

Ixabepilone and Other Epothilones: Microtubule-targeting Agents for Metastatic Breast Cancer

Patrick G. Morris, MD, and Monica N. Fornier, MD

Dr. Fornier is Assistant Member and Dr. Morris is Special Fellow in the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Address correspondence to:
Monica Fornier, MD
Breast Cancer Medicine Service
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY
Phone: (646) 888-4563
Fax: (646) 888-4555
E-mail: fornierm@mskcc.org

Abstract: Taxanes, derived from the bark of the Pacific yew tree, were the last major group of cytotoxic agents to be developed. Their proven efficacy in a variety of malignancies has constituted a real breakthrough in the treatment of cancer. Wider clinical use of taxanes has several important limitations, including acquired and intrinsic tumor resistance, hypersensitivity reactions, and cumulative neurotoxicity and hematopoietic toxicity. Epothilones, naturally occurring macrolide antibiotics that also act on the microtubule, are a novel class of compounds that may circumvent some of these problems. Many synthetic and semisynthetic epothilone analogs have been formulated and have undergone varying degrees of testing. These compounds have demonstrated activity in a variety of tumors, including in tumors and cell lines resistant to taxanes. So far only ixabepilone has been tested in phase II and III trials and licensed by the US Food and Drug Administration for the treatment of metastatic breast cancer. The main dose-limiting toxicity appears to be a sensory peripheral neuropathy, as commonly seen with drugs that act on the microtubule. Further clinical studies assessing the role of ixabepilone in other settings, as well as the clinical investigation of other epothilones, are eagerly awaited.

Introduction

For many years, cytotoxic chemotherapeutic agents have formed the backbone of treatment strategies for a variety of malignancies. Traditionally, novel agents were first tested in the metastatic setting, where a dearth of other treatment options existed, and then were gradually brought forward into the first-line metastatic setting and in some cases ultimately adopted as adjuvant therapy. An increased understanding of the molecular pathways of various malignancies has led to recent therapeutic developments focusing on so-called targeted agents. For example, following the widespread use of trastuzumab (Herceptin, Genentech) in the setting

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of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC), clinical trials demonstrated the benefit of trastuzumab in the adjuvant setting.¹⁻⁴ Since HER2 is overexpressed in only 20–30% of breast cancers and resistance to trastuzumab can be inherent or acquired, there is still a need for effective new therapies including new cytotoxic agents.⁵ Many targeted therapies, including trastuzumab, have proven to be more active in combination with cytotoxic chemotherapy than as single agents presumably because of our limited understanding of the molecular mechanisms of tumor growth and resistance. It appears, therefore, that cytotoxic agents will be used as part of the treatment paradigm for some time to come.

Taxanes were the last group of cytotoxic agents with a novel mechanism of action to be developed. Taxanes were originally derived from the bark of the Pacific yew tree and are active in a range of solid tumor malignancies. They are broadly used in clinical practice in a variety of settings and in combination with drugs with different mechanisms of action and nonoverlapping toxicity profiles. Broadly, taxanes are part of a myriad of drugs that interfere with the normal functioning of microtubules, which play an important role in a variety of cellular processes including transport, signaling, and mitosis. Until recently, taxanes were the only clinically important drugs that acted as microtubule stabilizers. The binding of taxanes to tubulin stabilizes the microtubule and inhibits its disassembly, ultimately leading to cell death by apoptosis.

While the development of taxanes has constituted a real breakthrough for a variety of malignancies, their clinical use has several important limitations. Acquired and intrinsic tumor resistance through various mechanisms remains a significant problem, and inevitably leads to tumor progression. One important resistance mechanism is the expression of multidrug resistance proteins such as P-glycoprotein, which belongs to a family of ATP-binding cassette transporters, expression of which results in the production of drug efflux pumps that prevent the accumulation of therapeutic intracellular concentrations of active drug. Other important mechanisms of resistance to taxanes include mutations in the β III isoform of tubulin, which is the taxane target, and altered expression of microtubule-associated proteins, which can also lead to prevention of drug binding.

Hypersensitivity reactions following taxane administration remain a significant clinical problem. Novel taxane formulations and various premedications have been used to circumvent these reactions, but the risk is not entirely eradicated. Ultimately, long-term taxane use in the metastatic setting is limited by both cumulative neurotoxicity and hematopoietic toxicity, which may depend somewhat on both the choice of taxane and the treatment schedule used. There exists an opportunity to develop new agents

that act on the taxane target of tubulin, but which are not associated with these problems.

Epothilones

Epothilones are naturally occurring macrolide antibiotics and are the first major new class of cytotoxic agents developed since taxanes. Derived from the myxobacterium *Sorangium cellulosum*, the natural epothilones A and B are cytotoxic in vitro.⁶ Epothilones have a similar mechanism of action to taxanes, which involves binding tubulin, causing microtubular stabilization and arrest of the cell cycle at the G2/M phase.^{7,8} This stabilization inhibits microtubular disassembly and leads to activation of pro-apoptotic signaling and ultimately to cell death. Differences exist in the precise mechanisms of apoptosis induction between taxanes and epothilones.⁹ While the taxanes and epothilones compete for the same binding pocket on β -tubulin, it is now thought that a common pharmacophore does not exist.¹⁰ Instead, it appears that tubulin displays a promiscuous binding pocket, in which contacts with different molecules are optimized according to the unique structure of the binding drug.¹⁰ Therefore, it is not surprising that the chemical structures of epothilones and taxanes are unrelated.

Initial in vitro studies with epothilones A and B demonstrated similar biologic activity to paclitaxel.⁸ More importantly, epothilones remain active in taxane-resistant and taxane-insensitive cell-lines that express multidrug resistance proteins, such as P-glycoprotein, or mutations in the β III isoform of tubulin.^{11,12} Due to this activity across a range of cell types, including in the face of drug resistance, epothilones represent an exciting therapeutic breakthrough.

Ixabepilone

Initial studies of naturally occurring epothilones A and B using in vivo cancer models revealed that the 2 compounds, despite their in vitro cytotoxicity, had only modest activity.¹¹ This was attributable in part to pharmacokinetic problems including poor metabolic stability and narrow therapeutic index.¹¹ Epothilones are 16-member ring macrolides combined with a methylthiazole side chain. Hundreds of synthetic and semisynthetic derivatives of epothilones have now been created with pharmacologic properties that vary depending on modifications in the macrolide ring.¹³ Thus, a large bank of molecules exists for testing in a variety of clinical settings. These compounds are at various stages of development. To date, the most widely tested epothilone is the semisynthetic ixabepilone (Ixempra, Bristol-Myers Squibb).

Ixabepilone is a rationally designed derivative of epothilone B, and is protected by degradation by human

hepatic esterases by the modification of a lactone ring to a lactam. Early preclinical studies showed that the cytotoxicity of ixabepilone was 2.5 times that of paclitaxel, although less than naturally occurring epothilone B.^{10,11} Importantly, this activity was maintained in taxane-resistant cell lines.¹¹ In addition, the predictable pharmacokinetics of ixabepilone made it a more appropriate drug for clinical investigation than its parent compound. Ixabepilone is more water-soluble than naturally occurring epothilone B, but formulation with polyoxyethylated castor oil is still required just as for paclitaxel.

Phase I Studies With Ixabepilone

Phase I studies with ixabepilone investigated 2 different dosing schedules.¹⁴⁻¹⁶ Abraham and colleagues carried out a phase I study in which patients received a 1-hour intravenous infusion of ixabepilone daily on days 1–5 of a 21-day schedule.¹⁴ The initial starting dose of 1.5 mg/m² per day was approximately one tenth of the severe toxic dose₁₀ used in rats.¹⁴ This study used an accelerated dose-escalation design, initially allowing dose escalation of 100% with consecutive patients. Twenty-seven patients with a variety of malignancies were treated and the maximum tolerated dose was determined to be 6 mg/m² per day. Patients previously treated with taxanes were preferentially enrolled and most patients were heavily pretreated; these patients received a median of 5 prior chemotherapy regimens. The main dose-limiting toxicity at the 8 mg/m² dose was neutropenia, regardless of filgrastim support. Other nonhematologic grade 3 toxicities included stomatitis and fatigue. Dose-limiting peripheral neuropathy was not observed. Encouragingly, some activity was noted in breast, cervical, and ovarian cancer.

Preliminary preclinical evidence has suggested that less frequent dosing might improve efficacy¹¹; it was also thought to be more convenient for patients. Thus, 2 phase I studies examined an intravenous infusion of ixabepilone given once every 3 weeks.¹⁵⁻¹⁶ Mani and associates¹⁵ treated 25 patients with a 1-hour infusion of ixabepilone at doses ranging from 7.4 mg/m² to 59.2 mg/m². All patients had metastatic solid organ tumors and had received up to 3 lines of chemotherapy for metastatic disease, although only 11 had received prior taxane therapy. Activity was seen in breast cancer and melanoma. Shimizu and coauthors also studied a 3-weekly dosing schedule, but infused ixabepilone over a 3-hour period.¹⁶ Fourteen patients were enrolled, half of whom had received prior taxane therapy. The patients previously received a median of 2 chemotherapy regimens. Activity was noted in patients with taxane-refractory non-small cell lung cancer (NSCLC). In these 2 studies the main dose-limiting toxicity was again

neutropenia.¹⁵⁻¹⁶ Both studies recommended a dose of 40 mg/m² for subsequent phase II studies.^{15,16}

Phase II Studies of Ixabepilone in Breast Cancer

Since taxanes are among the most active agents for breast cancer and activity of ixabepilone was already demonstrated in phase I studies, there was great interest in studying this agent in MBC. Several phase II studies have been conducted testing ixabepilone in a variety of settings, including the first-line metastatic setting, for patients who had taxane-naïve disease, and in heavily pretreated patients with taxane-resistant disease.¹⁷⁻²⁴ Table 1 shows a summary of the main phase II studies in MBC, including dosing schedules, response rates, and grade 3/4 toxicities. The initial dosing schedule of 50 mg/m² over a 1-hour infusion in 2 studies was changed ultimately to a 3-hour infusion of 40 mg/m² because of concerns of neurotoxicity and myelosuppression seen in other studies.^{18,21}

The phase II study by Perez and colleagues (Table 1) led to 1 of 2 indications for ixabepilone (as monotherapy for MBC in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine) that was approved by the US Food and Drug Administration.²⁰ In this study, resistance to anthracyclines and taxanes was defined as disease progression while receiving therapy in the metastatic setting (within 8 weeks of last treatment) or recurrence within 6 months of adjuvant or neoadjuvant therapy. Alternatively, patients could have demonstrated resistance to both taxanes and capecitabine and received a minimum cumulative anthracycline dose of 240 mg/m² of doxorubicin or an equivalent. Ixabepilone induced durable responses—for responders the median response duration was 5.7 months (95% confidence interval [CI], 4.4–7.3). The median progression free survival (PFS) was 3.1 months (95% CI, 2.7–4.2), and the median overall survival was 8.6 months (95% CI, 6.9–11.1). As expected, peripheral sensory neuropathy was the most common nonhematologic toxicity. During the study, 49% of patients developed grade 1/2 neuropathy and 13% developed grade 3/4 neuropathy.

Phase II Studies of Ixabepilone in Other Tumors

Numerous phase II studies, which have examined the activity of ixabepilone in a variety of other malignancies, have now been reported. Some of these studies have focused on tumors that are responsive to taxanes, such as prostate cancer and NSCLC.²⁵⁻²⁸ Other studies have investigated ixabepilone as a treatment for tumors for which a limited number of active chemotherapy drugs exist, such as melanoma, soft tissue sarcoma, and pancreatic and renal cell cancer; although activity in these tumors has been disappointing.²⁹⁻³²

Table 1. Phase II Studies in Metastatic Breast Cancer

Author	Inclusion Criteria (number of patients, N)	Dosing Schedule	% CR	% PR	% SD	Main grade 3/4 Toxicities
Low ¹⁷	LABC/MBC (37) Taxane-pretreated	Ixabepilone 6 mg/m ² 1 hour IV infusion d1–5 every 21 days	3%	19%	35%	Neutropenia 35% FN 14% Diarrhea 11%
Denduluri ¹⁹	MBC (23) No prior taxanes	Ixabepilone 6 mg/m ² 1 hour IV infusion d1–5 every 21 days	0	57%	26%	Neutropenia 22% Fatigue 13% Anorexia 9%
Roché ¹⁸	1st line MBC (65) Prior adjuvant anthracycline >1 year since any adjuvant taxane	Ixabepilone 50 mg/m ² 1 hour IV infusion every 21 days changed to 40 mg/m ² 3 hour IV infusion every 21 days	0	42%	35%	Protocol changed because of Grade 3-4 neuropathy at 1 hr infusion Sensory neuropathy 20% Neutropenia 27%
Thomas ²¹	MBC (49) Progressing on taxanes Prior anthracycline required	Ixabepilone 50 mg/m ² 1 hour IV infusion every 21 days changed to 3 hour infusion then changed to 40 mg/m ² 3 hour IV infusion every 21 days	0	12%	41%	Fatigue 27% Sensory Neuropathy 12% Myalgia 10%
Perez ²⁰	MBC (126) Resistant to taxanes, anthracyclines and capecitabine	Ixabepilone 40 mg/m ² 3 hour IV infusion every 21 days	0	18%	44%	Neutropenia 54% Fatigue 14% Sensory Neuropathy 13%
Baselga ²²	EBC (stage IIA-IIIb) (164)	Ixabepilone 40 mg/m ² 3 hour IV infusion every 21 days	pCR 19%	N/R	N/R	Neutropenia 19%
Bunnell ²³	MBC (62) Prior anthracycline and taxane	Ixabepilone 40 mg/m ² 3 hour IV infusion plus capecitabine 2,000 mg/m ² d-14 every 21 days	2%	28%	N/R	N/R
Moulder ²⁴	HER2+ MBC (59) No prior chemo for MBC Adjuvant trastuzumab allowed	Ixabepilone 15 mg/m ² and carboplatin (AUC=2) days 1, 8 and 15 of a 28-day cycle (max 6 cycles) and trastuzumab 4 mg/kg then 2 mg/kg weekly, then 6 mg/kg post chemo	5%	39%	24%	Neutropenia 50% Fatigue 12% Diarrhea 7% Sensory Neuropathy 7%

AUC=area under the time concentration curve; CR=complete response; EBC=early breast cancer; FN=febrile neutropenia; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; N=number of patients, N/R=not reported; PR=partial response; SD=stable disease.

Phase III Experience With Ixabepilone in MBC

To date, one phase III study with ixabepilone has been published and results of other ongoing studies will hopefully be reported in the near future. This was an international study of 752 patients with metastatic or locally-advanced breast cancer given capecitabine alone or in combination with ixabepilone.³³ The combination of capecitabine and ixabepilone is rational, as preclinical evidence of synergy between the drugs exists.³⁴ In addition,

capecitabine is widely used in the metastatic setting since many patients have received anthracyclines and taxanes in the adjuvant setting. In this trial, all patients had tumors resistant to taxanes and anthracyclines, defined as tumor progression during treatment or within 3 months of last dose in the metastatic setting or tumor recurrence within 6 months in the neoadjuvant or adjuvant setting. Patients were also eligible if they had received a cumulative doxorubicin dose of 240 mg/m² regardless of anthracycline

Table 2. Objective Tumor Responses in Patients Treated with Ixabepilone and Capecitabine or Capecitabine Alone

	Ixabepilone + Capecitabine (n=375)		Capecitabine (n=377)	
	Number of Patients	%	Number of Patients	%
Objective Response rate	130	34.7	54	14.3
Complete Response	1	<1	0	0
Partial Response	129	34	54	14
Stable Disease	155	41	175	46
Progressive Disease	58	15	102	27
Not determined	32	9	46	12

resistance. Up to 3 prior chemotherapy regimens in any setting were allowed. Patients with brain metastases and motor or sensory neuropathy grade 2 or higher were excluded. The primary endpoint of this study was PFS based on an intent-to-treat analysis.

Patients were stratified by presence of visceral metastases in the liver or lung, anthracycline resistance, prior chemotherapy for metastatic disease, and study site. Treatment consisted of random assignment to either ixabepilone 40 mg/m² intravenously on day 1 plus capecitabine 2,000 mg/m² per day (in 2 divided doses) on days 1–14 of a 21-day schedule or capecitabine alone 2,500 mg/m² per day (in 2 divided doses) on the same schedule. In total, 737 patients received treatment on this study and the baseline characteristics were well balanced between the 2 treatment groups. Tumors that overexpressed HER2 were present in 15% of patients. Patients in the combination arm received a median of 5 treatment cycles compared to a median of 4 cycles in the capecitabine-only arm. The addition of ixabepilone to capecitabine improved median PFS from 4.2 months (95% CI, 3.81–4.50) to 5.8 months (95% CI, 5.45–6.97). The response rates based on independent radiology review for the 2 treatments are shown in Table 2. The increase in PFS in favor of the combination was maintained across subgroups, including amongst 187 patients with triple negative (estrogen and progesterone receptor and HER2 negative) MBC, a disease subtype traditionally associated with a poor prognosis.

Treatment-related adverse events were mostly grade 1/2 and generally reversible; the toxicity profile of the combination reflected that of the individual agents. Myelosuppression was a common finding in patients treated with ixabepilone plus capecitabine, but was generally low grade with only a 5% incidence of febrile neutropenia. Twice as many patients treated with the combination complained of fatigue compared to those treated with capecitabine alone (40% vs 20%). The incidence of diarrhea and hand-foot syndrome was broadly equivalent

in the 2 groups, although there was more vomiting (39%) in patients receiving ixabepilone compared to single-agent capecitabine (24%). As expected with antimicrotubule agents, the addition of ixabepilone to capecitabine caused more myalgia (33% vs 4%), more arthralgia (20% vs 2%), and more nail changes (20% vs 8%)

The addition of ixabepilone increased peripheral neuropathy from 16% to 67%. This was mainly sensory, low-grade, and reversible; 21% of patients in the combination arm compared to no patients in the capecitabine alone arm developed grade 3/4 peripheral neuropathy. Peripheral neuropathy led to discontinuation of one or both study drugs in 21% of patients receiving combination therapy after a median of 6 cycles.

Twelve patients receiving ixabepilone in combination with capecitabine died from complications arising from neutropenia. Among 42 patients with grade 2 liver dysfunction at baseline, 5 of 16 (31%) patients receiving combination therapy died compared with 5 of 26 (19%) from the capecitabine group. In the combination group, these deaths were all related to neutropenia, while in the capecitabine monotherapy group they were due to progressive disease. In contrast, among patients with baseline grade 0/1 liver function tests, there was a much lower neutropenia-related death rate; 7 of 353 patients (1.9%) receiving combination therapy died and 3 of 342 patients (0.9%) treated with capecitabine monotherapy died.

The results of this study led to FDA approval for ixabepilone 40 mg/m² over 3 hours once every 21 days 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 resistant to taxanes and for whom further anthracycline therapy is contraindicated.

The results of the study are important because the activity of ixabepilone has now been demonstrated in a heavily pretreated population with MBC. This supports preclinical evidence and phase I/II data that suggested

that ixabepilone could be used in taxane-resistant cases. Etoposides, therefore, are the first new class of cytotoxic agents in over a decade to demonstrate clinical benefit in a phase III study. However, the addition of ixabepilone to capecitabine only modestly increased PFS by approximately 7 weeks. The cost in terms of toxicity was a high rate of neutropenia and neuropathy. The high rate of death in patients with baseline liver dysfunction is of concern given the fact that many patients with taxane- and anthracycline-resistant MBC might have underlying liver dysfunction related to disease burden. The study was subsequently amended to exclude patients with grade 2 or higher liver dysfunction and, therefore, this combination is recommended only for patients with normal or moderate liver dysfunction (grade 1).

While it can be argued that only 21% of patients treated with ixabepilone developed grade 3/4 neuropathy, this may somewhat underestimate the disability caused by this adverse event. In clinical practice the grading of sensory neuropathy is not absolute but a continuum, and is open to interpretation. The Common Terminology Criteria version 3 separates grade 2 sensory neuropathy—which interferes with function but not with activities of daily living—from grade 3, which also interferes with activities of daily living.³⁵ Clearly this separation is subjective and somewhat arbitrary. In this study, approximately 50% of patients experienced neuropathy (motor and sensory) of grade 2 or higher. This group of patients did not have debilitating neuropathy at baseline, as patients with grade 2 or higher neuropathy were excluded. Therefore, the potential neurotoxicity of ixabepilone in this setting should not be underestimated.

In this study the control group received capecitabine 2,500 mg/m² per day (in 2 divided doses) on days 1–14 every 21 days. This is the FDA approved dosing schedule, but the dosing commonly utilized in clinical practice is oftentimes lower. Indeed, 2,500 mg/m² per day may not be the ideal dose schedule for oral capecitabine. A novel dosing schedule developed from mathematical modeling of 2,000 mg (fixed dose) twice daily taken on days 1–7 every 14 days may allow for greater dose intensity, improve tolerability, and allow for prolonged administration.³⁶ However, the response rate for the control group is comparable to what has previously been seen in studies with single-agent capecitabine.^{37,38}

Since the treatment of MBC involves balancing the potential toxicities of therapy with maximizing the benefits, many clinicians opt for single-agent chemotherapy drugs used in sequence. The FDA approval of single-agent ixabepilone is based on phase II studies, the largest of which involved 126 patients. Further clinical studies with ixabepilone are needed to examine a number of important questions. Specifically, studies comparing

weekly ixabepilone dosing with treatment once every 3 weeks, comparing ixabepilone directly with taxanes, and assessing ixabepilone in the adjuvant setting are ongoing or planned. In addition, there is a need to investigate the activity of ixabepilone with approved novel targeted agents such as trastuzumab, lapatinib (Tykerb, Glaxo-SmithKline), and bevacizumab (Avastin, Genentech), as well as with investigational agents such as cetuximab (Bristol-Myers Squibb/ImClone).

Other Etoposides

Patupilone

Several other leading compounds from the etoposide family have reached clinical investigation. In vitro studies with patupilone (EPO 906, Novartis), naturally occurring etoposide B, have demonstrated that it is up to 20 times as potent as paclitaxel. This activity is maintained in taxane-resistant cell lines. Specifically, patupilone has demonstrated activity in cell lines from a variety of relatively rare malignancies such as myeloma, hepatocellular carcinoma, and glioma.^{39–41} Future clinical developments in these areas are anticipated.

Patupilone, unlike ixabepilone, is inactivated by esterases and this may partially explain the differing side effect profiles between the 2 drugs.⁴² The main dose-limiting toxicity is diarrhea, and there is minimal neurotoxicity and myelosuppression. These 2 substances are chemically similar and their differing side effect profile could be explained by tissue distribution and metabolism by esterases.⁴² Therefore, from a practical point of view patupilone could potentially be used in patients with pre-existing neurotoxicity.

The central nervous system is a sanctuary site for many cytotoxic agents, and limited treatment strategies exist for patients with brain metastases. Interestingly, patupilone crosses the blood brain barrier in 3 animal species and has demonstrable activity in brain tumor models.⁴³ Interim results of an ongoing phase II study in patients with refractory brain metastases from NSCLC were encouraging.⁴³ In this study, 5 of 13 patients (38%) showed response and the side effect profile was manageable. Another phase II trial of patupilone in patients with MBC and progressive brain metastases following whole brain radiotherapy is ongoing.⁴⁴ These are interesting and important studies because of the dearth of therapeutic options for these patients. For reasons that are not entirely clear, brain metastases are a relatively increasing clinical problem in a variety of malignancies including breast cancer. Improvements in the systemic control of breast cancer with modern therapies have not yet translated into improved outcomes within the central nervous system, and so this remains an important area for ongoing research.

Other Epothilone B Analogs

BMS-310705 is a semi-synthetic analog of epothilone B.⁴⁵ It is more water-soluble than ixabepilone, does not require formulation with polyoxyethylated castor oil, and therefore has been safely administered without the need for premedications.⁴⁵ In a phase I study, responses were seen in breast cancer as well as in gastric and ovarian cancer, but difficulties have arisen with both diarrhea and neurotoxicity, which may limit further clinical use.⁴⁵ ABJ-879 is also a semi-synthetic analog of epothilone B.⁴⁶ Compared to paclitaxel, ABI-879 has shown markedly more cytotoxicity in vitro and remains active against multidrug resistant cell lines.⁴⁶ Unfortunately, clinical studies with this compound are lacking.⁴⁶

The first fully synthetic epothilone is sagopilone (ZK-EPO).^{47,48} This compound is a rationally designed derivative of epothilone B, which has demonstrated both remarkable activity in a variety of cell lines and an ability to evade the cellular efflux pumps responsible for multidrug resistance.^{47,48} Preliminary results from a phase II study in 63 platinum-resistant ovarian cancer patients have been promising, and like ixabepilone, the main dose-limiting toxicity is peripheral neuropathy.⁴⁹

Epothilone D Derivatives

The in vitro activity of epothilone D is substantially less than that of epothilone B, but despite that some epothilone D derivatives have shown clinical promise.⁵⁰ One such derivative that has undergone clinical testing is KOS-862, which had particular activity against taxane-resistant cells in vitro.⁵⁰ Unfortunately, phase II studies in MBC, as well as in platinum-refractory NSCLC and metastatic hormone-refractory prostate cancer, have shown disappointing efficacy and patients suffered substantial neurotoxicity.⁵⁰⁻⁵² Another epothilone D derivative, KOS-1584, has shown activity in NSCLC, ovarian cancer, and head and neck cancer.⁵³ Like patupilone, the main dose-limiting toxicity with this drug is diarrhea.⁵³

Conclusion

Epothilones represent an exciting new class of cytotoxic agents with a distinctive target (the microtubule). Many synthetic and semisynthetic drugs have been formulated and have undergone varying degrees of testing. To date, only ixabepilone has emerged as an important clinical agent in MBC, although further developments with patupilone in brain metastases are eagerly awaited. The activity of ixabepilone has been demonstrated in one phase III study in combination with capecitabine and in phase II studies of up to 126 patients as monotherapy, leading to FDA approval for MBC. While the development of new agents for patients whose tumors are refrac-

tory to taxanes and anthracyclines is extremely welcome, the results to date are somewhat modest. Neuropathy has been identified as a major side effect, whereas myelosuppression is generally manageable. Further studies are needed to assess the role of ixabepilone earlier in the treatment paradigm in combination with targeted agents and in special subpopulations. FDA approval for ixabepilone should signal the start of clinical investigation and not the end. The development of other epothilones is also anxiously awaited.

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