Balancing the efficacy and safety of ixabepilone: optimizing treatment in metastatic breast cancer

Ellen Kossoff, PharmD, BCOP,[1] Nuttapong Ngamphaiboon, MD,[2] and Tracey L. O'Connor, MD[2]

[1]Department of Pharmacy, [2]Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York

Ixabepilone has been studied in the neoadjuvant setting, as first-line treatment of metastatic disease and in combination with other agents. The efficacy of ixabepilone in triple-negative breast cancer has been the focus of much research. Dose reduction is an effective strategy to manage adverse events associated with ixabepilone and does not result in diminished clinical outcomes. In addition, weekly administration of ixabepilone may decrease toxicity; however, this may come at the expense of lower progression-free survival but not overall survival. The optimal schedule and dosing of this agent will be clarified with the results of upcoming trials.

Ixabepilone is a semisynthetic analog of the natural product epothilone B that promotes cell cycle arrest and death by stabilization of microtubules. Ixabepilone (BMS-247550) binds to the same site of β-tubulin as do the taxanes, but in a different manner. This accounts for its utility against taxane-resistant tumors.[1-3] Indeed, findings from in vitro studies have shown that ixabepilone has low susceptibility to drug resistance in tumor cells, including mechanisms that increase drug efflux, a common cause of resistance to chemotherapy agents.[1,4,5] In the United States, ixabepilone is approved for the treatment of metastatic or locally advanced breast cancer in combination with capecitabine for patients whose disease is resistant to treatment with an anthracycline and a taxane, and as a monotherapy for patients whose disease is resistant or refractory to anthracyclines, taxanes, and capecitabine.[6]

Given the unique cytotoxicity profile of ixabepilone, the drug has been studied for first- and second-line treatment of metastatic disease[7,8] and as an agent in neoadjuvant regimens[9] (www.clinicaltrials.gov studies NCT00455533; NCT00821886; NCT00866905; NCT01097642) and adjuvant regimens (www.clinicaltrials.gov studies NCT00630032; NCT00789581). The efficacy of ixabepilone in subsets of breast cancer patients, notably those with triple-negative breast cancer (TNBC), is also the focus of much research[10] (www.clinicaltrials.gov studies NCT00633464; NCT01097642; NCT0078958; NCT00630032).

The standard dose of ixabepilone either alone or in combination with capecitabine, is 40 mg/m^2 administered as a 3-hour infusion once every 3 weeks.[6] In addition to the approved 3-week cycle, weekly administration of ixabepilone (15-20 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) is also of clinical and research interest[11-13] (www.clinicaltrials.gov study NCT00593827).

Ixabepilone regulatory trials

The safety and efficacy of ixabepilone plus capecitabine has been evaluated in 2 large phase 3 clinical trials in women with metastatic or locally advanced breast cancer.[14-16] The pivotal phase 3 trial enrolled 752 patients with metastatic breast cancer (MBC) resistant to taxanes and/or resistant to anthracyclines or heavily pretreated with anthracyclines.[14] Patients were randomized to receive ixabepilone (40 mg/m^2 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) or capecitabine alone (2,500 mg/m^2 also on days 1-14 of a 3-week cycle). Median independently assessed progression-free survival (PFS) was found to be significantly longer in patients who received the combination regimen, compared with

Manuscript received November 14, 2011; accepted May 23, 2012.
Correspondence: Ellen Kossoff, PharmD, Clinical Pharmacy Specialist, Breast Service, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 (Ellen.Kossoff@RoswellPark.org).
Disclosures: The authors have no conflicts of interest to disclose.

Commun Oncol 2012;9:222-228 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.cmonc.2012.06.001

those who received capecitabine alone (5.8 vs 4.2 months, respectively), equivalent to a 25% risk reduction for disease progression with combination therapy (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.64-0.88; $P = .0003$).[14] The Food and Drug Administration requested an analysis of the trial, which censored for PFS at the last tumor assessment date in patients who received subsequent therapy before the date of progression. The analysis reported an improved median PFS for ixabepilone plus capecitabine, compared with capecitabine alone (5.7 vs 4.1 months; HR, 0.69; 95% CI, 0.58-0.83; $P < .0001$).[17] Overall survival (OS) favored the combination arm, but it did not reach statistical significance (12.9 vs 11.1 months; HR, 0.9; 95% CI, 0.77-1.05; $P = .19$).[15]

A confirmatory trial was subsequently conducted in 1,221 women who had been pretreated with—or were resistant to—anthracyclines or taxanes. The findings from that study showed improved PFS of ixabepilone plus capecitabine, compared with capecitabine alone (6.2 vs 4.4 months, respectively; HR, 0.79; 95% CI, 0.69-0.90; $P = .0005$) and a trend toward improved OS (16.4 months vs 15.6 months; HR, 0.90; 95% CI, 0.78-1.03; $P = .1162$).[16] A significant improvement in OS in the combination treatment arm (HR, 0.85; 95% CI, 0.75-0.98; $P = .0231$) was reported in a predefined Cox regression analysis that was adjusted for prespecified baseline covariates (performance status, number of organ sites, visceral disease, and estrogen-receptor status).

The approval of ixabepilone as monotherapy in patients with MBC was based on the results of a phase 2 study that evaluated a dose of 40 mg/m^2 on day 1 of a 3-week cycle in 126 patients with locally advanced breast cancer or MBC who had progressed while receiving previous anthracycline, taxane, and capecitabine therapies.[18] The overall response rate (ORR) was 11.5% and an additional 50% of patients achieved stable disease (SD). Median duration of response (DOR) was 5.7 months and the median time to response was 6.1 weeks. Median PFS and OS were 3.1 and 8.6 months, respectively.

Tolerability

Tolerability is an important consideration when clinicians decide whether or not to treat a patient with monotherapy or a combination regimen. Hematologic toxicity is the most significant treatment-related adverse event (AE) with ixabepilone monotherapy. In two clinical trials of 50 or more patients, grade 3 or 4 neutropenia occurred in 54% and 58% of patients, and grade 3 or 4 leukopenia occurred in 49% and 50% of patients (Table 1). In these and other clinical trials of ixabepilone monotherapy, the nonhematologic AEs included grade 3 or 4 fatigue (range, 6%-27% [in all 5 studies]) and myalgia (range, 8%-10% [in 3 studies]; Table 1). Sensory neuropathy (49%-51% for grade 1 or 2; 12%-14% for grade 3 or 4) was observed at a rate similar to that reported in patients receiving taxanes.[18,19]

The combination of ixabepilone plus capecitabine improves PFS compared with capecitabine monotherapy, but incurs more grade 3 or 4 neuropathy (25% and 1%, respectively), fatigue (12% and 3%), neutropenia (73% and 9%), and leukopenia (63% and 7%) than does single-agent capecitabine.[16]

Patient selection

Cytotoxic chemotherapy is indicated in breast cancer patients with symptomatic visceral disease, hormone receptor–negative disease that is not localized to the bone or soft tissues, or hormone receptor–positive disease that is resistant to endocrine therapy.[22] MBC patients who do not respond to 3 or more sequential chemotherapy regimens or who have an Eastern Cooperative Oncology Group (ECOG) performance status > 3 should be considered for palliative care only. In this setting, balancing the treatment toxicity with preservation of quality of life is particularly important. Current approval for ixabepilone emphasizes its role as a third-line agent in the treatment of MBC, but because of the increasing use of anthracyclines and taxanes in the adjuvant setting, ixabepilone has been evaluated at various stages throughout the spectrum of breast cancer, including adjuvant and neoadjuvant therapy and in the first-line treatment of MBC.

Early breast cancer

A phase 2 study has examined the efficacy and safety of neoadjuvant ixabepilone in 161 women with previously untreated, invasive stage IIA-IIIB early breast cancer. Before surgery, patients received up to 4 cycles of ixabepilone (40 mg/m^2) followed by anthracycline-based adjuvant chemotherapy.[9] In all, 18% of patients achieved a pathologic complete response, 14% reported grade 3 or 4 neutropenia, and 1% reported grade 3 or 4 sensory neuropathy. A randomized trial of ixabepilone or paclitaxel as an adjuvant therapy of triple-negative breast cancer is ongoing (TITAN; www.clinicaltrials.gov study NCT00789581). This study is designed to evaluate the disease-free survival (DFS) of triple-negative, early-stage breast cancer patients through a comparison of standard doxorubicin plus cyclophosphamide (AC) followed by ixabepilone 40 mg/m^2 every 3 weeks for 4 cycles with standard AC followed by weekly paclitaxel for 12 cycles.[10]

First-line treatment of MBC

An increasing number of patients presenting for first-line chemotherapy in the metastatic setting are ineligible for further anthracycline therapy.[23] The need to identify

TABLE 1 Clinical experience with ixabepilone monotherapy: phase II clinical studies

Study	Ixabepilone Regimen (median cycles)	Patient group (n)	Efficacy	Grade 3/4 AEs
Denduluri,[20] 2007	6 mg/m^2 on days 1-5 of a 21-day cycle (8)	MBC with no previous taxane therapy (23)	Median DOR, 5.6 mo Median TTP, 5.5 mo PR, 57% SD, 26% PD, 17%	Neutropenia, 22% Fatigue, 13% Thrombocytopenia, 4% Arthralgia/myalgia, 4% Diarrhea, 4% *Discontinuation* Disease progression (14 patients), toxicity (4)
Low,[21] 2005	6 mg/m^2 on days 1-5 of a 21-day cycle (4)	Locally advanced or MBC previously treated with taxanes (37)	Median DOR, 118 days Median TTP, 80 days CR, 3% PR, 19% SD, 35%	Neutropenia, 35% Febrile neutropenia, 14% Fatigue, 14% Diarrhea, 11% Nausea/vomiting, 5% Myalgia/arthralgia, 3% Neuropathy, 3% *Discontinuation* Disease progression (29 patients), toxicity (5)
Perez,[18] 2007	40 mg/m^2 on day 1 of a 21-day cycle (4)	MBC resistant to anthracycline, taxane, and capecitabine therapy (126)	Median DOR, 5.7 mo Median PFS, 3.1 mo Median OS, 8.6 mo OR, 11.5% SD, 50%	Neutropenia, 54% Leukopenia, 49% Peripheral neuropathy, 14% Fatigue/asthenia, 13% Myalgia, 8% Thrombocytopenia, 8% Anemia, 8% Stomatitis/mucositis, 6% *Discontinuation* NA
Roche,[7] 2007	First line, 40 mg/m^2 on day 1 of a 21-day cycle (6)	MBC with previous adjuvant anthracycline therapy (65)	Median DOR, 8.2 mo Median TTP, 4.8 mo Median OS, 22 mo PR, 42% SD, 35% PD, 20%	Neutropenia, 58% Leukopenia, 50% Sensory neuropathy, 20% Myalgia, 8% Fatigue, 6% Febrile neutropenia, 8% *Discontinuation* Disease progression (52%), toxicity (34%
Thomas,[19] 2007	40 mg/m^2 on day 1 of a 21-day cycle (3)	MBC resistant to taxane therapy (49)	Median DOR, 0.4 mo Median TTP, 2.2 mo Median survival, 7.9 mo PR, 12% SD, 41%	Fatigue, 27% Sensory neuropathy, 12% Febrile neutropenia, 10 % Myalgia, 10% Nausea, 6% Vomiting, 6% *Discontinuation* Disease progression (74%), toxicity (16%)

Abbreviations: CR, complete response; DOR, duration of response; MBC, metastatic breast cancer; mo, month(s); n, number of patients; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

appropriate treatment options for these patients has led to an increased focus on the earlier use of ixabepilone for metastatic disease. Several lines of evidence suggest that ixabepilone use during earlier rounds of therapy might improve clinical outcomes.

In a pivotal phase 3 clinical trial, the HR for PFS was 0.75 (95% CI, 0.64-0.88) indicating a 25% reduction in risk of disease progression with ixabepilone-capecitabine combination therapy. Although 92% of the overall cohort was treated in second-line therapy,[14] a pooled analysis of PFS in the pivotal and confirmatory phase 3 clinical trials, which included only patients treated in the first-line setting, reported an HR of 0.58 (95% CI, 0.45-0.76), favoring the combination arm and indicating a 42% reduction in risk of disease progression in the first-line setting.[24] These data suggest an incremental benefit when ixabepilone is added to capecitabine in the first-line setting, compared with its use in later lines. Similarly, PFS data

from the confirmatory study also suggest that the benefit associated with combination therapy is greater among patients receiving ixabepilone during earlier rounds of treatment.[16] In this study, the HR for median PFS was 0.64 (95% CI, 0.47-0.87) favoring combination therapy in patients with no prior chemotherapy in the metastatic setting, compared with 0.84 (95% CI, 0.72-0.97) in those who had received at least 1 prior chemotherapy regimen.

A pooled analysis of data from the phase 3 clinical trials examining ixabepilone in the first-line treatment of MBC has indicated that ixabepilone plus capecitabine achieves better PFS than does capecitabine alone: The PFS was 5.6 months (95% CI, 4.6-6.9 months) and 2.8 months (95% CI, 2.2-3.7 months), respectively (HR, 0.58; 95% CI, 0.45-0.76).[24] In addition, the HR for median OS favored combination therapy over capecitabine monotherapy among MBC patients with no previous chemotherapy (HR, 0.89; 95% CI, 0.67-1.20), as well as the overall study population (HR, 0.9; 95% CI, 0.78-1.03) in the confirmatory phase 3 study.[16]

First-line ixabepilone monotherapy (40 mg/m^2 on day 1 of a 3-week cycle) of 65 women with MBC who had received previous anthracycline chemotherapy in the adjuvant setting produced a median DOR of 8.2 months and a median OS of 22 months.[7]

Efficacy in breast cancer subsets

Triple-negative disease

TNBC, which accounts for 15%-20% of breast cancer cases, does not express hormone receptors or the human epidermal growth factor receptor 2 (HER2).[25,26] Patients with TNBC can be difficult to treat since their tumors do not respond to endocrine or anti-HER2 therapies. Ixabepilone may be a promising agent for such patients. In a pooled analysis of results from the phase 3 clinical trials, ORR was 31% with the combination of ixabepilone plus capecitabine, compared with 15% with capecitabine monotherapy in patients with TNBC. The median PFS was 4.2 months and 1.7 months, respectively.[10]

Symptomatic disease

Ixabepilone plus capecitabine has shown an OS benefit, compared with capecitabine alone, in patients with symptomatic disease (Karnofsky performance status [KPS] score, 70-80); the median OS was 12.3 and 9.5 months, respectively (HR, 0.75; $P = .0015$).[27] The ORR was also significantly higher with combination therapy than with capecitabine monotherapy (35% and 19%), as was median PFS (4.6 and 3.1 months; HR, 0.76; $P = .0021$). Corresponding results in patients with high performance status (KPS score, 90-100) were a median OS of 16.7 and 16.2 months (HR, 0.98; $P = .8111$); an ORR of 45% and 28%; and a median PFS of 6.0 and 4.4 months (HR, 0.58; $P = .0009$), respectively.

A similar beneficial effect of combination therapy in patients with symptomatic disease was also noted in a prespecified secondary analysis of data from the pivotal phase 3 trial.[15] Ixabepilone plus capecitabine was associated with a clinically meaningful increase in OS in patients with a KPS of 70-80, compared with capecitabine monotherapy (10.1 and 7.8 months, respectively; HR, 0.75; 95% CI, 0.58-0.98).

Taxane-resistant disease

Ixabepilone plus capecitabine has also shown an OS benefit, compared with capecitabine alone, in 1,223 patients with taxane-resistant cancer (defined as disease progression within 4 months of receiving a taxane in the metastatic setting, or within 12 months of receiving adjuvant taxane). In this pooled analysis of phase 3 studies, the ORR was 39% with the combination, compared with 22% with capecitabine alone.[28] The median PFS was 5.1 months and 3.7 months, and the median OS was 13.3 and 11.6 months, respectively.

Alternative treatment schedules

Once-weekly paclitaxel is regarded as standard of care treatment for MBC.[29] In the Cancer and Leukemia Group B 9840 trial, once-weekly paclitaxel was significantly superior to administration once every 3 weeks.[30] Ixabepilone is pharmacologically similar to the taxanes, so weekly administration may be an equally appropriate treatment schedule. A phase 1 dose-escalation study[31] has reported the maximum tolerated dose of ixabepilone to be 25 mg/m^2, supporting the selection of 15-20 mg/m^2 for use in the clinic.[11] The results of clinical trials with weekly ixabepilone are summarized in Table 2.

Clinical experience

Weekly ixabepilone (15-20 mg/m^2) monotherapy was evaluated in 24 patients with heavily pretreated MBC (Table 2).[11] The median dose was 16 mg/m^2 and median treatment duration was 1.4 months. Partial response and SD were reported in 4% and 48% of patients, respectively. Doses were held because of toxicity in 37.5% of patients, and 84% of patients ultimately discontinued because of disease progression. The incidence of grade 3 or 4 fatigue (13%), neutropenia (4%), and neuropathy (8%) suggest a manageable toxicity profile.

In a direct comparison, once-weekly ixabepilone 16 mg/m^2 on days 1, 8, and 15 every 28 days seemed to be less effective than the 40 mg/m^2 regimen administered once every 3 weeks, but was associated with improved

TABLE 2 Clinical experience with weekly administration of ixabepilone

Study	Design	Regimen (Median doses)	Patient group	Efficacy	Grade 3/4 AEs
Smith,[13] 2010	Prospective phase II randomized trial First- or later-line therapy	Ixabepilone, 16 mg/m^2 on days 1, 8, and 15 of a 28-day cycle	176 patients with MBC 80% received previous chemotherapy for MBC TNBC, 22% ECOG PS 0/1/2: 46%, 48%, 6%	ORR, 8% Median PFS, 2.8 mo 6-mo PFS, 29% Median OS, 13.4 mo	Total, 28% Neuropathy, 11% Neutropenia, 7% *Discontinuation* Treatment-related AEs, 11% of patients
		Ixabepilone, 40 mg/m^2 every 3 weeks		ORR, 14% Median PFS, 5.1 mo 6-mo PFS, 42% (P = .05 vs weekly regimen) Median OS, 15.0 mo	Total, 69% Neuropathy, 20% Neutropenia, 40% *Discontinuation* Treatment-related AEs, 24%
Kossoff,[11] 2010	Retrospective chart review Late-line therapy	Ixabepilone, 15-20 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (6) Median treatment duration, 1.4 mo	24 patients with heavily pretreated MBC ≥ 4 lines of chemotherapy, 67% TNBC, 29% ECOG PS ≥ 2, 46%	Median TTP, 2.1 mo (range, 0.9-6.4)PR, 4% SD, 48% PD, 48% NE, 8%	Fatigue, 13% Neuropathy, 8% Neutropenia, 4% Nausea, 4% Lymphedema, 4% Diarrhea, 4% *Discontinuation* PD, 84%; toxicity, 8%
Moulder,[12] 2010	Phase II single-arm First-line setting	Trastuzumab, 4 mg/kg loading dose on day 1, cycle 1; then 2 mg/kg per week Ixabepilone, 15 mg/m^2, and carboplatin, AUC = 2 IV, on days 1, 8, and 15 of a 28-day cycle (6) 76% received all 6 cycles	59 patients with HER2+ MBC Previous neoadjuvant or adjuvant chemotherapy, 64% ECOG PS 0/1, 54%, 46%	Median TTP, 8.2 mo (95% CI, 6.3-9.9) CR, 7% PR, 37% SD, 25%; PD, 27% NE, 3%	Neutropenia, 49.1% Thrombocytopenia, 13.6% Anemia, 11.9% Fatigue, 11.9% Diarrhea, 6.8% Neuropathy, 6.8% Anorexia, 5.1% Dehydration, 5.1% *Discontinuation* PD, 66%; toxicity, 14%
Rugo,[30] 2009	Randomized phase II study	Ixabepilone, 16 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (6) plus bevacizumab 10 mg/kg every 2 weeks (6)	Women with no previous chemotherapy for locally advanced/MBC 46 patients	ORR, 50% 24-week PFS rate, 75%	Grade 3 peripheral neuropathy, 18% Grade 3/4 neutropenia, 11% Febrile neutropenia, 0%
		Ixabepilone 40 mg/m^2 on day 1 of a 21-day cycle (7), plus bevacizumab 15 mg/kg every 3 weeks (10)	45 patients	ORR, 71% 24-week PFS rate, 86%	Grade 3 peripheral neuropathy, 22% Grade 3/4 neutropenia, 55% Febrile neutropenia, 2%
		Paclitaxel 90 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (6.5), plus bevacizumab 10 mg/kg every 2 weeks (8)	32 patients	ORR, 56% 24-week PFS rate, 94%	Grade 3 peripheral neuropathy, 25% Grade 3/4 neutropenia, 22% Febrile neutropenia, 0%

Abbreviations: AUC, area under curve; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MBC, metastatic breast cancer; mo, month(s); NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer; TTP, time to progression.

tolerability.[13] In this phase 2 randomized trial, which included 176 patients with HER2-negative MBC, the ORR and PFS were significantly higher with the regimen administered every 3 weeks (Table 2), but grade 3 or 4 treatment-related AEs seemed lower with the once-weekly regimen (28%), compared with the regimen administered every 3 weeks (69%; neuropathy, 11% and 20%, respectively; neutropenia, 7% and 40%). Discon-

tinuations because of treatment-related AEs were 11% and 24% with the once-weekly and every-3-weeks regimens, respectively.

Weekly ixabepilone has been evaluated in the first-line setting in combination with trastuzumab and carboplatin[12] or bevacizumab[32] (Table 2). In 59 patients with HER2-positive MBC, weekly ixabepilone (15 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) plus trastuzumab and carboplatin achieved an ORR of 44%. Median time to progression and OS were 8.2 and 34.7 months, respectively. The toxicity profile was acceptable, with the most common grade 3 or 4 AEs including neutropenia (49%), thrombocytopenia (14%), fatigue (12%), diarrhea (7%), and neuropathy (7%).[12] This tolerability profile compares favorably with that of patients who were treated in the phase 3 pivotal trial and received ixabepilone (once every 3 weeks) plus capecitabine.[14] In that study, the incidences of grade 3 or 4 neutropenia (68%) and neuropathy (25%) seemed higher than those seen in the present study, whereas frequency of other grade 3 or 4 adverse events was similar. However, the higher degree of neuropathy observed in the pivotal phase 3 trial likely reflects cumulative toxicity because of previous taxane exposure.

Rugo and colleagues reported a preliminary result of a phase 2 study of weekly ixabepilone with or without bevacizumab, compared with paclitaxel with or without bevacizumab or nab paclitaxel with or without bevacizumab.[32] The weekly ixabepilone plus bevacizumab regimen for MBC was associated with a slightly lower response rate compared with ixabepilone plus bevacizumab administered every 3 weeks (50% vs. 71%, respectively), but much improved tolerability (grade 3 or 4 neutropenia, 11% and 55%).[32] At the recent annual meeting of the American Society of Clinical Oncology, Rugo and colleagues presented the findings of their randomized phase 3 study of weekly paclitaxel, compared with weekly nab paclitaxel or ixabepilone with or without bevacizumab as first-line chemotherapy for patients with chemotherapy-naïve locally advanced breast cancer or MBC. Their findings suggested that relative to paclitaxel, PFS was not superior with nab paclitaxel and ixabepilone when all are combined with bevacizumab (10.6, 9.2, and 7.6 months, respectively). In addition, weekly paclitaxel plus bevacizumab was better tolerated compared with the other regimens.[33]

Management of adverse events

Dose reduction is an effective strategy to manage AEs associated with ixabepilone, and does not result in declining clinical outcomes. In a pivotal phase 3 study, the median time from onset to improvement of grade 3 or 4 peripheral neuropathy by at least one grade was 4.1 weeks, and was 6 weeks to resolution to baseline or grade 1.[19] Most of the patients in the combination group received more than 70% of their overall planned relative-dose intensity (88% and 62% relative to the ixabepilone and capecitabine dose-intensity, respectively, compared with 82% in the capecitabine monotherapy group).

A review of 3 multicenter trials of ixabepilone involving almost 1,100 patients with MBC indicated that a dose reduction or delay either improved or did not worsen peripheral neuropathy symptoms in most patients.[34] After discontinuation, a resolution of peripheral neuropathy occurred in most patients (median time to resolution, 5-6 weeks). A median of 2 to 3 further treatment cycles were able to be given after dose reduction.

A retrospective analysis of pooled data from the phase 3 clinical trials also indicates that ixabepilone dose reductions do not impact overall efficacy in patients receiving ixabepilone plus capecitabine.[35] This analysis compared the clinical outcomes in 347 patients who required dose reduction before cycle 4 vs 219 patients who required either a dose reduction after cycle 4 or no dose reduction. The PFS was 7.0 months (95% CI, 6.5-7.5) in the early-reduction group and 7.2 months (95% CI, 6.6-8.0) in the late-reduction group. The ORR was 55.3% and 62.6%, respectively.

Dose reductions have also been described for the management of AEs in weekly ixabepilone, a schedule not approved by the Food and Drug Administration. In first-line patients with MBC, a starting dose of ixabepilone 15 mg/m^2, in combination with carboplatin and trastuzumab, could be further reduced to 12.5 mg/m^2 and then 10 mg/m^2 per week for grade 2 or higher hematologic and nonhematologic AEs (excluding alopecia) that were unresponsive to supportive therapy.[12]

Conclusions

Because anthracyclines and taxanes are the cornerstones of adjuvant chemotherapy regimens, future studies should continue to examine ixabepilone in the other treatment lines in metastatic disease and in specific phenotypic subsets. The unique cytotoxicity profile of ixabepilone coupled with preliminary clinical trial results support further evaluation of this agent in early breast cancer in the neoadjuvant and adjuvant setting. Findings from recent trials also support its use in the weekly setting and in combination with other biologic agents and other chemotherapies. It is important that the dosing regimen that offers the best balance between safety and efficacy is identified in each particular patient for optimization of treatment outcomes.

Acknowledgments

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise. They also wish to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing writing and editorial support. Neither Bristol-

Myers Squibb nor StemScientific influenced the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

References

1. Lee FY, Borzilleri R, Fairchild CR, et al. BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin Cancer Res*. 2001;7(5):1429-1437.
2. Lee FY, Borzilleri R, Fairchild CR, et al. Preclinical discovery of ixabepilone, a highly active antineoplastic agent. *Cancer Chemother Pharmacol*. 2008;63(1):157-166.
3. Nogales E, Wolf SG, Khan IA, Ludueña RF, Downing KH. Structure of tubulin at 6.5A and location of the taxol-binding site. *Nature*. 1995;375(6530):424-427.
4. Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. *J Clin Oncol*. 2004;22(10):2015-2025.
5. Lee FY, Smykla R, Johnston K, et al. Preclinical efficacy spectrum and pharmacokinetics of ixabepilone. *Cancer Chemother Pharmacol*. 2009;63(2):201-212.
6. Ixempra Kit [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2009.
7. Roché H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol*. 2007;25(23):3415-3420.
8. Fornier M. Ixabepilone plus capecitabine for breast cancer patients with an early metastatic relapse after adjuvant chemotherapy: two clinical trials. *Clinical Breast Cancer*. 2010;10(5):352-358.
9. Baselga J, Zambetti M, Llombart-Cussac A, et al. Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. *J Clin Oncol*. 2009;27(4):526-534.
10. Perez EA, Patel T, Moreno-Aspitia A. Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer. *Breast Cancer Res Treat*. 2010;121(2):261-271.
11. Kossoff EB, Ngamphaiboon N, Laudico TJ, O'Connor TL. Weekly ixabepilone administration in heavily pretreated metastatic breast cancer patients. *Med Oncol*. 2011;28(suppl 1):S115-S120.
12. Moulder S, Li H, Wang M, et al. A phase II trial of trastuzumab plus weekly ixabepilone and carboplatin in patients with HER2-positive metastatic breast cancer: an Eastern Cooperative Oncology Group Trial. *Breast Cancer Res Treat*. 2010;119(3):663-671.
13. Smith JW, Vukelja SJ, Rabe AC, et al. Final results of a phase II randomized trial of weekly or every 3-week ixabepilone in metastatic breast cancer (MBC) Poster presented at: 2010 American Society of Clinical Oncology Breast Cancer Symposium 2010, October 1-3, 2010; National Harbor, MD. Abstract 268.
14. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol*. 2007;25(33):5210-5217.
15. Hortobagyi GN, Gomez HL, Li RK, et al. Analysis of overall survival from a phase III study of ixabepilone plus capecitabine versus capecitabine in patients with MBC resistant to anthracyclines and taxanes. *Breast Cancer Res Treat*. 2010;122(2):409-418.
16. Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol*. 2010;28(20):3256-3263.
17. Thomas ES. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol*. 2008;26(13):2223.
18. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol*. 2007;25(23):3407-3414.
19. Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol*. 2007;25(23):3399-3406.
20. Denduluri N, Low JA, Lee JJ, et al. Phase II trial of ixabepilone, an epothilone B analog, in patients with metastatic breast cancer previously untreated with taxanes. *J Clin Oncol*. 2007;25(23):3421-3427.
21. Low JA, Wedam SB, Lee JJ, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. *J Clin Oncol*. 2005;23(12):2726-2734.
22. NCCN Practice Guidelines in Oncology–v.2.2011: Breast Cancer. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed October 28, 2011.
23. O'Shaughnessy J, Twelves C, Aapro M. Treatment for anthracycline-pretreated metastatic breast cancer. *Oncologist*. 2002;7(suppl 6):4-12.
24. Vahdat L, Fein LE, Karwal MW, et al. Ixabepilone plus capecitabine vs capecitabine in patients with metastatic breast cancer receiving ixabepilone in the first-line setting: a pooled analysis from two phase III studies. *Cancer Res*. 2009;69(2 suppl 1). http://dx.doi.org/10.1158/0008-5472.SABCS-6117.
25. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)–negative, progesterone receptor (PR)–negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer registry. *Cancer*. 2007;109(9):1721-1728.
26. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res*. 2007;13(8):2329-2334.
27. Roché H, Conte P, Perez EA, et al. Ixabepilone plus capecitabine in metastatic breast cancer patients with reduced performance status previously treated with anthracyclines and taxanes: a pooled analysis by performance status of efficacy and safety data from 2 phase III studies. *Breast Cancer Res Treat*. 2011;125(3):755-765.
28. Roché H, Li R, Ro J, et al. Ixabepilone plus capecitabine improves progression-free survival in patients with metastatic breast cancer resistant to taxanes: A pooled analysis from two phase III studies (Abstract 2015). *Cancer Res*. 2009;69(2 suppl 1). doi:10.1158/0008-5472.SABCS-2015.
29. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357(26):2666-2676.
30. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER2 overexpressors and random assignment to trastuzumab or not in HER2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol*. 2008;26(10):1642-1649.
31. Awada A, Piccart MJ, Jones SF, et al. Phase I dose escalation study of weekly ixabepilone, an epothilone analog, in patients with advanced solid tumors who have failed standard therapy. *Cancer Chemother Pharmacol*. 2009;63(3):417-425.
32. Rugo HS, Campone M, Amadori D, et al. Randomized phase II study of weekly versus every-3-week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC) [ASCO abstract 1029]. *J Clin Oncol*. 2009;27(suppl 1):S15.
33. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC) [ASCO abstr CRA1002]. *J Clin Oncol*. 2012;30(suppl).
34. Perez EA, Pivot X, Vrdoljak E, et al. A prospective characterization of the resolution of ixabepilone-induced peripheral neuropathy: data from a large registrational program in patients with metastatic breast cancer. *Cancer Res*. 2009;69(2 suppl 1). doi:10.1158/0008-5472.SABCS-6140.
35. Valero V, Bosserman LD, Yardley DA, et al. Maintenance of clinical efficacy following dose reduction of ixabepilone plus capecitabine (Cape) in patients (pts) with anthracycline (A) and taxane (T) pretreated (pretx) metastatic breast cancer (MBC): A retrospective analysis of pooled data from two phase III clinical studies (046/048)[ASCO abstract 1051]. *J Clin Oncol*. 2010;28(suppl 1):S15.