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Review

Activity of ixabepilone in oestrogen receptor-negative and oestrogen receptor-progesterone receptor-human epidermal growth factor receptor 2-negative metastatic breast cancer

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ABSTRACT

Oestrogen receptor (ER)-negative breast cancer, including oestrogen receptor-, progesterone receptor- and human epidermal growth factor receptor 2-negative (ER/PR/HER2-negative) breast cancer, is more aggressive than ER-positive disease. A major limitation in the treatment of ER-negative disease subtypes is the inherent insensitivity to hormonal agents (tamoxifen, aromatase inhibitors) that are widely used in the treatment of breast cancer. Thus, therapeutic options for poor prognosis patients with ER-negative breast cancer are limited to a handful of chemotherapeutic agents, and new agents are needed to improve the treatment of this disease.

Ixabepilone, a novel epothilone B analogue with low susceptibility to cellular mechanisms that confer resistance to taxanes and other chemotherapeutic agents, has demonstrated potent preclinical antitumour activity in multiple models, including those with primary or acquired drug resistance. This review summarises the results of a prospective subset analysis from a phase III clinical trial evaluating ixabepilone for the treatment of metastatic breast cancer (MBC), in which efficacy and safety were evaluated in patients with ER-negative and ER/PR/HER2-negative disease.

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1. Introduction

Breast cancer is a heterogeneous disease composed of multiple subtypes, as demonstrated by their different genetic profiles, proteomic expression patterns and biological properties, many of which have not yet been fully characterised.[1] Breast tumours can vary widely with respect to both morphology and pathology measures such as size, histological grade, invasiveness, ploidy and proliferation index. Among these variables, the expression levels of the hormone receptors for oestrogen (ER) and progesterone (PR) are of major relevance.[2] This is not only because ER expression modulates tumour sensitivity to hormonotherapy, but also because the ER status of a tumour may impact the efficacy of chemotherapy.[3–9] Similarly, but to a different extent, PR impact tumour sensitivity to hormonal therapy and chemotherapy.[10] ER and/or PR status has been correlated with age of onset of disease, tumour ploidy, tumour aggressiveness and disease outcomes.[8,10–13] These characteristics are not causally linked, and the relationships between them are not well understood.

Variability also exists for expression of growth factor receptors that regulate breast cancer growth, such as human epidermal growth factor receptor 2 (HER2). The overexpression of HER2 is associated with response to HER2-targeted therapy. In addition, HER2 expression levels may affect outcomes and susceptibility to chemotherapy.[14]

Breast cancer patients with ER-negative breast cancer, including those with ER/PR/HER2-negative tumours, typically have more aggressive disease and poor prognosis.[15] Compared with other breast cancer subtypes, ER/PR/HER2-negative breast cancer is associated with an earlier age of disease onset, more frequent local relapse, a higher proportion of visceral and brain metastases and shorter overall survival.[16–19]

Ixabepilone, a novel semisynthetic epothilone B analogue, has demonstrated significant activity against multiple cancer cell lines and xenograft tumour models, including those with primary or acquired drug resistance to paclitaxel and/or with multidrug resistant (MDR) phenotype.[20–24] Ixabepilone binds at or near the paclitaxel-binding site on the β-tubulin subunit of microtubules and stabilises their polymerisation, resulting in cell cycle arrest and apoptosis.[25–27] In contrast with taxanes, ixabepilone binds to multiple isotypes of β-tubulin, including the βIII isotype,[28] which may account in part for its ability to bypass or circumvent resistance associated with overexpression of βIII-tubulin.[20–22,28]

Multiple clinical trials have evaluated ixabepilone in drug-resistant breast cancer following varying degrees of pretreatment with chemotherapy.[29–38] A phase II study also demonstrated activity of single-agent ixabepilone in the neoadjuvant setting.[39] Patients with invasive breast adenocarcinoma (⩾3 cm diameter) not amenable to breast conservation surgery received ixabepilone (40 mg/m^2) as a 3-hour infusion on day 1 of a 21-day cycle for a maximum of four cycles. A pathologic complete response (pCR) was achieved in 18% of patients.[39] The primary aim of this phase II neoadjuvant breast cancer study had been to identify predictors of response to ixabepilone using gene expression profiling, and the analysis identified low ER gene expression as a predictor of clinical response to treatment with single-agent ixabepilone.[39,40] Significantly higher activity was observed in patients with ER-negative breast adenocarcinoma treated with neoadjuvant ixabepilone, with a pCR_B rate of 29% versus 18% in the total patient population.[39] Single-agent ixabepilone activity was also observed in patients with ER/PR/HER2-negative tumours, with a pCR_B rate of 26%.[38,39] These results highlighted a need to further explore ixabepilone's efficacy in patients with low ER expression.[40]

In the metastatic breast cancer (MBC) setting, five early phase II monotherapy studies and one recently completed phase III trial of ixabepilone in combination with capecitabine have demonstrated that this agent is effective in patients with metastatic disease.[29–33] In three of the monotherapy phase II trials, patients received ixabepilone 40 mg/m^2, administered as a 3-hour infusion on day 1 every 21 days (Table 1). A retrospective analysis was performed in patients with subtypes of ER-negative tumours in these three phase II ixabepilone monotherapy trials. Interestingly, in these three studies the response rate was similar in 71 patients with ER/PR/HER2-negative breast cancer (17%) and in 169 patients with non-ER/PR/HER2-negative disease (21%).[38] This analysis demonstrated that ixabepilone monotherapy was effective against ER/PR/HER2-negative disease despite the historically poor prognosis of this patient population. In order to assess the activity of the ixabepilone plus capecitabine doublet in these poor prognosis patient populations, a prospective subset analysis was planned and conducted as part of the subsequent phase III trial. The results of this analysis are discussed in this review.

2. Patients in the phase III trial and methods

The randomised phase III trial demonstrated efficacy of ixabepilone in combination with capecitabine versus capecitabine alone in 752 patients with locally advanced or MBC who were pretreated with or resistant to anthracyclines and resistant to taxanes.[34] Resistance to taxanes was defined as tumour progression during treatment or within 4 months of the last dose in the metastatic setting or 12 months in the adjuvant setting. Eighty-five percent of patients had progressed on prior taxane therapy for MBC, and 93% had received ⩾1 prior regimen for metastatic disease. In addition to being heavily pretreated, patients in this trial had widespread metastatic disease (84% had significant baseline visceral disease involving the liver and/or lung).

Patients received ixabepilone 40 mg/m^2, administered as a 3-hour infusion on day 1 every 21 days, plus capecitabine 2000 mg/m^2 daily on days 1 through 14 every 21 days; those treated with capecitabine alone received a dose of 2500 mg/m^2 daily on days 1 through 14 every 21 days. The primary end-point of the study was progression-free survival (PFS). Treatment with ixabepilone plus capecitabine resulted in a median PFS of 5.8 months compared with 4.2 months for capecitabine monotherapy, reflecting a 25% reduction in estimated risk of disease progression (hazard ratio [HR] = 0.75; $p = 0.0003$).(34) Response rates were also greater in the combination arm (35% versus 14%; $p < 0.0001$) (Table 2). Compared with the monotherapy arm, the combination regimen re-

Table 1 – Efficacy of ixabepilone in metastatic breast cancer.[35–38,41]

	Single-agent ixabepilone			Ixabepilone + capecitabine
Patient population	Tax^R, $Anth^R$, Cap^R $n = 126$[a]	Tax^R $n = 49$[b]	$Anth^{Pre}$ $n = 65$[c,d]	Tax^R $Anth^{Pre/R}$ $n = 375$[e,f]
Phase	II	II	II	III
Pretreatment characteristics	77% Visceral disease in liver and/or lung; 88% completed ⩾2 prior chemotherapy regimens for MBC (48% had ⩾3 lines)	All patients received ⩾1 prior taxane-based regimen (31% ⩾2); 98% received a taxane-based regimen as most recent MBC therapy; 73% progressed within 1 month of last taxane dose	77% at least two involved disease sites ($n = 50$) and/or visceral metastases; (85%; $n = 55$). 100% received ⩾1 anthracycline-containing regimen	84% visceral disease involving the liver or lung; 93% ⩾1 prior regimen for MBC; 85% progressed on prior taxane therapy for MBC
ORR (%)	11.5[g]	12[h]	41.5[h]	42[h]
Median DoR (mo)	5.7	10.4	8.2	6.4
SD (%)	50	41	35	41
Median PFS (mo)	3.1	2.2	4.8	5.3
Median OS (mo)	8.6	7.9	22.0	12.9

Anth, anthracycline; Cap, capecitabine; DoR, duration of response; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; Pre, pretreated; PFS, progression-free survival; R, resistant; SD, stable disease; Tax, taxane.

a Resistance in metastatic setting was defined as progression within 8 weeks of last treatment; for adjuvant/neoadjuvant therapy (anthracyclines or taxanes) defined as recurrence within 6 months of therapy completion.

b Resistance in metastatic setting was defined as progression during therapy or within 4 months of last treatment of docetaxel or paclitaxel; for adjuvant/neoadjuvant therapy defined as recurrence within 6 months of taxane therapy completion. Taxane was to be the last prior treatment in all patients.

c Patients must have received prior anthracycline-based adjuvant regimen.

d Patients may have received a taxane as part of an adjuvant regimen provided that ⩾1 year had elapsed since completion of treatment.

e Taxane resistance in metastatic setting was defined as tumour progression during treatment or within 4 months of last dose; for adjuvant/neoadjuvant therapy defined as recurrence within 12 months.

f Ixabepilone/capecitabine arm.

g IRF-assessed ORR based on 113 response evaluable patients.

h Investigator-assessed ORR.

Table 2 – Trial 046: efficacy in total, ER-negative and ER/PR/HER2-negative populations.[34,41,43]

	Overall population		ER-negative subgroup[a]		ER/PR/HER2-negative subgroup		ER-positive subgroup	
	Ixabepilone/ capecitabine (*n* = 375)	Capecitabine (*n* = 377)	Ixabepilone/ capecitabine (*n* = 202)	Capecitabine (*n* = 199)	Ixabepilone/ capecitabine (*n* = 91)	Capecitabine (*n* = 96)	Ixabepilone/ capecitabine (*n* = 173)	Capecitabine (*n* = 178)
Median PFS (mo) (95% CI)	5.8 (5.5–7.0)	4.2 (3.8–4.5)	4.4 (4.1–5.6)	2.8 (2.1–3.4)	4.1 (3.35–4.37)	2.1 (1.45–2.83)	7.6 (6.70–8.64)	5.7 (5.16–6.90)
Hazard ratio (95% CI)	0.75 (0.64–0.88)		0.65 (0.52–0.80)		0.68 (0.50–0.93)		0.81 (0.64–1.03)	
ORR (%)	35	14	30	10	27	9	40	19

ER, oestrogen receptor; CI, confidence interval; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; PR, progesterone receptor; ORR, objective response rate.
a Data include patients with documented ER-negative status (164/202, 161/199) and unknown ER status (38/202, 38/199) for the ixabepilone/capecitabine and capecitabine-only groups, respectively.

sulted in higher levels of grade 3/4 treatment-related sensory neuropathy (20.8% versus 0%), fatigue (9% versus 3.3%), and neutropaenia (68% versus 11%). Peripheral sensory neuropathy was generally reversible. Capecitabine-related toxicities were similar in both treatment groups.[34] (Table 3).

A prospectively defined subgroup analysis of this trial was conducted to evaluate the efficacy and safety of ixabepilone plus capecitabine in patients with anthracycline-pretreated or -resistant, and taxane-resistant, ER-negative MBC.[37] Kaplan–Meier methodology was used to estimate progression-free survival and duration of response; the HR was estimated using a stratified Cox proportional hazards model. Statistical comparison between groups for objective response was performed using the Cochran–Mantel–Haenszel test.

3. Results

3.1. *Efficacy and safety in patients with ER-negative breast cancer*

Of the 752 patients enrolled in the above phase III trial, 401 (53%) were found to have ER-negative tumours (Table 2). In the subgroup analysis, patients were equally distributed between the ixabepilone plus capecitabine arm (*n* = 202) and the capecitabine monotherapy arm (*n* = 199). The ER-negative subsets included patients with documented ER-negative status (164/202; 161/199), unknown ER status (1/202; 0/199) or ER status not reported (37/202; 38/199) for the ixabepilone plus capecitabine and capecitabine-only groups, respectively. Nearly all patients in the ER-negative subgroup were resistant to taxanes.[37]

In ER-negative patients, treatment with the combination regimen significantly prolonged median PFS compared with capecitabine alone (4.4 months versus 2.8 months) (Table 2). The HR of 0.65 indicated that ixabepilone plus capecitabine treatment was associated with a 35% reduction in risk of disease progression in patients with ER-negative tumours relative to the capecitabine monotherapy arm.[37] The observed magnitude of benefit in this ER-negative subset was higher than in the total population (HR = 0.75). Combination therapy with ixabepilone and capecitabine also increased the objective response rate (ORR) threefold compared with capecitabine alone in the ER-negative subgroup (30% versus 10%). This effect was similar to the benefit seen in the total patient population (35% versus 14%; $p < 0.0001$).[37]

The safety profiles of ixabepilone/capecitabine and capecitabine alone were similar for the ER-negative subgroup and for the overall population (Table 3). In the ER-negative subgroup, the incidence of treatment-related grades 3 and 4 neutropaenia was higher in the combination arm (28.2% and 39.5%, respectively) than with capecitabine alone (8.2% and 1.5%) (Table 3). Grade 3/4 febrile neutropaenia was 3.5% in the ixabepilone plus capecitabine arm. Two patients (1.0%) in the combination therapy group had grade 5 febrile neutropaenia (i.e. experienced neutropaenia-related death).

Neuropathy, mainly sensory, was the most common treatment-related non-haematologic adverse event noted with the combination regimen. Grades 3 and 4 peripheral sensory neuropathy occurred in 18.8% and 0.5% of ER-negative patients in the combination arm, respectively.[37] The incidence was sim-

Table 3 – Trial 046: selected treatment-related adverse events in total and ER-negative populations.[38,41]

Adverse event[a]	Overall population				ER-negative subgroup			
	Ixabepilone/capecitabine (*n* = 375)		Capecitabine monotherapy (*n* = 377)		Ixabepilone/capecitabine (*n* = 197)		Capecitabine monotherapy (*n* = 194)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Haematologic toxicity								
Neutropaenia	116 (32)	133 (36)	33 (9)	6 (2)	55 (28.2)	77 (39.5)	16 (8.2)	3 (1.5)
Leucopaenia	150 (41)	60 (16)	17 (5)	4 (1)	85 (43.6)	28 (14.4)	10 (5.2)	2 (1)
Febrile neutropaenia	13 (4)	3 (0.8)	2 (0.5)	0	6 (3)[b]	1 (0.5)[b]	1 (0.5)	0
Non-haematologic toxicity								
Peripheral sensory neuropathy	75 (20)	3 (0.8)	0	0	37 (18.8)	1 (0.5)	0	0
Peripheral motor neuropathy	18 (5)	0	0	0	12 (6.1)	0	0	0
Myalgia	29 (8)	0	1 (0.3)	0	N/A[c]			
Hand-foot syndrome	67 (18)	0	62 (17)	0				

CTCAE, common terminology criteria for adverse events; ER, oestrogen receptor.

a By patients' worse CTCAE v.3.

b Two patients (1.0%) in the combination therapy group had grade 5 febrile neutropaenia.

c Data were not available at the time of this publication.

ilar in the overall population, 20.0% and 0.8%, respectively.[34] Neuropathy was commonly observed, generally reversible, and managed by dose reductions. Among the 342 patients in the overall population who received at least two cycles of ixabepilone plus capecitabine, 63 (18.4%) required an ixabepilone dose reduction for management of peripheral neuropathy.[37] Patients received a 20% dose reduction upon experiencing moderate (grade 2) events lasting more than 7 days, or severe (grade 3) events lasting less than 7 days. Ixabepilone therapy was discontinued in cases of grade 3 peripheral neuropathy lasting longer than 7 days or any grade 4 event. Treatment was delayed if peripheral neuropathy did not resolve to grade 1 or baseline, with a maximum allowed treatment delay of 3 weeks.[42] Median time to grade 3/4 neuropathy symptom improvement (by at least one Common Terminology Criteria for Adverse Events [CTCAE] grade) was 4.1 weeks. Median time to resolution of neuropathy to grade 1 or baseline was 6 weeks.[37] Clinical data illustrate that ixabepilone was an effective and tolerable treatment option for patients with MBC.

In particular, the magnitude of benefit linked with ixabepilone exposure appears to be significantly higher in patients with ER-negative disease, despite a generally dismal prognosis for this subgroup.

3.2. *Efficacy and safety in patients with ER/PR/HER2-negative breast cancer*

The ER/PR/HER2-negative subset was prospectively analyzed in the phase III trial evaluating ixabepilone plus capecitabine combination versus capecitabine alone (Table 2). Response rates in the triple negative subgroup were 27% for ixabepilone plus capecitabine versus 9% with capecitabine alone.[38,41] The PFS was 4.1 months for ixabepilone plus capecitabine versus 2.1 months for capecitabine (HR = 0.68).[38,41] The observed magnitude of benefit of ixabepilone in this subset of patients with poor prognosis tumours was similar to the benefit observed in the total patient population (HR = 0.75). Adverse events with ixabepilone in combination with capecitabine were similar in this subset of patients in comparison with the total population, and they were manageable with dose adjustments.[41]

4. Discussion

Ixabepilone has proven activity in breast cancers that are resistant to or refractory to commonly used chemotherapy agents such as anthracyclines, taxanes and capecitabine.[43] This likely reflects not only the antitumour activity of ixabepilone but also its low susceptibility to multiple tumour resistance mechanisms, particularly those resulting in resistance to taxanes. In October 2007, based on its demonstrated clinical efficacy, ixabepilone was approved by the US Food and Drug Administration (FDA) in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to an anthracycline and a taxane, and as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer resistant or refractory to anthracyclines, taxanes and capecitabine. In November 2008, however, the European Medicines Agency

(EMEA)'s Committee for Medicinal Products for Human Use (CHMP) expressed a concern that the benefits of ixabepilone might not justify its risks in the patient populations who participated in the studies.

The CHMP opinion was based on outcomes in the population as a whole, which consisted of patients with extensive disease who had undergone multiple rounds of previous chemotherapy. Preliminary data suggest that ixabepilone may demonstrate considerable efficacy in earlier lines of therapy or in certain hard-to-treat subpopulations of breast cancer patients. For example, the aforementioned neoadjuvant phase II trial found that ER status is a significant factor related to the activity of ixabepilone, and retrospective analyses of patient subsets in phase II monotherapy studies showed that ixabepilone is active in ER-negative and ER/PR/HER2-negative tumour subtypes. Herein, a review of a subset analysis in a large phase III trial demonstrated that ixabepilone plus capecitabine is more active than capecitabine alone in MBC patients with ER-negative disease. Compared with capecitabine monotherapy, the combination regimen produced a substantial (35%) reduction in risk of disease progression in ER-negative patients versus the 25% reduction in risk of disease progression observed for the total patient population.[34] Toxicity profiles were similar between the ER-negative subgroup and the overall population following treatment with ixabepilone plus capecitabine, and the treatment-related adverse events were generally manageable in both groups.[37] These results indicate that ixabepilone has significant clinical activity in taxane-resistant MBC which is not diminished with ER-negative or ER/PR/HER2-negative disease.[38,41] Interestingly, in the ER/PR/HER2-negative subset of patients, the combination regimen also produced a substantial (32%) reduction in risk of disease progression, compared with the 25% reduction observed for the total patient population.[34] Moreover, the marginal performance of capecitabine alone in this population suggests that single-agent capecitabine may not be an efficacious choice for ER/PR/HER2-negative disease.

In conclusion, ixabepilone is an effective therapeutic option for patients with ER-negative or ER/PR/HER2-negative MBC. The combination of ixabepilone and capecitabine is clinically superior to capecitabine alone in patients with taxane-sensitive or taxane-resistant ER-negative tumours. Of note, the magnitude of benefit in the patient subsets with unfavourable prognosis was comparable to that of the total population. These results warrant further studies in the adjuvant setting to determine the efficacy and safety of ixabepilone in patients with ER-negative and ER/PR/HER2-negative breast cancer.[44]

Conflicts of interest statement

Xavier Pivot received a commercial research grant from Roche and speakers bureau honoraria from Roche and GlaxoSmithKline. He also served as a consultant on advisory boards for Bristol-Myers Squibb and Cephalon. Jacek Jassem and Henri Roché served as consultants on advisory boards for Bristol-Myers Squibb. Pralay Mukhopadyay is an employee of Bristol-Myers Squibb Company, Inc.

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