Acute Encephalopathy: A New Toxicity Associated with High-Dose Paclitaxel[1]

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ABSTRACT

The purpose of this study was to describe acute encephalopathy as a new toxicity associated with paclitaxel, when it is delivered at high doses (≥600 mg/m^2) with stem cell support. A total of 129 patients, included in clinical trials of paclitaxel-containing high-dose chemotherapy, were analyzed. A total of 114 patients received paclitaxel at a dose of ≥600 mg/m^2. Six patients presented acute encephalopathy starting between 7 and 23 days after paclitaxel treatment; two of them had received prior whole-brain irradiation. Paclitaxel was given alone (one patient), with cyclophosphamide and cisplatin (two patients), and with cyclophosphamide and cisplatin plus 1,3-bis(2-chloroethyl)-1-nitrosourea (three patients). Central nervous system toxicity consisted of rapid obtundation and coma (five patients) and severe confusional picture with paranoid ideations (one patient). Brain magnetic resonance imaging showed diffuse white matter atrophy (one patient) or multiple small infarcts (one patient), or it was normal (four patients). Other complementary tests, including cerebrospinal fluid analysis and electroencephalography, were nondiagnostic. An effect from concomitant psychotropic medications or from other organ toxicities was excluded in all patients. Three patients recovered after 8–15 days, either spontaneously (two patients) or after high-dose steroids (one patient). Three patients died of irreversible coma. Necropsy, performed in two patients, showed generalized white matter atrophy and multiple brain parenchymal infarcts, respectively. No pharmacodynamic correlation between the occurrence of encephalopathy and a pharmacokinetic parameter of paclitaxel could be identified. Paclitaxel-containing high-dose chemotherapy can cause severe acute encephalopathy. An aggravating effect from prior brain irradiation or concurrent 1,3-bis(2-chloroethyl)-1-nitrosourea seems possible.

INTRODUCTION

Paclitaxel is highly active against a variety of solid tumors, including breast, ovarian, lung, and head and neck cancer (1). *In vitro* data show that paclitaxel causes a dose- and schedule-dependent tumor cell kill (2–4). Clinical data suggest that the drug may also have a favorable dose-response effect *in vivo* (5). The toxic profile of paclitaxel at standard doses includes neutropenia, peripheral neuropathy, and myalgia as its most relevant side effects.

Stem cell support circumvents the myelotoxicity of many drugs and allows severalfold dose escalation. The University of Colorado Bone Marrow Transplant Program first showed the feasibility of a substantial dose escalation of paclitaxel with ASCT,[3] well beyond its MTD without ASCT (6). In a Phase I trial, paclitaxel was delivered over 24 h, in combination with fixed doses of CPA and cDDP, followed by ASCT. Paclitaxel was escalated up to 825 mg/m^2, and its MTD was established at 775 mg/m^2. Other clinical trials with paclitaxel-containing HDC are presently underway at our program and elsewhere (7–10).

When drugs are given at doses that require ASCT, a different nonhematological toxic profile is seen (11). We have previously reported that high-dose paclitaxel may cause pulmonary injury (12), a side effect very rarely seen with lower doses of the drug (13).

Here, we describe acute encephalopathy as a new toxicity associated with the use of paclitaxel, when it is used at doses of ≥600 mg/m^2, in combination with CPA and cDDP, with or without BCNU.

MATERIALS AND METHODS

Patients reported here received paclitaxel-containing HDC at the University of Colorado in four different clinical trials. Paclitaxel premedication and supportive measures described for trial 1 were the same in all four studies.

Trial 1. In this Phase I clinical study, paclitaxel was escalated with fixed doses of CPA and cDDP (6). Paclitaxel was delivered over 24 h in doses ranging from 135 to 825 mg/m^2. It was followed by CPA at 1875 mg/m^2 as a daily 1-h infusion for 3 days (total dose, 5625 mg/m^2) and cDDP at 165 mg/m^2 in a 72-h continuous infusion. The doses of CPA and cDDP were the

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[3] The abbreviations used are: ASCT, autologous stem cell transplant; CPA, cyclophosphamide; cDDP, cisplatin; HDC, high-dose chemotherapy; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; WBI, whole-brain irradiation; PK, pharmacokinetic; HPLC, high-performance liquid chromatography; CNS, central nervous system; MRI, magnetic resonance imaging; VOD, veno-occlusive disease.

Table 1 Clinical findings[a]

Patient	PTX[b] dose	BCNU	Brain metastases	Prior WBI	Other toxicities	Clinical picture	Onset (day)	Brain MRI	Outcome	Brain autopsy
1	600	200	Yes	Yes	Liver G3	Coma	+2	Normal	Death	Diffuse WM atrophy
2	600	550	No	No	Mucositis G3; ileus G3	Coma	+10	Normal	Resolution	N/A
3	775	200	No	No	Lungs G4	Coma	+5	Normal	Resolution	N/A
4	775		No	No	Mucositis G3; liver G3	Coma	+16	Multiple small infarcts	Death	Multiple small infarcts
5	825		Yes	Yes	Mucositis G3; renal G3	Coma	+3	Diffuse WM atrophy	Death	Not authorized
6	825		No	No	Renal G3	Severe confusion	0	Normal	Resolution	N/A

[a] Doses are given in mg/m^2.
[b] PTX, paclitaxel; WM, white matter; N/A, not applicable.

same as in the STAMP-I combination of CPA, cDDP, and BCNU (14). Stem cells were infused following HDC. Stem cell collection, vigorous i.v. hydration, continuous bladder irrigation during HDC, and other supportive care measures have been described previously (6) and were the same as in the other trials described below. Premedication for paclitaxel consisted of 20 mg of dexamethasone p.o. 14 and 7 h before, 300 mg of cimetidine p.o. 1 h before, and 50 mg of diphenhydramine p.o. 1 h before the infusion. All patients received prochlorperazine, diphenhydramine, and lorazepam as antiemetic therapy. Ciprofloxacin and rifampicin were used for infection prophylaxis from the next day to the end of HDC. This study included patients with refractory advanced cancer who were ineligible for Phase II or III trials. Nine patients had brain metastases, and one had prior WBI. A total of 49 patients were entered onto this study from February 1993 to March 1995. Dose-limiting toxicities were acute lung injury and encephalopathy. Other significant side effects encountered were nephrotoxicity, hepatic VOD, and mucositis. The final MTD of paclitaxel was established at 775 mg/m^2.

Trial 2. The three-drug combination of 775 mg/m^2 paclitaxel, 5875 mg/m^2 CPA, and 165 mg/m^2 cDDP is presently subject of study in a Phase II clinical trial for metastatic breast cancer with chemosensitive disease. Patients with brain disease are not eligible. Twenty-seven patients have been included as of January 1998.

Trial 3. This is a Phase II study for patients with relapsed germ cell tumors, using the same paclitaxel-CPA-cDDP combination described above. Brain metastases are an exclusion criteria. This study has accrued four patients since its inception.

Trial 4. This Phase I trial is presently exploring the addition and dose escalation of BCNU, infused at 5 mg/m^2 per min, to paclitaxel-CPA-cDDP, delivered as described previously . BCNU is administered at doses ranging from 200 to 550 mg/m^2 on day −3. A total of 49 patients have been treated since August 1995. Exclusion and inclusion criteria are identical to the first Phase I trial mentioned above.

Statistical Methods. The PK parameters of paclitaxel and BCNU were compared in patients with and without encephalopathy using the Kruskal-Wallis test (SAS software, Version 6.12).

PK Analysis. The PK analysis of paclitaxel has been described previously (6). Samples were drawn as follows: immediately before the infusion; every 3 h during the infusion; and 0.5, 1, 2, 5, 9, and 13 h after the end of the infusion. The drug was extracted with ethyl acetate, using diphenylhydantoin as an internal standard, and analyzed using a HPLC system. The resulting time/concentration data were analyzed with PCNONLIN Version 4.0 nonlinear regression software. PK analysis of BCNU was performed as described previously (15). Briefly, blood samples for BCNU were obtained in 10-ml air-evacuated, heparinized tubes with 3 ml of HPLC-grade ethyl acetate spiked with 50 μg/ml diphenylhydantoin as an internal standard. At 30, 60, and 120 min after the start of the infusion and 15, 30, 45, 60, 90, 120, and 240 min after the completion of the infusion, 3 ml of blood were drawn and injected to the ethyl acetate-containing tube and vortexed at the bedside. After centrifuge, the supernatant was dried under a nitrogen stream. The residues were reconstituted with 300 μl of methanol, and the entire volume was transferred to autosampler vials for HPLC analysis.

PK samples for CPA and cDDP were processed as described previously (15). Adequate data sets for PK analysis of paclitaxel, CPA, cDDP, and BCNU were available in 85, 534, 591, and 467 patients, respectively. Data from the latter three drugs include primarily patients treated with CPA, cDDP, and BCNU.

RESULTS

As of January 1998, a total of 129 patients have been included in these four paclitaxel-containing HDC clinical trials. A total of 114 patients received paclitaxel at doses of ≥600 mg/m^2. Six patients developed CNS abnormalities, characterized, in five of them, by rapid obtundation, that progressed in a few hours to coma. The remaining patient developed severe confusion with paranoid ideation and hallucinations. No cases of spinal cord dysfunction were seen.

Clinical Course. Table 1 summarizes the clinical findings in the six patients. Toxicities are graded according to Southwestern Oncology Group criteria (16). CNS symptom onset was between transplant days 0 and +16, that is, between 7 and 23 days after the infusion of paclitaxel. The dose of paclitaxel ranged from 600 to 825 mg/m^2. One patient (patient 5), who presented pulmonary edema with respiratory insufficiency starting immediately after the end of the infusion of paclitaxel, did not receive the rest of her chemotherapy program

with CPA and cDDP. Her respiratory complication resolved within 24 h. Ten days after paclitaxel treatment, she developed progressive obtundation and coma. She never regained consciousness and died 8 days later. In addition to paclitaxel-CPA-CDDP, three patients also received BCNU, at 200 mg/m^2 (two patients) and 550 mg/m^2 (one patient).

Three patients completely recovered of their encephalopathy. No memory loss or any other intellectual deficit was evidenced after recovery by gross function assessment. No specific follow-up neuropsychiatric testing was performed. Two patients (patients 3 and 6) spontaneously improved after 5 and 8 days, and symptoms eventually resolved. One patient (patient 2) received high-dose 6-methyl-prednisolone at 1 g/day in a tapering schedule. She started to improve after 8 days and eventually recovered completely and was discharged on day +42. Three patients died of irreversible coma, in combination with grade 3 hepatic toxicity in two of them, and with grade 3 nephrotoxicity in the third patient. Postmortem exams were authorized in two patients. In the first patient, it showed multiple small infarcts in the cerebral parenchyma, without signs of cerebral vasculitis or an external source of emboli being noticeable. The autopsy of the second patient, who had received prior WBI for metastases, showed diffuse white matter atrophy, with no residual tumor lesions.

Complementary Test Findings. A brain MRI was performed in all six patients (Table 1). It was normal in four patients (patient 1, 2, 3, and 6) but showed diffuse white matter atrophy in one patient (patient 5), and multiple small infarcts in another patient (patient 4). Patient 4 had a carotid Doppler study and a transesophageal echocardiogram, which did not show evidence of an emboli source; rheumatoid factor and antinuclear antibodies were negative, and erythrocyte sedimentation rate was normal. Lumbar puncture, performed in four patients, did not show cerebrospinal fluid abnormalities other than mild increase in protein. Because the lumbar puncture was performed >1 week after HDC, no PK analysis was performed on the cerebrospinal fluid. Electroencephalography performed on two patients while they were in coma was abnormal and showed diffuse nonspecific slowing (θ) with no epileptiform or focal features.

Concomitant Psychotropic Medications. Patient 5 was receiving morphine at 1 mg/h in continuous infusion at the time of her coma. A narcotic intoxication was excluded with a naloxone test. Two more patients (2 and 4) had received morphine for mucositis-related pain but were off the drug by the time of onset of encephalopathy, for 2 and 8 days, respectively. One patient (patient 6) was receiving prochlorperazine as an antiemetic for the stem cell infusion. Prochlorperazine was discontinued, with no neurological improvement in the subsequent 11 days.

Toxicities in Other Organs. Patient 3 presented grade 4 acute lung injury that started 8 days after the coma. Two patients (patients 1 and 4) experienced grade 3 VOD of the liver, starting 5 and 8 days before the beginning of the encephalopathy and with bilirubin peaks of 5.7 and 10.9 mg%, respectively. Their diagnosis was based on clinical (patient 1) and both pathological and clinical criteria (patient 4). In both cases, the bilirubin was decreasing when the patients developed a coma. Patient 6 presented, 4 days after the start of the encephalopathy, grade 3 renal failure with a blood urea nitrogen peak of 96 mg/dl 3 days later. The nephrotoxicity resolved completely before the resolution of the encephalopathy.

Peripheral polyneuropathy is a prominent and common toxicity from high-dose paclitaxel (7). This side effect was not evaluable in the three patients who died of encephalopathy. Patients who recovered of encephalopathy also experienced grade 2 ($n = 2$) and grade 3 ($n = 1$) peripheral neurotoxicity.

Prior Brain Metastases and WBI. Two patients with known brain metastases had been treated previously with WBI. Patient 1 received 30 Gy over 10 fractions 2 months before admission for HDC for three 1-cm parietal nodules. Patient 5 had one 1-cm occipital lesion treated with 40 Gy in 15 fractions 5 months prior to HDC. On admission, both patients were asymptomatic from a neurological viewpoint, and their brain computed tomography scans showed complete remissions of their brain lesions. They both had a brain MRI done after the start of their encephalopathy. The MRI performed on patient 1 was unremarkable. In patient 5, the brain MRI was showed generalized white matter atrophy. Both patients died. The postmortem exam in patient 1 showed diffuse white matter atrophy with no residual tumor foci, as mentioned previously.

PK Analysis. Paclitaxel PK were available in five of the six patients who had encephalopathy and in 86 patients treated with paclitaxel at doses >600 mg/m^2 and who did not have this toxicity (Table 2). A statistical comparison between both groups was performed with the Kruskal-Wallis test. There were no significant differences between the two groups in area under the concentration-time curve ($P = 0.638$), serum peak levels (C_{max}; $P = 0.78$), half-life ($P = 0.08$), or clearance of paclitaxel ($P = 0.589$).

The small sample size of patients treated with a paclitaxel-CPA-cDDP-BCNU who developed encephalopathy ($n = 3$) does not allow any statistical comparison between their BCNU PK parameters and those of the patients who received a BCNU-containing combination and did not present encephalopathy ($n = 467$). The PK parameters of CPA and cDDP were not significantly different between patients with and without encephalopathy (data not shown).

DISCUSSION

We describe acute encephalopathy as a complication of paclitaxel-containing HDC. Six patients who received paclitaxel at doses of ≥600 mg/m^2 developed this toxicity. In all of the cases, an effect from other CNS-acting drugs, metabolic disturbances, sepsis, hepatic encephalopathy, or hypoxia, were assessed to be unlikely primary causes of the CNS toxicity, based on data outlined above.

Two patients were diagnosed with grade 3 hepatic VOD prior to the encephalopathy. Although liver VOD is a fairly frequent complication of high-dose therapy, VOD-related encephalopathy is uncommon other than in severe grade 4 cases, defined by a bilirubin peak of >20 mg% and/or severe ascites (17). In those two cases the bilirubin levels had peaked at 5.7 and 10.9 mg% and were decreasing at the onset of their encephalopathy.

In the group of patients who experienced acute encephalopathy, paclitaxel was given alone (1 patient), with CPA and

Table 2 PK analysis

	Paclitaxel				BCNU	
	AUC[a]	C_{max}	$t_{1/2}$	Cl	AUC	C_{max}
Patients with encephalopathy						
1	6729	4.6	212	148.2	755	8.2
2	4078	2.9	157	147.1	488	4.2
3	2521	1.7	35	247.8	567	8.3
4	4397	3.3	126	176.2		
5	N/A	N/A	N/A	N/A		
6	5564	3.9	144	148.2		
Mean/SD	5327/1947	3.3/1.1	135/64	173/43	604/137	6.9/2
Patients without encephalopathy (mean/SD)						
Paclitaxel[b] (n = 86)	5609/4480	3.5/2.3	216/119	211/246		
BCNU (n = 467)					480/320	4/2

[a] AUC, area under the concentration-time curve; C_{max}, maximal concentration; Cl, clearance; $t_{1/2}$, half-life; N/A, not available. AUC, C_{max}, $t_{1/2}$, and Cl are expressed in μg · min/ml, μg/ml, min, and ml/min, respectively.

[b] Dose ≥ 600 mg/m^2.

cDDP (2 patients), and with CPA, cDDP, and BCNU (3 patients). CPA has not been reported to date to cause CNS toxicity. cDDP-related encephalopathy is most commonly associated with intracarotid administration of the drug (18). CNS toxicity from systemically delivered cDDP, although rare, has been described. Its first signs are in most cases acute cortical blindness and/or seizures (19), none of which were seen in the cases described here.

Because BCNU crosses the blood-brain barrier, it can potentially cause CNS toxicity. Single-agent BCNU-related encephalomyelopathy has been observed at doses of the drug of >1200 mg/m^2 (20, 21) and starting at a minimum of 35 days after BCNU treatment (22). When used in combination, BCNU is given at lower doses. An example is the STAMP-I regimen, where BCNU is given at 600 mg/m^2 with CPA and cDDP. Although post-STAMP-I subclinical white matter changes have been observed (23, 24), encephalopathy is a very uncommon occurrence. In 459 patients treated at the University of Colorado with STAMP-I as of January 1998, only 3 cases (0.65% incidence) of CNS complications (coma or severe confusional states) have been observed, at 50 days, 60 days, and 18 months after the BCNU treatment.[4] Two patients' symptoms resolved after administration of 6-methylprednisolone at 1 g/day in a tapering schedule. A third patient died. The doses of BCNU given, in conjunction with paclitaxel-CPA-cDDP, to three of the patients in the present report were 200 mg/m^2 (two patients) and 550 mg/m^2 (one patient). These doses of BCNU appear to be too low to be a primary cause of the neurotoxicity seen in these patients (19). Importantly, encephalopathy in these three patients appeared 4, 9, and 13 days after the BCNU treatment, which is much earlier than the pattern of encephalopathy caused primarily by BCNU, either as single agent or in combination. Although the encephalopathy of these three patients seems unlikely to have been caused by BCNU alone, an additive toxic effect of paclitaxel and BCNU seems possible.

The fact that three of the six patients did not receive BCNU strengthens the role of paclitaxel as the putative cause of the encephalopathy. Furthermore, one patient (patient 5) received only paclitaxel, as described previously. Paclitaxel is suspended at 6 mg/ml in Cremophor EL (polyoxyethylated castor oil; 527 mg per mg of paclitaxel) and 49.7% dehydrated alcohol. In patients receiving paclitaxel, the postinfusion plasma alcohol levels depend on the amount of alcohol delivered (proportional to the dose of paclitaxel) and on the infusion rate, as shown by Webster *et al.* (25) The elimination of ethanol in nonalcoholics follows zero-order kinetics with an elimination rate constant of 120 mg·kg·h^{-1} or 8.4 g/h per 70 kg (26). For a dose of paclitaxel of 700 mg/m^2 (total of 1190 mg per 1.7 m^2 of body surface area), the total amount of ethanol delivered is ~80 g (density, 0.789 g/ml), The infusion rate over 24 h would be ~3.3 g/h, which is within its normal systemic elimination rate range. Furthermore, the onset of neurological symptoms in these patients, more than 1 week after paclitaxel infusion, excludes a role for its alcohol vehicle.

Cremophor EL may be a cause of encephalopathy in patients treated with paclitaxel. Preclinical studies have shown electroencephalography changes and a decrease of cerebral flow in cremophor-treated animals (27, 28). Other studies show that Cremophor EL induces coagulation factor changes that may predispose to thrombotic-embolic events (29–31). It is noteworthy that patient 4 presented multiple CNS infarctions, with no recognized source of emboli.

Two of the three patients who died had received prior WBI 2 and 5 months before HDC. Their brain metastases experienced a clinical complete remission after the WBI. A brain postmortem exam was authorized in one of them, and no residual tumor was seen. The other patient had a brain MRI performed after the development of the encephalopathy that did not show any cerebral metastases. This makes tumor an unlikely cause of their coma. Radiation-related brain injury is a well-described phenomenon, caused by damage to the small- and medium-sized brain vessels and the myelin-producing oligodendroglia (32). Radiation-related brain necrosis usually presents as focal signs, seizures, or headache from 9 to 12 months after the delivery of large doses of

[4] University of Colorado Bone Marrow Transplant Program, Y. Nieto, P. J. Cagnoni, S. I. Bearman, E. J. Schpall, S. Matthes, and R. B. Jones, unpublished observations.

radiotherapy (33). This toxicity is usually seen on the computed tomography scan as an enhancing mass with substantial edema and midline shift. Treatment consists of excision of the necrotic mass. Radiation leukoencephalopathy is a dementia syndrome with cognitive deficits and gait abnormalities after a mean postradiation interval of 17 months. Imaging studies characteristically show decreased density of the cerebral white matter and ventricular dilation (34). Although it is unlikely that these patients' prior WBI could entirely explain their encephalopathy, it may have been an aggravating factor. A radiation-recall phenomenon, similar to those described with paclitaxel in the skin or lungs (35, 36), might be a plausible explanation. In addition, it is possible that WBI increases the penetration of paclitaxel across the blood-brain barrier by altering small vessel function.

In this small series of patients, we could not identify a correlation between any PK parameter of paclitaxel and the occurrence of encephalopathy. Within the conventional dose range, paclitaxel is extensively bound to plasma proteins, particularly albumin and α_1-glycoprotein, in a concentration-independent fashion. It might be that, at very high doses, protein-binding reaches a saturation point, causing the free fraction of paclitaxel to increase exponentially, as has been described in other drugs, such as melphalan (37). The unbound fraction would then cross the blood-brain barrier more readily than the protein-bound drug. It is possible that the patients who presented encephalopathy could have had a higher area under the concentration-time curve or C_{max} of unbound paclitaxel, which could not be detected using our PK methodology.

CNS toxicity related to standard-dose paclitaxel is extremely uncommon. To date, four cases have been reported of CNS toxicity, possibly related to standard-dose paclitaxel. Two patients presented grand mal seizures (38, 39), one of them in the context of enlarging brain metastases and subtherapeutic blood levels of phenytoin (38). Two other patients experienced a confusional picture with dysphasia (40). Paclitaxel is considered to have negligible CNS penetration at standard doses (41, 42).

These data, taken together, suggest to us that paclitaxel, as formulated, is a likely primary cause of acute encephalopathy in the patients described. Paclitaxel-related encephalopathy seems a new entity, different from the encephalopathy caused by irradiation or other drugs. Three of the patients in this series also received BCNU, although at much lower doses than the ones that have been associated with CNS toxicity. In addition, the timing of paclitaxel-related encephalopathy is much earlier than the encephalopathy primarily caused by BCNU. Concomitant antineoplastic drugs or prior WBI may increase the risk of paclitaxel-related encephalopathy. The potential benefit from high-dose steroids remains to be determined. A pathological review of the postmortem findings in two patients could not draw any firm conclusions regarding the histological features of paclitaxel-related brain injury. Future studies are necessary to characterize this toxic entity from a pathological standpoint. Because early recognition of a toxicity from a novel treatment modality is important, clinicians involved in paclitaxel-containing HDC trials need to be aware of this potentially fatal complication.

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