Neurophysiological Study of Peripheral Neuropathy after High-Dose Paclitaxel: Lack of Neuroprotective Effect of Amifostine

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ABSTRACT

Purpose: To determine if there is a beneficial effect of amifostine in preventing or reducing the neuropathy induced by high-dose paclitaxel.

Methods: Breast cancer patients receiving high-dose infusional paclitaxel (725 mg/m^2/24 h) in combination with doxorubicin (165 mg/m^2/96 h) and cyclophosphamide (100 mg/kg/2 h; ACT) were studied on two autologous peripheral blood stem cell transplant protocols, one with and one without amifostine (740 mg/m^2 administered over 10 min before and 12 h after initiation of the paclitaxel infusion). Patients were evaluated before ACT and $20–40$ days later with neurological examination, a composite peripheral neuropathy score, peroneal and sural nerve conduction studies, and quantitative sensory testing.

Results: There was no significant difference in paclitaxel maximum concentration, systemic clearance, or area under the curve determinations. Narcotic requirement as well as recovery of hematopoietic counts were also similar in subjects with or without amifostine. After ACT was administered, there was a decrease in peroneal nerve compound muscle action potential amplitude and sural nerve sensory action potential amplitude, as well as an increase in vibratory and cold detection thresholds. Clinical composite peripheral neuropathy scores were similar despite amifostine treatment; and logarithm to the base 2 ratios post/pre ACT showed no significant effect of amifostine on peroneal nerve compound muscle action potential, sural nerve sensory action potential, vibratory detection thresholds, or cold detection thresholds. All subjects had acroparesthesias and lost their ankle deep-tendon reflexes after administration of ACT.

Conclusions: Single high-dose paclitaxel produces predictable clinical and neurophysiological changes so that patients receiving high-dose therapy are ideal subjects to test the effectiveness of neuroprotective agents. Amifostine was ineffective in preventing or reducing the neurotoxicity of high-dose paclitaxel.

INTRODUCTION

Taxol (paclitaxel), a diterpene alkaloid drug is widely used as a chemotherapeutic agent primarily in breast, lung, and ovarian cancer. Peripheral neuropathy occurs after repetitive cycles of a standard dose paclitaxel (cycles of $135–250$ mg/m^2 every 3 weeks) or after a single high dose ($500–800$ mg/m^2; Refs. 1 and 2). Most neurophysiological studies of paclitaxel neuropathy have been performed in subjects receiving standard dose paclitaxel, often in combination with cisplatin (3–5). High-dose paclitaxel (725 mg/m^2 i.v. over 24 h) has been used in combination with doxorubicin and cyclophosphamide (ACT) followed by autologous peripheral blood stem cell transplantation in breast cancer patients (6). As anticipated (2, 7), the dose-limiting toxicity at 725 mg/m^2 was partially reversible peripheral neuropathy.

Peripheral neuropathy from paclitaxel produces primarily sensory symptoms and signs in the distal distribution of the longest nerves of the body, a postulated "dying back" axonopathy resulting from disruption of axoplasmic transport from the drug's effect on microtubule assembly (1). The identification of a safe and effective neuroprotective agent that does not reduce tumor cell cytotoxicity and that allows further dose escalation of paclitaxel would represent a significant medical advancement. Recently, glutamine was shown in a case control trial to reduce neuropathic symptoms and signs after high-dose paclitaxel (8). The present study investigates amifostine as a neuroprotective agent.

Amifostine, a cysteamine analog, has been used as a radioprotective agent in head and neck and rectal carcinoma (9), a hematopoietic progenitor cell protectant in bone marrow purging with 4-hydroperoxycyclophosphamide (10), and a cytoprotective agent in a number of chemotherapy trials (11, 12). Possible mechanisms include the scavenging of free radicals, decreasing DNA-DNA interstrand cross-links induced by alkylating drugs, and decreasing platinum-DNA adducts (13). The selective protection of amifostine (in normal rather than neoplastic cells) is postulated to be secondary to more efficient alkaline phosphatase activity in normal tissue, allowing greater dephosphorylation of amifostine to the active free thiol form, WR-1065 (14).

Amifostine has been proposed as a potential agent for protecting against chemotherapy-induced peripheral neuropathy

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(15). A beneficial effect of amifostine on peripheral neuropathy has been reported in a randomized study of 242 ovarian cancer patients treated with cisplatin and cyclophosphamide. The statistically significant benefit was based on "blinded" neurological examinations and assessment of toxicity criteria (16). Detailed comparison studies using quantitative sensory and nerve conduction tests in cisplatin neuropathy have not been done. For paclitaxel, an early study showed that amifostine allowed dose escalation beyond the anticipated neurotoxic level to 310 mg/m^2 with no subjects after the first cycle and only two of eight subjects after the second or third cycle developing grade 3 neurotoxicity (17). However, in patients receiving multiple courses of standard dose paclitaxel (250 mg/m^2), amifostine failed to prevent peripheral neuropathy, as indicated by patient questionnaires and neurological examination of muscle strength and vibratory sensation (18, 19). Quantitative sensory testing has been used to monitor patients receiving standard dose paclitaxel (4), but neither quantitative sensory tests nor nerve conduction tests were used in the studies that failed to show a neuroprotective effect of amifostine in patients receiving standard dose paclitaxel. There are no reports of these combinations of neurophysiological tests in patients receiving high-dose paclitaxel regimens with or without amifostine. In the present study, changes in neurological examination, composite neuropathy score, nerve conduction tests, and quantitative sensory tests were monitored in patients receiving ACT with or without the cytoprotective drug amifostine.

MATERIALS AND METHODS

Eligibility. Patients with high-risk breast cancer (stage II with ≥10 axillary lymph nodes involved, stage IIIA, or IIIB carcinoma) were eligible to receive ACT with or without amifostine, whereas patients with responsive or stable stage IV disease were eligible to receive ACT with amifostine. The following were required: Karnofsky performance status of ≥80%; age of ≤60 years; bilirubin within normal range; AST and ALT ≤2 × the upper limit of normal; a measured creatinine clearance ≥70 ml/min; cardiac left ventricular ejection fraction ≥55%; a forced expiratory volume in 1 s of ≥2 liters; and diffusion capacity of carbon monoxide >60% of that predicted. Patients with bone marrow or central nervous system metastases were excluded. Although patients were not randomized between the two treatments (ACT alone or ACT with amifostine), the two protocols ran concurrently, had similar eligibility criteria, and sequential patients on each underwent neurophysiological studies. The same technologist performed all nerve conduction studies and quantitative sensory tests. All patients participating in these studies signed informed consent documents approved by the City of Hope Institutional Review Board.

Treatment Plan. Granulocyte colony-stimulating factor (Filgrastim, Amgen Inc., Thousand Oaks, CA), 5 μg/kg bid, was administered s.c. On the 5th day, apheresis commenced and continued through collection of at least 2 × 10^6/kg CD34+ peripheral blood progenitor cells. Cells were collected and immediately cryopreserved as reported earlier (20). Ideal body weight was used when calculating doses. Doxorubicin (165 mg/m^2) was administered over 96 h, between days −9 and −5, followed by 100 mg/kg cyclophosphamide over 2 h on day −5.

A 24-h continuous i.v. infusion of 725 mg/m^2 paclitaxel was started on day −4. Amifostine (740 mg/m^2 over 10 min; ALZA Corporation, Mountain View, CA) was administered both before and 12 h into the paclitaxel infusion. Twenty-five percent of peripheral blood progenitor cells were reinfused on day −2 and 75% on day 0. Supportive care was provided as per institutional standards. Granulocyte colony-stimulating factor 5 μg/kg bid, i.v. was started with the first stem cell reinfusion and was continued until the absolute granulocyte count was ≥1 × 10^9/liters for 3 consecutive days.

Assessment of Peripheral Neuropathy. Neurological signs were recorded and neurophysiological tests (nerve conduction studies and quantitative sensory testing) obtained on consecutive patients before and 20–40 days after ACT chemotherapy. Peroneal nerve motor conduction studies were performed with the stimulating electrode at the ankle and the recording electrode 8 cm distally over the extensor digitorum brevis muscle. The sural nerve was stimulated antidromically in the posterior lower leg and recorded 14 cm distally at the lateral malleolus. Quantitative sensory testing of vibratory and cold detection thresholds was performed with the Case IV system one-time-period 4, 2, 1 Stepping Algorithm (21). The point of stimulation was immediately distal to the base of the nail of the right large toe for vibration and the dorsal surface of the right foot for cold. After paclitaxel treatment, the relative changes in nerve conduction and quantitative sensory tests were recorded and expressed as the logarithm to the base 2 of ratios of post-transplant/pretransplant determinations (a logarithm ratio of 0 indicates no change, −1 indicates the value was reduced by half, +1 indicates an increase by a factor of 2, −2 indicates a reduction by a factor of 4, and so forth).

Peripheral neuropathy scores were obtained by a modification of the method by Chaudhry *et al.* (3). As shown in Table 1, scores of 0–3 were given for each of the following seven categories: (category 1) sensory symptoms; (category 2) pin sensory loss; (category 3) vibration sensory loss; (category 4) strength; (category 5) deep tendon reflexes; (category 6) sural sensory nerve action potential (SNAP) amplitude; and (category 7) peroneal nerve compound muscle action potential (CMAP) amplitude. Percentage reduction of SNAP and CMAP were determined on the basis of the lower limit of the laboratory normal. Sum of scores could range from 0 (no impairment) to 21 (maximum impairment on this scale).

Pharmacokinetics. For those patients in whom pharmacokinetic studies were performed, peripheral blood samples were obtained immediately before the start of the paclitaxel infusion, at 3, 6, 12, 20, and 24 h during the paclitaxel infusion, then at 15 and 30 min and 1, 2, 3, 6, 12, and 24 h after completion of the paclitaxel infusion. The concentration of paclitaxel in plasma was measured in accordance with a HPLC method published previously (22). Pharmacokinetic data analyses of individual plasma drug concentration *versus* time curves were performed using ADAPT II software (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA). Paclitaxel areas under the curves (AUCs) were estimated using linear trapezoids, with the terminal area extrapolated to infinity, using both the measured and fitted drug concentrations. Paclitaxel systemic clearances (CL$_{sys}$) were determined using the following re-

Table 1   Peripheral neuropathy composite scores

Categories	Scores			
	0	1	2	3
(1) Sensory symptoms	None	Numbness/paresthesias feet	Numbness/paresthesias feet and hands	Dysesthesias
(2) Pin sensation	Normal	Decreased in feet	Decreased feet and ankles	Decreased feet and hands
(3) Vibration sensation	Normal	Decreased in toes	Absent toes	Absent toes and ankles
(4) Muscle strength	Normal	Weak toe extensors	Weak ankles	Generalized weakness
(5) DTR[a]	Normal	Ankle DTR decreased or absent	Ankle DTR absent, other DTRs reduced	Areflexia
(6) Sural SNAP	Decreased <10%	Decreased 10–25%	Decreased 25–50%	Decreased >50%
(7) Peroneal CMAP	Decreased <10%	Decreased 10–25%	Decreased 25–50%	Decreased >50%

[a] DTR, deep tendon reflexes; SNAP, sensory nerve action potential; CMAP, compound muscle action potential.

Table 2   Effect of amifostine on neurological examination and neurodiagnostic tests

Neurodiagnostic test (logarithm post transplant/pre transplant)

	Peroneal CMAP[a] amplitude	Sural SNAP amplitude	VDT	CDT
ACT (N = 12)	−2.5 ± 2.0	−0.52 ± 0.45	0.36 ± 0.24	0.12 ± 0.30
ACT and amifostine (N = 9)	−1.1 ± 0.9	−0.45 ± 0.44	0.36 ± 0.22	0.23 ± 0.24
P	0.08	0.97	0.97	0.31

Neurological examination

	Absent ankle DTR	Generalized areflexia	Decrease of vibration toes	Decrease of pin toes
ACT (N = 11)	100%	36%	91%	45%
ACT and amifostine (W = 13)	100%	54%	85%	54%
P	1	0.4	1	1

[a] CMAP, compound muscle action potential; SNAP, sensory nerve action potential; VDT, vibration detection threshold; CDT, cold detection threshold; ACT, doxorubicin, cyclophosphamide, paclitaxel.

lationship: CL_{sys} = dose/AUC. Peak plasma paclitaxel concentrations were defined as the actual paclitaxel levels measured immediately before the end of the infusion. The time that the plasma paclitaxel concentration remained above 0.05 μM was estimated by extrapolation of the model-derived fits of each individual patient's data.

Statistical Analysis. Not all patients provided blood samples for pharmacokinetic analysis, but all available data points were included in the data analysis. Wilcoxon Mann-Whitney rank-sum tests were used to compare determinations from patients treated with and without amifostine for pharmacokinetic measurements, duration of hematopoietic suppression or narcotic requirement, and changes from baseline of neurophysiological tests. Student's *t* tests were used for comparison of neurological signs.

RESULTS

Patients. Tables 2–4 present comparisons of ACT subjects who received amifostine (n = 14, age range 30–62, median 45) and those who did not receive amifostine (n = 17, age range 29–56, median 42). Karnofsky score was 90 or 100 in all subjects, although the percentage of subjects at Karnofsky 90 was greater in the amifostine group (50% compared with 29%). All subjects without amifostine had stage II/III disease whereas

six subjects receiving amifostine had stage IV disease. Of these six patients, two had complete response to chemotherapy, two had partial response, and two had stable disease before enrollment in the ACT plus amifostine protocol. Seventy to seventy-five percent of subjects in both groups had prior courses of either paclitaxel or docetaxel at standard doses. Of the patients with stage II-III disease, there was no significant difference in relapse-free survival between the two groups (P = 0.34; 95%

Table 3   Incidence of grade 3 or 4 toxicities (CTC[a], version 2.0) in patients treated with ACT or ACT and amifostine

	ACT (17) percentage grade 3 or 4	ACT and amifostine (14) percentage grade 3 or 4
Bone marrow	100%	100%
Febrile neutropenia	100%	100%
Gastrointestinal	100%	93%
Pain	24%	29%
Cardiovascular	12%	7%
Pulmonary	6%	14%
Musculoskeletal	6%	0%
Constitutional	6%	7%

[a] CTC, Common Toxicity Criteria; ACT, doxorubicin, cyclophosphamide, paclitaxel.

Table 4 Effect of amifostine on hematopoietic recovery, days of narcotic treatment, and paclitaxel pharmacokinetics

Hematopoietic recovery and days of narcotic treatment			
	Days to granulocytes >500/µl	Days to platelets >50,000/µl	Days to platelet independence	Days on narcotics
ACT[a] (N = 17)	9.1 ± 1.2	9.9 ± 1.7	5.4 ± 2.1	9.8 ± 1.9
ACT and amifostine (N = 13)	9.6 ± 1.0	9.5 ± 1.6	6.2 ± 1.9	9.3 ± 3.9
P	0.12	0.47	0.28	0.92

Paclitaxel pharmacokinetics			
	C_{MAX}(µM)	AUC(µM·h)	Cl_{sys}(1/h/m2)	T.05 µM(h)
ACT (N = 8)	4.0 ± 0.3	82 ± 5.3	10.4 ± 0.7	69 ± 16
ACT and amifostine (N = 11)	5.0 ± 1.4	95 ± 28	9.5 ± 2.6	61 ± 15
P	0.07	0.11	0.13	0.20

[a] ACT, doxorubicin, cyclophosphamide, paclitaxel; T.05, time paclitaxel concentration above 0.05 µM.

confidence interval for relative hazard, 0.3–1.5) with median follow-up of surviving patients 22 months (range 1.4–33 months). Four of the 17 ACT only patients have died, although there have been no deaths to date among the eight stage II-III patients who received ACT plus amifostine. Of the six stage IV patients treated with ACT and amifostine, median progression-free survival was 18 months, although median survival is undefined at a median follow-up of 21 months (range 4–30 months). The therapeutic efficacy of ACT plus amifostine could not be determined in these six subjects because none had a change in measurable disease following high-dose therapy.

The Effect of Amifostine on Neurological Examination and Neurophysiological Tests after High-Dose Paclitaxel. Fig. 1 shows results of neurophysiological tests in 21 patients before and after high-dose paclitaxel. There was a decrease in amplitude of peroneal CMAP in all subjects treated with and without amifostine. As shown in Table 2, the mean decrease of peroneal amplitude expressed as logarithm ratio was less in the amifostine group (−1.1 compared with −2.5 without amifostine), but this difference was not statistically significant (P = 0.08). There was also a decrease in sural SNAP amplitude both in subjects with and without amifostine as well as an increase in
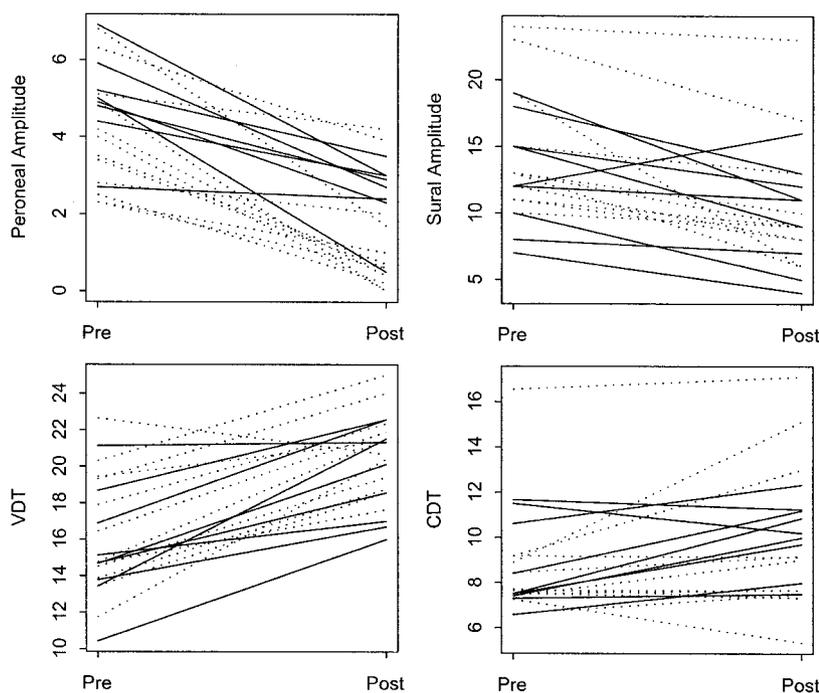

Fig. 1 Nerve conduction tests and quantitative sensory tests pre- and post-high-dose paclitaxel with (*solid lines*) and without (*dotted lines*) amifostine. Peroneal amplitude of compound muscle action potential (CMAP), sural amplitude of sensory nerve action potential (SNAP), vibration detection threshold (VDT), and cold detection threshold (CDT).

Fig. 2 Neuropathy scores pre- and post-high-dose paclitaxel. *A,* patients receiving doxorubicin, cyclophosphamide, paclitaxel (ACT) alone. *B,* patients receiving ACT and amifostine.
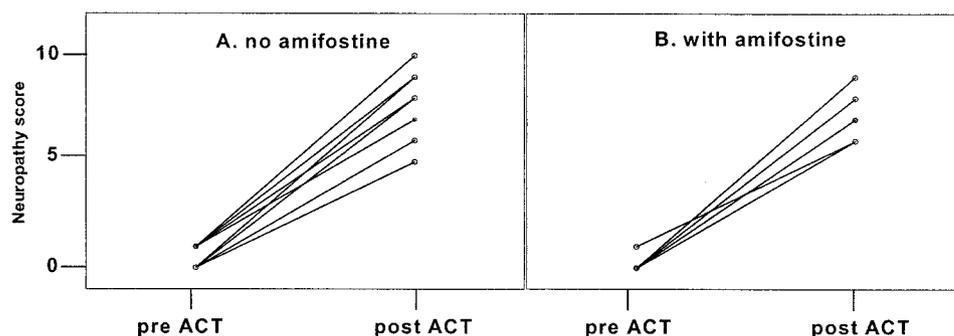
sensory detection thresholds for vibration and cold (Fig. 1). As shown in Table 2, the mean log ratios of sural SNAP amplitudes and the vibratory detection thresholds were essentially the same with and without amifostine. The mean increase in cold detection thresholds after paclitaxel was greater in the amifostine group, although the difference was not statistically significant. Of the 12 subjects treated without amifostine, nine had prior standard dose paclitaxel or docetaxel chemotherapy, and of the nine subjects receiving amifostine, six had prior paclitaxel or docetaxel. The degree of peroneal CMAP or sural SNAP amplitude drop-off or sensory threshold increase did not correlate with prior chemotherapy. Also, the extent of CMAP or SNAP amplitude drop-off did not predict the extent of threshold increases in quantitative sensory tests. Nerve conduction velocities and distal motor or sensory latencies were not consistently affected.

Paired neurological examinations were performed in 13 subjects treated with ACT and amifostine and 11 subjects treated with ACT alone. All 24 subjects reported acroparesthesias after ACT. As shown in Table 2, all patients had absent ankle deep tendon reflexes after ACT. None had weakness in toes or ankles, and none had proprioceptive abnormalities in the toes. Decreased vibratory sensation (128C tuning fork) on the toes was reported in 91% of subjects without and 85% of subjects treated with amifostine, and decreased pin sensation on the feet was recorded in 45% of subjects treated without and 54% of subjects treated with amifostine.

Fig. 2 shows changes in peripheral neuropathy composite scores in 17 subjects for which full clinical and neurophysiological data are available. Despite prior taxane exposure in 71%, only five subjects had pretransplant scores >0, and none had pretransplant scores >1. All subjects had an increase in peripheral neuropathy score after transplant with the maximum posttransplant score of 10 of a possible 21 on this scale. The increase in peripheral neuropathy scores was similar in patients receiving or not receiving amifostine.

The Effect of Amifostine on High-Dose Paclitaxel Toxicity, Hematological Recovery, Narcotic Requirement, and Paclitaxel Pharmacokinetics. Table 3 lists percentage grade 3 or 4 toxicity in 17 patients treated with ACT alone and 14 patients treated with ACT plus amifostine. A comparable pattern of toxicity was present in both groups. Similarly, the mean times of hematopoietic cell recovery and requirement for narcotic medication for mucositis pain were not different in subjects with

and without amifostine (Table 4). The median number of days of narcotics (10 days) was the same in both groups, and the median number of days after transplant for the platelet count to exceed $50,000/\mu l$ (10 days after transplant) was also the same in both groups. The median number of days after transplant for granulocytes to exceed $500/\mu l$ was 9 or 10, and the median number of days for platelet independence was 5 or 6 for the groups treated without and with amifostine, respectively.

As shown in Table 4, there was greater variability of paclitaxel pharmacokinetics in subjects who received amifostine. Although the mean C_{max} value was approximately 20% higher in amifostine-treated patients, the difference was not statistically significant. Furthermore, there was no significant difference in paclitaxel AUC, clearance, or time above $0.05 \mu M$ (Table 4).

DISCUSSION

Patients receiving high-dose paclitaxel are ideal subjects for trials of putative neuroprotective agents such as amifostine. In the present study, paclitaxel decreased peroneal motor nerve CMAP amplitude and sural SNAP amplitude. There was also an increase in sensory thresholds, loss of deep tendon reflexes, loss or decrease in vibration and to a lesser extent pin distally in the feet (Fig. 1 and Table 2), and an increase in composite neuropathy scores (Fig. 2). These results are comparable with earlier reports of high-dose paclitaxel given as monotherapy (500–825 mg/m^2/24 h; Refs. 2 and 23).

The results of pharmacokinetic studies revealed no significant effect of amifostine on paclitaxel C_{max}, systemic clearance, or AUC in patients receiving or not receiving amifostine. These data are in agreement with previous pharmacokinetic studies of paclitaxel at standard doses showing no effect of amifostine on paclitaxel AUC or clearance (18, 24, 25), or a lowering of paclitaxel AUC by amifostine (26). Amifostine also had no significant effect on percentage of patients with grade 3 or 4 toxicity (Table 3) and no significant effect on days of narcotic requirement or time required for hematopoietic cell recovery after high-dose paclitaxel (Table 4). This result on hematopoietic cell recovery is comparable with an earlier paclitaxel study in which amifostine did not alter the median days to leukocyte nadir (day 15) or percentage of patients with grade 4 neutropenia (47% with amifostine, 60% without amifostine; Ref. 18). Similarly, amifostine did not influence myelotoxicity

associated with standard dose docetaxel (27). Although the sample size in the present study is limited, the data do not suggest tumor protection.

A number of methods have been used to assess the incidence and severity of paclitaxel neuropathy. Most investigational studies have used practical measures such as neurological examination or standard toxicity scale measurements. Significant interobserver variability occurs in grading peripheral neuropathy by health care professionals (28), and as in other aspects of quality of life (29), the patients' own assessment of neuropathy symptoms and functional limitations may be more meaningful. Randomized double-blind trials of putative agents will be required to evaluate conclusively the presence or absence of a neuroprotective effect, and these trials will need to include patient questionnaires. However, for initial screening of potential neuroprotective agents such as amifostine or glutamine, an argument can be made to use objective measurements such as those from nerve conduction and quantitative sensory tests, although these tests have not been extensively used or validated in clinical studies of chemotherapy-associated neuropathies.

The present screening study showed no significant effect of amifostine on neuropathy in the following areas after high-dose paclitaxel: nerve conductions, quantitative sensory tests, and composite neuropathy scores. It is possible that the lack of an effect of amifostine was related to the schedule of administration. Amifostine was administered over 10 min just before and 12 h into the 24-h paclitaxel infusion. The potential for overlapping cardiovascular and other possible toxicities precluded a more sustained amifostine infusion in this exploratory trial. The lack of an effect of amifostine, however, may not be unexpected because the postulated cytoprotective mechanism of amifostine is at the level of DNA whereas paclitaxel neuropathy is thought to occur as a consequence microtubule assembly, disrupting axoplasmic transport (1). The present exploratory study suggests that a large, randomized trial of amifostine at the schedule used here to reduce neurotoxicity of high-dose paclitaxel is not warranted.

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