Peripheral Neuropathy Induced by Paclitaxel: Recent Insights and Future Perspectives

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Abstract: Paclitaxel is an antineoplastic agent derived from the bark of the western yew, *Taxus brevifolia*, with a broad spectrum of activity. Because paclitaxel promotes microtubule assembly, neurotoxicity is one of its side effects. Clinical use of paclitaxel has led to peripheral neuropathy and this has been demonstrated to be dependent upon the dose administered, the duration of the infusion, and the schedule of administration. Vehicles in the drug formulation, for example Cremophor in Taxol[®], have been investigated for their potential to induce peripheral neuropathy. A variety of neuroprotective agents have been tested in animal and clinical studies to prevent paclitaxel neurotoxicity. Recently, novel paclitaxel formulations have been developed to minimize toxicities. This review focuses on recent advances in the etiology of paclitaxel-mediated peripheral neurotoxicity, and discusses current and ongoing strategies for amelioration of this side effect.

Key Words: Taxol, cremophor, ABI-007, peripheral neuropathy.

INTRODUCTION

Chemotherapeutic agents can cause toxic effects on peripheral nerves. Severity may range from loss of sensory function and mild paresthesias to neuropathic pain, severe ataxia and weakness leading to pronounced disability. Involvement of autonomic nerve fibers with orthostatic hypotension, impotence and incontinence may further reduce the quality of life. Many cytotoxic agents are reported to be neurotoxic, but for only a few drugs such as paclitaxel is peripheral neuropathy an important and often dose-limiting side-effect.

Paclitaxel is an antineoplastic agent originally derived from the bark of the western yew tree, *Taxus brevifolia*, with activity against several tumors including carcinoma of the ovary, breast, lung and the head and neck. Paclitaxel exerts its antitumor activity by promoting microtubule assembly. As a consequence, neuropathy is one of its toxic side effects. Peripheral sensory neuropathy is the most commonly reported neurotoxic effect of paclitaxel and it limits treatment with high and cumulative doses of paclitaxel when given alone or in combination with other neurotoxic antineoplastic agents such as cisplatin.

PATHOGENESIS OF PACLITAXEL-MEDIATED NEUROPATHY

The primary site of pathogenesis of the peripheral neuropathy associated with paclitaxel therapy is not clear. In tissue culture, paclitaxel promotes the formation of abnormal bundles of microtubules within the cytoplasm, leading to the disruption of normal cell function and proliferation. In patients, this is results in the desired effect on the tumor, however, this is not without toxicity to normal tissue.

Microtubules are important for the development and maintenance of neurons. Microtubule elongation contributes toward the growth of neurites through interactions with the growth cone [1-3], and they are the major participating elements mediating axonal transport in the neuron [4]. Microtubules also provide important structural support for neurons. Given the fact that paclitaxel disrupts microtubule assembly, it is not unexpected that neuronal development and function could be dramatically impaired. *In vitro* studies have demonstrated that large abnormal microtubule arrays in spinal cord-sensory ganglion explant cultures are formed following exposure to paclitaxel [5, 6], resulting in abnormal neurite outgrowth and neuronal death [5-8].

Paclitaxel formulated in Cremophor-ethanol (Taxol[®]) has been shown to distribute within the central and peripheral nervous system in a rat model [9]. Paclitaxel was shown to accumulate in the dorsal root ganglia, as well as access the brain, albeit at very low concentrations. Intermediate concentrations of paclitaxel were present in the sciatic nerve and spinal cord, possibly due to paclitaxel transport along the centrifugal and centripetal branches of the dorsal root ganglia neuron axons [9]. Paclitaxel induced neuropathy is probably due to dysfunctional microtubules in dorsal root ganglia, axons and Schwann cells [10, 11]. *In vivo* studies have shown that direct injection of paclitaxel into the rat sciatic nerve causes the formation of unusual microtubule aggregates resulting in demyelination and loss of axoplasmic transport [10, 11].

Although *in vitro* studies have shown paclitaxel to affect Schwann cells, it is not clear that only a demyelinating process is involved. Overall, it is likely that paclitaxel induces both a sensory axonopathy and ganglioneuropathy, the latter occurring with higher single and cumulative doses, or in combination with cisplatin [12]. Risk factors that may predispose to developing severe peripheral neurotoxicity include significant prior exposure to known neurotoxic agents, and antecedent medical disorders that are also

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capable of inducing peripheral neurotoxicity, such as diabetes mellitus [13].

Efforts to examine the effects of paclitaxel on neurons *in vivo* involved direct injection of the drug into rat sciatic nerve [14, 15]. These studies demonstrated that paclitaxel induced the formation of unusual aggregates of microtubules in both axons and Schwann cells, resulting in acute demyelination and chronic loss of axoplasmic transport. Subsequent studies have shown that paclitaxel administration inhibits the usual regenerative response of axons and Schwann cells to nerve crush injuries in rodent models [16, 17]. Systemic administration of paclitaxel to mice results in an elevation of the tail-flick threshold (which tests the sensitivity to a thermal noxious stimulus), reduces the level of substance P (a neuropeptide involved in pain transmission) measured in the dorsal root ganglia, and reduces the action potential amplitude as recorded from the caudal nerve [11]. In this mouse model, nerve conduction velocities were not significantly affected by the administration of paclitaxel. In rat models, using different methods of administering paclitaxel, the predominant abnormalities included decreased nerve conduction velocities, dorsal root axonal degeneration, and demyelination, but without weakness and heat nociception [18, 19].

To gain an improved understanding of the pathogenesis of neurotoxicity associated with paclitaxel treatment, *in vivo* experiments have also been performed using a variety of animal models. Authier *et al.* described a new animal model of neuropathic pain produced by the single intraperitoneal administration of Taxol (32 mg/kg) to male Sprague-Dawley rats [20]. Taxol administration produced an important and rapidly developing mechanical hyperalgesia, a thermal hypoalgesia but no mechanical or thermal allodynia. Degenerative changes were observed in the sciatic nerve, the nerve fibres in the paw subcutaneous tissue and in the lumbar spinal cord. When Taxol or the Cremophor-ethanol vehicle were repeatedly injected once a week for 5 weeks, similar nociceptive disorders were observed in addition to a decrease in peripheral nerve conduction velocity. The selective dysfunction of high-diameter myelinated fibers observed after one single administration of Taxol (32 mg/kg) may be attributable to paclitaxel-induced neuropathy. However, other mechanisms causing neurochemical dysfunction must also be involved [20].

Rat models have also been used to establish an experimental paclitaxel-induced painful peripheral neuropathy. Adult male rats were given four intraperitoneal injections on alternate days of vehicle or 0.5, 1.0, or 2.0 mg/kg of paclitaxel (Taxol) [21]. Behavioral tests for pain using mechanical and thermal stimuli applied to the tail and hind paws, and tests for motor performance, were taken before, during, and after dosing for 22–35 days. All three doses of paclitaxel caused heat-hyperalgesia, mechano-allodynia, mechano-hyperalgesia, and cold-allodynia, but had no effect on motor performance. Neuropathic pain began within days and lasted for several weeks. No dose-response relationships were detected. Tests at the distal, mid, and proximal tail failed to show evidence of a length-dependent neuropathy. Vehicle control injections had no effect on any measure. No significant systemic toxicities were noted in the

paclitaxel-treated animals. Light-microscopic inspection of the sciatic nerve (mid-thigh level), L4–L5 dorsal root ganglia, and dorsal and ventral roots, and the gray and white matter of the L4–L5 spinal cord, showed no structural abnormalities. Electron microscopic examination of the sciatic nerve (mid-thigh level) and the L4–L5 dorsal root ganglia and dorsal horns demonstrated no degeneration of myelinated and unmyelinated axons in the sciatic nerve and roots, but revealed endoneurial edema [21]. This model may be useful in understanding a significant source of pain in cancer patients, and in finding ways to avoid the neurotoxicity that limits paclitaxel therapy.

CLINICAL PACLITAXEL-MEDIATED NEUROTOXICITY

The most common clinical neurotoxicity associated with paclitaxel administration is a predominantly sensory peripheral neuropathy. The neurotoxicity is dose- and infusion-duration related, and most frequently occurs when the dose of paclitaxel per administration exceeds 250 mg/m² infused over ≥24 hours [10, 12, 22]. Early on, infusion related reactions and neutropenia were the most common adverse effects seen with the use of paclitaxel. However, with the use of premedication and alteration of the infusion schedule these toxicities have decreased in frequency and severity. With the use of granulocyte colony-stimulating factors given in combination with paclitaxel, neurotoxicity becomes the dose-limiting toxicity [23]. The risk of developing neuropathy following treatment with paclitaxel is greater for patients who have preexisting conditions that may cause neuropathy (such as diabetes or kidney disease) or who have been previously treated with other neurotoxic chemotherapy such as cisplatin and vincristine [22].

Signs and symptoms of paclitaxel induced peripheral neuropathy may begin as early as 24–72 hours after administration of high single doses of paclitaxel [10, 12]. The severity of paclitaxel neuropathy is related to both the single and cumulative dose. It usually occurs at cumulative doses in excess of 1,400 mg/m² [24]. With lower doses of paclitaxel (135–200 mg/m²) or with weekly regimens, neuropathy is less common. Presenting symptoms include numbness, paresthesias and burning pain in a glove-and-stocking distribution [25]. Symptoms are often symmetrical, and usually have their origins distally in the lower extremities. Patients commonly report the simultaneous onset of symptoms in toes and fingers, but asymmetric presentations have been described. Facial involvement is less common, but has been reported [26]. Although mild symptoms have been reported to improve or resolve completely within several months after discontinuation of therapy [12, 27], the symptoms and deficits have been reported to persist longer in patients who develop severe neuropathy [12].

At the time of neurologic examination, the most common findings are diminished sensation to pain, temperature, vibration and/or proprioception, and loss of deep tendon reflexes [10]. These findings suggest that there is toxicity to both small- and large-sensory fibers, since large sensory fiber loss results in impaired vibratory and proprioceptive sensation and deep tendon reflexes. Small-diameter sensory

fibers convey pain and temperature sensation, although patients may complain of neuropathic pain or abnormal hypersensitivity to pain. Autonomic neuropathic manifestations, such as paralytic ileus and symptomatic orthostatic hypotension, have been observed but they are rare [25]. Other rare neurotoxicities observed with paclitaxel treatment include optic nerve disturbances, epileptic seizures and encephalopathy [28].

Unlike sensory neuropathy, motor neuropathy is not a frequent neurotoxicity of paclitaxel but has been observed in patients receiving higher doses of paclitaxel [29]. In these patients the weakness may present either proximally or distally. Distal motor neuropathy is generally described as being relatively mild, however, it progresses with treatment. In comparison, proximal motor neuropathy may be more severe, can present at any stage of treatment, and occurs independently of sensory neuropathy [29].

Transient myalgias are commonly observed after treatment with moderate to high paclitaxel doses administered over 6 to 24 hours [12]. These symptoms usually occur 2 or 3 days following treatment and typically resolve within 5 to 6 days. Myalgias are generally mild and occur rarely at doses below 170 mg/m². However, patients receiving doses from 200 to 250 mg/m² may experience myalgias more commonly, and these tend to be mild to moderate in severity [12].

PACLITAXEL DOSE AND ADMINISTRATION SCHEDULE DEPENDENT NEUROTOXICITY

The single paclitaxel dose, as well as the cumulative dose, seems to be related to the severity of the resulting neuropathy. Postma *et al.* [30] have reported the results of neurologic assessments in 27 patients who received 3-hour paclitaxel infusions at three different starting dose levels, 135, 175, and 250 to 300 mg/m². They reported neuropathic symptoms in 50%, 79% and 100% of patients, respectively, and neuropathic signs in 83%, 86%, and 100%, respectively. Dose-limiting neurotoxicity occurred in 0%, 21%, and 71% of patients, respectively [30]. In general, it appears that at lower dosages per cycle (135-200 mg/m²) neuropathy is usually mild, less frequent, and occurs at a higher cumulative dosage (>1400 mg/m²). At higher dosage per cycle (>250 mg/m²), a more severe neuropathy is frequent, which often starts in the days following the first cycle. Despite the frequent improvement before the next cycle, symptoms tend to increase after additional cycles.

Paclitaxel dosing and scheduling changes have been evaluated in several clinical studies in an effort to optimize therapeutic efficacy while minimizing toxicity. Most of these early investigations were done to extend the infusion duration in an effort to minimize the hypersensitivity reactions seen with shorter administration schedules. With proper premedication, shorter infusions became possible. The various infusion schedules which have been tried have made it possible to gain an increased understanding of toxicities related to infusion dose and duration, prompting pharmacokinetic analysis.

A higher incidence of paclitaxel neuropathy has been reported when paclitaxel is infused over three hours as

compared to 24 hours [31, 32]. One possible explanation is that the neuropathy may be related to peak blood concentrations. As a result, while <5% of patient with advanced ovarian cancer treated with cisplatin (75 mg/m²) and infusional paclitaxel (135 mg/m²) experienced Grade 3 neuropathy [33], 20-25% developed severe symptoms when treated with the same dose of cisplatin and paclitaxel in fused over 3 hours (175 mg/m²) [34, 35].

The effects of weekly short infusions of paclitaxel on the development of peripheral neuropathy were assessed in 92 patients with advanced cancer. Patients were randomized to treatment with 100 mg/m² of paclitaxel weekly infused over 1 versus 3 hours [36]. The development of peripheral neuropathy (PNP), a primary endpoint of the study, was evaluated by a clinical score including sensory symptoms, strength, tendon reflexes and vibratory sense (range 0-12; PNP >3 points). The probability to exceed a PNP score of 3 increased from 0.20 versus 0.30 after six to 0.68 versus 0.47 after 12 administrations (1 versus 3 h: *p* = 0.66). Following 12 weeks of treatment only 25% of assessable patients were free of peripheral neuropathy [36]. This study demonstrated a rapid increasing risk of developing peripheral neuropathy in the course of weekly treatment with paclitaxel. However a significant difference in the development of peripheral neuropathy was not observed between the two infusion schedules.

The lack of significant difference in the development of peripheral neuropathy between 1 and 3 hour weekly infusions of 100 mg/m² doses could have in part been related to the fact that a reduction in the infusion time decreases the area under the concentration-time curve (AUC) of unbound paclitaxel but not that of total paclitaxel [37]. The shortening of infusion time from 3 hours to 1 hour has been shown to increase the AUC of its vehicle Cremophor (CrEL), which is known to have neurotoxic potential as well (see below) [37, 38].

To better understand the role of paclitaxel pharmacokinetics on peripheral neuropathy, a prospective evaluation was conducted in 24 patients with advanced cancer. Patients were randomized to receive a maximum of 12 weekly-administered 1 or 3 hour infusions of 100 mg/m² of paclitaxel (as Taxol). Neurotoxicity was scored using a standardized clinical PNP system. Patients were questioned about their symptoms and underwent a clinical examination based on a tuning fork test, as well as an evaluation of strength and peripheral reflexes. This individual clinical score could range from 0 (best) to 12 (worst) points and PNP was defined as an event when the PNP score exceeded 3 for the first time. Patients who developed peripheral neuropathy (*n*=14) received more weeks of therapy and showed significantly higher overall systemic drug exposures for both total and unbound paclitaxel than those without peripheral neuropathy [39].

PACLITAXEL FORMULATION VEHICLE-ASSOCIATED NEUROPATHY

The most commonly used commercial preparation of paclitaxel is Taxol, which is formulated in a solvent system composed of CrEL and dehydrated ethanol USP (1:1, vol/vol). CrEL is widely used as a vehicle for the

solubilization of number of other hydrophobic drugs, including anesthetics, vitamins, sedatives, photosensitizers, and immunosuppressives such as cyclosporin. The amount of CrEL in paclitaxel per administration is relatively high (~25 mL at the recommended 3-weekly dose), and therefore its toxicological and pharmacological behavior in the context of chemotherapeutic treatment with paclitaxel is of major importance. While it is well known that the hypersensitivity reactions associated with Taxol infusion are caused, in part, by CrEL, it is less well known that CrEL can also cause neurotoxicity.

Experimental data has show that CrEL can cause peripheral neuropathy associated with paclitaxel chemotherapy [38, 40]. CrEL concentrations achieved with therapeutic doses of paclitaxel have been shown to produce axonal swelling, vesicular degeneration, and demyelination in rat dorsal root ganglion neurons exposed to this vehicle [41], which is consistent with the data from electrophysiologic studies in patients with neurotoxicity after treatment with paclitaxel [12].

Interestingly, in rats treated with CrEL-free ^3H -paclitaxel, paclitaxel was not detectable in the peripheral nervous system, indicating that the anticancer drug itself might not be responsible for the observed toxicity and could be caused by CrEL [42]. The hypothesis of CrEL-induced neurotoxicity is further supported by the fact that intravenously administered cyclosporine A causes neurotoxicity in approximately 25% of patients [43], while this side effect is rarely seen with oral administration. This is also consistent with a previous finding that CrEL is not absorbed intact when given orally as a result of intestinal degradation [44].

It has been postulated that the neurotoxic properties of CrEL might be caused by impurities present in the vehicle such as residual ethylene oxide and unsaturated fatty acids, possibly due to the appearance of peroxidation products.[45] Nonetheless, the ethoxylated derivatives of castor oil probably account for most of the neuronal damage observed with CrEL [45].

ALTERNATE DELIVERY STRATEGIES FOR PACLITAXEL

Despite attempts to minimize paclitaxel-induced neurotoxicity with changes in dose, infusion schedule and premedication or co-treatment with neuroprotective agents, paclitaxel-induced neurotoxicity remains dose-limiting in many instances and is a barrier to achieving the desired clinical response.

The toxicity associated with the presence of CrEL in the paclitaxel formulation has prompted extensive research to develop alternative delivery forms. Several strategies have been utilized to develop a CrEL free formulation of paclitaxel, including biological approaches (oral administration), chemical approaches (prodrugs, analogs), and pharmaceutical approaches (use of co-solvents, emulsions, liposomes, cyclodextrins, microspheres, nanoparticles) [46, 47].

TOCOSOL® Paclitaxel is an injectible, vitamin E based emulsion that is CrEL-free. This ready-to-use formulation of paclitaxel was granted Orphan Drug Designation by the FDA in 2003 for the treatment of nonsuperficial urothelial cancer.

In the Phase I evaluation of this agent (formerly S-8184), the dose limiting toxicities were neutropenia and febrile neutropenia. Grade 3 or greater neuropathy was not reported [48]. A Phase I/II study in patients with non-small cell lung cancer, transitional cell, ovarian or colorectal cancer in evaluated the weekly administration of TOCOSOL paclitaxel at doses of 100-120 mg/m² in 91 patients. Neuropathy was reported in 22% of patients (19/86) with grade 3 neuropathy been seen after a median of 9 weeks of therapy in 5 patients, 4 of whom had prior therapy with cisplatin [49].

The most extensively studied alternative paclitaxel preparation is a human albumin-stabilized, lyophilized nanoparticle formulation (i.e., ABI-007) that is free of CrEL. ABI-007 (Abraxane), has recently been approved by the US Food and Drug Administration for the treatment of metastatic breast cancer. Interestingly, ABI-007 was found to have significantly less toxicity than Cremophor-containing paclitaxel in mice [50].

In a Phase III study conducted in patients with metastatic breast cancer, patients treated with ABI-007 achieved a significantly higher objective response rate and time to progression than those treated with Cremophor-containing paclitaxel [51]. Patients were randomized to treatment every 3 weeks with either ABI-007 260 mg/m² intravenously (IV) without premedication to prevent hypersensitivity reactions (n=229) or Taxol 175 mg/m² IV with premedication (n=225). Grade 3 sensory neuropathy was higher in the ABI-007 arm (10%) than in the paclitaxel arm (2%), with no episodes of grade 4 neuropathy. This may be related to the administration of a 49% higher paclitaxel dose in the ABI-007 arm as compared to Taxol [52]. It is of interest to note that the incidence of neuropathy observed with ABI-007 at a dose of 260 mg/m² is substantially less than that seen with Taxol administered at a similar dose of 250 mg/m² [53]. Sensory neuropathy was improved to grades 1 or 2 within a median of 22 days if ABI-007 was withheld. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group. No differences in physician or patient grading of peripheral neuropathy were observed between the 2 groups when these parameters were analyzed on the basis of total paclitaxel dose administered [52].

Given its mechanism of action, peripheral neuropathy would be expected to occur with a solvent-free formulation paclitaxel. Consistent with this hypothesis, in the Phase I evaluation of Genexol-PM, a polymeric micelle formulated paclitaxel which does not contain CrEL, neuropathy and myalgia were both dose-limiting toxicities despite the absence of CrEL [54]. However, without the neurotoxicity induced by CrEL, neuropathy might be less severe and/or resolve more rapidly. In the Phase III comparative trial sensory neuropathy resulting from treatment with ABI-007 was reported to improved rapidly (median, 22 days) from grade 3 to lower grades with treatment interruption [52]. Available data on recovery from Taxol induced neuropathy suggests that the toxicity resolves within several months after stopping therapy [27].

NEUROPROTECTIVE AGENTS

Various attempts have been made to prevent chemotherapy-induced neuropathy with possible neuroprotective

agents. Presently, no therapeutic options are available once a patient develops chemotherapy-induced neuropathy. One can only try to diminish symptoms with symptomatic treatment, such as amitriptyline in case of a painful taxane-induced neuropathy. Prevention of toxic neuropathies by administration of rescue-drugs would have great clinical significance, as this could allow for increased dose-intensity for agents for which neuropathy is a dose-limiting toxicity. However, a prerequisite for the use of any such agent is that it should not reduce the antitumor activity of the anti-neoplastic therapy and/or alter the agent's pharmacokinetic profile.

Amifostine

Amifostine is an organic thiophosphate compound, which in animal models selectively protects normal tissue against the toxicity of both radiation and a variety of chemotherapeutic agents [55]. As a prodrug, amifostine is dephosphorylated at the tissue site to the active metabolite, WR-1065. In the cell, it is thought to act by binding to and detoxifying the reactive molecules of alkylating or platinum agents and by acting as a scavenger for the oxygen free radicals produced by ionizing radiation and certain chemotherapeutic agents [56]. Preclinical studies have shown that amifostine may offer cytoprotection of normal tissues from paclitaxel as well. *In vitro* studies compared the selective cytoprotection of amifostine on paclitaxel in culture [57].

The American Society Clinical Oncology Guidelines for the use of chemoprotectants does not support the routine use of amifostine [58]. At the time the guidelines were prepared, there were no data from phase II or III studies to evaluate whether amifostine protects against paclitaxel neurotoxicity. The available clinical data were from a phase I dose-escalation study of paclitaxel (3-hour infusion) and amifostine. Twenty-two patients with advanced malignancies were treated with 910 mg/m² of amifostine and escalating doses of paclitaxel starting at 135 mg/m² up to 310 mg/m² [58]. Higher doses of paclitaxel were reached when drug administration was preceded by amifostine. Two patients developed grade 3 neuropathy, which is less than what would be predicated based on previous studies of paclitaxel at these doses.

Following the evaluation of amifostine in the Phase I setting, a trial was conducted in 40 women with metastatic breast cancer to determine whether the neurotoxicity of paclitaxel 250 mg/m² given over 3 hours every 3 weeks could be reduced by pretreatment with amifostine 910 mg/m² [59]. Patients were randomized to receive either paclitaxel alone or paclitaxel preceded by amifostine. At baseline and after each cycle, all patients completed questionnaires for neurologic symptoms and had standardized neurologic examinations, including objective assessments of power and vibration sense. No differences were observed in any of the measures of neurotoxicity with this administration dose and schedule [59].

The protective effects of amifostine have also been assessed in 40 patients with germ cell tumors following treatment with conventional-dose paclitaxel, ifosfamide, cisplatin (TIP) and high-dose carboplatin, etoposide and thiotepa (CET) followed by peripheral blood progenitor cell

(PBPC) rescue. Patients were randomized either to receive one fixed dose of 500 mg amifostine per day of conventional-dose TIP and two fixed doses of 500 mg per day amifostine during high-dose CET (group A, n = 20) or no amifostine (group B, n = 20). Prior to the first cycle of TIP, one course of 175 mg/m² paclitaxel and 5 g/m² ifosfamide (TI) followed by granulocyte-colony stimulating factor (G-CSF) at 10 microg/kg/day were given for PBPC mobilization. Peripheral neurotoxicity (i.e., paresthesia or sensorymotor impairment), hearing impairment, hematologic toxicity, nephrotoxicity, nausea, myalgia, skin- and liver-toxicity did not differ significantly between the two patient groups, and the response rates to TIP and high-dose CET were comparable in patients with or without amifostine [60].

The benefit of amifostine in preventing or reducing the neuropathy induced by high-dose paclitaxel has been investigated in a study of patients with breast cancer treated with infusional paclitaxel (725 mg/m²/24-hour infusion) in combination with doxorubicin and cyclophosphamide on two autologous peripheral blood stem cell transplant protocols, one with and one without amifostine (740 mg/m² infused over 10 minutes before and 12 h after initiation of the paclitaxel infusion). Patients were evaluated before chemotherapy and 20-40 days later with neurological examination, a composite peripheral neuropathy score, peroneal and sural nerve conduction studies and quantitative sensory testing. Symptoms of distal symmetrical peripheral neuropathy in the feet and absent ankle deep tendon reflexes occurred in all patients after chemotherapy. There were no differences between the amifostine group and the chemotherapy only group in the percentage of patients with decrease in vibration or pin sensation, the median increase in vibratory and cold detection threshold, or the reduction in sensory nerve (sural nerve) or motor nerve (peroneal nerve) amplitudes. Amifostine was ineffective at preventing or reducing the neurotoxicity of paclitaxel in this setting [61].

Glutamate

Glutamate has been evaluated as a possible neuro-protectant of paclitaxel neurotoxicity in a rat model of cytotoxic neuropathy [62]. Neuropathy was manifest as a gait disturbance in 100% of paclitaxel treated animals after two weeks. Significant elevations of mean tail-flick threshold, a measure of sensory impairment, were observed. Impaired rota-rod performance was observed in both light and dark with paclitaxel, indicating motor neuropathy. In cytotoxic treated animals supplemented with oral sodium glutamate (approx. 500 mg/kg/day in drinking water) from 24 hours before chemotherapy, there was a significant delay in time to onset of gait disturbance allowing significantly higher mean doses to be tolerated. Mean tail-flick and rota-rod scores were unchanged from baseline suggesting a protective effect of glutamate on neuropathy in this model. Glutamate administered at this dose did not impair the cytotoxic efficacy of paclitaxel against a transplantable rat mammary adenocarcinoma grown subcutaneously in rats [62].

Nerve Growth Factor

Nerve growth factor (NGF) is necessary for the development of dorsal root ganglia and the maintenance of

normal ganglion function in adults [63]. A neuroprotective effect of nerve growth factor was suggested by several *in vitro* studies on cisplatin, paclitaxel, and suramin neurotoxicity [8, 41, 64, 65]. In animal models, NGF prevented the Taxol- and cisplatin-induced decreased of compound motor action potential, and the increase of the threshold of thermally induced pain [11, 63].

Insulin-like Growth Factor

Insulin like growth factor-1 is a factor probably involved in regulating body growth during development. It has a variety of other actions, including a stimulation of motor and sensory nerve regeneration. In animal experiments, it prevented the development of both vincristine- and paclitaxel-induced neuropathy [66, 67].

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC) is a naturally occurring compound with neuroprotective activity. The protective activity of ALC on paclitaxel-induced neuropathy has been assessed in a rat model. Sensory nerve conduction velocity (SNCV) was measured in rats before, at end, and after an additional follow up period following treatment with paclitaxel alone or in combination with ALC. A significant reduction in paclitaxel neurotoxicity was observed following ALC cotreatment. *In vitro* experiments in different tumor systems did not show loss of the antineoplastic activity of paclitaxel in the presence of ALC [68].

Vitamin E

Vitamin E is a fat soluble vitamin which has been used in many conditions including malabsorption disorders, hematologic disorders, and cardiovascular disease. A randomized pilot trial assessing the effects of vitamin E supplementation on chemotherapy-induced peripheral nerve damage was recently conducted in 31 patients with cancer treated with six courses of cumulative cisplatin, paclitaxel, or their combination regimens [69]. Patients were randomly assigned in two groups and followed by neurologic examination and electrophysiologic study. Patients assigned in Group I (n = 16) received oral vitamin E at a daily dose of 600 mg/day were during chemotherapy and 3 months after its cessation were compared to patients of Group II (n = 15), who received no supplementation and served as controls. The severity of neurotoxicity was summarized by means of a modified peripheral neuropathy score. The incidence of neurotoxicity differed between the two groups, occurring in 4/16 (25%) patients assigned in the vitamin E supplementation group and in 11/15 (73.3%) patients assigned in the control group (p = 0.019). Mean peripheral neuropathy scores were 3.4 +/- 6.3 for patients of Group I and 11.5 +/- 10.6 for patients of Group II (p = 0.026). The relative risk (RR) of developing neurotoxicity was significantly higher in case of control patients, RR = 0.34, 95% CI = 0.14 to 0.84.

CONCLUSIONS

Despite clinical efforts to minimize paclitaxel-induced neurotoxicity, peripheral neuropathy still remains an important toxicity that sometimes is dose-limiting, as in the case of high-dose Taxol. Clinicians must balance the potential for

therapeutic efficacy through maintenance of dose-intensity with that of potentially causing a painful peripheral neuropathy. Investigations to improve understanding of the pathogenesis of paclitaxel-induced neuropathy have been ongoing. However, various attempts to minimize toxicity through altered infusion schedules have not entirely eliminated the neurotoxicity of paclitaxel. Recently, a novel formulation of paclitaxel that lacks CrEL, ABI-007, has been developed to help improve tolerability. This is particularly important, since the concurrent administration of Taxol with neuroprotective agents has demonstrated little success in the clinical setting. Given the demonstrated efficacy in a variety of tumor types, continuing investigation into methods aimed at minimizing the neurotoxicity associated with paclitaxel administration are clearly needed.

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