Epothilones – Expanding the Options for Breast Cancer?

a report by
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Breast cancer is the most common cancer in women in the western world.[1] More than one million women worldwide are diagnosed with it each year.[2] Locally advanced breast cancer accounts for 10–15% of all newly diagnosed cases.[3] This stage of cancer is a difficult clinical problem as most patients progress to distant metastases and, eventually, death.[4–6] The goals of therapy are to extend survival and improve quality of life. Chemotherapy is often used in the neoadjuvant, adjuvant and metastatic settings, with anthracyclines and taxanes being the most active chemotherapeutic agents in the metastatic setting (see *Figure 1*). However, drug resistance and the dose-limiting toxicity of anthracyclines are significant barriers to goal attainment. Until recently, only capecitabine was approved as monotherapy in patients with locally advanced and metastatic breast cancer progressing on taxanes and an anthracycline-containing chemotherapy regimen. Other agents have shown only limited benefit.[7] Thus, there is a need for agents and strategies that optimise the treatment of locally advanced and metastatic disease in breast cancer patients.

Epothilones are microtubule-stabilising cytotoxic chemotherapeutic agents (see *Figure 2*).[8–11] Their mode of action includes induction of apoptosis and promotion of cell death.[7,12,13] These agents represent a novel class of microtubule inhibitors with efficacy and lower susceptibility to drug resistance in taxane-resistant tumours. Epothilones, including ixabepilone, patupilone, KOS-862, KOS-1584 and sagopilone, are under investigation for the treatment of various types of cancer.[8,9,14,15] Among this class, the most advanced in terms of clinical evaluation is ixabepilone, particularly for breast cancer treatment.[14]

Ixabepilone has been approved by the US Food and Drug Administration (FDA) as monotherapy for metastatic or locally advanced breast cancer resistant or refractory to anthracycline, taxanes and capecitabine, and as combination therapy with capecitabine following the failure of anthracycline and taxanes.[16] Its novel mechanism of action has also led to its evaluation as neoadjuvant and adjuvant therapy. The potential of ixabepilone in combination with targeted therapies for the treatment of breast cancer is also under investigation. This article will discuss the rationale for epothilones in the neoadjuvant and adjuvant settings and the potential role of epothilones as combination therapy with targeted agents.

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Rationale for Epothilones in the Neoadjuvant Setting

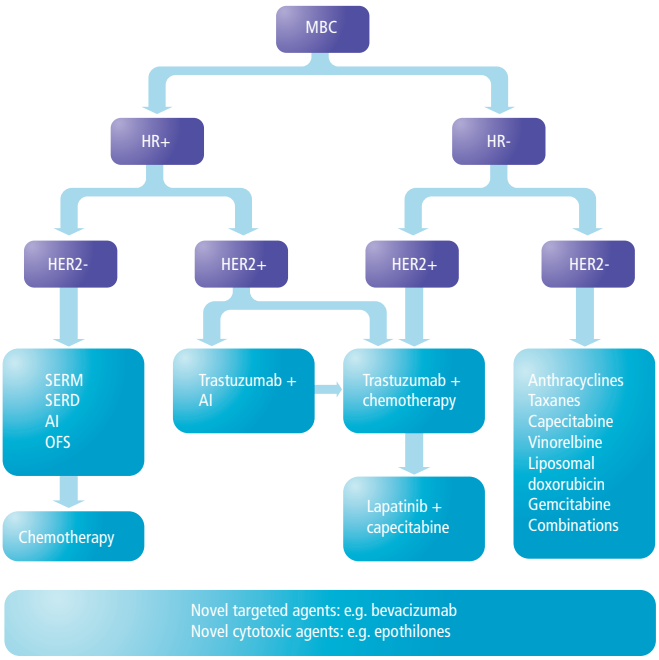
The clinical benefit of neoadjuvant chemotherapy in breast cancer patients has been shown by large multicentre randomised trials.[17–19] Chemotherapy in the neoadjuvant setting is currently the standard of care for the management of locally advanced invasive breast cancers.[20] It is also part of standard therapy for some stage IIA and IIB breast cancers.[20] The doxorubicin (Adriamycin®) plus cyclophosphamide (AC) regimen is frequently used in the neoadjuvant setting for operable breast cancer.[17–19] This regimen involves doxorubicin 60mg/m^2 plus cyclophosphamide 600mg/m^2 given intravenously (IV) on day one and then every 21 days for up to four cycles.[21] Clinical trials have also shown high response rates with taxane-containing regimens when used in the neoadjuvant setting.[22,23] While both the AC and taxane-containing regimens are also used to treat locally advanced invasive breast cancers, the chemotherapeutic agents are associated with drug resistance and toxicity. Thus, there is as yet no regimen recommended as treatment of choice for this stage of breast cancer.

Studies *in vitro* in tumour cell lines show that ixabepilone has greater antiproliferative and antitumour activity than the taxanes, especially under conditions of taxane resistance.[24–27] In clinical trials, ixabepilone has shown antitumour activity in patients with anthracycline-pre-treated, taxane-resistant and multidrug-resistant metastatic breast cancers.[10,28–31] The toxicity profile of ixabepilone is also similar to that of the taxanes. Therefore, it has been proposed that the epothilones may offer clinical benefit in the neoadjuvant setting for the treatment of patients with locally advanced and operable breast cancer.

Clinical Data for Neoadjuvant Epothilone Chemotherapy

The role of ixabepilone in the neoadjuvant setting has been evaluated in a phase II clinical trial (080).[32] This was an exploratory, single-arm, multicentre phase II study. The patients recruited were treatment-naïve women with locally advanced invasive breast cancer ≥3cm (stage IIA–IIIB) not amenable to breast conservation surgery (BCS). Each patient received a three-hour infusion of ixabepilone (40mg/m^2) every 21 days for up to four cycles, followed by surgical resection and an anthracycline-based adjuvant treatment regimen. Of interest to this article are the secondary objectives of the trial, which included assessment of the rate of pathological complete response (pCR) in breast

Figure 1: Treatment Algorithm for Metastatic Breast Cancer by Tumour Characteristics



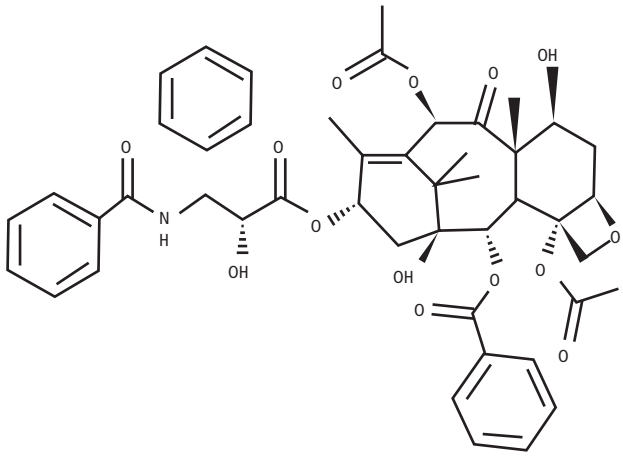
AI = aromatase inhibitor; HER2 = human epidermal growth factor receptor-2; HR = hormone refractory; MBC = metastatic breast cancer; OFS = ovarian function suppression; SERD = selective oestrogen downmodulator; SERM = selective oestrogen receptor modulator. Courtesy of PF Conte.

(B) and lymph nodes (L), the proportion of patients able to have BCS after treatment and the safety of ixabepilone. pCR is defined as the complete absence of intact tumour cells in the resected specimen; this end-point was used as it has been shown to be a good predictor of disease-free and overall survival.[33–35] The patient response rates and surgical outcomes are shown in *Tables 1* and *2*. Grade 3–4 adverse events were reported for 32% of patients.

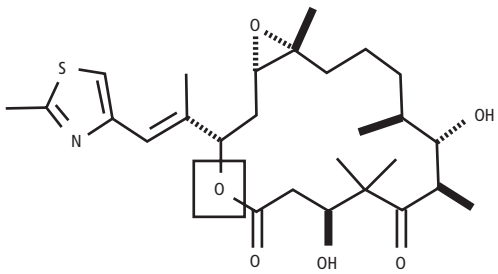
The 080 trial showed that the overall pCRB rate was 18% after four cycles of neoadjuvant ixbepilone (see *Table 1*). This is better than the rates achieved with four cycles of single-agent taxane in the neoadjuvant setting (pCR_B rate with docetaxel, paclitaxel 250mg/m^2 and paclitaxel 200mg/m^2: 10, 8 and 4%, respectively).[36–38] The pCR_B rate with ixabepilone was also better than that achieved with the anthracyclines (doxorubicin plus cyclophosphamide: 13%).[39] The 080 trial also showed a good pCR_L rate (see *Table 1*). This trial has shown encouraging data in terms of the antitumour activity of neoadjuvant ixabepilone in locally advanced invasive breast cancer (stage IIA–IIIB) patients.

Oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) are prognostic biomarkers in primary breast cancers. Patients with ER-negative, ER-/HER2-negative and ER-/PR-/HER2-negative (triple-negative) tumours have poor prognosis with the available treatment strategies. Interestingly, a subanalysis of the 080 trial showed that patients with these tumour characteristics respond to neoadjuvant ixabepilone chemotherapy (see *Tables 1* and *2*). An important goal of neoadjuvant chemotherapy in patients with cancers that are not amenable to BCS is to down-size the tumour and increase the rate of breast conservation therapy. This goal was achieved with neoadjuvant ixabepilone, as 32% of the patients underwent BCS (see *Table 1*).

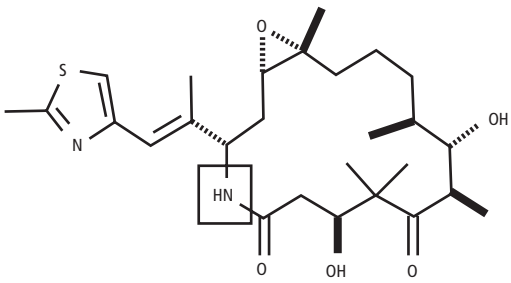
Figure 2: Ixabepilone Has Low Susceptibility to Multiple Mechanisms of Tumour Resistance



Paclitaxel



Epothilone



Ixabepilone

- *Low susceptibility to tumour resistance mechanisms such as beta III tubulin overexpression or multidrug-resistant phenotype.*
- *No structural relationship to taxanes.*
- *More potent than the taxanes.*
- *Active in taxane-resistant models.*
- *Pre-clinical syndergy with capecitabine.*

The results from the 080 trial emphasise the need for further studies of ixabepilone in the neoadjuvant setting. One such study is ongoing; its aim is to assess the efficacy of standard chemotherapy drugs versus a regimen combining standard chemotherapy plus ixabepilone when given to patients with ER-/HER2-negative locally advanced invasive breast cancer in the neoadjuvant setting.[40] Patients will be randomised to receive the AC regimen followed by either weekly paclitaxel 80mg/m^2 for 12 weeks or ixabepilone 40mg/m^2 for four cycles every three weeks. The primary outcome measure is the pCR rate in the two arms. Secondary outcome measures include the rate of BCS and safety of the AC plus ixabepilone treatment regimen.

Table 1: Patient Response Rates and Surgical Outcomes

Response Category	Patients with Response	Total Patients	%	95% CI
pCR_B				
All treated patients	29	161	18	12–25
ER-negative tumours*	21	72	29	19– 41
ER/PR*/HER2-negative tumours**	11	42	26	14–42
pCR_{BL}	17	161	11	6–16
All treated patients				
ER-negative tumours*	14	72	19	11–30
ER/PR/HER2-negative tumours**	8	42	19	9–34
End-point surgery (n=154)				
Breast conservation surgery	50	154	32	–
Mastectomy	104	154	68	–

CI = confidence interval; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; pCR_B = pathological complete response in the breast; pCR_{BL} = pathological complete response in the breast and lymph nodes; PR = progesterone receptor.
**ER and PR status was determined by immunohistochemistry (IHC).*
***HER2 status was based on fluorescence* in situ *hybridisation (FISH). IHC was used if FISH results were not available.*
Source: Baselga et al., 2009.[32]

Table 2: Patient Response Rates by Receptor Status

Patient Responses (pCR_B) by ER*/HER2** Status#	ER/HER2-negative	ER-negative/ HER2-positive
Number of responders	11	6
Number of non-responders	39	7
Response rate (%)	22.0	46.1

ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; pCR_B = pathological complete response in the breast.
**ER status was determined by immunohistochemistry (IHC).*
***HER2 status was based on fluorescence* in situ *hybridisation (FISH). IHC was used if FISH results were not available.*
#Data based on 134 patients for whom data for ER and HER2 expression were available.
Source: Baselga et al., 2009.[32]

Table 3: Ongoing Breast Cancer Studies of Ixabepilone In Combination with Targeted Agents

Study	Phase	End-point
Ixabepilone + trastuzumab vs docetaxel + trastuzumab	II	ORR
Three-arm trial of two schedules of ixabepilone + bevacizumab and paclitaxel + bevacizumab	II	ORR
Bevacizumab weekly + ixabepilone or paclitaxel or Nab-paclitaxel weekly	III	PFS
Ixabepilone vs ixabepilone + cetuximab in triple-negative MBC	II	ORR
Ixabepilone + lapatinib vs ixabepilone + lapatinib + capecitabine in pre-treated HER2+ LABC or MBC	I/II	MTD
Sorafenib + ixabepilone in HER2- MBC	I/II	PFS
Ixabepilone + carboplatin + trastuzumab as neoadjuvant therapy in LABC	II	pCR

ORR = objective response rate; HER2 = human epidermal growth factor receptor-2; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; MTD = maximum tolerated dose; pCR = pathological complete response; PFS = progression-free survival.
Source: clinicaltrials.gov

Rationale for Epothilones in the Adjuvant Setting

The current standard of care in adjuvant chemotherapy involves FEC100 (epirubicin 100mg/m^2 with 5-fluorouracil 500mg/m^2 and cyclophosphamide 500mg/m^2) given once every 21 days for up to six cycles, followed by three cycles of docetaxel. Ixabepilone's mechanism of action is similar to that of the taxanes; however, as previously discussed, it has better efficacy than the taxanes, especially under conditions of taxane resistance, sensitivity or insensitivity. Ixabepilone has demonstrated antitumour activity in breast cancer patients with locally advanced and metastatic disease.[28–31] The 080 trial has also shown the clinical benefit of ixabepilone in the neoadjuvant setting. These data have led to the proposal that epothilones may be effective in the adjuvant setting. The ongoing PACS 08 trial is investigating the role of ixabepilone in the adjuvant setting.[41] PACS 08 is a randomised, open-label, multicentre phase III trial. Patients recruited have non-metastatic, operable breast cancer, either triple-negative or PR-/HER2-negative, and are randomised to three cycles of FEC100 followed by three cycles of either docetaxel or ixabepilone. The primary objective is to evaluate the benefit of a sequential regimen involving ixabepilone against the standard epirubicin and docetaxel-based regimen, and the end-point is five-year disease-free survival. The secondary objectives include the assessment of the impact of ixabepilone on the five-year distant metastasis-free survival and overall survival.

The Role of Epothilones plus Targeted Therapy in Breast Cancer

There is little doubt that targeted therapies will play an important role in oncology as it has been demonstrated that in all stages of breast cancer they may induce tumour inhibition with little effect on normal tissue.[42] However, many targeted therapies are more effective when given in addition to chemotherapy.[42] Thus, combination therapy with cytotoxic drugs plus targeted therapy may be a more efficacious treatment strategy and such combinations have already shown substantial clinical benefits.[42,43] A recently reported phase II trial investigated the role of combination therapy with trastuzumab, ixabepilone and carboplatin in patients with HER2-positive treatment-naïve metastatic breast cancer.[44] The treatment cycle lasted for 28 days, with a maximum of six cycles.[45] Patients received trastuzumab (4mg/kg loading dose then 2mg/kg IV) over 30 minutes on days one, eight, 15 and 22 of the cycle, while ixabepilone (15mg/m^2) plus carboplatin (area under the concentration–time curve [AUC] 2) were given IV over one hour on days one, eight and 15 of the cycle.[45] Data from the study have been presented in abstract form.[44] Of the 57 patients evaluable for measurement of response, two achieved complete response (3.5%, 95% confidence interval [CI] 0.5–12.1), while 22 patients achieved partial response (38.6%, 95% CI 26–52.5).[44] Very few adverse effects were observed, with acceptable rates of neuropathy and neutropenia.[44] The results of this study suggest that combination therapy with trastuzumab, ixabepilone and carboplatin may be effective for the treatment of patients with HER2-positive metastatic breast cancer.

Further to this trial, a National Cancer Institute-sponsored phase II trial is currently under way. The aim of this trial is to evaluate the efficacy and safety of combination therapy with ixabepilone plus trastuzumab in patients with HER2-positive breast cancer.[46] Patients are stratified into two cohorts according to whether or not they have previously received chemotherapy and/or trastuzumab. The treatment protocol involves trastuzumab given IV over 30–90 minutes and ixabepilone given IV over three hours on day one, with these courses repeated every three weeks. Other ongoing phase II clinical trials are evaluating the role of neoadjuvant ixabepilone/carboplatin/trastuzumab in HER2-positive locally advanced breast cancers[47] and the combination of ixabepilone with bevacizumab as first-line therapy for metastatic breast cancer.[48] At present, clinical trials are evaluating the efficacy and safety of ixabepilone in combination with a variety of other targeted agents in patients with breast cancer (see *Table 3*).

Conclusions

Epothilones are a novel class of microtubule-stabilising cytotoxic chemotherapeutic agents. Among this class, the most advanced in terms of clinical evaluation is ixabepilone, particularly for breast cancer treatment. Drug resistance and toxicity of the anthracyclines and taxanes are significant barriers to goal attainment in the neoadjuvant, adjuvant and metastatic settings. Notably, ixabepilone has demonstrated antitumour activity in patients with anthracycline-, taxane- and/or capecitabine-resistant metastatic breast cancers. Therefore, it has been proposed that the epothilones may have a role in the neoadjuvant and adjuvant setting for the treatment of locally advanced invasive breast cancers (stage IIA–IIIB). Initial data have shown promise for the use of ixabepilone in the neoadjuvant setting, particularly for the difficult-to-treat, poor-prognosis ER-negative, ER-/HER2-negative and ER-/PR-/HER2-negative tumours. Combination therapies have also been investigated for the treatment of breast cancer, with cytotoxic agent plus targeted therapies showing substantial clinical benefit. Preliminary results have shown that ixabepilone/trastuzumab/carboplatin combination therapy can achieve complete or partial response in HER2-positive treatment-naïve metastatic breast cancer patients.

While emerging clinical data for the role of epothilones in the neoadjuvant and adjuvant settings and in combination therapy are promising, further clinical trials are needed to fully evaluate the role of the epothilones for the treatment of breast cancer using such strategies. ■

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