Novel tubulin-targeting agents: anticancer activity and pharmacologic profile of epothilones and related analogues

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Background: Epothilones are 16-member ring macrolides with antimicrotubule activity that share a similar mechanism of action to the taxanes but have demonstrated potent antiproliferative activity in several different multidrug-resistant and paclitaxel-resistant tumor cell lines in vitro and in vivo.

Design: This review summarizes data from preclinical and phase I clinical studies of epothilone B (patupilone; EPO960) and epothilone D (KOS-862) and their second-generation (ixabepilone, BMS-310705, KOS-1584) and third-generation (ZK-EPO, ABJ-879) derivatives. Data were identified by searches of PubMed and the Proceedings of the American Society of Clinical Oncology annual meetings from 2000 to 2006.

Results: Epothilones demonstrate a linear dose-dependent pharmacokinetic profile, are well tolerated, and exhibit antitumor activity in a variety of tumor types in phase I studies of patients with cancer. Although similar in chemical structure, the epothilones demonstrate a striking difference in toxicity profile in phase I studies. Diarrhea is the dose-limiting toxicity (DLT) associated with patupilone, whereas neurotoxicity and neutropenia are the DLTs most commonly encountered with other epothilones. Consistent with preclinical data, partial responses were observed with patupilone and ixabepilone in patients with breast cancer previously treated with taxanes.

Conclusion: The epothilones demonstrate promising antitumor activity in a broad spectrum of taxane-sensitive and -refractory tumors at doses and schedules associated with tolerable side-effects.

Key words: epothilone, mechanism of action, phase I study, preclinical, tubulin-targeting agents

introduction

Epothilones are naturally occurring macrolides that constitute a novel class of antimicrotubule-targeting agents. Although the epothilones share a similar mechanism of action to the taxanes, they exhibit more potent antiproliferative activity in various tumor cell lines, particularly in cases of taxane resistance [1–3]. The epothilones have also demonstrated high levels of antitumor activity in vitro against tumor cell lines that are naturally resistant to paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ) or acquire resistance to paclitaxel by specific point mutations in the β-tubulin gene [1, 4]. Recently, several derivatives of naturally occurring epothilones have been designed to optimize in vivo antitumor efficacy, improve pharmacologic properties, and enhance the ability to overcome multiple mechanisms of drug resistance.

Currently, epothilone B (patupilone; EPO960) and its four synthetic derivatives ixabepilone (aza-epothilone B; BMS-247550), BMS-310705 (a water-soluble analogue of epothilone B), ZK-EPO (ZK-219477), 20-desmethyl-20-methylsulfanyl epothilone B (ABJ-879), and epothilone D (desoxy-epothilone B; KOS-862) and its derivative KOS-1584 are under clinical investigation for the treatment of cancer. This review briefly summarizes the current understanding of the mechanism of action and data from preclinical and phase I clinical studies of the epothilones.

chemical structure

The naturally occurring epothilones A and B were isolated from the myxobacterium Sorangium cellulosum more than a decade ago [5]. Subsequently, numerous natural epothilone variants have been described. The epothilones are 16-member ring macrolides that are combined with a methylthiazole side chain (Figure 1). Naturally occurring epothilones are classified as either epoxides (epothilones A, B, E, and F) or olefins (epothilones C and D) based on the presence or absence of an epoxide group in the C-12 to C-13 position of the macrolide ring.

Modifications to the chemical structure of the macrolide ring have been shown to alter the biologic activity and pharmacologic properties of the epothilones [6, 7]. Second- and third-generation derivatives of epothilone B have been synthesized that possess greater antitumor potency and enhanced water solubility compared with the original natural products. The second-generation semisynthetic epothilone B derivative ixabepilone was synthesized by the substitution of an azide group for oxygen at position 16 of the macrolide ring.
Ixabepilone possesses increased water solubility and plasma stability compared with epothilones B and D, but it exhibits one-fold reduction in cytotoxicity compared with epothilone B [6]. Additionally, a second semisynthetic derivative of epothilone B, BMS-310705, which was created by the substitution of the hydroxyl group with an amino group at position C-21 of the methylthiazole side chain, is ~10-fold more water soluble than epothilone B and is more cytotoxic than epothilone D in human tumor cell lines [2]. This improved water solubility allows for the development of a clinical formulation that does not contain Cremophor®-EL (BASF, Ludwigshafen, Germany). Collaboration between research groups has led to the discovery of 20-desmethyl-20-methylsulfanyl epothilone B, referred to as ABJ-879, which exhibits more potent cytotoxicity than epothilone B in human tumor cell lines [6]. The synthesis of the first fully synthetic third-generation epothilone B derivative, ZK-EPO (ZK-219477), was recently reported by a group of German investigators [8]. This agent exhibits greater potency in vitro relative to the other epothilones and retains activity even in multidrug-resistant cancer cells. Unlike paclitaxel, ZK-EPO has been shown to cross the blood–brain barrier, indicating the potential for penetration into the central nervous system (CNS). Electron crystallography studies comparing the binding of epothilone A and paclitaxel indicate that epothilone A binds to the tubulin-binding pocket of microtubules in a manner that is unique and independent of that of the taxanes [12]. Unlike the taxanes, the epothilones stimulate the formation of microtubules from tubulin purified from the yeast Saccharomyces cerevisiae. These findings indicate that the interaction of epothilones with microtubules is functionally distinct from that of the taxanes [13].

**mechanism of action**

Epothilones bind to the β-tubulin subunit of the α,β-tubulin dimer of microtubules and induce microtubule polymerization and stabilization, resulting in G2/M arrest and the induction of apoptosis. The mechanism by which the epothilones suppress microtubule dynamics appears to be similar to that of the taxanes. The binding site of epothilones on the β-tubulin subunit of tubulin is not known; however, data from studies of tubulin-binding dynamics indicate that the epothilones share common or overlapping pharmacophores with taxanes on the β-tubulin subunit [9–11]. However, evidence from other studies highlights the potential differences in the mechanisms of action of the epothilones and taxanes.

**preclinical studies**

In preclinical studies, the epothilones exhibit a broad spectrum of potent antitumor activity in vitro in a variety of taxane-sensitive and -resistant cell culture models [14, 15] and in vivo in murine xenograft tumor models [16–18].

**tumor cell lines**

The epothilones are roughly one order of magnitude more potent in cell culture models than is paclitaxel, with a median inhibitory concentration (IC_{50}) in the sub or low nanomolar...
Table 1. Cytotoxicity (IC_{50}) in nm of epothilones in comparison to paclitaxel in human tumor cell lines [6]

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Epothilone A</th>
<th>Epothilone B</th>
<th>Epothilone C</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT116 (colon)</td>
<td>2.51</td>
<td>0.32</td>
<td>NA</td>
<td>2.79</td>
</tr>
<tr>
<td>SW620 (colon)</td>
<td>0.1</td>
<td>NA</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>SW620AD (paclitaxel-resistant colon carcinoma subline)</td>
<td>NA</td>
<td>0.3</td>
<td>NA</td>
<td>250</td>
</tr>
<tr>
<td>PC-3M (prostate)</td>
<td>4.27</td>
<td>0.52</td>
<td>NA</td>
<td>4.77</td>
</tr>
<tr>
<td>A549 (lung)</td>
<td>2.67</td>
<td>0.23</td>
<td>NA</td>
<td>3.19</td>
</tr>
<tr>
<td>MCF-7 (breast)</td>
<td>1.49</td>
<td>0.18</td>
<td>2.90</td>
<td>1.80</td>
</tr>
<tr>
<td>MCF-7/ADR (breast)</td>
<td>27.50</td>
<td>2.92</td>
<td>NA</td>
<td>9105</td>
</tr>
<tr>
<td>KB-31 (epidermoid)</td>
<td>2.10</td>
<td>0.19</td>
<td>2.70</td>
<td>2.31</td>
</tr>
<tr>
<td>CCRF-CEM (leukemia)</td>
<td>0.35</td>
<td>9.5</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NA, data not available.

range in breast, lung, colon, prostate, and ovarian cell lines (Table 1) [14, 15]. Ixabepilone has demonstrated potent cytotoxicity across a panel of cancer cell lines: breast (35 cell lines, including MCF7/ADR, an established multidrug-resistant cell line), colon (20 cell lines, including the multidrug-resistant HCT116/VM46 cell line), and lung (23 cell lines), with the majority of IC_{50} values between 1.4 and 45 nm [19]. The synthetic derivative of epothilone B, ABJ-879, has exhibited greater potency than patupilone and paclitaxel across a panel of human tumor cell lines [20]. The average IC_{50} of ABJ-879 on a panel of drug-sensitive human tumor cell lines was 0.09 nm, compared with 0.24 and 4.7 nm for patupilone and paclitaxel, respectively. Importantly, in contrast to paclitaxel, ABJ-879 retained full activity against cancer cells overexpressing the drug efflux pump P-glycoprotein (Pgp) or harboring tubulin mutations. KOS-862 exhibits reduced antiproliferative activity in human cancer cell lines compared with patupilone (Table 1), which may be related to its reduced cellular uptake compared with patupilone.

The epothilones have also demonstrated potent antiproliferative activity in multidrug-resistant and paclitaxel-resistant cell lines. The overexpression of drug efflux transport proteins such as Pgp has been implicated as an important mechanism of resistance to the taxanes. Although the IC_{50} of paclitaxel is increased significantly in multidrug-resistant cell culture models, the overexpression of Pgp has minimal effect on the cytotoxicity of patupilone, ixabepilone, and KOS-862. KOS-862 appears to be least affected by the overexpression of Pgp, whereas ixabepilone is most affected. Additionally, the epothilones retain significant antiproliferative activity in cell lines harboring the specific mutations of the β-tubulin that confer resistance to paclitaxel [1]. Although these findings indicate that the epothilones may be more effective than the taxanes in patients with malignancies characterized by high levels of Pgp expression or taxane resistance, the clinical significance of these data needs to be established.

**xenograft models**

The broad-spectrum in vitro antineoplastic activity demonstrated in cancer cell lines was also evident in vivo by the robust efficacy of epothilones against a wide array of human cancer xenografts in mice. In vivo studies using different formulations and schedules of administration of patupilone, ixabepilone, and KOS-862 indicate that they are active in paclitaxel-sensitive and -resistant tumor models. Ixabepilone is highly active in a variety of human cancer xenografts when administered intravenously (using an ethanol/Cremophor® formulation) or orally to mice using intermittent daily or weekly schedules [15]. At doses producing clinically relevant exposures, ixabepilone has demonstrated significant antitumor activity in 33 of 35 human cancer xenografts evaluated [19]. In the majority of tumors, prolonged tumor growth delay ≥1 log cell kill was achieved, which was accompanied by significant tumor regression rates. In addition, cures were observed in ~50% of the tumor types. Ixabepilone also exhibited potent antiproliferative activity in tumors expressing the Pgp-mediated multidrug-resistance phenotype in vivo, reversing the multidrug resistance of four established multidrug-resistant models: MCF7/ADR and 16C/ADR breast, Pat-7 ovarian, and HCT116/VM46 human colon carcinoma [19].

Similarly, patupilone produces either growth inhibition or tumor regression in lung, breast, colon, and prostate xenografts when administered intravenously (in a PEG300/water formulation) on a weekly schedule [16]. The intravenous and intraperitoneal administrations of KOS-862, BMS-310705, and ZK-EPO have also been reported to induce the regression of taxane-sensitive and -resistant tumors in certain xenograft tumor models [18]. More recently, ZK-EPO has demonstrated marked tumor growth inhibition in breast cancer models of brain and bone metastasis [21]. ABJ-879 induces transient regressions and inhibition of tumor growth in human xenograft models of slow-growing NCI H-596 lung adenocarcinoma tumors and difficult-to-treat NCI H-460 large cell lung tumors [20]. A single administration of ABJ-879 has also been reported to induce long-lasting regressions and cures in a xenograft model of paclitaxel-resistant KB-8511 epidermoid carcinoma [20].

Although patupilone exhibits more potent antiproliferative activity in vitro, its therapeutic efficacy in vivo is limited by substantial toxicity in animal tumor models. KOS-862 is less toxic than patupilone and demonstrates greater therapeutic efficacy than patupilone in vivo. Drug schedule had a significant impact on the antitumor activity and toxicity of epothilones in experimental models of human tumor xenografts. For example, the antitumor activity of KOS-862 was enhanced when this agent given intravenously or intraperitoneally every 2 days; however, toxicity associated with a rapid infusion over 6 h resulted in death in animal models [16].

**clinical development**

The promising antitumor activity and improved biopharmaceutical properties of the epothilones and their synthetic derivatives have prompted a further evaluation of these compounds in the clinical setting (Table 2) [22–36]. Phase I data have been reported in the literature for patupilone and ixabepilone in a variety of different solid tumor types. Phase I data on BMS-310705, ZK-EPO, KOS-862, and KOS-1584 are limited and have been reported primarily in abstract form.
Three schedules of patupilone administration have been reported in phase I studies [22, 23, 37]. Calvert et al. [22] investigated a three-weekly schedule of patupilone in 42 patients with solid tumors; diarrhea was the dose-limiting toxicity (DLT) when the medication was given at 8 mg/m². A partial response to treatment was reported in one patient with a cancer of unknown primary site. A second phase I study investigated two schedules of patupilone in patients with advanced solid tumors [23]. In this study, patients received patupilone, 0.3–3.6 mg/m², administered on a 6-weeks-on/3-weeks-off (n = 54) or 3-weeks-on/1-week-off (n = 37) schedule. After a short infusion, patupilone blood concentrations declined in a multiphasic manner, with a terminal half-life of 4 days. The maximum tolerated dose (MTD) was 2.5 mg/m², with diarrhea being the most common DLT for both schedules above this dose. No neurologic toxicity or hypersensitivity reactions were observed with patupilone. Partial responses were reported in three patients, two of whom had received previous taxane therapy [23]. More recently, the three-weekly schedule of patupilone, 6.5–11.0 mg/m², has been reexplored in a phase I/II study of 42 patients with non-small-cell lung cancer (NSCLC) using an intensive program of diarrhea management [37]. As a result, the dose of patupilone has been escalated to 11.5 mg/m². DLTs have included fatigue and diarrhea, and neurotoxicity has also been noted. At the time of reporting, the MTD had not been reached, and partial responses were noted in four patients. Patupilone is mainly metabolized by the enzyme carboxylesterase-1 to its hydrolytic-derived metabolite; the oxidative metabolism by cytochrome P450 enzyme plays a minimal role [38]. Based on data from other ongoing phase I/II studies, a dose of 10 mg/m² every 3 weeks has been chosen for randomized phase III trials [39–41].

**ixabepilone, a second-generation epothilone B**

Four different dosing schedules of ixabepilone (1.5 to 65 mg/m²) have been evaluated in phase I studies [24–28]. Ixabepilone is formulated in polyoxyethylated castor oil, and

### Table 2. Summary of clinical studies of epothilones in patients with advanced malignancies

<table>
<thead>
<tr>
<th>Epothilones</th>
<th>Patient (no.)</th>
<th>Drug/schedule evaluated</th>
<th>Dose (mg/m²)</th>
<th>General toxicity</th>
<th>DLT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixabepilone</td>
<td>27</td>
<td>Days 1–5 of a 21-day cycle</td>
<td>1.5–8.0</td>
<td>Neuropathy, neutropenia, HSR, fatigue, and hyponatremia</td>
<td>Neutropenia at 8 mg/m²/day; MTD 6 mg/m²</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Days 1–3 of a 21-day cycle</td>
<td>8–10</td>
<td>Neuropathy at 8 mg/m²/day</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>Weekly infusion every 21 (n = 34) or 28 (n = 52) days</td>
<td>1–30</td>
<td>Grade 3 fatigue at 30 mg/m²/day; MTD 25 mg/m²</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Day 1 of a 21-day cycle</td>
<td>7.4–65.0</td>
<td>Neutropenia, abdominal pain at 50–56 mg/m²; MTD 40 mg/m²</td>
<td>24–26</td>
<td></td>
</tr>
<tr>
<td>Patupilone</td>
<td>91</td>
<td>Days 1, 8, and 15 of a 28-day cycle</td>
<td>0.3–3.6</td>
<td>Diarrhea, fatigue, nausea, and vomiting</td>
<td>Diarrhea; MTD 2.5 mg/m²</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>Day 1 of a 21-day cycle</td>
<td>0.3–8.0</td>
<td>Diarrhea at 8 mg/m²/day; MTD 2.5 mg/m²</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>KOS-862</td>
<td>13</td>
<td>Days 1–3 of a 21-day cycle</td>
<td>16–100</td>
<td>Neuropathy, fatigue, nausea, and vomiting</td>
<td>Unknown</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Days 1, 8, and 15 of a 28-day cycle</td>
<td>20–50</td>
<td>Neuropathy</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>On day 1 of a 21-day cycle</td>
<td>9–185</td>
<td>Grade 3 chest pain, impaired gait, and cognitive/perceptual changes</td>
<td>Neuropathy</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Day 1 of a 14-day cycle, over 24 h</td>
<td>1–6 mg/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Day 1 of a 14-day cycle, over 72 h</td>
<td>1–1.7 mg/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-310705</td>
<td>21</td>
<td>Days 1, 8, and 15 of a 28-day cycle</td>
<td>5–30</td>
<td>Grade 2 diarrhea, and HSR</td>
<td>Grade 3 diarrhea at 30 mg/m²</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>Day 1 of a 21-day cycle</td>
<td>0.6–70</td>
<td>Grade 3/4 neuropathy, neutropenia, fatigue, diarrhea, and HSR</td>
<td>Grade 4 hyponatremia, neutropenia at 70 mg/m²</td>
<td>31</td>
</tr>
<tr>
<td>ZK-EPO</td>
<td>Day 1 of a 21-day cycle</td>
<td>0.6–29</td>
<td>Neuropathy, fatigue, and ataxia</td>
<td>Unknown</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>KOS-1584</td>
<td>12</td>
<td>On days 1, 8, and 5 of a 28-day cycle</td>
<td>0.8–7.5</td>
<td>Fatigue and anorexia</td>
<td>Unknown</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Day 1 every 21 days</td>
<td>0.8–11.3</td>
<td>Diarrhea and fatigue</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

DLT, dose-limiting toxicity; HSR, hypersensitivity reaction; MTD, maximum tolerated dose.
as a result, hypersensitivity reactions were seen in all phase I studies, necessitating the use of prophylactic antihistamines. Three studies have investigated the administration of ixabepilone as a 1-h infusion given every 3 weeks [24–26]. In these studies, the MTD was 40 mg/m² and the DLT was neutropenia. Grade 1 or 2 neuropathy was reported in all patients treated at the MTD. The recommended dose of ixabepilone for phase II studies of the three-weekly schedule is 25 mg/m². The mean clearance, volume of distribution (Vss), and apparent terminal elimination half-life at the 40 mg/m² dose were 21 l/h/m², 826 l/m², and 35 h (excluding one outlier of 516 h), respectively [24]. In one study [24], partial responses occurred in two patients with paclitaxel-refractory ovarian cancer, one patient with taxane-naïve breast cancer, and another patient with docetaxel-refractory breast cancer. Similar findings were observed in a second study that evaluated a once-every-3-week schedule in 17 cancer patients [25].

The final results of a third study investigating the weekly schedule of ixabepilone were recently reported in abstract form [29]. In this study, ixabepilone was administered weekly as a 30-min infusion every 3 weeks or every 4 weeks. Due to neurotoxicity, infusion time was increased to 1 h with a 1-week break allowed. Doses ranged from 1 to 30 mg/m². Thirty-four patients were treated with the once-every-3-weeks schedule, and 54 patients were treated with the once-every-4-weeks schedule. The DLT was grade 3 fatigue, which occurred at the 30 mg/m² dose level with the once-every-3-weeks schedule. No DLTs were seen at doses of 25 mg/m² on the once-every-3-weeks schedule or at doses of 15, 20, or 25 mg/m² on the once-every-4-weeks schedule. Thus, the MTD was established at 25 mg/m². Partial responses were noted in five patients. The recommended doses for phase II studies of weekly ixabepilone are 25 (30-min weekly infusion, 3-week schedule) and 20 mg/m² (1-h weekly infusion, 4-week schedule) [29]. The oxidative metabolism by CYP3A4/5 appears to be a prominent route of transformation in vitro [38].

Two phase I studies have evaluated ixabepilone given as a 1-h infusion daily for either 3 (8–10 mg/m²) or 5 (1.5–8 mg/m²) consecutive days every 3 weeks [27, 28]. Neutropenia was the DLT with both schedules. Other grade 3 non-hematologic toxic effects included fatigue, anorexia, and stomatitis. Peripheral neuropathy was also reported but was generally mild. The MTDs were 6 and 8 mg/m²/day with the 3- and 5-day schedules, respectively. Antitumor activity was observed in a number of tumor types, including mesothelioma, ovarian, and renal cell carcinoma.

BMS-310705, a second-generation epothilone B

Two phase I studies have evaluated the water-soluble, second-generation, semisynthetic derivative of epothilone B, BMS-310705 [30, 31]. In phase I studies, BMS-310705 was administered as a 15-min infusion given either every 3 weeks or weekly for three consecutive weeks [30]. Preliminary pharmacokinetic data show increases in area under the time-concentration curve (AUC) and maximum plasma concentration (Cmax) that are dose related and are similar between cycles 1 and 2. For the 40 mg/m² dose in cycle 1, mean pharmacokinetic values were Cmax, 3936 ng/ml; AUC, 2823 ng/h/ml; elimination half-life, 42 h; clearance, 277 ml/min/m²; and steady-state Vss, 443 l/m². Neutropenia, diarrhea, and sensory neuropathy were the most common toxic effects associated with BMS-310705. In contrast to ixabepilone, no hypersensitivity reactions were observed with this compound in phase I studies. Partial responses to BMS-310705 treatment were reported in one patient with ovarian cancer treated at 40 mg/m² and one patient with bladder cancer treated at 30 mg/m². A complete response was achieved by one patient with NSCLC treated with 40 mg/m² [31]. Objective responses were also observed with the weekly schedule of BMS-310705 in one patient with gastric cancer and two patients with breast cancer [30].

ZK-EPO, a third-generation epothilone B

One phase I study of ZK-EPO in patients with advanced solid tumors has been reported in abstract form [42]. In this study, ZK-EPO was given as a 30-min induction once every 3 weeks from a starting dose of 0.6 mg/m². At the time of reporting, 47 patients had been treated with ZK-EPO at doses of up to 29 mg/m². With regard to toxicity, the most common adverse events were peripheral sensory neuropathy and nausea. The DLT was grade 3 peripheral neuropathy; grade 3 ataxia occurred in one patient each at the 16- and 29-mg/m² dose levels. The MTD has not been reached. Two partial responses were noted in patients with taxane-pretreated breast cancer.

KOS-862, epothilone D

Three phase I studies have investigated several dosing schedules of KOS-862 in patients with various malignancies [32–34]. Similar to ixabepilone, a Cremophor®-based formulation has been used in phase I studies. Linear pharmacokinetics were reported in studies that evaluated KOS-862 given as a 90-min infusion, 16–100 mg/m², three of every 4 weeks; a single dose of 9–185 mg/m² every 3 weeks; or a 20- to 50-mg daily dose given for three consecutive days every 3 weeks [32, 33]. The safety of two (24- and 72-h) continuous intravenous schedules of KOS-862 administered every 2 weeks has also been investigated in 24 patients [34]. Neurologic toxicity was dose limiting in all phase I studies of KOS-862. Neuropathy, fatigue, nausea, and vomiting were also observed, though to a lesser degree. Evidence of antitumor activity was noted in patients with pancreatic, breast, testicular, and ovarian cancers.

KOS-1584, a second-generation epothilone D

Two phase I studies of the epothilone D derivative KOS-1584 have recently been reported in abstract form (Table 2) [35, 36]. KOS-1864, at doses of 0.8–11.3 mg/m², given as a 3-h infusion once weekly every 3 weeks, was evaluated in 27 patients with solid tumors. At the time of reporting, no DLT was observed in cycle 1, and common toxic effects included...
gastrointestinal disorders, fatigue, and increased aspartate aminotransaminase levels. Linear pharmacokinetics were reported over the dose range tested. The mean clearance, \( V_{\text{ss}} \), and apparent terminal elimination half-life were 30.2 l/h, 741 l, and 17.7 h, respectively. The \( V_{\text{ss}} \) and apparent terminal elimination half-life were five- and two-fold higher with KOS-1864 than with KOS-862.

Similar findings were reported in a second study investigating the administration of KOS-1584, 0.8–7.5 mg/m², given as a 1-h infusion three times weekly every 4 weeks to 12 patients with advanced solid tumors [35]. A slower clearance of KOS-1584, as determined by a higher \( C_{\text{max}} \) and AUC, total values, was noted with the 1-h infusion than with the 3-h infusion of the 5.0 mg/m² dose. No DLT had been reached at the time of reporting, and accrual is ongoing.

**conclusion**

The epothilones and their structural derivatives have demonstrated improved pharmacologic and resistance profiles when compared with the taxanes in *in vitro* and *in vivo* preclinical tumor models. The clinical profile of epothilones is clearly different, with diarrhea being the most common DLT encountered with patupilone and neutropenias and sensory neuropathy being the most common toxic effects observed with the other epothilones. The incidence of neuropathy induced by ixabepilone may be schedule dependent and is less common on daily schedules than on weekly or 3-week schedules. Data from phase I studies indicate that the epothilones are active in a broad spectrum of taxane-sensitive and –resistant tumor types, including breast, lung, and prostate cancer. Phase II studies are ongoing in specific tumor types, and data from these studies will further clarify the role of epothilones in the treatment of patients with cancer.

**disclosures**

PF has reported that he has acted as a consultant for GlaxoSmithKline and Sanofi-Aventis, and that he has acted as a speaker for Pfizer and Sanofi-Aventis.

**references**


