Epothilones in prostate cancer: review of clinical experience

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Background: Hormone-refractory prostate cancer (HRPC) is a progressive chemotherapy-resistant disease that remains a challenge to manage. Despite the recent approval of docetaxel (Taxotere) for the treatment of HRPC, the need exists for additional novel agents that can further improve patient outcomes. The epothilones are potent antimicrotubule agents that have demonstrated activity in the setting of taxane resistance. They are structurally distinct compounds that appear to lack cross-resistance with the taxanes.

Design: This review summarizes current preclinical and clinical data on the safety and efficacy of the epothilones ixabepilone (BMS-247550) and patupilone (EPO906) for the treatment of prostate cancer. Data were identified by searches of PubMed and the Proceedings of the American Society of Clinical Oncology annual meetings from 2000 to 2006.

Results: The epothilones have demonstrated potent antitumor activity in vitro and in experimental animal models of prostate cancer. In clinical studies, the epothilones have demonstrated potent activity in HRPC, including no cross-resistance with the taxanes and a manageable toxicity profile. Phase II studies of single-agent ixabepilone in patients with HRPC have reported a confirmed prostate-specific antigen (PSA) response rate of 33%. Higher PSA response rates have been reported in studies that assessed the combination of ixabepilone and estramustine in patients with HRPC.

Conclusions: The epothilones are promising new chemotherapeutic agents that have demonstrated single-agent antitumor activity in HRPC in the phase II setting. Phase III trials are needed to confirm the activity of the epothilones in tandem with docetaxel, given the experience to date.

Key words: clinical trial, epothilone, prostate cancer

Introduction

Hormone-refractory prostate cancer (HRPC) is a progressive androgen-independent disease that is challenging to manage. Although a variety of cytotoxic agents have been actively investigated for the treatment of patients with HRPC, most agents tested have demonstrated only marginal efficacy and, at best, have extended survival only 10–12 months [1]. More recently, docetaxel-based chemotherapy has been shown to provide survival and palliative benefits when compared with mitoxantrone and prednisone after androgen ablation therapy has failed in patients with HRPC [2, 3]. However, the survival benefit of docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ) is modest—2 to 3 months—and a large proportion of patients with advanced prostate cancer become refractory to taxane-based treatments. Thus, the need exists for additional novel agents that can provide further improvement in patient outcomes.

The clinical success of the taxanes has led to more intensive investigation of this class of agents. Currently, a number of novel antimicrotubule agents are in phase I and II trials. Of these, the epothilones have recently emerged as a promising treatment for patients with HRPC. In preclinical studies, epothilone B (patupilone; EPO906) and its semisynthetic derivative ixabepilone (BMS-247550) have demonstrated more potent antiproliferative activity than paclitaxel (Taxol, Bristol-Myers Squibb, New York) in human tumor cell culture assays [4] and in murine xenograft models of androgen-independent prostate cancer [5, 6]. The epothilones have also demonstrated a lower susceptibility to certain resistance mechanisms, including P-glycoprotein-mediated efflux and specific tubulin mutations that confer resistance to taxanes [7].

Currently, epothilone B and ixabepilone are under clinical investigation for the treatment of patients with HRPC. This review highlights preclinical data and data emerging from clinical trials of the epothilones ixabepilone and patupilone in patients with prostate cancer. Preliminary data from phase I/II trials of ixabepilone in combination with estramustine are also presented.

Preclinical Studies

Although the mechanism of action of the epothilones is similar to that of the taxanes, the epothilones represent a functionally
and structurally distinct class of antimicrotubule agents. Currently, four forms of epothilones, labeled A through D, have been identified. Similar to the taxanes, the epothilones promote microtubule stabilization, the formation of microtubule bundles, and multipolar spindles that result in mitotic arrest at the G2/M phase of the cell cycle and eventual apoptosis. However, increasing evidence indicates that the epothilones differ from the taxanes with respect to binding and interaction with β-tubulin [8, 9]. Preclinical studies have shown that the epothilones are more potent inducers of tubulin polymerization than paclitaxel and inhibit cell growth across a broad panel of taxane-sensitive and taxane-resistant human tumor cell lines [7]. In cell culture assays of prostate cancer cell lines DU145 and PC-3M, patupilone was 10-fold more cytotoxic than paclitaxel, with respective mean inhibitory concentrations of 0.31 and 0.52 nm [4]. Epothilone A and the desoxy derivatives of epothilones A and B also inhibited the growth of prostate cancer cell lines, but they were less potent than patupilone. Synergistic antitumor activity has been reported with the combination of epothilones and farnesyl transferase inhibitors (FTIs) in DU145, a cell line that is not particularly sensitive to FTIs [4]. These findings indicate that the combination of a FTI and an epothilone may represent a new clinical strategy for the treatment of patients with advanced prostate cancer.

Patupilone has been shown to inhibit the growth and metastasis of experimental prostate tumors in vivo. The administration of patupilone to athymic mice bearing human prostate cancer xenografts (subcutaneous DU145 and PC-3M, orthotopic PC-3M) was associated with the inhibition of tumor growth, followed by protracted regression in DU145 and PC-3M xenograft models [6]. In the mice with orthotopic PC-3M tumors, patupilone also enhanced survival, with only transient body weight loss. In other studies, a novel fluorinated epothilone, 26-fluorooepothilone B, demonstrated potent antitumor activity against human MDA PCa 2b- and PC3-derived prostate tumors in murine xenograft models and was superior to paclitaxel at equivalent toxic doses [5]. In cell culture assays, growth inhibitory concentrations for 26-fluorooepothilone B ranged from 0.5 to 4 nm. Treatment of athymic mice bearing human prostate tumors with 2 or 10 mg/kg of 26-fluorooepothilone B per kg body weight resulted in 58% and 80% maximal reduction of tumor size, respectively, compared with tumor growth in the saline control group [5].

**phase I clinical studies**

Promising preclinical antitumor activity has prompted the clinical evaluation of several epothilones including epothilones B and D and their synthetic derivatives. Currently, patupilone, ixabepilone, and epothilone D (KOS-862) are the furthest along in clinical development. Phase I data for these epothilones have been published in the literature or in abstract form.

A variety of schedules of ixabepilone, including a single 60-min infusion every 3 weeks, a weekly schedule, a five-times-daily every-3-weeks schedule, and a three-times-daily every-3-weeks schedule, in patients with advanced cancer have been evaluated in phase I studies [10–14]. The major dose-limiting toxic effects associated with ixabepilone treatment were sensory neuropathy and neutropenia. Antitumor responses were reported in patients with ovarian cancer, non-small-cell lung cancer, and breast cancer; many of these patients had previously been treated with paclitaxel- or docetaxel-containing regimes [10, 12]. Based on findings of phase I studies of ixabepilone, the recommended dose of ixabepilone for phase II studies is 40 mg/m² for the every-3-weeks schedule [11, 12] and 25 mg/m² for the weekly schedule [15].

Phase I studies of patupilone have also been reported in the literature [16] and in abstract form [17]. In contrast to ixabepilone, the major dose-limiting toxic effects associated with patupilone treatment were diarrhea and fatigue. The safety profile of patupilone in phase I studies was favorable when compared with that of docetaxel. Antitumor responses were reported in patients with taxane-sensitive, taxane-resistant, and taxane-refractory tumors. The combination of patupilone and estramustine has also been reported. Wojtowicz et al. [18] investigated the combination of patupilone and estramustine in a phase I dose-finding study that involved 14 patients with advanced cancer. The majority of the patients had stage III/IV prostate or breast cancer and a performance status of two or less and had received prior taxane therapy. Patients received weekly oral estramustine (280 mg twice daily) on days 1 through 3 and weekly patupilone (0.5–2.5 mg/m²) on day 2 for 3 weeks, followed by 1 week of rest. The most common toxic effects reported were diarrhea, fatigue, and vomiting. The maximum tolerated dose (MTD) of patupilone in combination with estramustine was 2.5 mg/m². Preliminary tumor assessment showed that one patient had a partial response and eight patients had disease stabilization (in three patients for 4 months and in five patients for 2 months).

**phase II clinical studies**

Data from several phase II studies of epothilones have recently been reported in the literature or in abstract form (Table 1) [19–23]. Single-agent ixabepilone [21] and patupilone [20] have demonstrated promising antitumor activity in patients with HRPC. A phase II study of KOS-862 in patients with HRPC was closed after interim analysis showed lack of efficacy. More recently, the efficacy of ixabepilone in combination with estramustine for the treatment of patients with HRPC has been reported [19]. A review of these studies and of ongoing studies follows.

**single-agent studies**

A phase II trial of ixabepilone for the treatment of HRPC has been reported in the literature [21]. This study involved 42 patients [median age, 73 years; median prostate-specific antigen (PSA) level, 111 ng/ml] with chemotherapy-naïve metastatic prostate cancer in whom androgen deprivation therapy and antiandrogen withdrawal had failed. Patients received ixabepilone 40 mg/m² over 3 h using the once-every-3-weeks schedule. All patients were premedicated with oral diphenhydramine 50 mg and ranitidine 150 mg 1 h before receiving ixabepilone therapy to prevent...
The primary objective of the study was to assess the PSA response to ixabepilone, defined as (i) ≥50% reduction in PSA levels from baseline on two successive evaluations done a minimum of 4 weeks apart, and (ii) a minimum objective disease response status of stable disease or better. Of the 42 patients treated with ixabepilone, 14 patients (33%) had a confirmed PSA response. Among the 20 patients with measurable disease, one patient had unconfirmed complete response and two patients had unconfirmed partial response, for an objective response rate of 16%. The estimated progression-free survival was 6 months, and the median survival was 18 months. The most common toxic effects included neutropenia and neuropathy. These findings demonstrated that ixabepilone is active in patients with chemotherapy-naive metastatic HRPC.

A multicenter, noncomparative, randomized phase II study (NCI 6046) that evaluated the safety and activity of ixabepilone in patients with metastatic prostate cancer unresponsive to paclitaxel, docetaxel, or hormone therapy has recently been completed and reported in abstract form [22]. This study involved a total of 82 patients who were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2) and then randomized to receive either ixabepilone 35 mg/m² every 3 weeks or mitoxantrone 14 mg/m² plus oral prednisone 5 mg twice daily on days 1 through 21 of an every-3-weeks schedule. For both regimens, the courses were repeated every 21 days in the absence of disease progression or unacceptable toxicity. Patients who progressed while on treatment after at least two courses or who discontinued treatment for toxicity were

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of eligible patients</th>
<th>Schedule</th>
<th>PSA response no. of patients (%)</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain et al. [21]</td>
<td>42</td>
<td>40 mg/m² 3-h infusion every 3 weeks</td>
<td>14 (33%) confirmed, 2 (5%) unconfirmed</td>
<td>6 months (95% CI, 4–8 months)</td>
<td>18 months (95% CI, 13–24 months)</td>
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<tr>
<td>Smaletz et al. [23]</td>
<td>12 chemotherapy naive</td>
<td>Ixabepilone 35 mg/m² (n = 13) or 40 mg/m² (n = 6) every 3 weeks plus EMP 280 mg t.i.d. on days 1–5</td>
<td>11 had ≥50% decline in PSA levels</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Galsky et al. [19]</td>
<td>89 chemotherapy naive</td>
<td>Ixabepilone 35 mg/m² (n = 45) every 3 weeks or Ixabepilone 35 mg/m² every 3 weeks plus EMP 280 mg t.i.d. on days 1–5 (n = 47)</td>
<td>21/44 (48%) with ≥50% decline in PSA levels on Ixabepilone alone; 31/45 (69%) with ≥50% decline in PSA levels on Ixabepilone plus EMP</td>
<td>Time to PSA progression: NR</td>
<td>12.5 months for mitoxantrone plus prednisone</td>
</tr>
<tr>
<td>Lin et al. [22]</td>
<td>82 taxane-resistant HRPC</td>
<td>Mitoxantrone 14 mg/m² every 3 weeks and prednisone 5 mg p.o. b.i.d. (n = 41) or Ixabepilone 35 mg/m² every 3 weeks (n = 41)</td>
<td>21/44 (48%) with ≥50% decline in PSA levels on Ixabepilone alone; 31/45 (69%) with ≥50% decline in PSA levels on Ixabepilone plus EMP</td>
<td>NR</td>
<td>13.0 months for Ixabepilone</td>
</tr>
<tr>
<td>Patupilone</td>
<td>Hussain et al. [20]</td>
<td>Patupilone 2.5 mg/m² once weekly for 3 weeks, with 1 week of rest between cycles</td>
<td>8 (22%) with partial PSA response 6 (16%) with disease stabilization</td>
<td>NR</td>
<td>NR</td>
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HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; CI, confidence interval; t.i.d., three times a day; NR, not reported; p.o., by mouth; b.i.d., twice a day; EMP, estramustine phosphate; MP, mitoxantrone/prednisone.

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allowed to cross over to the other study arm and receive treatment as above, beginning within 12 weeks of the last study treatment on the original arm. Patients were followed every 3 months. The study’s primary end point was to detect a ≥50% PSA decline by consensus criteria in at least 25% of second-line patients (H₀ = 10%, α = 0.04, β = 0.18 for each group). At the time of reporting, the median number of treatment cycles administered to each second-line treatment group was 3 (range, 1–8 cycles ixabepilone; 1–12 cycles mitoxantrone plus prednisone) and patients had been followed for a median of 5.0 months (range, 0.3–19.5 months). Median survival was similar between the treatment groups: 13.0 months with ixabepilone and 12.5 months with mitoxantrone plus prednisone (Figure 1). PSA responses were observed in 17% of the ixabepilone-treated patients [95% confidence interval (CI), 7% to 32%] and in 20% of the patients treated with mitoxantrone plus prednisone (95% CI, 9% to 35%).

Of those patients with measurable disease, partial responses were observed in one of 18 patients treated with ixabepilone (6%; 95% CI, 0.1% to 27.3%) and in one of 15 patients treated with mitoxantrone plus prednisone (7%; 95% CI, 0.2% to 31.9%). Crossover to third-line treatment occurred in 39% and 68% of the patients treated with ixabepilone and mitoxantrone plus prednisone, respectively. Confirmed third-line PSA response was observed in three of the 24 (31%) patients treated with ixabepilone and in four of the 13 (12.5%) patients treated with mitoxantrone plus prednisone. With respect to toxicity, the most common grade 3/4 toxicity associated with second-line treatment was neutropenia (41% of ixabepilone patients and 54% of mitoxantrone plus prednisone patients). These findings indicate that ixabepilone and mitoxantrone plus prednisone appear to have only modest activity as second- and third-line treatment in this highly selected taxane-resistant HRPC population [22].

A phase II study of patupilone administered on a weekly schedule to patients with metastatic HRPC has been reported in abstract form [20]. This study involved 37 patients (median age, 68 years), 29 of whom had received a maximum reported in abstract form [20]. This study involved 37 patients (median age, 68 years), 29 of whom had received a maximum reported in abstract form [20]. This study involved 37 patients (median age, 68 years), 29 of whom had received a maximum reported in abstract form [20]. This study involved 37 patients (median age, 68 years), 29 of whom had received a maximum reported in abstract form [20]. This study involved 37 patients (median age, 68 years), 29 of whom had received a maximum

**combination studies**

Two studies evaluating the combination of ixabepilone and estramustine in patients with metastatic prostate cancer have been reported in the literature [19, 23]. A small pilot study that evaluated the combination of ixabepilone and estramustine demonstrated a high rate of PSA response in patients with chemotherapy-naive castrate metastatic prostate cancer [23].

**Figure 1.** Median overall survival of patients treated with ixabepilone or mitoxantrone and prednisone as second-line therapy. Reprinted with permission from Lin et al. [22].

In this study, 13 patients were treated with ixabepilone 35 or 40 mg/m² and oral estramustine 280 mg three times daily for 5 days, once every 3 weeks. Dose-limiting grade 4 neutropenia occurred at the 40-mg/m² dose level, establishing 35 mg/m² as the MTD. Sensory neuropathy was observed in eight patients and was clinically significant (grade 2) in six patients (46%). Neurotoxicity appeared to correlate with increasing dose levels and infusion rates of ixabepilone. Of the 12 patients providing assessable data, 11 patients (92%) had a decline in PSA of ≥50% (95% CI, 76% to 100%). Of the seven patients with measurable disease at baseline, one patient (14%) had a complete response, three patients (43%) had a partial response, one patient (14%) had stable disease, and one patient (14%) had progression of disease. One patient was not evaluable. This patient developed liver metastases from a second malignancy. Most notably, three patients who experienced disease progression while on ixabepilone and estramustine responded to subsequent taxane-based regimes. These findings indicate a possible noncross-resistant mechanism of action between the epothilones and taxanes.

Similar findings were reported in a second randomized phase II study that investigated the antitumor activity and safety of ixabepilone, with or without estramustine, in chemotherapy-naive patients with progressive, castrate metastatic prostate cancer [19]. A total of 92 patients were randomized to receive single-agent ixabepilone 35 mg/m² once every 3 weeks (n = 45) or the same schedule of ixabepilone plus estramustine 280 mg orally three times daily on days 1 through 5 (n = 47). The primary objective of the study was detection of a confirmed PSA response, defined as a ≥50% decline in post-therapy PSA levels compared with baseline. A higher proportion of patients treated with ixabepilone plus estramustine had a PSA response than did patients receiving single-agent ixabepilone (69% versus 48%). The time to PSA progression was similar in both groups: 4.4 months (95% CI, 3.1–6.9 months) in the single-agent ixabepilone group and 5.2 months (95% CI, 4.5–6.8 months) in the combination therapy group. In patients with measurable disease, partial responses were observed in eight (32%) of 25 patients (95% CI, 14% to 50%) in the single-agent ixabepilone group and in 11 (48%) of 23 patients (95% CI, 27% to 68%) in the combination
therapy group. Negative bone scans were found in 78% and 60% of patients in the two groups, respectively. The most common toxic effects were neutropenia and neuropathy. Neuropathy occurred in 84% of patients but was tolerable (grade 1 or 2); grade 3 neuropathy occurred in 7%–13% of patients. Febrile neutropenia and thrombosis occurred at a higher rate in patients treated with combination therapy.

cross-resistance with taxanes

More recently, a retrospective analysis of second-line taxane-based therapy in patients who received first-line ixabepilone therapy has been reported. Evidence from preclinical and clinical studies indicates a lack of cross-resistance between the epothilones and the taxanes. To further examine the clinical cross-resistance of the taxanes and epothilones and determine the role of these agents in second-line therapy for patients with HRPC, Rosenberg et al. [24] retrospectively analyzed the efficacy of taxane therapy in a cohort of HRPC patients who had previously been treated with ixabepilone. For this analysis, 49 patients were identified who had received ixabepilone with estramustine (n = 28) or ixabepilone alone (n = 21) and who had subsequently received second-line taxane-based chemotherapy. Of these patients, the majority (79%) received docetaxel plus estramustine or docetaxel monotherapy as second-line treatment. A PSA response was achieved by 51% of the patients treated with second-line taxane therapy. The median time to PSA progression with second-line taxane-based therapy was 4.6 months. Second-line PSA responses were achieved by 61% of the patients (95% CI, 42% to 78%) who achieved a first-line PSA response with ixabepilone, compared with only 33% of the patients (95% CI, 13% to 59%) who did not (P = 0.08). Patients who discontinued first-line ixabepilone treatment because of disease progression were less likely to achieve a PSA decline of ≥50% in response to second-line taxane-based therapy compared with patients who discontinued treatment because of toxicity or patient preference (36% versus 71%; P = 0.01). Although patients with ixabepilone-refractory disease were less likely to respond to second-line taxane chemotherapy, one-third of these patients did achieve a PSA response. The median survival time in this cohort was 10.7 months from the initiation of second-line taxane-based therapy. These findings indicate that the epothilones and taxanes are not cross-resistant and may be useful when administered in tandem.

ongoing studies

A phase II study sponsored by the ECOG (E3803) is currently investigating a weekly schedule of ixabepilone in patients with metastatic HRPC. A total of 69 patients who were chemotherapy naive (n = 32) or had prior exposure to taxane (n = 37) have been enrolled [25]. Patients were treated with i.v. ixabepilone 20 mg/m² weekly ×3 in 4-week cycles. The primary objective of the study is to detect a 50% PSA reduction using consensus criteria in at least 50% (91% power, α = 0.10) of chemotherapy-naive patients and 30% (90% power, α = 0.10) of prior taxane-treated patients. At the time of reporting, median follow-up was 1.8 and 4.1 months for chemotherapy-naive and prior taxane exposure groups, respectively. Neutropenia, neuropathy, and fatigue were the most common clinically significant toxic effects, with grade 3/4 neutropenia occurring in 10 patients (five chemotherapy-naive, five prior taxane-treated), grade 3/4 neuropathy occurring in seven patients (two chemotherapy-naive, five prior taxane-treated), and grade 3 fatigue occurring in eight patients (three chemotherapy-naive, five prior taxane-treated). Of note, grade 3 diarrhea occurred in five patients (four chemotherapy-naive, one prior taxane-treated). Myelosuppression appeared to be improved, as compared to historical data, with the every-3-weeks schedule, using this dose and schedule. At the time of reporting, PSA and objective responses have been observed, but no conclusions have been drawn regarding the activity of ixabepilone in the first- or second-line setting, as the response assessment is ongoing.

A second multicenter trial, sponsored by the National Cancer Institute, is examining the use of second-line ixabepilone versus mitoxantrone plus prednisolone in patients with metastatic disease and progressive disease after taxane therapy. The primary objective of this phase I trial is to assess the safety and MTD of ixabepilone and mitoxantrone when given together with prednisone. The phase II part of the study will assess the efficacy of this regimen, as measured by a reduction in PSA level, in patients with metastatic HRPC. During the phase II study, cohorts of three to six patients receive escalating doses of mitoxantrone given over 30 min, ixabepilone given as a 3-h infusion on day 1, and oral prednisone administered twice daily on days 1 through 21. Treatment is repeated every 21 days for at least three courses in the absence of disease progression or unacceptable toxicity. The target enrollment for the study is 94 patients. During the phase II study, patients will receive mitoxantrone, ixabepilone, and prednisone at the MTD determined in phase I. PSA response will be assessed every 3 months. A third phase II study is evaluating the safety and efficacy of ZK-epothilone, a novel third-generation derivative of epothilone B, given with prednisone to patients with androgen-independent prostate cancer.

conclusion

Although phase II trials of the epothilones are ongoing, ixabepilone and patupilone have thus far provided the most convincing data regarding activity in patients with HRPC, including no cross-resistance with the taxanes. Therefore, the logical next step will be to pursue definitive phase III trials to confirm the activity of the epothilones in tandem with docetaxel, given the clinical findings to date. Such trials will lay the foundation for defining the role of the epothilones in the first- and second-line settings in HRPC. The distinct toxicity profiles of each of these drugs will probably influence their future development and their use in combination therapy with existing chemotherapy regimens.

disclosures

NAD has reported no financial relationships with companies whose products are mentioned in this supplement.


22. Lin AM, Rosenberg JE, Weinberg VK. Clinical outcome of taxane-resistant (TR) hormone refractory prostate cancer (HPRC) patients (pts) treated with subsequent chemotherapy (ixabepilone (Ix) or mitoxantrone/prednisone (MP)). Proc Am Soc Clin Oncol 2006; 24 (Suppl): 231s (Abstr 4558).

