

Neuropathy Associated with Microtubule Inhibitors: Diagnosis, Incidence, and Management

Sandra M. Swain, MD, and Joseph C. Arezzo, PhD

Dr. Swain is Medical Director of the Washington Cancer Institute at the Washington Hospital Center, in Washington, DC. Dr. Arezzo is Vice Chair, Department of Neuroscience at Albert Einstein College of Medicine in The Bronx, NY.

Address correspondence to:
Sandra M. Swain, MD
Medical Director,
Washington Cancer Institute
Washington Hospital Center
110 Irving Street, NW
Washington, DC 20010
Phone: 202-877-8112
E-mail: sandra.m.swain@medstar.net

Abstract: Microtubule inhibitor (MTI)-based chemotherapies used in the treatment of breast cancer—including vinca alkaloids, taxanes, and epothilones—are known to be associated with peripheral neuropathy. The incidence and severity of neuropathy, most frequently sensory in nature, depend on the agent used, absolute and cumulative drug dose, administration schedule, and presence of comorbidities. Although some first-generation vinca alkaloids, such as vincristine, were associated with severe mixed sensory/motor neuropathy, the deficits associated with newer agents in this class (eg, vinflunine) are generally milder and limited to distal sensory signs and symptoms. Among the taxanes, sensory neuropathy is reported more often with administration of paclitaxel and albumin-bound paclitaxel and less frequently with docetaxel. Epothilones, a new class of MTI, may be associated with grade 3/4 peripheral neuropathy; however, the neuropathy associated with ixabepilone, a novel epothilone B analog, is generally mild to moderate and reversible to baseline or grade 1 levels. The neuropathy induced by MTI therapy is best managed with dose adjustments and/or treatment delay. This article provides an overview of the incidence, characteristics, and management of MTI-associated neurotoxicities for known vinca alkaloids and taxanes, as well as newer agents, such as vinflunine and ixabepilone.

Microtubule inhibitors (MTIs) comprise a group of chemotherapeutic agents that share a broad mechanism of action, targeting cytoskeletal microtubules that are critical to many intracellular functions of cancer cells.¹ This class includes distinct types of agents: the vinca alkaloids, which are microtubule-destabilizing; the taxanes; the natural epothilones; and the semisynthetic epothilone analogs, which are microtubule-stabilizing.^{1,2} Microtubules play a key role in both the structure and the function of neurons; therefore, MTI therapy is generally associated with some form of neuropathy. The induced neuropathy can vary in time of onset, rate of progression, severity, pattern, and reversibility as a function of the specific inducing agent and

Keywords

Sensory neuropathy, microtubule inhibitor, vinca alkaloid, taxane, epothilone, ixabepilone.

dose, but it is often dose-limiting and can significantly affect patient quality of life.^{3,4} In this review, we present data on the incidence and characteristics of MTI-associated neuropathy. Management of peripheral neuropathy associated with the recently developed epothilone B analog ixabepilone (Ixempra, Bristol-Myers Squibb)⁵ is also discussed in detail.

Mechanisms of MTI-associated Neuropathy

Although the precise mechanisms of neurotoxicity associated with MTIs have not been fully defined, preclinical physiologic and histopathologic studies indicate that the pathogenesis of MTI-associated neuropathy is principally a consequence of the interruption of axonal transport within neurons.⁶ Intact microtubules and their associated neurofilaments are essential for both anterograde and retrograde axonal transport. Because of the excessive length of peripheral axons, MTI-induced deficits are especially disruptive to axons forming peripheral nerves. The relative fenestration of the blood-nerve barrier at the level of the dorsal root ganglia⁷ results in a greater effect of MTIs on sensory versus motor nerves. Generally, MTI-induced neuropathies are considered length-dependent distal sensory axonopathies,⁸ but in some cases there can also be involvement of motor and/or autonomic axons, as well as damage to myelin and Schwann cells.^{3,9} In vivo studies performed in rats demonstrated aggregation of microtubules in both neuronal axons and Schwann cells after local injection of paclitaxel.¹⁰ Additional in vitro studies using rat dorsal root ganglia cultures suggested the reversibility of paclitaxel-induced neuropathy after exposure of 1–3 days.¹¹

A vehicle commonly used in the formulation of lipophilic chemotherapy agents for intravenous administration is Cremophor-EL (polyethoxylated castor oil; BASF). A phase III trial of paclitaxel in metastatic breast cancer (MBC) suggested that Cremophor-EL may contribute to MTI-associated neuropathy.¹² However, a pharmacokinetic study of paclitaxel in patients with advanced cancer does not support this hypothesis,¹³ and a Cremophor-free taxane formulation, albumin-bound paclitaxel (Abraxane, Abraxis/AstraZeneca), is associated with neuropathy (Table 2).¹² Thus, a potential role for this vehicle in the development of peripheral neuropathy remains undefined.

Diagnosis of MTI-associated Neuropathy

Peripheral neuropathies associated with MTIs may vary in nature depending on the type of nerve fibers involved: sensory, motor, or autonomic.^{14,15} Positive sensory manifestations may include paresthesia, pain or burning, and allodynia.^{15,16} Negative signs and sym-

ptoms include hyperesthesia or numbness, decreased vibratory perception, and reduced or absent Achilles tendon reflex.^{3,14,17} These deficits are usually symmetric and progress along a distal-to-proximal gradient. The characteristic pattern of findings adheres to a classic “stocking-and-glove” distribution, with the most severe symptoms generally appearing first in the lower extremities. Diminished vibration sensitivity (ie, elevated threshold) is commonly one of the earliest manifestations of MTI-induced neuropathy. Loss of proprioception (limb-position sense) is a late event and usually limited to patients with grade 3/4 sensory neuropathy.³

Motor deficits are less frequent with MTIs than sensory symptoms; however, generalized muscle weakness, decreased deep tendon reflexes, diminished fine motor skills, and vocal cord dysfunction have been reported. Autonomic motor effects such as abdominal cramping, constipation or severe ileus, and urinary retention have also been linked to vinca alkaloids and, less commonly, to other MTIs.^{14,18,19} Autonomic symptoms, which may be severe, generally occur with high-dose vincristine therapy.¹⁹

Ideally, the clinical assessment of peripheral neuropathy should include a combination of signs (eg, reflexes, strength), symptoms (eg, pain, paresthesia), laboratory tests (eg, quantitative sensory testing, electrophysiology), and measures of activities of daily living.³ In practice, the standardized criteria established by the National Cancer Institute (NCI; Table 1)²⁰ and the Eastern Oncology Cooperative Group²¹ are commonly used to grade the severity of symptoms and the progression of the neuropathy. For instance, early diagnosis and management of mild to moderate (grade 1/2) symptoms is important to prevent progression to severe neuropathy.³ Recently, the use of the Total Neuropathy Score in addition to the NCI scale has been advocated in a multicenter clinical trial of chemotherapy-induced peripheral neuropathy.²² Although sensory neuropathy is usually self-evident, several confounding factors that may be experienced by patients (eg, upper extremity lymphedema and nail toxicity) can hamper an accurate diagnosis. There is compelling evidence that treatment-induced peripheral neuropathy is underreported.¹⁷

Objective tests added sensitivity and specificity to the assessment of neuropathy, although they are often costly and complex and, in many cases, their predictive validity has not been fully established.²³

Neuropathy Associated With Chemotherapeutic Agents

Platinum-based chemotherapy is often associated with the development of neuropathy, which is typically dose-

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Table 1. NCI-CTCAE v 3.0 Grading Criteria for Sensory Neuropathy

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4
Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling

ADL=activities of daily living; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 2. Incidence of Vinca Alkaloid- and Taxane-associated Peripheral Neuropathy

	Dose per Cycle, mg/m ²	Schedule	Grade 3/4 Sensory Neuropathy, %	First Author
Vinca alkaloids				
Vincristine (liposomal)	2	q14d	31	Sarris ²⁶
Vinorelbine	25–30	weekly	0–6*	Vogel ²⁷ ; Fumoleau ²⁸ ; Zelek ³⁰
Vinflunine	320	q3w	0	Campane ²⁹
Taxanes				
Paclitaxel [†]	175	q3w	2–12	Gradishar ¹² ; Jones ³⁴ ; Winer ³⁵ ; Nabholz ³⁶ ; Seidman ³⁸
	210		19	Winer ³⁵
	250		12–32	Seidman ³⁷ ; Smith ³⁹ ; Winer ³⁵
	160	d1 and d8 q3w	4	Blum ⁴⁰
	80–100	weekly	9–24*	Seidman ³⁸ ; Perez ⁴¹ ; Miller ⁴²
Paclitaxel, albumin-bound [‡]	260	q3w	10	Gradishar ¹²
	100	weekly	4	Lee ³
	125		11	O’Shaughnessy ⁵⁹
Docetaxel [§]	75	q3w [¶]	4*	Alba ⁶⁰
	100	q3w	0–17*	Bonnetterre ⁴³ ; Jones ³⁴ ; Taberero ⁶¹ ; Eniu ⁶²
	35–40	weekly	2*	Taberero ⁶¹ ; Eniu ⁶²

*Reported as unspecified neuropathy, peripheral neuropathy, neurocortical toxicity, or neurotoxicity; †Cremophor-based;

‡Cremophor-free; §Polysorbate 80-based; ¶In combination with doxorubicin 50 mg/m².

d=day(s); q14d=every 14 days; q3w=every 3 weeks.

dependent and predominantly sensory.¹⁷ For cisplatin, the neurotoxic cumulative dose is 300–400 mg/m², resulting in up to 64% grade 3/4 peripheral neuropathy.^{17,24} Generally, the onset of platinum-induced neuropathy is delayed and symptoms can manifest several weeks after final dose.¹⁵ Sensory symptoms are similar to MTI-induced neuropathy and can occur 3 weeks to 6 months after final dose. Motor symptoms are rare but

have been seen with high doses.¹⁵ Of note, approximately 75% of patients receiving cisplatin experience high-frequency hearing loss or tinnitus.¹⁷ Cisplatin-induced neuropathy is irreversible in approximately 30–50% of patients, even after treatment has been discontinued.²⁵

The etiology of MTI-related neuropathic effects has been examined primarily for the vinca alkaloids and taxanes, and these effects have been found in preclinical

and clinical use to be both dose- and schedule-dependent (Table 2).³ Specifically, the incidence and severity of neuropathy depend on the agents, absolute dose, cumulative dose, treatment schedule, duration of infusion, and presence of concomitant medications and comorbidities.^{3,23} Predisposing conditions include diabetes, alcoholism, nutritional deficiencies, infectious diseases such as AIDS and Lyme disease, and inherited neuropathies.^{4,17} Concurrent administration of cisplatin- or carboplatin-based therapies is an established risk factor for the development of taxane-related peripheral neuropathy.^{3,14,17}

Vinca Alkaloids

Peripheral neuropathy is an adverse event observed to varying degrees during treatment with the vinca alkaloids vincristine, vinorelbine, and vinflunine (Table 2).²⁶⁻³⁰ Among the first-generation vincas, vincristine has been associated with a severe, mixed sensory/motor polyneuropathy, which is frequently dose-limiting.^{18,31} Grade 3/4 motor or sensory neuropathy was reported in 31% of patients with relapsed non-Hodgkin lymphomas who were treated with 2 mg/m² liposomal vincristine every 2 weeks, according to early results of an ongoing phase II trial.²⁶ In addition, off-therapy worsening of signs or symptoms (“coasting”) occurred in a substantial subset ($\leq 30\%$) of patients who received vincristine.³¹ Symptoms of autonomic neuropathy (including generally mild-to-moderate constipation) occurred with vincristine, and cases of paralytic ileus or megacolon have been reported.¹⁹

In contrast to the first-generation vincas, peripheral neuropathy associated with vinorelbine and vinflunine is primarily sensory in nature, mostly mild to moderate in severity, cumulative, and generally reversible after discontinuation.^{28,29,32,33} In a study of anthracycline- and taxane-pretreated patients with MBC, 5% of patients treated with vinorelbine 25–30 mg/m² experienced grade 3 peripheral neuropathy and 8% experienced grade 3 ileus.³⁰ Peripheral neuropathy is reported less frequently with vinflunine than with vinorelbine. In a phase II study of 60 women with MBC who received prior anthracyclines and taxanes first-line in the metastatic setting, vinflunine was administered at 320 mg/m² every 3 weeks.²⁹ Grade 1/2 sensory neuropathy occurred in 13% of patients, and no patient experienced a grade 3 event; 2 patients (3%) had grade 3 ileus.

Taxanes

A large body of clinical evidence (from the 1990s to the present) on the use of taxanes for the treatment of breast cancer contributes to our understanding of taxane-associated neuropathy. Clinical studies have consistently shown that peripheral neuropathy associated with taxane administration is generally sensory in nature.^{3,12,34-43} The

onset of peripheral neuropathy with this class of agents is correlated with the cumulative dose delivered, with many trials reporting a mean cumulative dose to onset, or cycles to onset.³ For example, the mean cumulative dose to onset of grade 2 or higher peripheral neuropathy was 371 mg/m² for docetaxel (Taxotere, Sanofi-Aventis) and 715 mg/m² for paclitaxel.³⁴ A major finding to emerge from clinical studies is that the rate of taxane-associated neuropathy is specifically related to the dose per treatment cycle (Table 2). For example, across several breast cancer trials in which paclitaxel was infused over 3 hours once every 3 weeks, the incidence of grade 3/4 sensory neuropathy increased from 2–12% at a dose of 175 mg/m² to 12–32% at a dose of 250 mg/m².^{12,34-39} The clear relationship between the dose of taxane and incidence of neuropathy has resulted in a gradual adoption of lower taxane dosing as the standard of care.³⁵

The incidence of neuropathy also appears to be correlated with the schedule of administration, as illustrated by a study comparing weekly with every-3-weeks administration of paclitaxel (Table 2).³⁸ The rate of grade 3 sensory neuropathy was increased with more frequent administration in this trial (weekly, 23%, vs every 3 weeks, 12%); however, it should be noted that the dose intensity was higher with weekly administration. In addition, it is possible that patients who received weekly infusions may have had closer monitoring of symptoms, thereby possibly affecting the reported incidences of this adverse event.¹³

The duration of infusion may also be a contributing factor to the incidence of neuropathy.³ One study reported that the incidence of grade 3/4 sensory neuropathy was 13% when high-dose (250 mg/m²) paclitaxel was infused over 3 hours, and 7% when the infusion time was extended to 24 hours.³⁹ However, decreased neurosensory toxicity was offset by increased hematologic toxicity, and progression-free and overall survival were not improved with continuous high-dose infusion in this study. Finally, the absolute dose and duration of infusion are not necessarily independent factors because both affect overall drug exposure over time. A pharmacokinetic study of paclitaxel—in which development of peripheral neuropathy was a primary endpoint—identified a threshold of exposure time (approximately 11 hours) above a defined paclitaxel concentration (0.05 $\mu\text{mol/L}$) as the only independent risk factor.¹³

In a study that directly compared docetaxel 100 mg/m² with paclitaxel 175 mg/m² (both administered every 3 weeks), the incidence of grade 3/4 peripheral neuropathy was slightly higher with docetaxel (7% vs 4%, respectively); however, this difference did not reach statistical significance.³⁴ It has been noted that the safety profiles of these taxanes may have been affected by the greater number of treatment cycles administered for the more

active agent, docetaxel, in this trial.⁴⁴ Severe sensory neuropathy was not observed in a smaller study of docetaxel in MBC.⁴³ Studies with a Cremophor-free taxane formulation, albumin-bound paclitaxel, also showed a dose-dependency for grade 3/4 peripheral neuropathy when doses of 100 mg/m² or 125 mg/m² were infused over 30 minutes weekly (Table 2).³ A higher incidence of severe peripheral neuropathy also appeared to be related to more frequent administration of albumin-bound paclitaxel (ie, weekly vs every 3 weeks).

Taxane-associated peripheral neuropathy has been managed in clinical trials with dose reduction or delay and treatment discontinuation, when indicated. Neurosensory symptoms generally resolve or improve after completion or discontinuation of therapy, although specific data on the time course of this process are reported infrequently. In an early study of patients with anthracycline-resistant breast cancer treated with high-dose (250 mg/m²) paclitaxel, symptoms improved in approximately 50% of patients within 9 months after cessation of therapy.⁴⁵ Peripheral neuropathy associated with docetaxel in MBC is also generally reversible. Limited follow-up data indicate spontaneous reversal of symptoms in a median of 9 weeks (range, 0–106 weeks) from the time of onset.⁴⁶ However, isolated cases of symptom worsening after discontinuation of docetaxel have been reported.⁴⁷

A significantly higher incidence of grade 3 peripheral neuropathy was reported in the phase III study comparing albumin-bound paclitaxel with standard paclitaxel (10% vs 2%, respectively; $P < .001$).¹² Consistent with the concept of a class effect for taxanes irrespective of the presence of Cremophor-EL, this higher rate was attributed to delivery of a higher active taxane dose. Grade 3 neuropathy improved by 1 or 2 grades in a median of 3 weeks from onset of the event after treatment interruption; the rate of complete resolution to baseline was not stated. Taken together, the safety data from a large number of studies—including the dose and schedule dependency, sensory nature, and reversibility of taxane-associated peripheral neuropathy—provide a context for understanding this adverse event during therapy with the more recently developed MTIs.

Clinical Experience With Epothilone-associated Neuropathy

The epothilones are a new class of antineoplastic drug with a lower susceptibility to chemotherapy-resistance mechanisms, which limit the effectiveness of other agents such as taxanes.^{1,2,5} This class includes the natural epothilones—epothilone B (EPO906, patupilone) and epothilone D (KOS-862)—as well as the semisynthetic epothilone analogs ixabepilone and ZK-EPO. The epothi-

lones differ from other MTIs in their precise binding sites and/or affinities for tubulin isoforms; however, because of their microtubule-targeting mechanism of action, these drugs can be associated with neurotoxic effects.

Peripheral neuropathy with patupilone has been primarily grade 1/2 in phase I and II studies in multiple solid tumor types, and the primary dose-limiting toxicity is severe diarrhea.^{48,49} The reasons for this distinct toxicity profile are unknown, but may relate to differential *in vivo* tissue distribution and metabolism.¹ Neurotoxicities associated with KOS-862 include both peripheral sensory neuropathy and central neuropathy characterized by impaired gait, cognition/perception defects, and fatigue.¹

The novel epothilone B analog ixabepilone has shown significant preclinical activity against a range of tumor types, including taxane-sensitive and -resistant tumors.⁵⁰ The incidence, severity, and nature of peripheral neuropathy have been relatively consistent across clinical studies of ixabepilone, from phase I through phase III, in patients with various malignancies, including MBC resistant to multiple chemotherapeutic agents (Table 3). Phase II trials evaluated ixabepilone monotherapy in the neoadjuvant setting,⁵¹ as well as in patients with anthracycline-pretreated,⁵² taxane-resistant,⁵³ or multiresistant (anthracycline-/taxane-/capecitabine [Xeloda, Roche]-resistant) MBC.⁵⁴ Ixabepilone was administered at 40 mg/m² intravenously over 3 hours every 3 weeks.

Peripheral neuropathy was primarily sensory, with rates for all grades of sensory peripheral neuropathy ranging from 20% in untreated early breast cancer⁵¹ to 63% in rapidly progressing taxane-resistant MBC.⁵³ Grade 3 sensory neuropathy was reported in 1% of patients in the neoadjuvant setting, in 12% of taxane-resistant patients, in 13% of patients with anthracycline-, taxane-, and capecitabine-resistant disease, and in 20% of anthracycline-pretreated patients.⁵¹⁻⁵⁴ Grade 4 sensory neuropathy was rare, occurring in a single patient across all of these phase II studies. A lower incidence and severity of peripheral sensory neuropathy was observed when ixabepilone was administered at 6 mg/m²/day on days 1–5 of a 3-week cycle. Among 37 taxane-pretreated⁵⁵ and 23 taxane-naïve patients,⁵⁶ grade 1/2 sensory neuropathy occurred in 54% and 52% of patients, respectively; one grade 3 event was reported.⁵⁵

Results of a large randomized phase III study of ixabepilone in combination with capecitabine administered to patients with MBC who were anthracycline-pretreated or -resistant and taxane-resistant were recently reported.⁵⁷ Combination therapy was administered as ixabepilone (40 mg/m² IV over 3 hours every 3 weeks) plus capecitabine (2 g/m² PO in 2 divided doses on days 1–14 every 3 weeks). The adverse event profile of the combination regimen was consistent with profiles of the individual

Table 3. Peripheral Neuropathy in Ixabepilone-treated Patients With Metastatic Breast Cancer

		<i>Dose per Cycle</i>	<i>N</i>	<i>All Grades, %</i>		<i>Grade 3, %</i>		<i>Grade 4, %</i>		<i>First Author</i>
Breast Cancer Setting				Sensory	Motor	Sensory	Motor	Sensory	Motor	
Neoadjuvant—Phase II		40 mg/m ² d1 q3w (maximum 4 cycles)	161	20	N/R	1	N/R	0	N/R	Baselga ⁵¹
Metastatic—Phase II										
Taxane-naive		6 mg/m ² d1–5 q3w	23	52	8	0	4	0	0	Denduluri ⁵⁶
Anthracycline-pretreated		40 mg/m ² d1 q3w	65	71	6	20	5	0	0	Roche ⁵²
Taxane-pretreated		6 mg/m ² d1–5 q3w	37	54	0	3	0	0	0	Low ⁵⁵
Taxane-resistant		40 mg/m ² d1 q3w	49	63	2	12	0	0	0	Thomas ⁵³
Anthracycline-/taxane-/capecitabine-resistant		40 mg/m ² d1 q3w	126	60	10	13	<1	1	0	Perez ⁵⁴
Metastatic—Phase III										
Anthracycline-/taxane-resistant	Ixabepilone + capecitabine*	40 mg/m ² d1 q3w	369	64	16	20	5	<1	0	Thomas ⁵⁷
	Capecitabine†		368	16	<1	0	0	0	0	

*Capecitabine 2,000 mg/m² d1–14 q3w in combination with ixabepilone; †Capecitabine 2,500 mg/m² d1–14 q3w as monotherapy.

N/R=not reported; q3w=every 3 weeks.

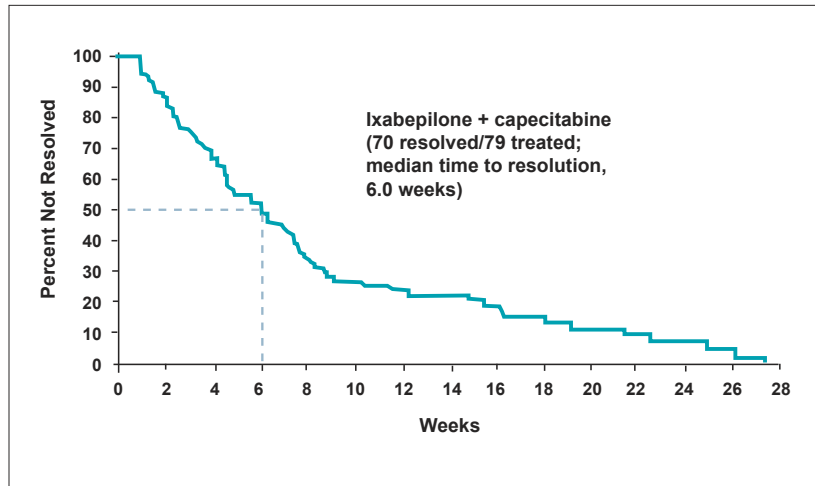
drugs when given as single agents; thus, the incidence of peripheral neuropathy was similar to the phase II experience (Table 3). Sixty-seven percent of patients experienced any treatment-related peripheral neuropathy (all grades), and in the vast majority (64%) these were sensory; grades 3 and 4 peripheral sensory neuropathy were reported in 20% and less than 1% of patients, respectively. Ixabepilone-associated peripheral neuropathy was cumulative in nature, with onset of grade 3/4 events occurring after a median of 4 treatment cycles. This allowed administration of sufficient treatment cycles to achieve the objective responses observed.⁵⁷

Peripheral neuropathy has been effectively and successfully managed with dose reduction across all clinical trials. Seventy-two percent of patients who received ixabepilone plus capecitabine in the phase III study and experienced neuropathy that qualified for dose reduction (persistent grade 2 or transient grade 3) had their dose reduced from 40 mg/m² to 32 mg/m² (and further reduced

to 25 mg/m², if needed, depending on tolerability).⁵⁷ Symptoms of neuropathy either improved to baseline or grade 1, or did not worsen, in 80% of this group after dose reduction. For many patients, treatment resumption at a reduced dose of ixabepilone has been possible after resolution of symptoms of peripheral neuropathy to grade 1 or baseline. For example, 22% of patients in the phase III MBC study continued therapy after dose reduction and received a median of three (range, 1–16) additional treatment cycles.⁵⁷

For a minority (21%) of patients treated with ixabepilone plus capecitabine, peripheral sensory neuropathy led to permanent discontinuation. However, among the cohort of patients with grade 3/4 peripheral neuropathy, symptoms either completely resolved to baseline or lessened in severity in 70 of 79 patients (Figure 1). The median time to resolution (to grade 1 or baseline severity) was 6 weeks (95% confidence interval [CI], 4.6–7.6), and 70% of patients experienced complete resolution within

Figure 1. Resolution of grade 3/4 peripheral neuropathy in patients receiving ixabepilone plus capecitabine. Seventy-nine patients had grade 3/4 treatment-related peripheral neuropathy that occurred within 30 days of their last ixabepilone dose. Neuropathy resolved in 70 patients in a median of 6 weeks (95% confidence interval, 4.6–7.6); 9 patients were censored due to subsequent receipt of other neurotoxic chemotherapy, ongoing treatment with ixabepilone, loss to follow-up, unknown status, or death.⁵⁷



approximately 8 weeks. However, in 1 patient, symptoms persisted for up to 28 weeks before completely resolving. The median time to symptom improvement by one grade was 4 weeks (95% CI, 2.9–6.0).⁵⁷

The reversibility of ixabepilone-associated peripheral neuropathy, both in patients whose dose was reduced and those who required permanent discontinuation, contrasts somewhat with clinical experience using other microtubule-targeting agents. For example, neurotoxicity has been reported to worsen, rather than resolve, with early-generation vinca alkaloids³¹ and docetaxel.⁴⁷ Moreover, although taxane-related neuropathy is also managed successfully with dose reduction and delay, the available data suggest that resolution of ixabepilone-associated neuropathy may occur more rapidly.

Low-grade preexisting neuropathy does not appear to be a significant risk factor for newly developing peripheral neuropathy among patients treated with ixabepilone. Baseline grade 1 peripheral neuropathy was present in a substantial fraction—24%—of patients in the large phase III MBC study. However, the rates of newly developing grade 3/4 sensory neuropathy were similar whether patients had grade 1 neuropathy before study entry (26%) or not (20%).⁵⁷ Although there are no published ixabepilone data examining a role for other established risk factors (eg, preexisting conditions and prior neurotoxic therapies), patients with diabetes may be at increased risk for developing severe neuropathy.

Practical Management of MTI-associated Neuropathy

Management of ixabepilone-associated neuropathy, as with other MTIs, relies on dose adjustment (Table 4).

Table 4. Dose Adjustments for Management of Neuropathy With Ixabepilone Monotherapy and Ixabepilone Plus Capecitabine Combination Therapy⁵⁷

Grade and Duration of Neuropathy	Ixabepilone Dose Adjustment
Grade 2 lasting ≥7 days	Decrease by 20% (to 32 mg/m ²)
Grade 3 lasting <7 days	Decrease by 20%
Grade 3 lasting ≥7 days or any grade 4	Discontinue

Dosing is reduced by 20% (to 32 mg/m²) for symptoms of grade 2 neuropathy lasting 7 or more days, and by 20% for grade 3 neuropathy lasting less than 7 days. For grade 3 neuropathy lasting 7 or more days or grade 4 neuropathy of any duration, ixabepilone is discontinued. Treatment is resumed after symptoms improve to grade 1 or resolve to baseline. Similar dose adjustments have been used for grade 3 sensory neuropathy associated with albumin-bound paclitaxel.¹² The drug was withheld until symptoms resolved to grade 1/2, and the dose was reduced from 260 mg/m² to 220 mg/m² in subsequent cycles; it was further reduced to 180 mg/m² for recurrence of grade 3 neuropathy.

A variety of neuroprotective agents have been developed or used in the attempt to prevent or treat neuropathies associated with MTIs and other chemotherapies (eg, platinum-based therapies) and thus maintain relative dose intensity. These include acetyl-L-carnitine, AM424,

amifostine, amitriptyline, dimesna, gabapentin, glutamine, lamotrigine, and vitamin E.^{3,4} However, only a few small phase II studies have specifically examined the putative activity of these agents in MTI-treated patients, and specific guidelines of the American Society of Clinical Oncology do not support the use of these agents.⁵⁸ The lack of effective agents to counteract MTI-associated neuropathy highlights the need for early identification and proactive management of this adverse event.

Supportive care measures may be of help in managing symptoms of neuropathy and are based on careful evaluation of patient symptoms and functional impairment in activities of daily living.^{4,17} A variety of approved and experimental agents have been used to control neuropathic pain, including anticonvulsants, tricyclic antidepressants, opioids, cannabinoids, and topical agents; however, much of the data supporting their use are empirical or derived from small nonrandomized trials or animal studies.¹⁷ Patient education about self-care measures is a critical function of advanced practice nursing and should include suggested modifications of the home environment (eg, adequate lighting, handrails, and nonslip floors) to minimize falling hazards for patients with diminished proprioception and deep tendon reflexes. Avoidance of cold exposure and burning/scalding hazards are important for comfort as well as safety in patients with impaired temperature sensation.¹⁷ Finally, orthopedic aids, prescribed physical therapy, and moderate exercise may enhance patient mobility and safety.^{4,17}

Conclusion

Because MTIs may be associated with dose-limiting peripheral neuropathy, timely recognition and proactive management of this adverse event is critical to achieve optimal efficacy with these agents. Peripheral neuropathy that occurs with taxanes and the novel epothilone ixabepilone is generally sensory in nature, and its incidence and severity are both dose- and schedule-dependent. The incidence of taxane-related grade 3/4 sensory neuropathy is generally higher with solvent- and albumin-based formulations of paclitaxel than with docetaxel, but slightly lower than with ixabepilone. The rate of grade 3 peripheral sensory neuropathy reported in patients with MBC who received ixabepilone monotherapy ranged from 3% to 20%. Among patients who received ixabepilone in combination with capecitabine, the incidence of grade 3 peripheral sensory neuropathy was 20%, which was similar to that observed in patients with MBC who received taxanes. MTI-associated neuropathy is managed through dose adjustments. After dose reduction of ixabepilone, symptoms improve or stabilize in most patients and, importantly, peripheral neuropathy is reversible to baseline or grade 1 following dose adjustments.

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