Breast Cancer: Basic and Clinical Research

REVIEW

Ixabepilone as Monotherapy or in Combination with Capecitabine for the Treatment of Advanced Breast Cancer

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Abstract: Breast Cancer is the most prevalent cancer in the world with 4.4 million survivors up to 5 years following the diagnosis.[1] In the US alone approximately forty thousand women die annually of metastatic breast cancer (MBC). Despite many effective systemic treatment options approximately 50% of women with MBC succumb to the disease within 24 months of the diagnosis.[2] Ixabepilone is a novel, first in class member of the epothilone class of antineoplastic agents. Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and Capecitabine. Ixabepilone is also indicated in combination with Capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Ixabepilone was extensively studied as a single agent in patients with MBC and was found to be effective and well tolerated with a predictable and manageable safety profile. Not surprisingly prior exposure to anthracyclines and taxanes affects significantly the potential for response to therapy with single agent Ixabepilone in metastatic setting. MBC patients with taxane resistant MBC have objective response rate (RR) of 12%, patients with prior low exposure to taxanes and/or resistance RR = 22%, Ixabepilone treatment after adjuvant anthracycline therapy exposure renders RR = 42% and in Taxane naïve patients RR = 57%. In two large phase III studies of Ixabepilone + Capecitabine versus Capecitabine alone, progression free survival (PFS) and overall response rates (RR) were higher in the combination treatment arms, but no survival advantage was seen overall. Treatment with Ixabepilone + Capecitabine in a phase II study resulted in an overall response rate (ORR) of 23% in ER/PR/HER2 negative, triple-negative breast cancer patients (TNBC) while ORR of 31% was seen in a preplanned pooled analysis of TNBC in the phase III trials of Ixabepilone + Capecitabine. Significantly prolonged median PFS was seen for TNBC treated with the combination of Ixabepilone + Capecitabine compared to Capecitabine alone 4.2 vs. 1.7 months respectively. Ixabepilone as single agent appears to show excellent antitumor activity in patients with TNBC MBC. Addition of Ixabepilone to Capecitabine results in approximately doubling in median PFS for TNBC versus Capecitabine alone. Single agent Ixabepilone is generally well tolerated, and its toxicity profile does not overlap with that of Capecitabine and therefore depending on prior exposure to chemotherapy both single agent Ixabepilone or in combination with Capecitabine can be used safely and effectively for treatment of advanced breast cancer.

Keywords: Ixabepilone, metastatic breast cancer, monotherapy, in combination with capecitabine, triple negative breast cancer

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Introduction

Breast cancer is the most common malignancy diagnosed in women in the US[2] and it is also a major global problem, with approximately 1 million cases occurring each year.[1,3] Breast Cancer is the most prevalent cancer in the world with 4.4 million survivors up to 5 years following the diagnosis.[1] Majority of women in the US present with early stage, potentially curable disease, only about 6% of newly diagnosed patients present with advanced or MBC.[4] However, an estimated 40% of patients initially presenting with localized disease eventually progress to metastatic breast cancer.[3] In the US alone approximately forty thousand women die annually of MBC and despite many effective systemic treatment options approximately 50% of women with MBC succumb to the disease within 24 months of the diagnosis.[2] Recently significant improvements in median survival with MBC have been noted from 1.28 yrs in 1991–1994 to 2.57 years in 2003–2006, this impressive increase in median survival appears to be primarily due to the effect of new systemic treatments introduced in recent years such as new hormonal treatments for MBC (HR = 0.72,); taxanes at first line (HR = 0.69,); trastuzumab at first line (HR = 0.63,).[5] Many treatment options exist for MBC and the choice of systemic therapy depends on host and disease/tumor specific factors. Well established targets for therapy such as tumor expression of estrogen and/or progesterone receptors frequently preclude the use of endocrine manipulations first before chemotherapy is considered. Another established target for therapy in MBC is the HER2/neu which if amplified in the tumor mandates therapy with HER2 targeted agents such as Trastuzumab or Lapatinib in conjunction with chemotherapy.[6–16] Majority of patients with MBC are offered systemic treatments to control/palliate the symptoms of the disease soon after diagnosis is made. Based on NCCN guidelines patients with symptomatic visceral involvement due metastatic disease such as liver, lung and bone marrow are recommended systemic chemotherapy.[17] Several chemotherapy agents alone and in combination are FDA approved for management of MBC. As of October 2007 Ixabepilone is one of newest US FDA approved antineoplastic agents for treatment of locally advanced and MBC. Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and Capecitabine. Ixabepilone is also indicated in combination with Capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or ≤6 months in the adjuvant setting or 3 months in the metastatic setting while taxane resistance is defined as progression while on therapy or ≤12 months in the adjuvant setting or 4 months in the metastatic setting. (http://packageinserts.bms.com/pi/pi_ixempra.pdf)

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Mechanism of action

Ixabepilone is the first in class member of epothilone class of antineoplastic agents a relatively new class of antimicrotubule agents. Epothilones are cytotoxic macrolides with a similar mechanism of action to paclitaxel but with the potential advantage of activity in taxane-resistant settings in preclinical models.[18] The antineoplastic activity of epothilones has been linked to stabilization of microtubules, which results in mitotic arrest at the G2/M transition. Ixabepilone (BMS-247550) is a semisynthetic analog of epothilone B designed to optimize the characteristics of its natural precursor. It is distinct from other antineoplastic agents because it has low susceptibility to common mechanisms of tumor resistance, including those mediated by P-glycoprotein a multidrug resistance protein. In addition the microtubule-stabilizing agents such as Ixabepilone prolong activation of the spindle assembly checkpoint which may promote cancer cell death in mitosis or following mitotic exit.[19] Significant alterations of dynamic instability of microtubules occur with a variety of antimitotic antineoplastic agents that interact with tubulin. A number of such compounds displaying great structural diversity are currently used in the clinic for treatment of solid tumor malignancies and many of these agents were initially isolated from natural sources.[20] Compounds such as paclitaxel or docetaxel; complex diterpenes inhibit tubulin polymerization, and lead to mitotic arrest and stabilization of microtubule assembly. The non-taxoid com-

pounds, macrolides epothilones have also been shown to stabilize microtubules. The taxanes are widely used for treatment of various malignancies, but primary and acquired resistance to these antineoplastic agents remains a significant clinical concern.[21] Class 1,2,3,4 and 5 beta-tubulin isotypes are expressed in human tumors. Overexpression of the beta3-tubulin isotype is one mechanism that can render tumor cells resistant to taxanes. The significant antitumor activity of Ixabepilone in taxane-resistant tumors may be related to its preferential suppression of the dynamic instability of alpha/beta3-microtubules in cells expressing high levels of beta3-tubulin.[22] Epothilone B analoge (EpoB) Ixabepilone has also been shown to induce apoptosis via a Bcl-2-suppressible pathway that controls a conformational change of the proapoptotic Bax protein. The enhanced cytotoxicity of EpoB by blocking Bcl-2 at mitochondria implies a potential application of the combination of EpoB and Bcl-2 antagonists in the treatment of human breast cancer.[21,23]

Metabolism

Ixabepilone is metabolized in the liver and caution should be used when considering patients with liver impairment for therapy with this agent. Ixabepilone exposure is greater in patients with hepatic impairment and those receiving concomitant strong cytochrome P-450 CYP3A4 inhibitors. Dose adjustments and restrictions are recommended according to the degree of hepatic impairment, whether Ixabepilone is administered alone or in combination with Capecitabine if a strong CYP3A4 inhibitor is being coadministered.[24] In patients without liver dysfunction the recommended dose of Ixabepilone is 40 mg/m^2 administered intravenously (IV) over 3 hours every 3 weeks. Patients with mild hepatic impairment with AST and ALT $\leq 10 \times$ upper limit of normal (ULN) and bilirubin $\leq 1.5 \times$ ULN should be dose reduced to 32 mg/m^2 every 3 weeks. For moderate liver dysfunction defined as AST and ALT $\leq 10 \times$ ULN and bilirubin $> 1.5 \times$ ULN $\leq 3 \times$ ULN 20–30 mg/m^2 every 3 weeks should be used initially, or a dose of 20 mg/m^2 can be used in the 1st cycle and, then in subsequent cycles Ixabepilone may be escalated up to, but not exceeding, 30 mg/m^2 if tolerated. Use of Ixabepilone in patients with AST or ALT $> 10 \times$ ULN or bilirubin $> 3 \times$ ULN is not recommended as limited data are available for patients with severe liver dysfunction. (http://packageinserts.bms.com/pi/pi_ixempra.pdf). The use of concomitant strong CYP3A4 inhibitors should be avoided (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, or voriconazole). Coadministration of ketoconazole with Ixabepilone resulted in a 79% increase in area under the curve AUC.[25] Grapefruit juice may increase plasma concentrations of Ixabepilone and should be avoided. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall by certain compounds present in grapefruits.

If a strong CYP3A4 inhibitor must be used a 50% dose reduction to 20 mg/m^2 is required. On the other hand the use of concomitant strong CYP3A4 inducers should also be avoided (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital) because these can increase metabolism of Ixabepilone and decrease its efficacy. Markedly overweight patients with body surface area (BSA) greater than 2.2 m^2 should have their dose calculated based on 2.2 m^2 BSA. All patients should be monitored closely while on treatment and therapy should be delayed to allow recovery from severe toxicities. Briefly the following guidelines can be considered for Ixabepilone monotherapy and in combination with Capecitabine and include discontinuation of the agent/s for any grade 4 toxicity and unresolved grade 3 neuropathy lasting for ≥ 7 days. Twenty percent dose adjustments are required for unresolved grade 3 neuropathy lasting < 7 days or grade 2 neuropathy lasting for ≥ 7 days and any other grade 3 toxicity. If toxicities recur despite previous 20% dose reduction an additional 20% dose reduction should be made.

Pharmacokinetic profile

The pharmacokinetic profile of Ixabepilone and 2 of its chemical degradation products (the oxazine derivative BMS-249798 and the diol derivative BMS-326412) was assessed in a phase I dose escalation study for 1 and 3-hour infusion and showed multiexponential drug disposition. Ixabepilone concentrations decreased to less than 10% of peak concentration by 8 hours from the start of the 1- or 3-hour infusion. The pharmacokinetic profile of Ixabepilone was similar during cycles 1 and 2. Plasma concentrations of BMS-249798 and BMS-326412 were much less than plasma concentrations of

Ixabepilone. Systemic exposure to BMS-249798 and BMS-326412 was less than 4% of systemic exposure to Ixabepilone.[26] Another phase I study with Ixabepilone was conducted to determine pharmacokinetic profile and assess toxicities of the daily schedule for 5 days every 21 days and showed that the mean terminal half-life of Ixabepilone was 16.8 ± 6.0 hours, the volume of distribution at steady-state was 798 ± 375 L, and the clearance was 712 ± 247 mL/min.[27]

Phase I studies of single agent Ixabepilone

Various schedules of single agent Ixabepilone were studied in phase I, dose escalation studies to assess maximum tolerated dose (MTD), dose limiting toxicity (DLT) and pharmacokinetic and pharmacodynamic profile of Ixabepilone in solid tumor malignancies and lymphomas. The following schedules were tested, 1 and 3 hour infusion once every 21 days, 30 minutes weekly infusion continuous on 21 day schedule without interruption weekly, 1 hour infusion 3 out of 4 weeks every 28 days daily infusion on days 1–3 and 1–5, every 21 days (Table 1). All schedules mentioned above showed acceptable and manageable side-effect profiles.

A Phase I study of Ixabepilone as a 1-hour iv daily for 3 consecutive days every 21 days (N = 26) was done. The starting dose of Ixabepilone was 8 or 10 mg/m^2 per day for 3 consecutive days. The MTD was 8 mg/m^2 per day of Ixabepilone administered as a 1-hour intravenous infusion daily iv for 3 consecutive days every 21 days. DLT was neutropenia, peripheral neuropathy was mild, even after multiple cycles of therapy, and was not dose limiting. Other nonhematologic grade 3 toxicities included fatigue, hyponatremia, anorexia, ileus, stomatitis, and vomiting. The recommended Phase II dose of Ixabepilone on the daily schedule for 3 days was 8–10 mg/m^2 per day.[28] Another phase I study of Ixabepilone as a 1-hour iv daily for 5 consecutive days every 21 days was conducted (N = 27) without and with Filgrastim in the first cycle. The MTD was 6 mg/m^2 administered as a 1-hour iv daily for 5 consecutive days every 21 days. Neutropenia was the DLT at a dose of 8 mg/m^2/d with or without filgrastim support. Other nonhematologic grade 3 toxicities included fatigue, stomatitis, and anorexia. The recommended phase II dose of Ixabepilone on the daily schedule for 5 days was 6 mg/m^2/d every 21 days. Peripheral neuropathy was mild, even after multiple cycles of therapy, and was not dose limiting.[27]

A phase I dose escalation study in patients (N = 61) with advanced solid tumors or refractory non-Hodgkin's lymphoma with Ixabepilone administered as a 1-hour infusion every 21 days.[26] used an initial accelerated dose-escalation phase followed by a standard dose-escalation phase, with doses of Ixabepilone ranging from 7.4 to 65 mg/m^2. The most common DLTs were neutropenia, stomatitis/pharyngitis, myalgia, and arthralgia and the most frequent grade 3/4 adverse events were sensory neuropathy (13%), fatigue (13%), myalgia (10%), arthralgia (7%), and nausea (5%). The recommended phase II dose of Ixabepilone was 50 mg/m^2 over 1 hour every 21 days and was initially used as the starting dose in phase II trials. However this dose was eventually decreased to 40 mg/m^2 over 3 hours every 21 days due to the early safety results which showed increased severe grade 3 and 4 neuropathy with the 1 hour infusion schedule.

Another single-arm, dose-escalation study of Ixabepilone delivered as 30-min, weekly iv on a 21-day schedule (N = 33) established the weekly dose of Ixabepilone of 25 mg/m^2/week as the phase II recommended dose. Grade 3 fatigue was the DLT in 2/4 patients treated at 30 mg/m^2, overall Ixabepilone was well tolerated at the MTD and myelosuppression was rare, with no Grade 3/4 neutropenia. Due to the potential for cumulative neurotoxicity, the protocol was amended eventually to the following schedule, Ixabepilone 1-hour infusion, weekly for 3 out of 4 weeks. No DLT occurred at starting doses of 15, 20 and 25 mg/m^2 on this modified schedule (N = 51), although overall toxicity was less at 15 and 20 mg/m^2 than 25 mg/m^2. Ixabepilone had an acceptable safety profile at the MTD of 25 mg/m^2 as a 30-min weekly infusion on a continuous 21-day schedule and at 20 mg/m^2 as a 1-hour weekly infusion on a modified 28-day schedule.

Phase II studies with single agent Ixabepilone in locally advanced and MBC

Ixabepilone was extensively studied in several phase II studies as a single agent in patients with MBC with various exposures to prior chemotherapy and was found to be effective and well tolerated with a predictable and manageable safety profile.

Table 1. Phase I studies with single agent ixabepilone and Ixabepilone with capecitabine.

Author	Dose range and schedule	Number of pts (N)	Recommended phase II dose	Maximum tolerated dose	Dose limiting toxicities
Aghajanian[26]	7.4 to 65 mg/m^2, 1-hour infusion every 3 weeks	61	50 mg/m^2, 1 hour every 21 d this dose was eventually decreased to 40 mg/m^2 over 3 hours every 21 d due to early safety signals showing increased severe grade 3–4 neuropathy with the 1 hour infusion schedule	50 mg/m^2 1-hour infusion every 21 d	Neutropenia, stomatitis, pharyngitis myalgia, arthralgia
Zhuang[28]	8 or 10 mg/m^2/day, 1-hour infusion daily on 3 consecutive d every 21 d	26	8–10 mg/m^2 per day	8 mg/m^2 per day, 1-hour infusion daily for 3 consecutive days every 21 d.	Neutropenia
Awada[43]	Dose escalation, 30 min/week	33		25 mg/m^2/week 30-min infusion on continuous	Grade 3 fatigue at 30 mg/m^2 dose Myelosuppression was rare, no Grade 3/4 neutropenia. Due to the potential for cumulative neurotoxicity protocol was amended to 1 hour, 3 out of 4 wks schedule
	15, 20 and 25 mg/m^2/wk3 out of 4 weeks every 28 d	51		21-day schedule 20 mg/m^2 (as a 1-h weekly infusion every 28-days	
Bunnell Phase I/II[44]	**Schedule A** (ixabepilone 40 mg/m^2 on day 1 + capecitabine 1650–2000 mg/m^2 on days 1–14 of a 21-day cycle)	74		40/2000 mg/m^2 dose was defined as the MTD for schedule A	Grade 3 plantar-palmar erythrodysesthesia (PPE) Grade 3/4 Treatment-related events in phase II fatigue (34%), PPE (34%), myalgia (23%), nausea (16%), peripheral neuropathy (19%), diarrhea/vomiting (10%). Grades 3/4 neutropenia (69%) and leukopenia (55%) were managed primarily by dose reduction/treatment interruption
	Schedule B (ixabepilone 8–10 mg/m^2 on days 1–3 + capecitabine 1650 mg/m^2 on days 1–14 of a 21- day cycle			No (DLTs) were observed in the 1650 mg/m^2 and 1650 mg/m^2 cohorts	
Abraham[27]	Dose escalation daily for 5 consecutive days every 21 d	27	daily schedule for 5 d is 6 mg/m^2/d	6 mg/m^2 iv daily for 5 consecutive days every 21 d	Neutropenia with (8mg/m^2/d)or with-out filgrastim support. Nonhematologic grade 3 toxicities included fatigue (7 cycles), stomatitis (2 cycles), and anorexia (1 cycle).

Table 2. Phase II single arm studies with Ixabepilone in metastatic breast cancer, study endpoint overall response rate (ORR) for all studies.

Author	Ixabepilone dose	Patient population	Number of patients	Overall response rates (ORR) (%)	Safety GR3/4 toxicity in ≥10% of patients
THOMAS[39]	40 mg/m^2, 3 hour infusion q 21 d	Taxane-resistant	49	12%	Fatigue-27%, Costitutional-27% GI-20%, Neurology-14% sensory neuropathy-12%,
LOW[33]	6 mg/m^2, 1 hour infusion days 1–5 q 21 d	Taxane-pretreated/ resistant	37	22% SD = 35%	Neutropenia (35%), Febrile neutropenia (14%), Fatigue (14%) Diarrhea (11%) Nausea/vomiting (5%), Myalgia/arthralgia (3%) Sensory neuropathy (3%)
ROCHE[29]	40 mg/m^2 3 hour infusion Q 21 d	Anthracycline-pretreated First-line metastatic	65	41.5%	Neutropenia-58% Leucopenia-50% Sensory Neuropathy-20% Most common GR 1/2 treatment-related adverse events other than alopecia included mild to moderate neuropathy, which was primarily sensory and mostly reversible.
DENDULURI[31,32]	6 mg/m^2/d, days 1–5 1 hour infusion Q 21 d	Taxane-naive	23	57%	Fatigue-13% Neutropenia-13%
BASELGA[42]	40 mg/m^2, 3 hour infusion, Q 21 d	Neoadjuvant T ≥3 cm primary invasive breast cancer	161	In breast PCR = 18% PCR = 29% for ER-negative ER gene expression (ER1) was inversely related to pCR in breast	Grade 3 to 4 adverse events (AEs) were reported for 32% of pts. Except for neutropenia and leukopenia, all grade 3 to 4 AEs occurred in ≤3% of patients. Reversible peripheral neuropathy was experienced by 3% of patients.

Roche et al[29] conducted a phase II single arm study of Ixabepilone in women with MBC (N = 65) who received previously an anthracycline-based regimen as adjuvant treatment. Ixabepilone was administered initially at 50 mg/m^2 defined before iv over 1 hour every 21 days but due to increased signals of toxicity (grade 3/4neuropathy) the infusion length was increased to 3 hours. Later due to increased rate of GI toxicities observed in another phase I study conducted in parallel the dose of Ixabepilone was decreased to 40 mg/m^2 IV over 3 hours every 21 days. Objective response rate (primary end point) for this study was 41.5% (95% CI, 29.4%–54.4%), median duration of response was 8.2 months (95% CI, 5.7–10.2 months), and median time to response was 6 weeks (range, 5–17 weeks). Median survival was 22.0 months (95% CI, 15.6–27.0 months). Treatment-related adverse events were manageable and mostly grades 1/2; the most common side effects other than alopecia were mild to moderate neuropathy, primarily sensory and mostly reversible in nature.[29,30]

A phase II study of Ixabepilone in patients with Taxane-naive MBC (N = 23) used a different Ixabepilone schedule; 6 mg/m^2/d IV on days 1 through 5 every 21 days until unacceptable toxicity or disease progression.[31] In addition patients underwent pre and post-treatment tumor tissue biopsies which were analyzed for acetylated -tubulin, tau-1, and p53 expression. Partial responses were seen in 13 patients (57%; 95% CI, 34.5%–76.8%) and 6 patients (26%) had stable disease, median time to progression and duration of response were 5.5 and 5.6 months respectively. Dose reductions for neutropenia, neuropathy, or fatigue were required in a minority of patients and grade 3/4 toxicities were uncommon and included neutropenia, fatigue, anorexia and motor neuropathy. Grade 1/2 peripheral sensory neuropathy was seen in 52% of patients but no patient experienced grade 3/4 sensory neuropathy. Six out of 23 patients had paired biopsies pre and post treatment with Ixabepilone and all had increases in tumor-tubulin acetylation after treatment however baseline or cycle 2 acetylated -tubulin, tau-1, or p53 expression did not correlate with clinical response. The authors concluded that women with Taxane-naive MBC have a meaningful and durable response to single-agent Ixabepilone therapy with minimal hematologic toxicity and no grade 3/4 sensory neuropathy noted.[32]

In another phase II study of single agent Ixabepilone delivered at 6 mg/m^2/day IV on days 1–5 every 21 days, women with MBC (N = 37) with measurable disease who had paclitaxel and/or docetaxel as prior neoadjuvant, adjuvant, or metastatic therapy were treated.[33] One hundred fifty three cycles were delivered, in this previously taxane exposed patient population 8 out of 37 (22%) patients had objective response; complete response was seen in 1 patient (3%), partial responses in 7 (19%), and stable disease in 13 (35%) patients. Again the most common grade 3/4 toxicities included neutropenia (35%), febrile neutropenia (14%), fatigue (14%), diarrhea (11%), nausea/vomiting (5%), myalgia/arthralgia (3%), and sensory neuropathy (3%). Two patients discontinued therapy with Ixabepilone due to prolonged grade 2 or 3 neurotoxicity, and 3 patients due to other grade 3 and 4 nonhematologic toxicities.

Efficacy and safety of Ixabepilone was studied by Perez and colleagues[34] in a multicenter single arm phase II study in patients with MBC (N = 126) resistant to an anthracycline, a taxane, and Capecitabine. Patients with measurable disease who progressed while receiving prior therapy with anthracycline, taxane, and Capecitabine were treated with Ixabepilone 40 mg/m^2 monotherapy as a 3-hour IV every 3 weeks. The primary end point was objective response rate (ORR), assessed by an independent radiology facility (IRF). Off 126 treated patients 113 were assessable for response. Participants were "heavily pretreated", 88% had received at least two lines of prior chemotherapy in the metastatic setting. IRF-assessed ORR was 11.5% (95% CI, 6.3%–18.9%) for response-assessable patients, while investigator-assessed ORR for all treated patients was 18.3% (95% CI, 11.9%–26.1%). Fifty percent of patients achieved stable disease (SD) and 14.3% achieved SD ≥6 months. Median duration of response and progression-free survival were 5.7 and 3.1 months, respectively with a median overall survival of 8.6 months. Median of 4.0 treatment cycles (range, 1–16 cycles) were delivered, and a quarter of patients received ≥8 cycles. Grade 3/4 treatment-related toxicity events included peripheral sensory neuropathy (14%) and resolution of grade 3 and 4 peripheral sensory neuropathy occurred after a median period of 5.4 weeks. Fatigue/asthenia (13%), myalgia (8%), and stomatitis/mucositis (6%) were the other most common grade 3 and 4 toxicities. The authors concluded that Ixabepilone demonstrated clear activity and a manageable safety profile in patients with MBC resistant to anthracycline, taxane, and Capecitabine, durable responses were observed in patients who previously did not respond to multiple other therapies.

Combination of Ixabepilone and Capecitabine in Metastatic Breast Cancer

Effective treatment options for patients with metastatic breast cancer resistant to anthracyclines and taxanes are limited. Ixabepilone has single-agent activity in this patient population and preclinical synergy with Capecitabine has been demonstrated.[35] Two large phase III studies were done to evaluate efficacy of Ixabepilone in combination with Capecitabine in MBC patients, in both trials the control arm consisted of Capecitabine 2500 mg/m^2 total daily dose in 2 divided doses on days 1–14 of a 21 day treatment cycle. Neither trial was designed to allow crossover

to single agent Ixabepilone treatment at the time of progression on Capecitabine. In an international phase III study Thomas et al[35] studied the efficacy of the combination of Ixabepilone + Capecitabine compared to Capecitabine alone in patients with anthracycline-pretreated or -resistant and taxane-resistant expousre locally advanced or MBC, up to 3 lines of prior chemotherapy exposure were allowed. Seven hundred fifty-two patients were randomly assigned to Ixabepilone 40 mg/m^2 given IV over 3 hours on day 1 of a 21-day cycle + Capecitabine 2,000 mg/m^2 orally on days 1 through 14 of a 21-day cycle, or Capecitabine alone 2,500 mg/m^2 on the same schedule. The primary end point was progression-free survival (PFS) evaluated by blinded independent review. Ixabepilone + Capecitabine treatment resulted in prolonged PFS relative to Capecitabine (median, 5.8 v 4.2 months), with a 25% reduction in the estimated risk of disease progression (hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P = 0.0003). Objective response rate was also increased with the combination (35% v 14%; $P < 0.0001$). Grade 3/4 treatment-related sensory neuropathy (21% v 0%), fatigue (9% v 3%), and neutropenia (68% v 11%) were more frequent with combination therapy. Capecitabine-related toxicities were similar for both treatment groups. The investigators concluded that Ixabepilone + Capecitabine combination demonstrated superior efficacy to Capecitabine alone in patients with MBC pretreated or resistant to anthracyclines and resistant to taxanes.

The second large 2 arm phase III trial was done to compare the efficacy of the combination of Ixabepilone + Capecitabine with Capecitabine alone.[36] In this study the investigators sought to determine whether the combination of Ixabepilone + Capecitabine improved overall survival (OS) compared with Capecitabine alone in patients with MBC previously treated with anthracyclines and taxanes, up to 2 lines of prior therapy were allowed. A total of 1,221 patients with MBC previously treated with anthracycline and taxanes were randomly assigned to Ixabepilone (40 mg/m^2 IV on day 1) + Capecitabine (2,000 mg/m^2 orally on days 1 through 14) or Capecitabine alone (2,500 mg/m^2 on the same schedule) given every 21 days. The trial was powered to detect a 20% reduction in the hazard ratio (HR) for death. There was no significant difference in OS between the combination of Ixabepilone + Capecitabine and Capecitabine monotherapy arm, the median survival was 16.4 v 15.6 months respectively, HR = 0.9; 95% CI, 078 to 1.03; P = 0.1162). The treatment arms were well balanced with the exception of a higher prevalence of impaired performance status (Karnofsky performance status-KPS 70% to 80%) in the combination arm (32% v 25%). In a secondary Cox regression analysis adjusted for performance status and other prognostic factors, OS was improved for the combination (HR = 0.85; 95% CI, 0.75–0.98; P = 0.0231). Patients with measurable disease (79%) treated with the combination had a significantly improved (PFS; median, 6.2 v 4.2 months; HR = 0.79; P = 0.0005) and response rate (43% v 29%; $P < 0.0001$). Grade 3/4 neuropathy occurred in 24% treated with the combination, but was reversible. This study confirmed the findings from the Thomas trial demonstrating improved PFS and response for the Ixabepilone + Capecitabine combination compared with Capecitabine alone, although survival was equivalent in both groups of patients.

ER/PR/Her2 negative Subset of MBC Patients

Patients with ER/PR/HER2-negative, triple negative breast cancer (TNBC) are not candidates for hormonal or HER2-targeted therapy and in general do not derive as much benefit from standard chemotherapy[35,37] agents approved for treatment of MBC. Perez and colleagues[38] analyzed efficacy and safety data of Ixabepilone in patients with TNBC from 5 phase II and 2 phase III trials. Of 2,261 patients evaluated in these trials 24.5% had TNBC tumors. In the neoadjuvant setting, Ixabepilone produced a pathologic complete response rate in the breast of 26% in TNBC vs. 15% in the non-triple-negative population. In patients with MBC whose pretreatment status ranged from no prior therapy to progression on several classes of agents, overall response rates (ORR) in the phase II Ixabepilone monotherapy trials ranged from 6 to 55% and was similar to patients with non-triple-negative tumors. In addition treatment with the combination of Ixabepilone + Capecitabine in the phase II study resulted in an ORR of 23% in TNBC while ORR of 31% was seen in a preplanned pooled analysis of TNBC in the phase III trials of Ixabepilone + Capecitabine. The median progression-free survival (PFS) was significantly longer for TNBC treated with Ixabepilone + Capecitabine combination vs. Capecitabine

alone (4.2 vs. 1.7 months) respectively. Responses to Ixabepilone in TNBC are therefore comparable to those seen in patients with non-triple-negative tumors and no apparent increase in toxicity was noted in the TNBC subgroup compared with other groups of patients.

Safety of Ixabepilone

Hematological toxicity

Ixabepilone is contraindicated in patients with a neutrophil count <1500 cells/mm^3, with single agent therapy myelosuppression is dose-dependent and primarily manifested as neutropenia. Ixabepilone-associated hematologic abnormalities ($>40\%$) include neutropenia, leukopenia, anemia, and thrombocytopenia. Dose reductions are recommended in patients who experience severe neutropenia or thrombocytopenia. Neutropenia-related deaths however are rare and occurred in 0.4% of 240 MBC patients treated with Ixabepilone as monotherapy. Grade 3/4 neutropenia was observed in 54% of patients and leucopenia in 49% of patients in one phase II study of Ixabepilone monotherapy in MBC but the rate of grade 3 febrile neutropenia was 3%.[34] Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving Ixabepilone. Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with Ixabepilone in combination with Capecitabine.[35]

Non-Hematological Toxicity

Neurotoxicity

Peripheral neuropathy was common in clinical trials with Ixabepilone although many patients who entered these trials had preexisting peripheral neuropathy due to prior exposure to other neurotoxic chemotherapy agents (Taxanes).[24,35,39,40] In fact prior history of peripheral neuropathy did not predict the occurrence of peripheral sensory neuropathy symptoms in patients receiving Ixabepilone. Patients treated with IxabepiloIne should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Neuropathy primarily sensory and peripheral due to Ixabepilone tends to occur early during therapy and majority of patients (~75%) develop symptoms of new onset or worsening neuropathy during the first 3 cycles of treatment with Ixabepilone. Patients experiencing new or worsening peripheral neuropathy may require dose delays and or dose reductions mentioned earlier in this manuscript. In some cases discontinuation of Ixabepilone is necessary due to severe and unresolving symptoms. Neuropathy symptoms were the most frequent cause of treatment discontinuation due to drug toxicity in clinical trials in patients with MBC. Patients with other medical conditions with higher incidence of preexisting peripheral neuropathy such as diabetes mellitus should be approached with caution and followed closely while on treatment with Ixabepilone as they may have significant worsening of their preexisting peripheral neuropathy.

Hypersensitivity reactions

Patients should be premedicated with an histamine receptor 1 (H1) and an histamine receptor 2 (H2) antagonist approximately 1 hour before Ixabepilone infusion and observed for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm). Premedication with corticosteroids in the first cycle is not routinely required. In case of severe hypersensitivity reactions, infusion of Ixabepilone should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started. Patients who experience a hypersensitivity reaction in the first cycle of Ixabepilone must be premedicated in subsequent cycles with a corticosteroid in addition to the H1 and H2 antagonists, and extension of the infusion time can be considered. Ixabepilone should be avoided in patients with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to other agents containing Cremophor EL or its derivatives (eg, polyoxyethylated castor oil).

Cardiac safety

Ixabepilone is not considered cardiotoxic however caution should be exercised in patients with a history of cardiac disease and Ixabepilone should be discontinued in patients who develop cardiac ischemia or impaired cardiac function while on therapy. Isolated reports of cardiovascular adverse reactions such as (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction) have been reported clinical trials with Ixabepilone. Although small the frequency of cardiac adverse reactions (myocardial

ischemia and ventricular dysfunction) was higher in the treatment arm with Ixabepilone in combination with Capecitabine (1.9%) as compared to Capecitabine monotherapy (0.3%) treatment group.[35]

Other toxicities

Besides peripheral sensory neuropathy, the most common adverse reactions (≥20%) seen in patients receiving Ixabepilone were fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain.[41] The following additional adverse events occurred in ≥20% in combination with Capecitabine: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation.[35] Drug-associated hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

Dose reduction of Ixabepilone and efficacy of therapy

The efficacy data (overall response rate-ORR and disease free survival-DFS) from the 2 phase III studies of Ixabepilone with Capecitabine vs. Capecitabine were reanalyzed retrospectively looking at the possible effect of protocol specified, early versus delayed or no dose reduction of Ixabepilone due to toxicities.[45] Only patients with measurable disease who received 4 or more cycles of therapy were analyzed (N = 652), the median number of cycles was 7 for both early and late/no dose reduction groups. There was no difference in the ORR (62.6% vs. 52.3%) and median PFS

Table 3. Phase III studies with Ixabepilone with capecitabine versus capecitabine alone.

Phase III studies study author	Ixabepilone + capecitibine versus capecitabine	Patient population	Number of patients	Response rates (%) based on independent review	Safety GR3/4 toxicities
Thomas ES[35]	Arm I- Ixabepilone 40 mg/m^2, 3 hour infusion q 21 d plus Capecitabine 2,000 mg/m^2 orally on days 1 through 14 of a 21-day cycle Compared to Arm II Capecitabine 2,500 mg/m^2 orally on days 1 through 14 of a 21-day cycle	anthracycline-pretreated or -resistant and taxane-resistant locally advanced or metastatic breast cancer, ≤3 lines of prior chemotherapy	752	PFS primary endpoint 5.8 v 4.2 months HR 0.75; 95% CI 0.64–0.88; $P = 0.0003$ ORR 35% v 14%; $P < 0.0001$	Ixabepilone + Capecitabine v Capecitabine Sensory neuropathy (21% v 0%). Fatigue (9% v 3%) Neutropenia (68% v 11%) Death as a result of toxicity (3% v 1%, with patients with liver dysfunction [≥grade 2 liver function tests] at greater risk
Sparano JA[36]	Ixabepilone 40 mg/m^2 intravenously on day 1 of 21-day cycle plus Capecitabine 2,000 mg/m^2 on day 1–14 of a 21-day cycle Compared to Capecitabine 2500 mg/m^2 on day 1–14 of a 21 day cycle	MBC previously treated with anthracycline and taxanes, ≤2 lines of prior chemotherapy	1221	Primary endpoint OS similar for both treatment arms (median, 16.4 v 15.6 months; HR = 0.9; 95% CI, 078 to 1.03; $P = 0.1162$) PFS; median, 6.2 v 4.2 months; HR = 0.79; $P = 0.0005$) and response rate (43% v 29%; $P < 0.0001$) better for the combination treatment	Grade 3 to 4 sensory neuropathy in 24% treated with the combination, reversible

(7.2 vs. 7.0 months) respectively for early vs. late or no dose reduction with a HR of 0.98 (0.83–1.17). Median duration of response was 5.8 vs. 6.2 months respectively.[45]

Efficacy: single agent Ixabepilone versus Ixabepilone + Capecitabine doublet

Single agent activity of Ixabepilone in MBC is seen in heavily pretreated patients deemed resistant to Taxanes and anthracyclines. Several single arm phase II studies with different schedules of Ixabepilone and in different patient populations with a range of prior exposure to chemotherapy were conducted. Not surprisingly prior exposure to anthracyclines and taxanes therapy affects significantly the potential for response to therapy with single agent Ixabepilone in metastatic setting with the best responses seen in patients with minimal prior exposure to chemotherapy. MBC patients with taxane resistant disease have objective response rate (RR) of 12% (N = 49),[39] patients with prior low exposure to taxanes and/or resistance have RR = 22% (N = 37),[33] Ixabepilone after adjuvant anthracycline therapy exposure renders RR = 41.5% (N = 65)[29]; in taxane naïve patients RR = 57% (N = 23)[31] while in neoadjuvant setting overall complete pathologic response (pCR) rate was 18% in breast and 29% in estrogen receptor (ER) -negative patients.[42]

Two large phase III trials with similar eligibility criteria included (N = 752 + 1221) patients with locally advanced and MBC anthracycline-pretreated or resistant and taxane-resistant[35,36] and failed to show survival benefit for combined therapy with Ixabepilone with Capecitabine as compared to Capecitabine alone. Neither trial was designed to allow crossover to Ixabepilone after progression on Capecitabine. The Sparano trial was powered to detect a 20% reduction in the hazard ratio (HR) for death and no significant difference in OS between the combination (Ixabepilone + Capecitabine) and Capecitabine monotherapy arm was found (median survival was 16.4 v 15.6 months; HR = 0.9; 95% CI, 078 to 1.03; P = 0.1162). In this trial the treatment arms were unbalanced for higher prevalence of impaired performance status (KPS 70% to 80%) in the combination arm (32% v 25%). A secondary Cox regression analysis was adjusted for performance status and other prognostic factors and showed improved OS was for the combination (HR = 0.85; 95% CI, 0.75–0.98; P = 0.0231).[36] For both phase III trials PFS and overall response rates were higher in the combination treatment arms as compared to single agent therapy with Capecitabine.[35,36] Progression free survival for Ixabepilone + Capecitabine vs Capecitabine single agent therapy was (median, 5.8 v 4.2 months) for Thomas trial[35] and (median 6.2 v 4.2 months) for Sparano trial.[36] The objective response rate was also increased with the combination in both studies (35% v 14%; $P < 0.0001$) and (43% v 29%; $P < 0.0001$) respectively.

Patient preference

Literature review provided no published reports on patient self reported preference of therapy with single agent Ixabepilone versus in combination with Capecitabine, however Ixabepilone is generally well tolerated, and its toxicity profile does not overlap with that of Capecitabine. Myelosupression (leucopenia/neutropeniaI) and peripheral sensory neuropathy are the most common toxicities associated with Ixabepilone and can be effectively managed by dose reductions and delays where appropriate based on the severity of the side-effects. Ixabepilone dose reductions are recommended for most grade 3 toxicities, excluding transient fatigue, arthralgia, and myalgia. Treatment discontinuation is recommended for persistent grade 3 neuropathy or any grade 4 nonhematological toxicity. Caution should be used when treating patients with moderate and severe hepatic impairment which is associated with greater Ixabepilone exposure and more severe toxicity. Patients on concomitant strong cytochrome P-450 CYP3A4 inhibitors should have dose adjustments whether Ixabepilone is administered alone or in combination with Capecitabine, and whether a strong CYP3A4 inhibitor is being coadministered. Premedication with H1 and H2 blockers to prevent hypersensitivity reactions is required but unlike with paclitaxel corticosteroid premedication is not required unless a hypersensitivity reaction occurred previously with Ixabepilone or during treatment with another Cremophor-containing agent.

Conclusions

Ixabepilone a semisynthetic analog of epothilone B is the first in class US Food and Drug Administration approved member of epothilone class of antineoplastic

agents a relatively new class of antimicrotubule agents. Ixabepilone is FDA approved for treatment of MBC which is resistant to anthracyclines, taxanes and Capecitabine and in combination with Capecitabine for patients previously exposed to anthrayclines and taxanes. Epothilones are cytotoxic macrolides with a similar mechanism of action to taxanes but with the potential advantage of activity in taxane-resistant settings in preclinical models.[18] The antineoplastic activity of Ixabepilone has been linked to stabilization of microtubules, which results in mitotic arrest at the G2/M transition. Unlike many other antineoplastic agents it has low susceptibility to common mechanisms of tumor resistance, including those mediated by P-glycoprotein a multidrug resistance protein. In addition the microtubule-stabilizing agents such as Ixabepilone prolong activation of the spindle assembly checkpoint which may promote cancer cell death in mitosis or following mitotic exit.[19]

Ixabepilone is metabolized in the liver and caution should be used when considering patients with liver impairment for therapy with this agent. Ixabepilone exposure is greater in patients with hepatic impairment and those receiving concomitant strong cytochrome P-450 CYP3A4 inhibitors. Dose adjustments and restrictions are recommended according to the degree of hepatic impairment, whether Ixabepilone is administered alone or in combination with Capecitabine if a strong CYP3A4 inhibitor is being coadministered.[24]

Various schedules of single agent Ixabepilone were studied in phase I, dose escalation studies to assess maximum tolerated dose, dose limiting toxicity and pharmacokinetic and pharmacodynamic profile of Ixabepilone in solid tumor malignancies and lymphomas. The following schedules of Ixabepilone were tested 1 and 3 hour infusion once every 21 days, 30 minutes weekly infusion continuous on 21 day schedule without interruption, weekly, 1 hour infusion 3 out of 4 weeks every 28 days, daily infusion on days 1–3 and 1–5, every 21 days (Table 1). All schedules mentioned above showed acceptable and manageable side-effect profiles.

Ixabepilone was also extensively studied in several phase II studies (Table 2) as a single agent in patients with MBC and was found to be effective and well tolerated with a predictable and manageable safety profile. Not surprisingly prior exposure to anthracyclines and taxanes therapy affects significantly the potential for response to therapy with single agent Ixabepilone in metastatic setting. MBC patients with taxane resistant disease have objective response rate (RR) of 12%, patients with prior low exposure to taxanes and/or resistance RR = 22%, Ixabepilone after adjuvant anthracycline therapy exposure renders RR = 42% and in taxane naïve patients RR = 57%.

Effective treatment options for patients with MBC resistant to anthracyclines and taxanes are limited. Ixabepilone has single-agent activity in this patient population and preclinical synergy with Capecitabine has been demonstrated.[35] Two large phase III trials (N = 752 + 1221) in patients with locally advanced and MBC anthracycline-pretreated or resistant and taxane-resistant[35,36] were conducted to evaluate efficacy of Ixabepilone 40 mg/m^2 as 3 hour infusion every 3 weeks in combination with Capecitabine 2000 mg/m^2 total daily dose total daily dose, in both trials the control arm consisted of Capecitabine 2500 mg/m^2 total daily dose in 2 divided doses on days 1–14 of a 21 day treatment cycle. Neither trial was designed to allow crossover to single agent Ixabepilone treatment at the time of progression on Capecitabine and both trials failed to show survival benefit for combined therapy with Ixabepilone + Capecitabine as compared to Capecitabine alone. Progression free survival and overall response rates were higher in the combination treatment arms as compared to single agent therapy with Capecitabine. Ixabepilone + Capecitabine PFS relative to Capecitabine was (median, 5.8 v 4.2 months) for Thomas trial[35] and (median 6.2 v 4.2 months) for Sparano trial.[36] The objective response rate was also increased with the combination in both studies (35% v 14%; $P < 0.0001$) and (43% v 29%; $P < 0.0001$) respectively.

Responses to Ixabepilone in triple-negative MBC are comparable to those seen in patients with non-triple-negative tumors and no apparent increase in toxicity was noted in the triple-negative subgroup compared with other groups of patients. Treatment with Ixabepilone + Capecitabine in the phase II study resulted in an overall response rate (ORR) of 23% in TNBC while ORR of 31% was seen in a preplanned pooled analysis of TNBC in the phase III trials of ixabepilone + Capecitabine. Significantly prolonged median PFS was seen for TNBC treated with the combination of Ixabepilone + Capecitabine compared to Capecitabine alone 4.2 vs. 1.7 months

respectively.[38] Ixabepilone as single agent therapy appears to show excellent antitumor activity in patients with triple-negative MBC and the addition of Ixabepilone to Capecitabine results in approximately doubling in median PFS for TNBC patients versus Capecitabine alone.

Literature review provided no published reports on patient self reported preference of therapy with single agent Ixabepilone versus in combination with Capecitabine, however Ixabepilone is generally well tolerated, and its toxicity profile does not overlap with that of Capecitabine and therefore depending on prior exposure to chemotherapy both single agent Ixabepilone or in combination with Capecitabine can be used safely. Myelosupression (leucopenia/neutropeniaI) and peripheral sensory neuropathy are the most common toxicities associated with Ixabepilone and can be effectively managed by dose reductions and delays where appropriate based on the severity of the side-effects. In addition recent reports indicate that early into treatment Ixabepilone dose reductions do not affect the efficacy of this agent and certainly should be considered when required based on the observed side-effects.

In summary Ixabepilone as single agent or in combination with Capecitabine is an effective therapy for MBC which is anthracycline and taxane resistant. Significant activity is seen in ER, PR, HER2 negative TNBC patients with MBC. As expected the efficacy of Ixabepilone is higher in less heavily pretreated patients and this agent can be considered in these settings.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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