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ORIGINAL ARTICLE

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The pharmacokinetics and pharmacodynamics of high-dose paclitaxel monotherapy (825 mg/m^2 continuous infusion over 24 h) with hematopoietic support in women with metastatic breast cancer

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Abstract *Purpose*: We evaluated the pharmacokinetics and pharmacodynamics of high-dose paclitaxel (HDP) monotherapy (825 mg/m^2 continuous infusion over 24 h) with peripheral blood progenitor cell (PBPC) and G-CSF support in 17 women with metastatic breast cancer. *Methods*: Pharmacokinetic and pharmacodynamic data were collected in 17 women entered in a phase II trial of sequential HDP, and high-dose melphalan and cyclophosphamide/thiotepa/carboplatin. *Results*: The maximal plasma concentration (C_{max}), area under the plasma concentration time curve (AUC), apparent clearance (Cl_{app}), duration of plasma concentration above 0.05 μM ($t > 0.05$ μM) for paclitaxel were (means ± SD): 9.11 ± 7.45 μM, 145 ± 88 μM·h, 8.06 ± 2.90 l/h per m^2 and 82.4 ± 31.2 h, respectively. There was a significant correlation between the plasma paclitaxel concentration at 1 h ($r^2 = 0.87$), 12 h ($r^2 = 0.85$) and 23 h ($r^2 = 0.92$) and the AUC ($P < 0.0001$). Duration of neutropenia was brief (median 3 days, range 0–5 days) and neutrophil recovery occurred earlier (median 6 days, range 0–7 days) than could be attributed to infused PBPC. Median nadir count for platelets was 66×10^9/l (range 13–160×10^9/l). Pharmacodynamic analysis showed no correlation between pharmacokinetic parameters (C_{max}, AUC, $t > 0.05$ μM) and time to neutropenic nadir, duration of neutropenia, platelet count nadir and grades of neuropathy or mucositis. In ten patients in whom detailed neurologic and nerve conduction studies were performed, linear regression analysis showed a significant correlation between pre- and post-HDP treatment total neuropathy scores ($r^2 = 0.46$, $P = 0.03$). *Conclusions*: HDP (825 mg/m^2 continuous infusion over 24 h) did not appear to be myeloablative. The degree of neurotoxicity subsequent to HDP was associated with the degree of baseline neuropathy but was not predictable from pharmacokinetic parameters.

Key words Paclitaxel · Three-compartment nonlinear model · Neurotoxicity

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Introduction

Paclitaxel has activity in a number of solid malignancies including breast cancer [1]. In patients undergoing multiple cycles of standard-dose paclitaxel, the dose-limiting toxicities have been both hematological and nonhematological, notably peripheral neuropathy [1, 2]. Although controversial, high-dose chemotherapy with progenitor cell support may improve outcome in some patients with advanced breast cancer and is currently under study [3]. Preclinical data in breast cancer cell lines and MCA-4 transplanted tumors in C3Hf/Kam mice support a dose-concentration/response effect for paclitaxel in breast cancer [4, 5]. High-dose paclitaxel (HDP) has thus been included in sequential and combination high-dose regimens with peripheral blood progenitor cell (PBPC) support [6, 7, 8] in women with breast cancer. The nonlinear pharmacokinetics and pharmacodynamics of single-agent paclitaxel have been

extensively studied at conventional doses [9, 10, 11], but are less well documented at doses above 450 mg/m^2.

In a phase I trial of sequential HDP, and high-dose melphalan and cyclophosphamide/thiotepa/carboplatin (CTCb) in women with metastatic breast cancer, the maximum tolerated dose of paclitaxel was determined as 825 mg/m^2 [7]. We report here the pharmacokinetics and pharmacodynamics of HDP (825 mg/m^2) as a continuous infusion (CI) over 24 h with PBPC and G-CSF support in 17 women with metastatic breast cancer entered in a phase II trial of this sequential regimen.

Patients and methods

Complete paclitaxel pharmacological data were collected in 17 women with metastatic breast cancer enrolled in a phase II trial of sequential HDP, and high-dose melphalan and CTCb with hematopoietic cell and G-CSF support [12]. All patients had adequate hepatic (bilirubin not more than twice normal, transaminases not more than 1.5 times normal) and renal function (creatinine less than 1.5 times normal). Patients with central nervous system metastasis or pre-existing National Cancer Institute Common Toxicity Criteria (NCI-CTC) neuropathy of grade 3 or more were ineligible. Paclitaxel 825 mg/m^2 was administered as a CI over 24 h on day –4 with PBPC reinfusion on day 0. Patients were premedicated with dexamethasone 20 mg, cimetidine 300 mg and diphenhydramine 50 mg. G-CSF (5 μg/kg per day) was administered subcutaneously following PBPC reinfusion and continued until recovery from neutropenia (absolute neutrophil count $>1 \times 10^9$/l). The next sequential treatment of melphalan, and then CTCb, each with PBPC and G-CSF support, was given following marrow recovery to a leukocyte count of at least $>2 \times 10^9$/l, and platelets to $>20 \times 10^9$/l [7]. This study was approved by the institutional review board and written informed consent was obtained according to institutional requirements.

Plasma sampling and paclitaxel assay

Blood samples collected in heparinized tubes were obtained before the start of the paclitaxel infusion, and then at 1, 12, 23, 24.5, 25, 26, 28, 30, 48, 72 and 84 h. Samples were obtained from a well-flushed drug administration line, centrifuged, and the resulting plasma was stored in polypropylene cryovials at –20ºC until analysis. Plasma paclitaxel concentrations were quantified using the high-performance liquid chromatography (HPLC) method of Vergniol et al. [13] as modified for paclitaxel analysis. Briefly, plasma extraction of paclitaxel was accomplished by adding 1 ml 30% acetonitrile and 50 μl docetaxel (2 ng/μl, as internal standard) to a 1 ml plasma sample. The mixture was vortexed and applied to a preconditioned 100 mg/ml C18 solid phase extraction cartridge (Varian, Harbor City, Calif.). The sample cartridge was preconditioned with 1 ml methanol followed by 1 ml deionized water (dH_2O). Immediately following the addition of the sample mixture, the column was washed with 1 ml dH_2O followed by 1 ml 50% methanol. The absorbed paclitaxel was eluted with 250 μl 90% methanol and 200 μl was loaded onto the HPLC column for analysis. The HPLC system consisted of a Hewlett Packard 1090 M liquid chromatograph, DR5 solvent delivery system (Hewlett Packard, Waldbronn, Germany), a Spheri-5 ODS 220 × 4.6 mm column (Applied Biosystems, Foster City, Calif.) and an RP-18 guard column (Perlin Elmer, Norwalk, Ct.). Samples were chromatographed with 67.5% methanol/32.5% H_3PO_4 (0.3%) at a flow rate of 1 ml/min, and the eluate was monitored at 228 nm with a UV diode array detector. The retention time of paclitaxel was 6.95 min. The intraassay and interassay coefficients of variation were below 10%.

Pharmacokinetics

A previously described three-compartment, nonlinear distribution and elimination model was fitted to the plasma concentrations of paclitaxel from each patient [14]. This was done with the ADAPT II program [15] and MAP Bayesian weighting. Individual patient parameters were then used to simulate complete concentration versus time courses from which were calculated AUC and the time that plasma paclitaxel concentration remained above 0.05 μ*M*. Peak paclitaxel concentrations (C_{max}), area under the concentration versus time curve (AUC), apparent clearance (Cl_{app}) and time for which the concentration of paclitaxel was greater than 0.05 μ*M* ($t > 0.05$ μM) were determined for each patient. Linear regression analysis was performed to determine the association between plasma paclitaxel concentration at 1 h, 12 h and 23 h versus AUC.

Neurologic studies

Before and after HDP infusion, motor and sensory neuropathy were graded according to the NCI-CTC. In ten patients detailed clinical and neurophysiological examinations were performed before HDP and these were repeated at approximately 4 weeks, prior to high-dose melphalan. Changes in sensory symptoms, strength, pin perception, vibration, tendon reflexes and nerve conduction studies (NCS) were scored from 0 (none) to 3 (severe) according to the total neuropathy (TN) score of Chaudhry et al. [16], modified to include changes in amplitude, velocity and latency of motor (unilateral median and peroneal) and sensory (unilateral median and sural) nerves (Table 1).

Hematologic studies

The number of days to neutrophil nadir, duration of neutropenia (absolute neutrophil count (ANC) $< 0.5 \times 10^9$/l) and days to ANC recovery $> 0.5 \times 10^9$/l following the nadir were recorded, with the day of PBPC reinfusion designated day 0. For platelets, days to platelet nadir, nadir platelet counts and percentage reduction in platelets were recorded.

Statistical analysis

Nonparametric Spearman's coefficients were estimated. Univariate linear regression was performed using a significance level of 0.05.

Results

Pharmacokinetic data were assessed in 17 patients receiving paclitaxel 825 mg/m^2 as a CI over 24 h. Patient characteristics are shown in Table 2. Mean pharmacokinetic parameters estimated from the nonlinear model are shown in Table 3. A representative plasma paclitaxel concentration versus time curve is shown in Fig. 1. There was a significant correlation between the plasma paclitaxel concentration at 1 h ($r^2 = 0.87$), 12 h ($r^2 = 0.85$) and 23 h ($r^2 = 0.92$) and the AUC ($P < 0.0001$). No correlation between paclitaxel concentration or AUC and time above 0.05 μ*M* was found.

There were no deaths or irreversible grade 4 toxicities following the HDP therapy. Pre- and post-HDP CTC grades and hematopoietic parameters were available in 16 patients. One patient refused further hematologic and neurologic testing following HDP and withdrew from the protocol. A blood count obtained from this patient on day +8 following HDP showed full hematologic recovery.

Table 1 Total neuropathy score of peripheral neuropathy which includes scores of toxicity for clinical and nerve conduction studies (modified from Chaudhry et al. [16]). Total neuropathy score range is 0–51

Toxicity	0	1	2	3
Sensory symptoms	None	Paresthesia/numbness in feet	Paresthesia/numbness in feet and hands	Functionally disabling paresthesia/numbness/myalgia
Strength	Normal	Weak toe extension	Weak toe extension and finger abduction	Generalized weakness
Tendon reflexes	Normal	Ankle jerks reduced or absent	Ankle jerks absent, distal reduced	All absent
Pin prick	Normal	Decreased in toes	Decreased in toes to ankle or fingers	Decreased above ankle and wrist
Vibration	Normal	Decreased in toes	Decreased in toes and ankle or fingers	Decreased in hands
Motor (conduction velocity ↓, latency ↑, amplitude ↓)[a]	0–10%	10–25%	25–50%	> 50%
Sensory (conduction velocity ↓, latency ↑, amplitude ↓)[a]	0–10%	10–25%	25–50%	> 50%

[a] For unilateral motor (peroneal and median) nerves and sensory (median and sural) nerves, conduction velocity, latency and amplitude were each scored. The values indicate percent change from normal or baseline values for pre- and post-high-dose paclitaxel, respectively

Table 2 Clinical characteristics of 17 women with stage IV breast cancer receiving high-dose paclitaxel (825 mg/m^2 continuous infusion over 24 h) with hematopoietic support (*HDP* high-dose paclitaxel)

Age (years)	Median (range)	44 (24–58)
Previous chemotherapy		
Number of prior regimens	Median (range)	2 (1–3)
Taxane-containing regimen		12/17 (71%)
Non-taxane-containing regimen		5/17 (24%)
$CD34^+$ cells $\times 10^6$/kg reinfused post-HDP	Median (range)	2.68 (1.21–5.2)
NCI-CTC grade III toxicity post-HDP		
Neurosensory		10/16 (63%)[a]
Neuromotor		0/16 (0%)[a]
Stomatitis/esophagitis		2/17 (12%)
Neutropenic fever		6/17 (35%)

[a] One patient refused post-HDP neurologic evaluation

Table 3 Pharmacokinetic parameters of 17 women with stage IV breast cancer receiving high-dose paclitaxel (825 mg/m^2 continuous infusion over 24 h) with hematopoietic support. A three-compartment, nonlinear distribution and elimination model was fitted to the plasma concentrations of paclitaxel from each patient using the ADAPT II program [15] and MAP Bayesian weighting (C_{max} peak paclitaxel concentrations, *AUC* area under the concentration versus time curve, Cl_{app} apparent clearance, $t > 0.05$ μM time (h) for which the concentration of paclitaxel was greater than 0.05 μ*M*)

Pharmacokinetic parameter	Mean	SD	Range
C_{max} (μ*M*)	9.11	7.45	2.63–35.56
AUC (μ*M*·h)	145	88	65–472
Cl_{app} (l/h/m^2)	8.06	2.90	2.05–14.94
$t > 0.05$ μ*M* (h)	82.4	31.2	50.5–150

Prior to HDP, 12 of 17 patients had residual neuropathy from previous chemotherapy. Ten of these 12 patients (83%) had received taxane-containing regimens. Pre- and post-HDP CTC grades and TN scores are shown in Fig. 2. All 16 assessable patients experienced new or increased but reversible neuropathy following the HDP. Nerve conduction studies confirmed an axonal sensorimotor neuropathy in the ten patients in whom these studies were performed. Linear regression analysis showed a significant correlation between pre- and post-TN scores in these ten patients ($r^2 = 0.46$, $P = 0.03$), but no correlation between pharmacokinetic parameters (C_{max}, AUC, $t > 0.05$ μ*M*) and post-HDP TN scores. There was also no correlation between these pharmacokinetic parameters and CTC grades for neuropathy, mucositis and occurrence of neutropenic fever.

The median duration of ANC $< 0.5 \times 10^9$/l was 3 days (range 0–5 days), the median number of days to neutrophil nadir after PBPC reinfusion was 3 days (range 0–4 days), and median days to ANC recovery $> 0.5 \times 10^9$/l was 6 days (range 0–7 days). A representative neutrophil count versus time plot is shown in Fig. 3. The median days to platelet nadir was 4 days (range 3–7 days) and median platelet nadir count was 66×10^9/l (range 13–160 $\times 10^9$/l). There may be an association between percentage reduction in platelets and $t > 0.05$ μ*M* but this was not statistically significant ($P = 0.07$). There was no correlation between pharmacokinetic parameters (C_{max}, AUC, $t > 0.05$ μ*M*) and any of the other hematologic parameters studied.

The phase II trial was designed to assess response at the end of the sequential cycles of paclitaxel, melphalan

and CTCb [12]. Thus the response to paclitaxel alone was not determined. Following the sequential high-dose chemotherapy, 9 of 16 patients either remained without evidence of disease or had bone-only disease and were not evaluable, and the remaining evaluable patients showed no correlation of overall response with paclitaxel pharmacokinetics (data not shown).

Discussion

Paclitaxel has nonlinear pharmacokinetics, with saturable distribution and elimination features [10]. Cremophor EL used for the intravenous formulation of paclitaxel may contribute to the nonlinear pharmacokinetics [17]. The pharmacokinetic model of paclitaxel developed previously proved applicable to the data generated in the current study. Consistent with previous data for conventional doses of paclitaxel, there is a disproportionate increase in AUC in relation to increased dose, reflecting the nonlinear pharmacokinetics [10]. The interpatient variability in AUC and C_{max} was similar in magnitude to that seen at lower doses. The correlation of plasma concentration with AUC at 23 h suggests that a limited sampling strategy may provide information about both AUC and C_{max} at this dose of paclitaxel, but requires further prospective validation.

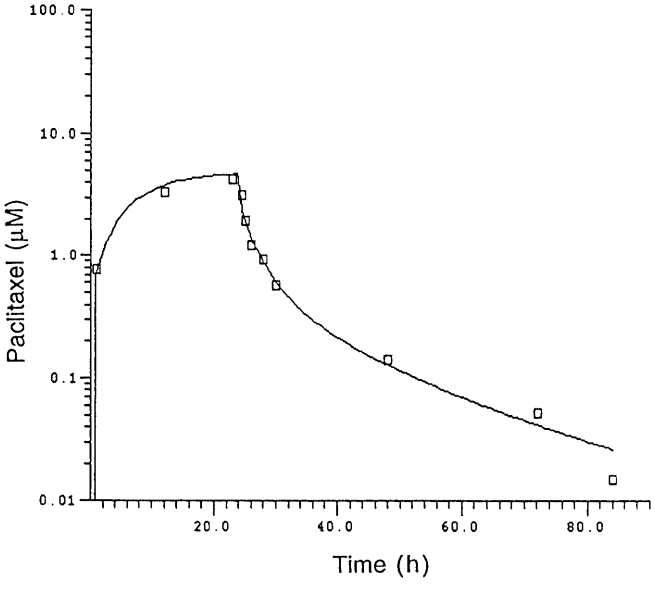

Fig. 1 Three-compartment model fit line through representative data of paclitaxel concentration versus time from a patient receiving paclitaxel 825 mg/m^2 as a continuous infusion over 24 h

Neurotoxicity is the dose-limiting toxicity of paclitaxel 825 mg/m^2 administered as a CI over 24 h [7]. In patients treated with single-agent paclitaxel CI (500–800 mg/m^2 over 24 h), Iniguez et al. found no significant correlation between dose escalation and severity of peripheral neuropathy. Dose escalation of paclitaxel did correlate with duration of symptoms and delay in improvement [8]. Preliminary data from 34 patients in the phase I study of our sequential HDP regimen (400–825 mg/m^2 CI over 24 h), found that severity of neurologic symptoms is not dose-dependent but gait difficulties are more common in patients receiving >700 mg/m^2 [7, 18]. Since patients receive high-dose carboplatin as a component of the CTCb therapy in our sequential regimen, we were unable to assess duration of paclitaxel-induced neuropathy independent of that contributed by the carboplatin. Stemmer et al. have studied the pharmacokinetics of paclitaxel (135–825 mg/m^2 CI over 24 h; one patient at the 825 mg/m^2 dose level) administered in combination with cyclophosphamide and cisplatin in 35 patients, using a zero-order intravenous input and first-order output two-compartment model [6]. These authors found a significant correlation between AUC and C_{max} and severity of neuropathy and mucositis using the SWOG toxicity grading.

As the majority of our patients receiving paclitaxel at 825 mg/m^2 developed CTC grade 3 sensory neuropathy,

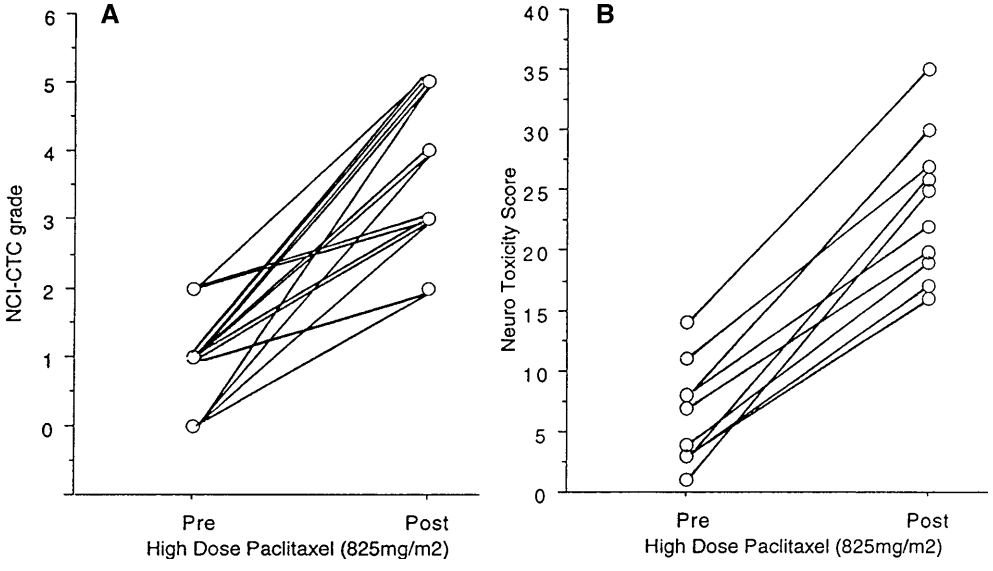

Fig. 2A, B Cumulative neurotoxicity pre- and post-high-dose paclitaxel (825 mg/m^2 as a continuous infusion over 24 h). **A** Combined neurosensory and neuromotor toxicity in 16 patients as graded by NCI-common toxicity criteria. **B** Total neuropathy scores in 10 patients as determined from Table 1

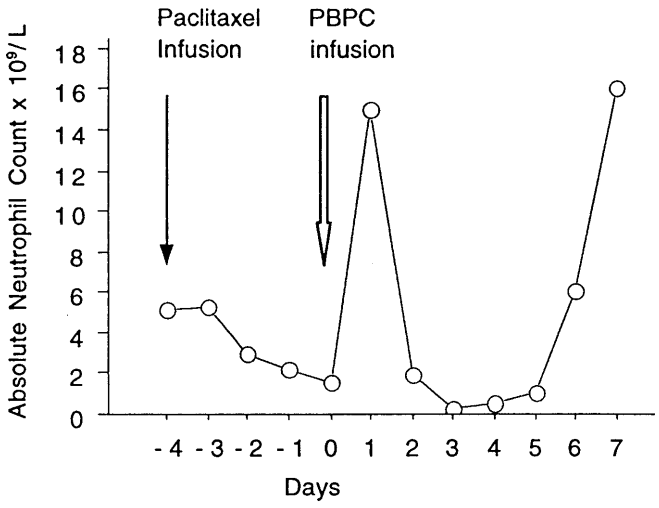

Fig. 3 Data of absolute neutrophil count versus time (days) from a typical patient receiving paclitaxel 825 mg/m^2 as continuous infusion over 24 h on day –4, followed by peripheral blood progenitor cell reinfusion on day 0, and G-CSF until recovery from neutropenia. The duration of ANC $< 0.5 \times 10^9$/l was 2 days, the number of days to neutrophil nadir after PBPC re-infusion was 3 days, and days to ANC recovery $> 0.5 \times 10^9$/l was 5 days

it is not unexpected that we found no such correlation despite a log difference in the range of C_{max} and a 50% difference in the AUC range for paclitaxel. A more detailed TN score in ten patients, nine of whom had had prior taxane therapy, also failed to show any significant correlation with pharmacokinetic parameters. Regression analysis of the TN score in these ten patients showed a significant positive correlation between pre- and post-HDP neuropathy. Thus at a dose of 825 mg/m^2, the degree of neurotoxicity subsequent to HDP appears to be associated with the degree of baseline neuropathy but is not predictable from pharmacokinetic parameters. These results need to be interpreted with caution due to the small number of subjects.

We have previously shown that at doses of paclitaxel in the range 400–825 mg/m^2 given as a 24-h CI with PBPCs and G-CSF, the median duration of ANC $< 0.5 \times 10^9$/l is 4 days [19]. All patients recovered ANC and platelet counts within 7 days of infusion of $\geq 1 \times 10^6$ CD34$^+$ cells/kg. Engraftment attributable to reinfused PBPCs prior to day 7 is unusual even at doses $> 15 \times 10^6$ CD34$^+$ cells/kg [20]. These results suggest that paclitaxel is not myeloablative at doses in the range 400–825 mg/m^2, nor is there a clinically relevant dose-dependent effect in this dose range. In the cohort of 17 patients receiving 825 mg/m^2 reported in the present study, the lack of correlation between pharmacokinetic and hematologic parameters provides further support for this clinical observation. At standard doses of paclitaxel, evidence suggests that neutropenia is more likely related to the time that the plasma paclitaxel concentration remains at or above a threshold concentration of 0.05 μM [10]. Although the reinfusion of PBPC and use of G-CSF precludes any definitive conclusions from our study, there appears to be no cumulative toxicity in hematopoietic progenitor cells exposed to a paclitaxel concentration > 0.05 μM beyond 50 h in duration. This observation is substantiated in patients treated with paclitaxel (140 mg/m^2) as a CI over 96 h, who despite a mean duration of paclitaxel concentration > 0.05 μM of 68 h, had resolution of granulocytopenia within 5 days [21]. Similarly, Socinski et al. have reported grade 4 neutropenia of less than 7 days duration in all patients receiving paclitaxel (140–200 mg/m^2) as CI over 96 h followed by G-CSF [22]. As with standard-dose paclitaxel, neither the peak plasma concentration nor AUC appear to be the pharmacokinetic parameters relevant to neutropenia or thrombocytopenia with HDP.

Pharmacokinetic parameters for HDP at 825 mg/m^2 have a wide range of interpatient variability and do not predict toxicity. Pre-existing neuropathy correlates with severity of neuropathy following HDP and due vigilance is required in patients previously treated with neurotoxic drugs, particularly taxanes, which are now routinely used in the setting of adjuvant and metastatic breast cancer. There is debate regarding the dose-response of paclitaxel beyond a plateau concentration [23]. In light of the 63% incidence of grade III neurotoxicity in our patients and the reported fatal encephalopathy following the use of paclitaxel-containing combination high-dose chemotherapy regimens [24], the strategy of including HDP in sequential regimens for breast and other malignancies is controversial and awaits confirmation of clinical efficacy.

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