Beyond Anthracyclines and Taxanes – Epothilones for Metastatic Breast Cancer

a report by
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Breast cancer is the most common female malignancy worldwide, with an annual global incidence of over 1 million and a resulting 450,000 deaths.[1] Despite progress in early diagnosis, approximately 10% of breast cancer patients present with metastatic disease.[2,3] In addition, around 30% of patients undergoing primary treatment will develop distant metastases.[2] Whereas patients whose tumours are hormone-receptor-positive are typically managed with endocrine-based therapies, chemotherapy remains the mainstay of treatment in patients with hormone-negative tumours.

The introduction of new cytotoxic and biological agents in metastatic breast cancer (MBC) has resulted in slightly improved survival. Nevertheless, the prognosis of MBC remains poor, median survival rates from the development of metastases are in the range of two to three years and a cure remains elusive.[4] The most frequently used agents in MBC are anthracyclines and taxanes, which in multidrug schedules produce response rates in the range of 50–70%.[5] However, median time to disease progression following chemotherapy for MBC is only six to 10 months as a proportion of patients are primarily resistant to anthracyclines and taxanes, and of those who initially respond the majority will subsequently develop resistance. Additionally, an increasing proportion of early breast cancer patients are given anthracyclines and taxanes as part of their adjuvant treatment, and the number of MBC patients who develop resistance to these agents may further increase. Hence, there is a need for new effective agents at the time a relapse occurs.

This article reviews current knowledge on epothilones, a new class of cytotoxic agents that have recently shown activity in MBC that is resistant to multiple prior therapies.

Mechanisms of Resistance to Anthracyclines and Taxanes in Breast Cancer

Resistance to chemotherapy manifests as tumour insensitivity to initial treatment (known as intrinsic or primary resistance) or occurs after an initial response to therapy (acquired resistance). Acquired resistance may develop during chemotherapy due to the emergence of a subpopulation of intrinsically resistant cells. The main cellular mechanisms involved in the development of tumour resistance to treatment include alterations in drug efflux, microtubule alterations, inadequate induction of apoptotic signalling and altered drug metabolism. Of these, the most recognised are alterations of drug efflux mechanisms involving members of the adenosine–triphosphate (ATP)-binding cassette (ABC) membrane transporter family, particularly P-glycoprotein (P-gp) encoded by the *MDR1* gene, multidrug-resistant protein 1 (MRP1) and breast cancer-resistance protein (BRCP) encoded by the *MXR* gene.[6,7]

MDR1 P-gp alterations have been demonstrated to confer multidrug resistance *in vitro*.[8] A meta-analysis of studies has calculated that approximately 40% of all breast tumours express *MDR1* P-gp, although there was substantial heterogeneity across the individual studies, probably due to the various assays used.[9] Prior exposure to chemotherapy or endocrine therapy increases the proportion of tumours expressing *MDR1* P-gp by around 1.8-fold.[9] Patients with *MDR1* P-gp expression have a three-fold higher risk of failure of response to chemotherapy compared with those without expression, and this difference may be even higher following exposure to chemotherapy.[9,10] It is of note that both the anthracyclines and taxanes are among the substrates of P-gp, a finding that may explain the common occurrence of cross-resistance between these two classes of drug in MBC.

The MRP family is another group of transporter proteins associated with tumour resistance. Expression of MRP1, the best known of the MRPs, confers resistance to anthracyclines, antifolates and vinca alkaloids, and is associated with poor prognosis.[11] Similarly to MDR1 P-gp, expression of MRP1 may increase following exposure to chemotherapy. BRCP was found to be expressed in a range of cultured breast cancer cells. Specific point mutations in the gene encoding BRCP may result in tumour resistance to mitoxantrone, anthracyclines, methotrexate and topoisomerase I inhibitors, which are commonly used in breast cancer.[12,13]

Microtubules play an important role in cell transport, signalling and mitosis. The β-subunit of tubulin in microtubules is the binding site for paclitaxel, and β-tubulin III isoform overexpression may inhibit the activity of this agent in MBC.[14] Pre-clinical data suggest that mutations in the α-tubulin gene may also exert taxane resistance.[15] In the clinic, overexpression of β-tubulin III in breast cancer was associated with resistance to paclitaxel and docetaxel.[16,17] However, the clinical implications of β-tubulin III expression as a marker of response to taxanes require further study.

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Table 1: Phase II Trials of Single-agent Ixabepilone in Metastatic Breast Cancer

Authors	Exposure to Chemotherapy	No. Patients	Dose and Schedule	Overall Response Rate (%)	Sensory Neuropathy Grade ≥2 (%)
Roché et al.[32]	Prior anthracycline in adjuvant setting	65	40mg/m^2 q3w	41	20
Denduluri et al.[33]	No prior taxane	23	6mg/m^2 daily for 5d q3w	57	13 (grade >3)
Low et al.[34]	Prior taxane (adjuvant, neoadjuvant or metastatic)	37	6mg/m^2 daily for 5d q3w	22	25
Denduluri et al.[35]	Prior taxane (adjuvant, neoadjuvant or metastatic)	12	8mg/m^2 daily for 3d q3w (cycle 1) ‡10mg/m^2 daily for 3d	0	25
Thomas et al.[36]	Prior taxane in the metastatic setting	49	40mg/m^2 q3w	12	45
Perez et al.[37]	Resistant to anthracycline, taxane and capecitabine	126	40mg/m^2 q3w	12	55

Another mechanism associated with acquired resistance is inadequate initiation of chemotherapy-induced apoptotic cell death owing to malfunctioning of apoptotic genes.[8] These mutations were found to be associated with resistance to tubulin-binding agents and anthracyclines.[18] In the latter case, impaired apoptosis was also due to the loss of DNA mismatch repair, which keeps the cell from detecting DNA damage and activating the cell death cycle.

Topoisomerase II is a key enzyme in DNA replication and the main target of several anticancer drugs, in particular anthracyclines. Several mechanisms, including chemotherapy-induced point mutation in the topoisomerase II-encoding gene, may exert inhibition of topoisomerase II, resulting in a resistance to drugs that target this enzyme.[19] Impaired drug metabolism may also be due to alterations in the activity of other enzymes: gluthathione-S-transferase, aldehyde-dehydrogenase and dihydrofolate-reductase.[6]

Options for Patients Pre-treated with Anthracyclines and Taxanes

There are relatively few therapeutic options available for MBC patients with tumours resistant to both anthracyclines and taxanes. Increased use of anthracyclines and taxanes in adjuvant and neoadjuvant settings has further restricted the applicability of these classes of drug in patients with relapse. Until recently, the only cytotoxic agent approved in the US and Europe in anthracycline- and taxane-pre-treated or -resistant tumours was capecitabine. Capecitabine monotherapy in this setting is associated with response rates of 20–30%.[20,21] The main adverse events of capecitabine include gastrointestinal disorders and hand–foot syndrome. Several other compounds, including antimetabolites (gemcitabine, capecitabine), vinca alkaloids (vinorelbine) and platinum salts, have shown some activity in anthracycline and taxane pre-treated MBC and are used at the physician's discretion[22–24] Another class of drugs found to be active in taxane-refractory breast cancer is that of new taxanes: nanoparticle albumin-bound paclitaxel and larotaxel.[25,26] In patients resistant to anthracyclines, taxanes and capecitabine ('triple-refractory'), therapeutic options are scarce and no particular agent has been recommended in this setting.

Epothilones

The natural epothilones and their analogues are macrolide antibiotics and represent a novel class of antimicrotubule agents. Naturally occurring epothilone A and B were first isolated in 1987 from a culture broth of myxobacterium *Sorangium cellulosum*. Like the taxanes, the epothilones are promoters of tubulin polymerisation and have strong antiproliferative activity in paclitaxel-sensitive human cancer cells.[27] Epothilone A and B compete with paclitaxel for the same binding sites on microtubules. However, their chemical structure is distinct and they bind to the tubulin-binding pocket in a specific and independent manner. The major strength of the epothilones is their activity in human cancer cells overexpressing P-gp, which are resistant to the taxanes.[27–31]

Ixabepilone

The most extensively studied epothilone in breast cancer is ixabepilone (BMS 247550). Ixabepilone is a second-generation semi-synthetic epothilone B derivative. In phase I studies, several schedules of ixabepilone were studied, including daily one-hour infusions for three or five days every three weeks, single three-hour infusions every three weeks and weekly administration.

A series of phase II trials investigated the efficacy of single-agent ixabepilone at various schedules in heavily pre-treated MBC patients (see *Table 1*). Roché et al.[32] demonstrated overall response rate of 41% with ixabepilone at 40mg/m^2 as a three-hour infusion every three weeks used as first-line therapy in MBC patients who had received prior adjuvant anthracycline. In this series, only 17% of patients had additionally received a taxane as part of an adjuvant regimen. In a small study including MBC patients with no prior taxane exposure, Denduluri et al.[33] demonstrated an overall response rate of 57%. Other phase II studies included MBC patients previously treated with the taxanes. In the study by Low et al.[34] including patients who had previously received at least one treatment with paclitaxel or docetaxel in the neoadjuvant, adjuvant or metastatic setting, the overall response rate was 22%. In this study, ixabepilone was administered in a one-hour infusion for five consecutive days repeated every three weeks. In another study using administration of ixabepilone for three consecutive days and repeated every three weeks, no patients showed a response but 83% experienced stable disease for at least six weeks.[35] Thomas et al.[36] achieved a response rate of 12% in a strictly defined population of patients who had progressed on docetaxel or paclitaxel as the most recent therapy within four months of the last dose or within six months of adjuvant treatment. In the registration phase II study, single-agent ixabepilone 40mg/m^2 as a three-hour infusion every three weeks was investigated in 126 MBC patients whose disease was resistant to anthracyclines, taxanes and capecitabine.[37] The overall response rate based on independent radiological review was 12%, and an additional 13% of patients experienced stable disease for at least six months. Across all phase II studies of single-agent ixabepilone, the most common grade 3 or 4 toxicities in these heavily pre-treated populations included neutropenia, peripheral sensory neuropathy, myalgia, arthralgia, stomatitis/mucositis,

vomiting and fatigue/asthenia. Of these, the most troublesome is cumulative sensory neuropathy, which however appears to be reversible with treatment discontinuation or by reducing the ixabepilone dose. In two phase III trials, the median time to onset of grade 3/4 sensory neuropathy associated with ixabepiloe has been shown to be 2.9 to three months and the median time to resolution of the grade 3/4 sensory neuropathy was around six weeks.[38,39]

In one phase II study, ixabepilone 40mg/m^2 as a three-hour infusion every three weeks was used as primary therapy in patients with locally advanced or large operable breast cancer.[40] The overall complete pathological response rate in the breast was 18%, and this rose to 29% in a subset of oestrogen-receptor-negative patients.

Ixabepilone has also been tested in combination with capecitabine. The rationale for combining these two agents included their distinct mechanisms of actions and non-overlapping toxicities. Based on promising phase I/II studies,[41–43] two large, open-label phase III trials have been launched to compare the efficacy of ixabepilone plus capecitabine combination with capecitabine alone in MBC patients previously exposed to anthracyclines and taxanes. A pivotal phase III study included 752 patients with anthracycline-pre-treated or -resistant and taxane-resistant locally advanced breast or MBC.[44] Patients could have up to three prior chemotherapy regimens (including both adjuvant and MBC treatment). Capecitabine was administered at a daily dose of 2,000mg/m^2 in the combination arm and 2,500mg/m^2 in the single-agent arm on days one to 14 every three weeks. Ixabepilone 40mg/m^2 was administered over three hours on day one every three weeks. Treatments were continued until disease progression or unacceptable toxicity. The primary end-point was progression-free survival (PFS), assessed by blinded independent radiology review. The combination of capecitabine plus ixabepilone was significantly superior to capecitabine alone in PFS (hazard ratio 0.75, 95% confidence interval [CI] 0.64–0.88; stratified log-rank p<0.001). Median PFS in the combination and capecitabine alone arms was 5.8 and 4.2 months, respectively. A pre-defined subset analysis demonstrated that the PFS benefit was maintained in most subgroups, including patients with triple-negative tumours. Overall response also favoured the capecitabine plus ixabepilone arm (35 versus 14% in capecitabine alone arm; p<0.001). The use of ixabepilone was associated with an increased rate of peripheral sensory neuropathy (grade 3–4 in 21% of patients versus 0% with capecitabine alone), with a median time to resolution of six weeks after treatment discontinuation or dose reduction. Additionally, in the capecitabine plus ixabepilone arm more patients experienced grade 3/4 neutropenia (68 versus 11%, respectively) and fatigue (9 versus 3%, respectively). Among the patients with initial liver dysfunction there were more toxic deaths in the capecitabine–ixabepilone arm, in all instances related to neutropenia. A rapid protocol amendment excluding these patients lowered the incidence of toxic deaths to 2%. The second phase III study compared the same chemotherapy regimens in 1,221 patients with anthracycline-pre-treated and taxane-resistant advanced breast cancer.[38] In this study patients could have up to two prior chemotherapy lines (including both adjuvant and MBC treatment). There was no significant difference in overall survival, the primary end-point in this study (14.0 and 11.3 months, respectively; p=0.0189), whereas the combination arm was more effective in terms of PFS (median 6.2 and 4.4 months, respectively; p=0.0005) and overall response (43 and 29%, respectively). A pooled analysis of both phase III studies showed that in a subset of patients with triple-negative tumours the response rate and progression-free survival favoured a doublet regimen, with a trend towards improved survival that did not reach statistical significance.[45]

Other Epothilones

Patupilone (EPO906), a natural epothilone B, showed activity in various malignancies, including breast cancer, in phase I studies.[45,46] The dose-limiting toxicity was diarrhoea and the recommended dose was 2.5mg/m^2 using either a six weeks on/three weeks off or a three weeks on/one week off weekly schedule. In a phase II study including 46 MBC patients with progression after one prior taxane and/or anthracycline regimen in the adjuvant or metastatic settings, the overall response rate was 11% and the most common grade 3 event was diarrhoea.[48]

BMS-310705, a water-soluble semi-synthetic analogue of epothilone B, was evaluated in phase I trials in patients with advanced solid tumours.[49,50] The dose-limiting toxicity was diarrhoea. Overall, partial response was achieved in three of nine patients with breast cancer.

KOS-862, an epothilone D analogue, was evaluated as a single agent in phase I trials.[51–53] In another phase I study, a combination of KOS-862 with trastuzumab was investigated in 13 MBC patients, most of whom had been previously treated with taxanes and trastuzumab.[54] Two patients had a partial response. The main treatment-related toxicity was sensory neuropathy. In a phase II trial including MBC patients treated previously with taxane and anthracycline, the overall response rate was 14%.[55]

ZK-EPO, a fully synthetic derivative of epothilone B, was investigated in a phase I dose-escalation study including 46 patients with advanced solid tumours.[56] There were 15 partial responses including two in taxane-pre-treated MBC patients. The most common toxicity was peripheral sensory neuropathy and nausea.

Conclusions

Epothilones are a new class of cytotoxic agent with promising activity in breast cancer and a manageable toxicity profile. The best-studied epothilone, ixabepilone, has shown compelling efficacy in patients with advanced breast cancer that had been heavily pre-treated or was resistant to taxanes, anthracyclines and other agents. The activity of ixabepilone includes patients with triple-negative (ER-/PgR-/HER2-) tumours. In the phase III trials including poor-prognosis patients with anthracycline-pre-treated or -resistant and taxane-resistant advanced breast cancer, ixabepilone plus capecitabine significantly improved PFS and response rate. These studies corroborate pre-clinical findings of a low ixabepilone susceptibility to the tumour resistance mechanisms and a lack of cross-resistance with the taxanes. The most common toxicities associated with single-agent ixabepilone are neutropenia and peripheral sensory neuropathy. Although the latter generally resolves on treatment discontinuation or dose reduction, it has apparently slowed down the clinical development of ixabepilone.

The clinical benefit of adding ixabepilone to capecitabine is achieved at the expense of increased frequency and severity of treatment-related adverse effects, which in fragile patients may be life-threatening. Particular caution should be given to patients with moderate and severe liver dysfunction, who are at increased risk of developing fatal neutropenic episodes. Currently, ixabepilone is mostly

used in patients who progress after previous anthracycline and taxane therapy. However, the exact role of this drug in the cascade of advanced breast cancer treatment remains to be established.

The encouraging results of ixabepilone in advanced and heavily pre-treated breast cancer patients call for testing of its efficacy in the adjuvant setting. The development of predictive markers of response to ixabepilone may allow better selection of patients for this therapy. Further studies are also needed to elucidate the mechanisms of neurotoxicity, the most common side effect of ixabepilone, to identify patients at risk and to devise preventative measures.

Other epothilones are still in early stages of clinical development in breast cancer. Further studies are warranted to define their role in this malignancy both as single agents and in combination with novel cytotoxic or molecularly targeting agents. ■

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