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New Therapeutic Options for Chemotherapy-Resistant Metastatic Breast Cancer

The Epothilones

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Abstract

When taxanes were introduced as anticancer agents some 20 years ago, their broad spectrum of activity was striking and engendered renewed hope for cancer patients. However, they were not without their problems, including a susceptibility to drug resistance caused by the drug efflux pump protein, P-glycoprotein. The epothilones are a new class of chemotherapeutic agents that have a mechanism of action similar enough to the taxanes to retain their broad spectrum of activity, but different enough to escape the multidrug resistance caused by P-glycoprotein. These properties are especially promising for patients with metastatic breast cancer who have run out of therapeutic options as a result of multidrug resistance.

Ixabepilone, a semi-synthetic analogue of epothilone B, has recently been granted US FDA approval for the treatment of chemotherapy-resistant advanced breast cancer. Approval was based on results from a phase III study of ixabepilone in combination with capecitabine, as well as phase II studies of ixabepilone monotherapy. Significantly prolonged progression-free survival and increased objective response rates were demonstrated in the phase III study when ixabepilone was administered in combination with capecitabine compared with capecitabine alone. The phase II trials demonstrated robust antitumour activity with single-agent ixabepilone in women with metastatic breast cancer that was resistant to taxanes, anthracyclines and capecitabine. Early data from phase I trials of KOS-1584 and sagopilone are positive and suggest that these drugs may also develop into useful chemotherapeutic agents.

Significant, but manageable, toxicities have been observed with the epothilones. In particular, neuropathy has led to the uneven and slower than expected clinical development of ixabepilone as optimal administration regimens were established. Some differences in tolerability profiles exist between the different analogues. Overall, it is expected that the epothilones will play an important role in the treatment of breast cancer and other tumour types.

Every year, more than 1 million women worldwide are diagnosed with breast cancer.[1] It is the most common form of cancer among females and the fifth most common cause of cancer mortality (regardless of sex) throughout the world.[2] Although breast cancer survival is estimated to be 73% in the developed world, it is somewhat less in the developing world (57%), and the total number of deaths in 2005 reached just over 500 000.[1,2]

Many of the deaths that occur in breast cancer patients are due to metastatic disease. The introduction of cytotoxic anticancer drugs, such as the anthracyclines in the 1970s and the taxanes in the 1990s, has seen a prolongation of treatment-associated survival in patients with metastatic breast cancer (MBC),[3] but a cure remains elusive. Response rates to first-line anthracyclines and taxanes are approximately 60%, with a median time to disease progression between 6 and 9 months.[4] However, development of resistance to these agents is common and the efficacy of second and subsequent lines of chemotherapy is poor, with response rates of 10–30% and median overall survival durations typically being between 6 and 12 months.[5] Moreover, it is expected that the number of patients with MBC who develop resistance to chemotherapy will continue to increase as use of anthracyclines and taxanes in early breast cancer adjuvant regimens continues to rise.

There are very few treatment options available to women with MBC whose cancer has failed to respond, or has relapsed, after receiving both anthracyclines and taxanes. Until the recent approval of ixabepilone combination therapy, single-agent capecitabine was the only treatment approved in this situation.[6] However, around 70–80% of tumours do not respond to capecitabine monotherapy and even those patients who initially respond will all eventually go on to have disease progression, with a median time to progression of approximately 3–5 months.[7,8] Thus, there is clearly a need for new therapies that are effective in patients with heavily pretreated MBC that is resistant to multiple prior agents. In pursuing this need, a novel class of cytotoxic agents, known as the epothilones, has been synthezised from the myxobacterium *Sorangium cellulosum*.[9]

Epothilones act in a manner similar to that of taxanes, by targeting and stabilizing microtubules.[10] However, they differ in terms of their low susceptibility to multiple mechanisms of drug resistance.[11-13] There are several epothilone analogues currently under investigation and one of these, ixabepilone (BMS-247550), has recently been approved by the US FDA for the treatment of chemotherapy-resistant breast cancer.

1. Mechanisms of Acquired Resistance to Chemotherapeutic Agents

Intrinsic and acquired drug resistance are the fundamental reasons for clinical failure in advanced breast cancer. General mechanisms involved in acquired drug resistance include (i) over-expression or activation of the drug efflux pump protein, P-glycoprotein (P-gp), encoded by the *mdr1* gene;[14,15] (ii) inadequate induction of apoptotic signalling;[16,17] (iii) qualitative and quantitative changes in the drug target (i.e. topoisomerase II or tubulin);[18] and (iv) altered drug metabolism.[14,17]

Cross-resistance between anthracyclines and taxanes, common in MBC, is illustrative of the multidrug-resistant (MDR) phenotype. MDR, caused by the over-expression of P-gp, is one of the most well defined mechanisms of drug resistance and is closely linked with resistance to both taxanes and anthracyclines.[17,19] Taxanes and vinca alkaloids, which are both tubulin-binding agents, are strong substrates for P-gp,[20,21] and research has shown that many MDR cell lines contain reduced drug concentrations as a result of increased drug efflux.[17]

Research into the other mechanisms of acquired resistance is still in its infancy, but preliminary explorations indicate that inadequate initiation of cell death may stem from mutations in genes that usually lead to apoptosis. These mutations impair gene function and cause apoptotic cascades to cease, thus preventing death in cells damaged by tubulin-binding agents.[17,22,23] Impaired apoptosis is also associated with anthracycline resistance, not only as a result of malfunctioning apoptotic genes,[24] but in response to a loss of DNA mismatch repair, which keeps the cell from detecting DNA damage and activating the cell death cycle.[25]

Topoisomerase II is an enzyme essential for separating replicated chromosomes during cell division and is the main target of several antitumour drugs, including anthracyclines. It has been shown that inhibition of topoisomerase II causes resistance to drugs that target this enzyme.[18] One possible mechanism is by chemotherapy-induced point mutations in the gene encoding topoisomerase II, leading to altered drug binding.[14] Several mechanisms of altered drug metabolism leading to drug resistance have been postulated, including alterations in gluta-

thione-S-transferase, aldehyde-dehydrogenase and dihydrofolate-reductase enzymatic activities.[14]

In addition, there are several mechanisms of acquired drug resistance that specifically affect antitubulin agents. Tubulins are the building blocks of microtubules, which, in turn, are critical and dynamic components in mitosis, intracellular transport, and the development and maintenance of cell structure and shape. Point mutations in β-tubulin have been shown to induce taxane resistance. For example, the substitution of a threonine residue for an alanine residue at point 364 of the β-tubulin genome confers resistance to paclitaxel.[26] In addition, altered drug-microtubule interactions have been shown to be the result of mutations at tubulin binding sites, changes in total tubulin content and/or tubulin polymerization dynamics, changes to tubulin isotype content or from mutations in tubulin isotype genes.[16,26]

2. Epothilones

Naturally-occurring epothilone A and epothilone B (patupilone; EPO-906) [figure 1] were first discovered during screening tests for antifungal agents.[27] However, their cytotoxic properties were quickly recognized and further research determined that epothilones have a similar mechanism of action to taxanes and vinca alkaloids.[10,12,17] Epothilones work by stabilizing, and thus suppressing, microtubule activity and by interfering with spindle formation so that the microtubules are unable to capture and align chromosomes during the metaphase and anaphase stages of cell division. This causes the cell cycle to stop and cell death to occur.[10,28]

In spite of their mechanistic similarities to taxanes, epothilones are structurally distinct and appear to be minimally affected by the over-expression of P-gp. *In vitro* studies show that the naturally occurring epothilones mimic the effects of paclitaxel, have a broad range of anticancer activity and competitively inhibit paclitaxel binding to microtubules, but retain potency against MDR cancer cell lines, including those with primary and secondary resistance to paclitaxel.[10,12] These are very promising results; however, *in vivo* investigations have proved disappointing as a result of the epothilones' metabolic instability, pronounced toxicity and unfavourable pharmacokinetics.[29] Fortunately (unlike paclitaxel), epothilones have proved amenable to

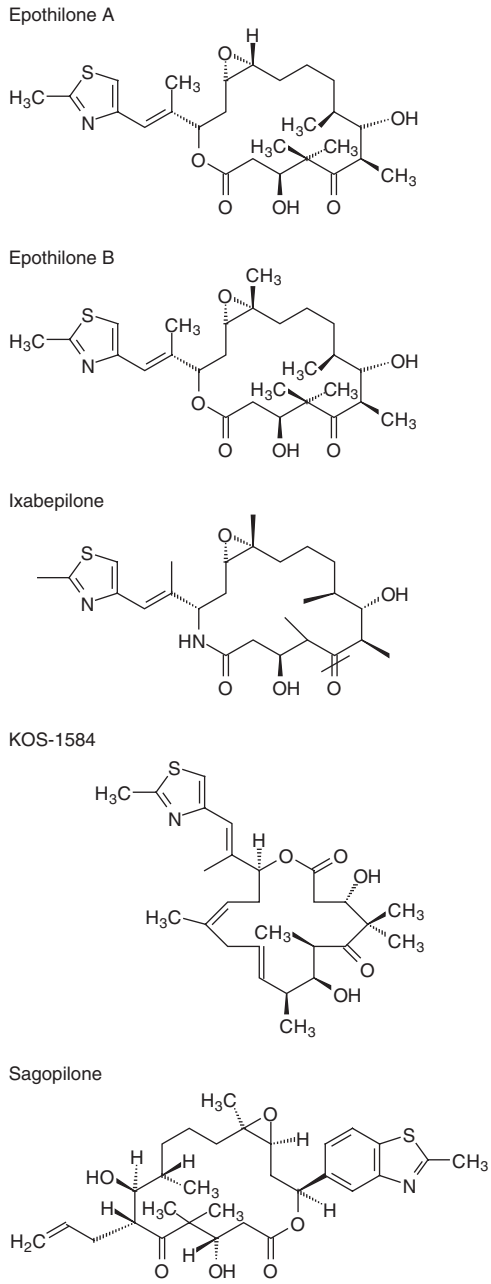

Fig. 1. Chemical structures of the epothilones.

complete synthesis and chemical manipulation. This has subsequently led to the development of a number of epothilone analogues (figure 1) and the establishment of a new 'epothilone class' of microtubule-

stabilizing agents that have shown promise in the treatment of patients with MBC.[12,29] Compounds from this class currently undergoing clinical development in various cancer types include ixabepilone, patupilone, KOS-1584 (R1645) and sagopilone (ZK-EPO). Patupilone is primarily undergoing development in tumour types other than metastatic breast cancer so will not be discussed further in this review.

Phase I and II clinical data suggest that these new compounds have a broad range of therapeutic antitumour activity at doses and regimens associated with acceptable tolerability (see sections 2.1, 2.2 and 2.3).[30-32] However, slight differences in tolerability profiles are apparent from the clinical trials discussed in this review. Neoadjuvant studies have also been conducted, and phase III studies in advanced breast cancer are either underway or have been recently completed.[33]

2.1 Ixabepilone

Ixabepilone (IXEMPRA™)[1] is a semi-synthetic epothilone B analogue (figure 1), which has emerged as a particularly promising agent. It has recently been approved in the US for the treatment of chemotherapy-resistant breast cancer and is awaiting approval in Europe. Ixabepilone is also undergoing phase III development for other solid tumours and as neoadjuvant therapy in patients with breast cancer; however, further mention of these indications is beyond the scope of this review. FDA approval was granted both as monotherapy for the treatment of locally advanced or metastatic breast cancer that is resistant or refractory to anthracyclines, a taxane and capecitabine, and as combination therapy with capecitabine for the treatment of locally advanced or metastatic breast cancer that is resistant to treatment with an anthracycline, a taxane or for patients whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

In *in vitro* studies, ixabepilone was 2.5 times more potent than paclitaxel at stabilizing microtubule dynamics and demonstrated a broad spectrum of activity against various human carcinoma cell lines.[12] In particular, the potential potency of ixabepilone against breast cancer was reflected in the low concentration to produce 50% inhibition (IC_{50}) values of 2.5 and 2.3 nmol/L observed in cytotoxic tests against the MCF-7 and SKBR3 breast cancer cell lines, respectively. Ixabepilone was also consistently active against various taxane-sensitive and -resistant cell lines, including those with over-expression of P-gp (HCT116/VM46 cell line; IC_{50} = 24.5 nmol/L) and those with mutations in tubulin proteins (A2780Tax ovarian carcinoma cell lines; IC_{50} values of 2.6 and 4.9 nmol/L), in keeping with the parent epothilone B molecule.[12]

In vivo antitumour investigations of ixabepilone were performed in murine Pat-21 breast cancer xenografts using cells taken from a patient with MBC heavily treated with multiple antineoplastic agents, including taxanes and anthracyclines. Ixabepilone exhibited significant antitumour response in this model with a log cell kill of 1.6, whereas other agents tested were completely inactive. The log cell kills were 0.3 for paclitaxel, 0.2 for docetaxel and 0.1 for vinorelbine.[11,12]

Early phase I clinical trials involving patients with resistant MBC showed objective responses following intravenous administration of ixabepilone on one of the following two schedules: (i) daily for 5 days every 3 weeks; or (ii) once every 3 weeks.[34,35] Ixabepilone has also been evaluated as a daily dose for 3 days every 3 weeks and as a weekly schedule.[36,37] The recommended dose of ixabepilone for phase II trials was set at 40 mg/m^2 (given as a 1-hour infusion every 3 weeks) and was based on the findings of one of these phase I studies. This study assessed 25 patients with solid tumours and observed two partial responses in patients with breast cancer, including one patient with docetaxel-refractory disease. At doses >40 mg/m^2, neutropenia was the principal dose-limiting toxicity. Among 12 patients who received the 40 mg/m^2 dose, three had grade 3 and two had grade 4 neutropenia. In terms of non-haematological toxicity, grade 3–4 fatigue, abdominal pain, diarrhoea and neuropathy was experienced by one patient each at the 40 mg/m^2 dose level. All 12 patients receiving this dose also experienced grade 1–2 neuropathy.[35]

The positive results from these early clinical studies were subsequently confirmed in four phase

1 The use of trade names is for identification purposes only and does not imply endorsement.

Table I. Key features of phase II studies of ixabepilone therapy in breast cancer (reproduced from Gianni,[42] with permission from the American Society of Clinical Oncology)

Reference	Disease characteristics	Prior taxane treatment (% patients)	Ixabepilone dose and schedule (every 3 weeks)	ORR (% patients)	Patients with sensory neuropathy grade ≥2 (% patients)
Denduluri et al.[38]	MBC	0	6 mg/m^2 daily for 5 days in 1 h	57	13
Roché et al.[40]	MBC, resistant to anthracyclines	17	40 mg/m^2 in 3 h	41.5	20 (grade ≥3)
Thomas et al.[41]	MBC, resistant to taxanes	100	40 mg/m^2 in 3 h	12	45
Perez et al.[39]	MBC, resistant to anthracyclines, taxanes and capecitabine	100	40 mg/m^2 in 3 h	18.3	41

MBC = metastatic breast cancer; **ORR** = objective response rate.

II trials involving patients with MBC who were taxane-naive, or taxane-resistant, or refractory or resistant to other chemotherapeutic agents.[38-41] Table I summarizes the clinical efficacy data for ixabepilone in each of these trials. All four studies demonstrated that ixabepilone had robust antitumour activity in women with MBC, most notably in women whose cancer was resistant to all three major chemotherapy groups (i.e. taxanes, anthracyclines and capecitabine). This is an extremely important finding because no other drug has consistently shown efficacy in this heavily pretreated, strongly resistant patient group before.

For the most part, treatment-related adverse events were of grade 1–2 in severity and were entirely manageable. The most common adverse events of grade 3 or greater across the four studies were peripheral sensory neuropathy, myalgia, arthralgia, stomatitis/mucositis, vomiting, fatigue/asthenia, neutropenia, febrile neutropenia and leukopenia.[38-41]

Despite encouraging efficacy, the risk of neurotoxicity associated with ixabepilone has led to an uneven and slower than expected clinical development.[42] As with other tubulin-active agents, ixabepilone has been shown to cause a cumulative, paclitaxel-like neuropathy (mainly sensory neuropathy; table I); however, this appears to be slowly reversible in most patients and could be managed by reducing the ixabepilone dose.[40,43]

Most recently, the results of a large, multicentre, randomized, phase III trial of ixabepilone in combination with capecitabine have been reported.[44,45] A total of 752 patients with MBC who were previously treated with, or were resistant to, an anthracycline and who were resistant to taxanes, were randomized to receive capecitabine alone or capecitabine plus ixabepilone. Ixabepilone was given intravenously over 3 hours at a dose of 40 mg/m^2 every 3 weeks. Capecitabine was administered orally at a dose of 1000 or 1250 mg/m^2 twice daily every 14 days. Ixabepilone in combination with capecitabine was found to be superior to capecitabine alone, with significant benefits observed for progression-free survival and objective response rates (table II). Grade 3–4 treatment-related sensory neuropathy occurred in 21% of patients receiving ixabepilone plus capecitabine, compared with 0% of those receiving capecitabine alone. In each instance, neuropathy was cumulative and reversible with a median time to resolution of 6 weeks. Grade 3 and 4 neutropenia were reported in 32% and 36% of ixabepilone plus capecitabine patients, respectively. Corresponding rates in patients receiving capecitabine alone were 9% and 2%. Other grade 3–4 adverse events observed with combination therapy were hand-foot syndrome (18%), fatigue (9%) and febrile neutropenia (4%). Patients receiving capecitabine monotherapy also experienced hand-foot syndrome (17%) and fatigue (3%).

2.2 KOS-1584

KOS-1584, a second-generation epothilone D compound (figure 1), has been selected to proceed to phase II clinical development for the treatment of breast and other solid tumours.[46] KOS-1584 is a natural polyketide product that also inhibits tumour growth by inducing tubulin polymerization and microtubule stabilization. A first-generation epothilone D compound known as KOS-862 was

Table II. Efficacy of ixabepilone plus capecitabine compared with capecitabine alone in patients with chemotherapy-resistant metastatic breast cancer[44,45] (reproduced from Vahdat et al.,[45] with permission from the American Society of Clinical Oncology)

Endpoint	Ixabepilone plus capecitabine	Capecitabine alone	p-Value
Median PFS (mo) [95% CI] – IRC	5.8 [5.5, 7.0]	4.2 [3.8, 4.5]	0.0003
Median PFS (mo) – INV	5.3	3.8	0.0011
12-Week PFS (%)[a]	71	55	<0.0001
ORR (%) – IRS	35	14	<0.0001

a Not stated if IRC or INV.

INV = investigator assessment; **IRC** = independent review committee assessment; **ORR** = objective response rate: **PFS** = progression-free survival.

previously being developed, but this has been discontinued in favour of KOS-1584, which has increased potency and an improved pharmacological profile.[47]

No full papers had been published concerning KOS-1584 at the time of writing this review, but phase I efficacy and safety data were reported in abstract form at the Annual Meeting of the American Society of Clinical Oncology in 2007.[32] In this study, patients with advanced solid tumours (n = 37) were given a 1-hour infusion of KOS-1584 on days 1, 8 and 15, every 4 weeks at doses ranging from 0.8 to 25 mg/m^2. Some antitumour activity was observed in the study; one patient with non-small cell lung cancer had a confirmed partial response, one patient with head and neck cancer achieved stable disease and another patient with ovarian cancer experienced a 40% reduction in cancer antigen-125 levels. Dose-limiting diarrhoea occurred at the 20 and 25 mg/m^2 dose levels. The most common drug-related adverse events were gastrointestinal (nausea 51% of patients, diarrhoea 49%, vomiting 32%, constipation 24%), fatigue (49%), anorexia (24%), peripheral sensory neuropathy (19%) and anaemia (16%). All patients who were given doses of 16–25 mg/m^2 experienced grade 1–2 neutropenia or leukopenia. One patient also had grade 3 weakness, neutropenia and peripheral sensory neuropathy that was dose limiting.

2.3 Sagopilone

Sagopilone is a fully-synthetic epothilone (figure 1) that has been designed specifically to overcome multidrug resistance. It is currently undergoing development in patients with MBC as a single agent.[33] Confirmed partial responses have so far been observed in two taxane-pretreated breast cancer patients involved in a phase I study, including one patient with taxane-resistant disease.[31] These patients were part of a broader study initiated to determine the maximum tolerated dose and dose-limiting toxicity of sagopilone. The study was ongoing when results were reported in 2005. At the time, it had enrolled 47 patients who had been given doses ranging from 0.6 to 29 mg/m^2 as a 30-minute intravenous infusion once every 3 weeks. The two breast cancer patients whose tumours responded to treatment received doses of 12 and 16 mg/m^2, respectively. An additional 13 patients with various advanced solid tumours achieved stable disease lasting between 3 and >16 months. The maximum tolerated dose had not been reached at the time of reporting and only two patients had experienced dose-limiting toxicities (grade 3 peripheral neuropathy at 16 mg/m^2 and grade 3 ataxia at 29 mg/m^2). The most common adverse events overall were grade 1–2 peripheral sensory neuropathy (34% of patients) and nausea (17%).

3. Conclusions

Increasingly poor response rates and increasingly shorter times to disease progression with second and subsequent lines of chemotherapy clearly demonstrate a need for new therapies that are effective in patients with heavily pretreated MBC that is resistant to multiple prior agents.

The natural epothilones and their synthetic analogues are a new, structurally distinct, class of chemotherapeutic compounds in development for a variety of tumour types. These microtubule-stabilizing agents, derived from the myxobacterium *S. cellulosum*, bind tubulin and cause apoptotic cell death.

The semi-synthetic epothilone B analogue, ixabepilone, has recently been approved by the US FDA for the treatment of chemotherapy-resistant advanced breast cancer. Phase III results demonstrated that ixabepilone, given in combination with capecitabine, significantly prolongs progression-free survival and increases objective response rates compared with capecitabine alone in patients with chemotherapy-resistant MBC. In addition, a phase II study demonstrated robust antitumour activity with ixabepilone monotherapy in women with MBC that is resistant to taxanes, anthracyclines and capecitabine.

Other epothilones currently in clinical development for the treatment of MBC include KOS-1584 and sagopilone. Early data from phase I trials are positive and suggest that these agents may also develop into useful additions to the chemotherapeutic armamentarium.

In terms of safety and tolerability, observations suggest that epothilones have significant but manageable toxicities, neuropathy in particular, and that some differences in tolerability profiles exist. Attempts to establish optimal administration regimens have been complex and it is likely that their clinical use will require some training.

Overall, it is expected that the epothilones will play an important role in the treatment of breast cancer and other tumour types, and additional phase III results are eagerly awaited.

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