior history of alcohol abuse, but alcohol could not be detected. The symptoms resolved spontaneously after 5 h. The patient received a second infusion with paclitaxel with the same dosage 3 weeks later and developed the same confusional condition. Again, this resolved spontaneously, within 4 h. Therapy with paclitaxel was stopped because of progressive systemic disease and the patient died 6 months later. Permission for autopsy was not granted.

Discussion
Peripheral neurotoxicity is a well recognized phenomenon, whereas CNS toxicity is a rare observation in association with paclitaxel administration. In contrast to our observation of acute onset, two publications reported delayed (1–3 weeks) encephalopathy after paclitaxel treatment.

In the first report [8], two women with breast cancer, treated with normal dose paclitaxel, developed a clinical state characterized by confusion, word-recollection difficulty and behavioral changes. These symptoms appeared 1 week after paclitaxel infusion and recovered spontaneously. Cerebral metastases or any other cause for the encephalopathy were ruled out. Also, delayed encephalopathy (1–3 weeks) related to high-dose paclitaxel with stem cell support is described [9]. A total of 114 patients received paclitaxel at a dose of ≥600 mg/m². Six patients presented acute encephalopathy starting between 7 and 23 days after paclitaxel treatment. Two of them had prior WBI. CNS toxicity consisted of rapid obtundation and coma (five patients) and a severe confusional picture with paranoid delusions (one patient). Three patients recovered after 8–15 days, either spontaneously (two patients) or after high-dose steroids (one patient). Three patients died of irreversible coma.

After standard-dose paclitaxel, McGuire et al. [6] and Brown et al. [10] reported two patients who experienced general mal seizures. However, one patient had brain metastases and a sub-therapeutic blood level of phenytoin [10]. The second patient had two generalized seizures 2 h after her first paclitaxel treatment. MRI and lumbar puncture (LP) in this patient were normal, and her electroencephalography (EEG) demonstrated unpecific changes. Because of epileptic status within 5 h of restarting the paclitaxel infusion, these seizures may have been caused by CNS toxicity. A 31-year-old patient with advanced ovarian carcinoma developed disseminated intravascular coagulation with subsequent multiterritory embolic infarction 3 days after paclitaxel [11], but the mechanism and the relationship to paclitaxel was unclear.

Paclitaxel is normally undetectable in the CSF in humans after i.v. administration [12, 13]. Animal studies have shown that paclitaxel concentrations are negligible in CSF and absent in normal brain [14]. However, our patients differ from these observations in that their blood–brain barrier had been disrupted by brain metastases as well as previous brain surgery and WBI. It has to be shown that these procedures cause damage to the small and medium sized brain vessels and the oligodendrogli [15]. Therefore, we speculate that disruption of the blood–brain barrier played a facilitating role in the occurrence of the observed encephalopathy.

The fact that platin derivates do not commonly cause acute encephalopathy, except in very rare conditions [16, 17], supports the role of paclitaxel as the putative reason for the encephalopathy. Paclitaxel is dissolved at 6 mg/ml in Cremophor EL (poloxymethylated castor oil; 527 mg/mg of paclitaxel) and 49.7% dehydrated alcohol. The post-infusion plasma alcohol is proportional to the dose of paclitaxel and the infusion rate, as shown by Webster et al. [18]. Cremophor EL itself is known to be a neurotoxic agent and could therefore be a cause of encephalopathy in patients treated with paclitaxel. Cremophor-treated animals showed changes in the electroencephalography and a decrease of cerebral blood flow [19, 20]. It induces procoagulatory effects that may predispose to thrombotic–embolic events [21, 22]. None of the patients had radiological evidence of CNS infarctions in CT scans or MRI of the brain, but we are not able to fully exclude Cremophor EL as a cause for the transient syndrome.

In our patients, other causes of encephalopathy (drug or analgesic toxicity, brain metastases, leptomeningeal carcinomatosis, metabolic disturbances and liver disease) were ruled out by neuroimaging and evaluation of CSF and blood serum. The strongest evidence for our hypothesis is provided by the fact that a repeated episode due to a rechallenge with paclitaxel (patient 3) led to a very similar clinical picture.
In conclusion, we suggest that paclitaxel, as formulated, is a likely primary cause of acute early-onset encephalopathy and is a distinguishable entity, for which patients with previous radiotherapy and/or brain surgery seem to be at risk.

References