MINI REVIEW

Optimizing ixabepilone treatment schedules in patients with advanced or metastatic breast cancer

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Abstract The epothilone B analog, ixabepilone, demonstrates low susceptibility to drug resistance mechanisms and has demonstrated clinically meaningful efficacy in patients refractory to other chemotherapeutic options. Ixabepilone is approved by the FDA for treatment of patients with metastatic breast cancer (MBC) progressing after taxanes and anthracyclines, either in combination with capecitabine or as monotherapy if the patient has already progressed on capecitabine. Ixabepilone is generally well tolerated at the approved dose and administration schedule of 40 mg/m^2 every 3 weeks. The most commonly observed dose-limiting adverse events (AEs) associated with ixabepilone are myelosuppression and peripheral neuropathy. Dose modification including dose reduction and dosing schedule modification may be utilized to manage toxicities, but this must be based on careful hematologic, neurologic, and liver function monitoring. Other ixabepilone dose schedules are being evaluated to further improve the risk/benefit profile. Weekly and daily schedules of ixabepilone have shown useful efficacy and reasonable tolerability. A recent phase II trial compared the tolerability of ixabepilone dosed once weekly (16 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) or every 3 weeks (40 mg/m^2 on Day 1 of each 21-day cycle) in patients with MBC. Preliminary data showed that both dosing schedules had an acceptable safety profile; however, more AEs were reported in patients receiving ixabepilone every 3 weeks. Ixabepilone is also being evaluated in combination with other anticancer agents (e.g., bevacizumab and lapatinib), in earlier breast cancer settings and in other indications.

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Introduction

Epothilones are cytotoxic metabolites from the myxobacterium *Sorangium cellulosum* that stabilize microtubules. They induce cell death by apoptosis [1] via a mechanism that is similar to that of taxanes [2]. Ixabepilone, a novel semisynthetic analog of epothilone B [3], has been modified to retain cytotoxic activity while improving the stability and pharmacokinetic properties of the agent. Ixabepilone binds to a site similar to the taxane binding site on the β subunit of the tubulin heterodimer, but in a qualitatively different manner than paclitaxel [4]. Ixabepilone is able to competitively inhibit paclitaxel binding [2, 5].

Unlike taxanes, ixabepilone demonstrates low susceptibility to drug resistance mechanisms, including those associated with resistance to multiple drug classes (such as high expression of the drug efflux proteins P-glycoprotein and multidrug resistance protein) and those specifically associated with taxane resistance (such as high expression of ßIII-tubulin, an isotype of tubulin to which taxanes cannot bind) [6–8]. These features, coupled with the tubulin binding differences between epothilones and taxanes, may open the door for the treatment of taxane-resistant tumors [9].

Ixabepilone was approved by the FDA in October 2007 for treatment of patients with MBC progressing after taxanes and anthracyclines, either in combination with capecitabine, or as monotherapy if the patient has already progressed on capecitabine [10]. Given ixabepilone has been available for a number of years, we believe it useful to review the current approved dosing. This paper summarizes the supporting data for the current approved dosing schedule,

as well as the other treatment schedules that have been investigated to optimize clinical efficacy and tolerability. In addition, situations for which the dose of ixabepilone may need to be altered and special administration considerations will be discussed.

Ixabepilone monotherapy doses and schedules

The approved dose of ixabepilone for treating metastatic breast cancer (MBC) is 40 mg/m^2 infused over 3 h every 3 weeks [10]. The dose of ixabepilone is the same for monotherapy and for combination therapy with capecitabine. Ixabepilone is currently supplied as a lyophilized powder with a polyoxyethylated castor oil/ethanol (Cremophor EL$^®$) vehicle to improve solubility. Data supporting this dosage are discussed.

Preclinical trials established that the maximum tolerated dose (MTD) for ixabepilone was 10 mg/kg in mouse xenograft models [11]. The dose shown to give equivalent exposure in humans was 40 mg/m^2. This dose also produced clinically relevant antitumor activity in patients [8].

Phase I trials in patients with solid tumors assessed a number of different dosing schedules of the Cremophor-based formulation [12]. In a study by Mani et al. [13], 40 or 50 mg/m^2 dosed once every 3 weeks was recommended for phase II trials. Once-daily dosing for 3 days (MTD 8–10 mg/m^2) [14] or 5 days (MTD 6 mg/m^2) every 3 weeks [12] was assessed in two separate studies. More recently (2009), Awada and colleagues [15] assessed a weekly dosing schedule of MTD 25 mg/m^2 as a 30-min infusion every week continuously or 20 mg/m^2 as a 1-h infusion for 3 weeks with a 1-week break.

Phase II and phase III clinical trials in heavily pretreated patients with MBC generally utilized a dosing schedule of 40 mg/m^2 once every 3 weeks. This regimen was effective and well tolerated. Table 1 summarizes the phase II clinical trials and dosing schedules that have been investigated (registrational and non-registrational trials included) [16–22]. Daily ixabepilone, administered at a dose of 8–10 mg/m^2 for 3 days, did not demonstrate meaningful efficacy in patients with MBC previously treated with taxanes, although it was well tolerated [21]. However, in a phase II trial in patients with MBC who had not received prior taxane treatment, the 6 mg/m^2 daily schedule (five consecutive days every 3 weeks) was well tolerated and demonstrated clinically meaningful efficacy (57% had partial responses) [19]. Recently, Smith et al. [22] presented toxicity results from a phase II randomized trial comparing ixabepilone dosed once weekly (Arm 1: 16 mg/m^2 over 1 h on Days 1, 8, and 15 of each 28-day cycle) vs. every 3 weeks (Arm 2: 40 mg/m^2 over 3 h on Day 1 of each 21-day cycle) in patients with MBC. Preliminary data

showed that both dosing schedules had an acceptable safety profile; however, more adverse events (AEs) were reported in patients in Arm 2 compared with Arm 1 (grades 3–4 treatment-related AEs: 57% vs. 22%; serious AEs: 36% vs. 28%; grades 3–4 treatment-related neutropenia: 33% vs. 5%, respectively). Other grades 3–4 treatment-related AEs occurring in >5% of patients were reported more frequently in Arm 2 than in Arm 1 (fatigue: 16% vs. 5%; neuropathy: 14% vs. 5%; dehydration: 10% vs. 1%; and vomiting: 6% vs. 0%, respectively). More patients in Arm 2 discontinued the study due to treatment-related AEs (14% vs. 7%).

Doses and schedules in combination with other agents

Ixabepilone and capecitabine

Synergistic effects between ixabepilone and capecitabine were demonstrated in pre-clinical studies [23]. A phase I/II trial assessed suitable treatment schedules for combination therapy of ixabepilone and capecitabine [24]. In the phase I, dose escalation study, patients received either a schedule A regimen (ixabepilone 40 mg/m^2 intravenously on Day 1 plus capecitabine 1,650–2,000 mg/m^2 on Days 1–14 of a 3-week cycle) or a schedule B regimen (ixabepilone 8–10 mg/m^2 on Days 1–3 plus capecitabine 1,650 mg/m^2 on Days 1–14 of a 3-week cycle). The MTD for schedule A was the 40/2,000 mg/m^2 dose. During phase II of the study, this dosing schedule showed promising efficacy (objective response rate [ORR] = 30%) and was generally well tolerated, with grade 3/4 events that included fatigue (34%), hand-foot syndrome (34%), myalgia (23%), nausea (16%), peripheral neuropathy (19%), and diarrhea/vomiting (10%).

The large ($N = 752$) pivotal phase III trial utilized ixabepilone at 40 mg/m^2 infused over 3 h on Day 1 of a 3-week cycle, in combination with oral capecitabine 2,000 mg/m^2 on Days 1–14 of a 3-week cycle. Patients in the comparator arm received capecitabine 2,500 mg/m^2 alone on the same dosing schedule [25]. The combination dose was well tolerated, with mostly grade 1/2 AEs that were manageable and reversible. The most frequent grade 3/4 AEs in the combination group were peripheral sensory neuropathy, hand-foot syndrome, fatigue, myalgia, asthenia, and diarrhea. The capecitabine group experienced grade 3 hand-foot syndrome and diarrhea at incidences similar to those for the combination arm. The ORR in the preliminary analysis was higher for the combination arm than for capecitabine alone (35% vs. 14%; odds ratio, 3.2; $P < 0.0001$) [25]. This efficacy was confirmed in the final analysis, with response rates of 42 and 23% for the two arms, respectively [26]. Data showed that progression-free survival (PFS) was significantly higher for patients receiving ixabepilone plus capecitabine than for those receiving capecitabine alone

Table 1 Summary of phase II trials exploring different doses/schedules of ixabepilone monotherapy in patients with metastatic breast cancer

Trial	Dosing schedule	MBC patient population	N	ORR	Grade 3/4 AEs $\geq$5%
Perez et al. [16]	40 mg/m^2, 3 h infusion; once every 3 weeks	Progression after anthracyclines, taxanes, and capecitabine	126	11.5%	CIPN sensory (14%); fatigue/asthenia (13%); myalgia (8%); stomatitis/mucositis (6%)
Thomas et al. [17]	50 mg/m^2, 1 h infusion; modified to 3 h infusion; modified to 40 mg/m^2; once every 3 weeks	Progression after taxanes	49	12%	GI (20%); fatigue (27%); CIPN sensory (12%); pain (10%); myalgia (10%); febrile neutropenia (10%); blood/bone marrow (6%)
Roche et al. [18]	50 mg/m^2, 1 h infusion; modified to 3 h infusion; modified to 40 mg/m^2; once every 3 weeks	Progression after adjuvant anthracyclines	65	41.5%	Neutropenia (58%); leukopenia (50%); CIPN sensory (20%); myalgia (8%); vomiting (7%); fatigue (6%); infection (6%); arthralgia (5%); CIPN motor (5%); neuropathic pain (5%); stomatitis (5%)
Denduluri et al. [19]	6 mg/m^2; 1 h infusion; Days 1–5 every 3 weeks	No previous taxane treatment	23	57%	Neutropenia (22%); fatigue (13%); nausea (9%)
Low et al. [20]	6 mg/m^2; 1 h infusion; Days 1–5 every 3 weeks	Previous exposure to taxanes	37	22%	Neutropenia (35%); GI (21%) febrile neutropenia (14%); fatigue (13); thrombocytopenia (8%)
Denduluri et al. [21]	8–10 mg/m^2; Days 1–3 every 3 weeks	Previous exposure to taxanes	12	0%	Leukopenia (four patients); neutropenia (two patients); thrombocytopenia (one patient); allergy (one patient)
Smith et al. [22]	Arm 1: 16 mg/m^2, 1-h infusion, on Days 1, 8, and 15 of each 28-day cycle weekly	No limit to prior chemotherapy or hormonal therapy	Arm 1 = 85	NR	Arm 1 vs. Arm 2
	Arm 2: 40 mg/m^2, 3-h infusion, on Day 1 of each 21-day cycle every 3 weeks		Arm 2 = 88		Neutropenia (5% vs. 33%); fatigue (5% vs. 16%); neuropathy (5% vs. 14%); dehydration (1% vs. 10%); vomiting 0% vs. 6%)

CIPN chemotherapy-induced peripheral neuropathy; *GI* gastrointestinal symptoms; *ORR* overall response rate; *NR* not reported

(5.3 vs. 3.8 months; HR 0.78; 95% CI, 0.67–0.91; $P = 0.0011$) [26]. The dose reduction rates for the combination arm were similar to those reported for capecitabine plus docetaxel [27]. Data from this phase III trial were further analyzed in order to assess the "trade-off" between toxicities and PFS ("Q-TWiST" analysis = quality-adjusted time without symptoms or toxicities). Results supported a positive risk/benefit to combination therapy with ixabepilone and capecitabine, compared with capecitabine alone (3.8-week improvement in quality-adjusted mean survival; $P = 0.0227$) in patients with advanced or MBC refractory to anthracyclines and taxanes [28]. Further subanalysis (pooled patients with poor prognostic features: "triple-negative" phenotype or symptomatic KPS 70–80 or post-adjuvant rapid relapse) supported these results, affirming a positive risk/benefit ratio of ixabepalone plus capecitabine, compared with capecitabine alone. The greatest difference in quality-adjusted survival was found in the post-adjuvant rapid relapse subgroup (45.6% vs. 36.0% for combination vs. monotherapy, respectively; 9.6% difference; $P = 0.0007$) [29].

Ixabepilone and bevacizumab

There is preclinical evidence for synergy between ixabepilone and bevacizumab [30]. A recent (2009) randomized phase II trial investigated this combination as first-line therapy for MBC by comparing a weekly ixabepilone-based regimen (16 mg/m^2 weekly for 3 weeks, every 4 weeks, plus bevacizumab 10 mg/kg every 2 weeks; Arm A) and an every-3-week ixabepilone-based regimen (40 mg/m^2 every 3 weeks plus bevacizumab 15 mg/kg every 3 weeks; Arm B) to a combination of paclitaxel and bevacizumab (90 mg/m^2 weekly, plus bevacizumab at the same dose and schedule as Arm A; Arm C) [31]. There was an automatic dose reduction of ixabepilone 40–32 mg/m^2 after the fourth treatment cycle. The preliminary analysis revealed comparable response rates (Arm A, 50% [34.9–65.1]; Arm B, 71% [55.7–83.6]; and Arm C, 56% [37.7–73.6]) and 24-week PFS rates (Arm A, 75% [62.4–87.9]; Arm B, 86% [75.7–96.4]; and Arm C, 94% [85.4–100]) for all three arms, indicating that both schedules of ixabepilone are as efficacious as weekly paclitaxel when combined with bevacizumab. The most significant grade 3/4 AEs included peripheral neuropathy (Arm A, 18%; Arm B, 22%; and Arm C, 25%) and neutropenia (Arm A, 11%; Arm B, 55%; and Arm C, 22%). Febrile neutropenia rates were <2% in all arms. The fact that rates of AEs were similar to those observed with ixabepilone monotherapy at these schedules suggests that ixabepilone does not exacerbate the AE profile of bevacizumab. Notably, although the trial investigated ixabepilone in combination with bevacizumab, this trial is the first to compare weekly ixabepilone to the approved

every 3-week schedule. The outcomes suggest that efficacy and tolerability of weekly ixabepilone might be comparable to the every 3-week schedule, and evaluation of these two schedules (ixabepilone monotherapy) in MBC is currently underway (ClinicalTrials.gov identifier: NCT00593827).

Ixabepilone and lapatinib

The therapeutic potential of combining ixabepilone and lapatinib was recently (2009) evaluated in a preclinical study in breast cancer cell lines. Results showed that the combination of these two agents significantly reduced cell proliferation compared with the non-Her-2-amplified control ($P < 0.001$ at 120 h) [32]. Based on the favorable results of this study, a phase I dose escalation trial of ixabepilone (32 mg/m^2 intravenous once every 3 weeks) in combination with lapatinib (1,000 mg orally once daily), with or without capecitabine (1,650 mg/m^2 orally twice a day for 14 days), for up to 54 weeks depending on response, has been initiated in patients with Her-2 positive, taxane- and trastuzumab-resistant advanced breast cancer (NCT00634088). At the time of this publication, patient accrual is still underway; however, RECIST (response evaluation criteria in solid tumors) responses have been confirmed in two of the first three patients enrolled in this trial [32].

Predicting response: gene expression patterns

Recent studies have investigated the use of gene expression patterns to predict response to ixabepilone. Baselga et al. [33] evaluated the safety, efficacy, and genomic predictors of neoadjuvant ixabepilone therapy (40 mg/m^2, 3-h infusion every 21 days, up to four cycles) in a single-arm, phase II study in patients with invasive breast cancer. Investigators identified estrogen receptor (ER) and microtubule-associated protein *tau* as predictive markers for pathologic complete response to ixabepilone as neoadjuvant therapy (*tau* gene expression inversely correlated with ixabepilone sensitivity). Further, data from Horak et al. [34] indicated a higher βIII-tubulin expression in patients with "triple-negative" (negative or low expression of ER, PR, and HER2) breast cancer with basal-like tumors (breast cancer subtype defined by gene expression and protein expression profiles; often considered synonymous with triple-negative breast cancer). Investigators noted that βIII-tubulin overexpression might contribute to the aggressiveness of "triple-negative" breast cancer and that increased levels may be a predictor of response to treatment with ixabepilone. These studies indicate that the use of gene expression analysis prior to initiating ixabepilone therapy maybe be used to

select patients who might derive clinical benefit from this treatment.

Dose modifications reductions

Cytotoxic chemotherapy requires balancing risk and benefit. Dose modification is used to manage the toxicities associated with therapy relative to the patient's ability to tolerate the therapeutic regimen. Dose modification to mitigate toxicity can be achieved either by reducing the dose administered, increasing/delaying the time between treatment periods, or altering the infusion time in order to maintain drug exposure but limit the peak plasma drug concentration often associated with toxic events.

In the clinical setting

Dose modifications of ixabepilone were necessary in many clinical trials to mitigate the AEs experienced by study participants or patients. Although 50 mg/m^2 had been identified as the MTD in one phase I trial, the dose in two subsequent phase II trials was reduced from 50 to 40 mg/m^2 to reduce the incidence of myelosuppression and mucositis. Additionally, in these studies, the 1-h infusion was lengthened to 3 h due to treatment-limiting neurotoxicity with the shorter infusion time [17, 18]. Data from these studies led to the use of a 3-h infusion of ixabepilone at 40 mg/m^2 in subsequent clinical trials and is the approved dosing as monotherapy and in combination with capecitabine [12, 18, 25].

In the phase II registrational trial of ixabepilone monotherapy in MBC patients following a taxane, anthracycline, and capecitabine, dose reductions to 32 or 25 mg/m^2 were made based on tolerability to ixabepilone in the previous cycle [16]. Seventy percent of patients received ≥90% of their planned relative dose intensity, and 80% of the cycles in the trial were administered at 40 mg/m^2 as planned.

In the pivotal phase III ixabepilone/capecitabine combination trial, 51 and 45% of patients in the combination arm required dose reduction of ixabepilone and capecitabine, respectively, compared with dose reductions in 37% of patients in the single-agent capecitabine group [25]. The majority of patients received ≥70% of their planned relative dose intensity: in the combination group, 88 and 62% received ≥70% of their relative ixabepilone and capecitabine (2,000 mg/m^2) dose intensity, respectively, compared with 82% in the capecitabine group (2,500 mg/m^2).

In clinical practice

The main dose-limiting AEs in patients treated with ixabepilone are neutropenia and peripheral sensory neuropathy.

Both of the AEs are manageable, reversible, and responsive to dose reduction or delay [10]. However, patients with ≥grade 2 neuropathy were excluded from the ixabepilone studies, and caution should be used when treating patients with diabetes mellitus or pre-existing peripheral neuropathy. In patients who have baseline neutrophil count <1,500 cells/mm^3, or baseline platelet count <100,000 cells/mm^3, ixabepilone is contraindicated.

Combination therapy with ixabepilone and capecitabine is contraindicated for patients whose levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceed 2.5 times the upper limit of normal (ULN) or patients whose bilirubin exceeds ULN. Based on liver enzyme levels, patients may receive ixabepilone monotherapy at a reduced dose. However, the ixabepilone prescribing information provides specific guidelines for dose reduction or delay in several situations, including AEs, impaired hepatic function, and potential drug–drug interactions (Table 2) [10]. Doses for patients whose body surface area exceeds 2.2 m^2 should be calculated based on 2.2 m^2 [10]. In order to ensure that each patient is receiving the optimal dose, all patients should be routinely monitored for AEs that may signal that a dose reduction is necessary; i.e., regular complete blood counts, neurological exams, and liver function tests [10]. There is no antidote for ixabepilone overdose [10], and patients should be monitored and offered supportive care for any presenting clinical manifestations. Overdosage has been reported for one patient who received 100 mg/m^2 (total 185 mg); however, the effects were minor (grade 1 fatigue and myalgia), and the patient made a full recovery [10].

Drug interactions

Ixabepilone is a weak inhibitor of human CYP3A4, but it is not expected to alter the plasma concentrations of other drugs [10]. Its main route of metabolism is via CYP3A4, and substances that inhibit CYP3A4 activity may decrease metabolism, thereby increasing plasma concentrations of ixabepilone. When ixabepilone is coadministered with strong inhibitors of CYP3A4, such as ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, and voriconazole, there is a significant increase in exposure to ixabepilone, and alternative therapeutic agents that do not inhibit CYP3A4 should be considered. In cases where coadministration of a strong CYP3A4 inhibitor cannot be avoided, a 50% dose reduction of ixabepilone should be considered in order to adjust the ixabepilone area under the curve to that observed in the absence of concurrent CYP3A4 inhibitors, and patients should be monitored closely for acute toxicities [10].

Table 2 Recommended ixabepilone dose reductions and treatment discontinuations [10]

Issue	Recommendations
Monotherapy OR combination therapy dose modifications	
Non-hematologic adverse events[a]	
Grade 2 neuropathy lasting ≥7 days	Decrease dose by 20%
Grade 3 neuropathy lasting <7 days	Decrease dose by 20%
Grade 2 neuropathy lasting ≥7 days, or disabling neuropathy	Discontinue treatment
Any grade 3 toxicity other than neuropathy	Decrease dose by 20%
Transient grade 3 arthralgia/myalgia	No change in dose
Transient grade 3 fatigue	No change in dose
Grade 3 hand-foot syndrome	No change in dose
Any grade 4 toxicity	Discontinue treatment
Hematologic adverse events[a]	
Neutrophils <500 cells/mm^3 for ≥7 days	Decrease dose by 20%
Febrile neutropenia	Decrease dose by 20%
Platelets <25,000/mm^3	Decrease dose by 20%
Platelets <50,000/mm^3 with bleeding	Decrease dose by 20%
Potential drug interactions	
Concomitant strong CYP3A4 inhibitor	Decrease dose to 20 mg/m^2
Monotherapy dose modifications	
Baseline hepatic impairment	
AST *and* ALT ≤2.5 *and* bilirubin ≤1 × ULN[b]	No change in dose of monotherapy or combination therapy
AST *and* ALT ≤10 *and* bilirubin ≤1.5 × ULN[b,c]	Decrease monotherapy dose to 32 mg/m^2
AST *and* ALT ≤10 *and* bilirubin >1.5–≤3 × ULN[b,c]	Decrease monotherapy dose to 20–30 mg/m^2
Combination therapy dose modifications	
Baseline hepatic impairment	
AST *or* ALT >2.5 *or* bilirubin >1 × ULN[b]	Combination therapy is contraindicated

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

[a] Toxicities graded in accordance with the National Cancer Institute (NCI) Common terminology criteria for adverse events (CTCAE v3.0)

[b] Excludes patients whose total bilirubin is elevated due to Gilbert's disease

[c] Applies to ixabepilone monotherapy only. Ixabepilone and capecitabine combination therapy is contraindicated in this setting

Alternatively, coadministration of substances that induce CYP3A4 activity, such as dexamethasone, phenytoin, carbamazepine, rifampin, and phenobarbital, may lead to subtherapeutic levels of ixabepilone, as they may increase ixabepilone metabolism, leading to a decrease in plasma concentration. In these patients, therapeutic agents with low enzyme induction potential for coadministration with ixabepilone may be considered. St. John's Wort should be avoided, as its effect on ixabepilone plasma concentrations is unpredictable [10].

Other administration issues

The Cremophor vehicle of ixabepilone can elicit hypersensitivity reactions (HSRs), but these can be prevented if patients receive oral H$_1$ and H$_2$ antihistamines approximately 1 h prior to infusion [10, 12]. In contrast to standard formulations of the taxanes, corticosteroid premedication is not mandatory before ixabepilone infusion, unless the patient has experienced a previous hypersensitivity reaction to ixabepilone [10]. In patients who have a known history of severe hypersensitivity reactions to a drug formulated with Cremophor, ixabepilone is contraindicated.

The initial labeling in 2007 recommended that, after reconstitution, ixabepilone be further diluted using only Lactated Ringer's Injection, USP. This restriction was deemed necessary in order to maintain ixabepilone at a pH between 6.0 and 9.0, in order to maintain its stability. New labeling released in 2009 permits two alternative choices for infusion liquids, including PLASMA-LYTE A Injection, pH 7.4, or 0.9% Sodium Chloride Injection, USP, with the pH adjusted to between 6.0 and 9.0 using two molar equivalents (mEq) Sodium Bicarbonate Injection, USP. In order to obtain the desired pH, 2 ml of an 8.4% w/v solution or 4 ml of a 4.2% w/v solution of sodium bicarbonate must be added to each 250- or 500-ml bag of Sodium Chloride Injection before the addition of reconstituted ixabepilone.

Summary and conclusions

Clinically meaningful efficacy with ixabepilone is demonstrated in patients refractory to other chemotherapeutic

options. Ixabepilone is generally well tolerated at the approved dose and administration schedule of 40 mg/m^2 every 3 weeks. The most commonly observed dose-limiting AEs associated with ixabepilone are myelosuppression and peripheral neuropathy (primarily sensory). Dose modification including dose reduction and dosing schedule modification may be utilized to manage toxicities, but this must be based on careful hematologic, neurologic, and liver function monitoring. Other ixabepilone dose schedules are being evaluated to further improve risk/benefit, and weekly and daily schedules have shown useful efficacy and reasonable tolerability. Ixabepilone is also being evaluated in combination with other anticancer agents, in earlier breast cancer settings and in other indications.

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