Pilot study of epothilone B analog (BMS-247550) and estramustine phosphate in patients with progressive metastatic prostate cancer following castration

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Background: Several trials have demonstrated that the response proportions to microtubule agents in patients with prostate cancer are increased by the addition of estramustine phosphate (EMP). The epothilone B analog BMS-247550 is a novel microtubule agent that has shown activity in taxane-resistant tumors. We conducted a dose-escalation study to determine a safe dose of BMS-247550 to combine with EMP in patients with metastatic prostate cancer.

Patients and methods: Chemotherapy-naive patients with castrate-metastatic prostate cancer were treated with intravenous BMS-247550 and oral EMP (280 mg three times daily for 5 days) every 3 weeks.

Results: Thirteen patients were treated at two dose levels (35 and 40 mg/m²). Three of six patients treated at 40 mg/m² developed grade 4 neutropenia, establishing 35 mg/m² as the maximum-tolerated dose. Significant peripheral neuropathy (grade ≥ 2) was related to dose level and infusion rate. A decline in prostate-specific antigen (PSA) of ≥50% was seen in 11 of 12 evaluable patients (92%) (95% confidence interval 76% to 100%). There were objective responses in soft tissue (57%) and bone metastasis (40%).

Conclusions: The phase II dose of BMS-247550 combined with EMP is 35 mg/m² over 3 h every 3 weeks. This combination is safe and ≥50% post-therapy declines in PSA were seen in 11 of 12 patients (92%).

Key words: clinical trial, epothilone, estramustine phosphate, prostatic neoplasms

Introduction

The paradigm characterizing castrate-metastatic prostate cancer as a chemotherapy-resistant tumor has changed since the observation that cytoskeletal targeting agents induce significant antitumor effects. Drugs such as vinblastine, paclitaxel and docetaxel have modest activity when given as monotherapy in patients with castrate-metastatic disease, with <30% of cases showing an objective and biochemical response [1–3]. Combined with estramustine phosphate (EMP), response proportions increase to 50–68% [4–8]. These observations are confirmed by two randomized studies comparing vinblastine or paclitaxel with or without EMP. In both trials, the combinations proved superior with respect to time to progression and post-therapy prostate-specific antigen (PSA) decline [9], with a trend towards a survival benefit [10, 11]. These studies have demonstrated that EMP is at least additive to other microtubule agents and further development schema with novel microtubule drugs should consider early combination studies with EMP.

The epothilones A and B form a new class of cytotoxic agents, obtained by the fermentation broth of the myxobacterium Sorangium cellulosum [12], with antineoplastic activity against a range of tumors insensitive or resistant to paclitaxel [13]. Their mechanism of action is similar to that of paclitaxel: microtubular stabilization resulting in mitotic arrest at the G2/M transition [14]. Antitumor effects have been observed in vitro [15] and in vivo [16]. BMS-247550, an epothilone B analog, was developed to optimize the antitumor efficacy and therapeutic index of this chemical class [13]. In phase I studies, BMS-247550 has shown acceptable toxicity and clinical activity in patients with taxane-refractory malignancies [17].

To rapidly develop this class of microtubule drugs in prostate cancer, we designed a two-step program. The initial phase included a dose-escalation study to evaluate a safe combination of BMS-247550 and EMP. Once a safe dose was established, a multicenter randomized phase II trial was designed to test the safety and clinical activity of BMS-247550 with and without EMP. This report summarizes the results of the dose-escalation phase.
Patients and methods

Patient eligibility and evaluation

Patients with histologically proven adenocarcinoma of the prostate that progressed after castration (androgen-independent) and who had not received prior chemotherapy were eligible for enrollment. Progressive castrate disease was defined as serum testosterone of ≤30 ng/ml and one of the following: a minimum of three consecutive rises in PSA (with the last value ≥4 ng/ml); new metastatic lesion on bone scan; and/or new or progressive soft tissue masses on a computed tomography (CT) scan or magnetic resonance image (MRI). Patients were required to have progressive disease after discontinuation of an antiandrogen or megestrol acetate. Those who did not undergo orchectomy were required to continue medical castration with a gonadotropin-releasing hormone analog. Additional eligibility criteria required patients to be ≥18 years of age, with a Karnofsky performance status ≥70%, and adequate hematological function [white blood count ≥3000/µl, absolute neutrophil count (ANC) ≥1500/µl; platelet count ≥100000/µl], hepatic function (bilirubin level within normal limits, aspartate aminotransferase (AST) and alanine aminotransferase ≤2.5 x upper limit of normal (ULN)], and renal function (serum creatinine level ≤1.5 x ULN). No more than one course of prior palliative radiation therapy and no prior radioisotope therapy with strontium-89 or samarium-153 were allowed. Patients with known brain metastases or concurrent active malignancy other than non-melanoma skin cancer were excluded. Other exclusion criteria included significant heart disease, bleeding disorder or recent gastrointestinal bleeding that would preclude anticoagulation, history of hemorrhagic or thrombotic cerebral vascular accident, deep venous thrombosis or pulmonary embolism within 6 months before starting therapy. Patients with a history of allergic reactions to compounds of similar composition to the epothilones were not eligible. Patients had to discontinue all alternative (PC-Spes, Saw Palmetto, etc.) and could not start to the epothilones were not eligible. Patients had to discontinue all alternative (PC-Spes, Saw Palmetto, etc.) and could not start bisphosphonate therapy immediately before or during the study. The protocol was approved by the institutional review board and written informed consent was obtained before study entry.

The following radiological studies were carried out within 4 weeks of starting therapy: chest radiograph, CT scan or MRI of the abdomen and pelvis, and radionuclide bone scan. During the study, patients underwent a weekly complete blood count. A prothrombin time was done weekly in the first cycle then every 3 weeks thereafter. The comprehensive profile and tumor markers (PSA/acid phosphatase) were repeated every 6 weeks. Measurable disease, when present, was re-evaluated every 12 weeks (four cycles) and patients with osseous metastases had a bone scan repeated every 12 weeks (four cycles).

Design of the study

The primary objective of the study was to determine the maximum-tolerated dose (MTD) of BMS-247550 when given in combination with EMP every 3 weeks. Four BMS-247550 levels were initially planned: 35, 40, 45 and 50 mg/m². No intra-patient dose escalation was permitted. Three patients per complete blood count. A prothrombin time was done weekly in the first cycle concurrent active malignancy other than non-melanoma skin cancer were provided by CTEP.

Treatment

BMS-247550 is manufactured by Bristol-Myers Squibb (New York, NY) and was provided by CTEP.

Chemotherapy was given in an outpatient setting. Patients received EMP 280 mg orally three times daily on days 1–5. The 5-day schedule was chosen to minimize EMP-related toxicities while maximizing interaction between both drugs [8]. On day 2, BMS-247550, supplied as a white to off-white color, whole or fragmented cake, was diluted in Lactated Ringer’s to a final concentration ranging from 0.1 to 0.6 mg/ml in a non-polyvinyl chloride container. BMS-247550 is formulated in polyoxyethylated castor oil (Cremophor®EL), which can cause a hypersensitivity reaction during infusion. Therefore, 1 h before administration all patients received diphenhydramine 50 mg and ranitidine 150 mg orally. Premedication with steroids was not indicated unless patients developed a grade ≥2 hypersensitivity reaction with a prior administration.

Based on emerging data in other microtubule agents that neuropathy may be related more to peak concentration than to the overall area under the plasma concentration versus time curve, the infusion was prolonged from 1 to 3 h. Warfarin 2 mg orally was given daily as thromboembolic prophylaxis.

Patients received subsequent cycles of therapy approximately every 21 days if ANC was ≥1500/mm³, platelets were ≥100 000/mm³ and treatment-related non-hematological toxicity had resolved to baseline or grade ≤1 (except fatigue or alopecia grade 2). If these criteria were not met, treatment was delayed a maximum of 3 weeks. The dose of BMS-247550 was reduced by 5 mg/m² on subsequent cycles for: (i) grade 4 neutropenia ≥7 days; (ii) febrile neutropenia; (iii) grade ≥3 thrombocytopenia; (iv) >1 week delay in retreatment due to drug toxicity; (v) grade 3 nausea/vomiting or diarrhea; and (vi) grade 2 neuropathy (motor or sensory) lasting ≥7 days or grade 3 neuropathy lasting ≤7 days. EMP was withheld in case of: (i) grade ≥2 nausea/vomiting; (ii) grade ≥2 diarrhea; and (iii) bilirubin elevation of ≥1.5 x ULN or AST elevation of ≥5 x ULN. EMP was reintroduced with a 50% dose reduction (140 mg orally three times daily) after the toxicity resolved. If patients could not tolerate EMP, this could be discontinued and the patient could continue BMS-247550 alone. In the case of deep venous thrombosis, full anticoagulation was instituted and patients continued EMP at the investigator’s discretion. However, in the case of pulmonary embolism or acute myocardial infarction, discontinuation of EMP was indicated.

Response evaluation

Outcomes were assessed independently using CT or MRI, radionuclide bone scans and post-therapy changes in serum PSA [18]. For measurable disease, the Response Evaluation Criteria in Solid Tumors guidelines [19] were used and radiographs reviewed independently, with the reviewer (L. S.) blinded to clinical outcome. All bone scans were reviewed independently, with the reviewer (T. Akerlund) blinded to clinical outcome. Bone scans were classified as stable/improved versus progression. A stable/improved bone scan required no new lesions or new pain in an area previously visualized, and progression signified new areas of focal uptake.

PSA levels were measured every 3 weeks. Post-therapy declines in PSA were reported based on the degree of change from baseline: normalization, ≥80% and ≥50%, confirmed by three successive evaluations at least 2 weeks apart. Post-therapy declines of <50% were reported as stable. PSA progression was defined as three consecutive increases in PSA from nadir or baseline, each measurement at least 2 weeks apart. Time to PSA progression was calculated from start of therapy to the time of the first PSA rise after the nadir confirmed by two consecutive PSA rises, at least 2 weeks apart.

Results

Patient characteristics

Thirteen patients were accrued to this study; their clinical characteristics are summarized in Table 1. One patient in the 35 mg/m² cohort was not assessable for response because he developed an allergic reaction to the first infusion of BMS-247550 and was not
Sixty cycles of chemotherapy were delivered in 12 patients, with a median of five cycles per patient (range two to seven cycles). One patient was unable to complete the first cycle because of an allergic reaction to the initial BMS-247550 infusion.

**Hematological.** Anemia was present in the majority of the patients (92%), but only grade 1 or 2. Grade 3 or 4 neutropenia or leukopenia was documented in four patients (31%), three of them in the 40 mg/m² cohort, but were short in duration (<7 days). No case of febrile neutropenia was observed. Grade 1 thrombocytopenia occurred in nine patients (69%), six in the 35 mg/m² cohort and three in the 40 mg/m² cohort.

**Gastrointestinal.** Five patients (38%) had grade ≤2 diarrhea but only two were clinically significant (grade 2). Grade 3 nausea developed in two patients (15%) and required dose reduction of EMP.

**Cardiovascular.** Edema in the lower extremities was observed in five patients (39%). Two patients (15%) presented with thromboembolic events. The first patient developed a thrombus of the left popliteal vein. The second patient had a left internal jugular vein thrombosis, preceded by a left arm cellulitis and associated with progressive soft tissue disease in the left supraclavicular fossa. Both patients recovered after anticoagulation and treatment was discontinued based on progressive disease.

**Neurological.** Eight patients (62%) developed sensory neuropathy, which was clinically significant (grade >2) in six patients (46%) (Table 3). The sensory neuropathy presented primarily with paresthesias in the feet and progressed to numbness, paresthesias and a burning sensation in the hands and feet in the more severe cases. This occurred after a median of five cycles (range three to six cycles) and presented in two patients at 35 mg/m² and in four at 40 mg/m². With respect to infusion duration, grade 2 neuropathy developed in three patients who received at least one cycle of 1-h BMS-247550 infusion and in one patient who received only 3-h infusions, whereas both cases of grade 3 neuropathy occurred in patients treated with 1-h infusions only (Figure 1). Of the six patients with grade ≥2 neuropathy, this had resolved in two patients (grade 2 to grade 0 in both), improved in two patients (grade 3 to grade 2 in both) and stabilized (at grade 2) in two patients at last follow-up (median of 40 weeks since the last infusion of BMS-247550, range 15–55 weeks).

**Dose adjustments and termination of therapy**

The dose of BMS-247550 was attenuated in four patients (31%). In one patient, treated at 35 mg/m², the dose was reduced secondary to seven cycles). One patient was unable to complete the first cycle because of an allergic reaction to the initial BMS-247550 infusion.
to neuropathy. The dose was reduced in the other three patients, treated at 40 mg/m²; for grade 3 nausea, prolonged fatigue and neuropathy. The dose of EMP was decreased by 50% in two patients due to nausea. Four patients (31%) had treatment delays of ≥ 1 week secondary to toxicity. One patient, treated at 35 mg/m², had a treatment delay secondary to neuropathy. Reasons for treatment delay in the other three patients, treated at 40 mg/m², were fatigue (two patients) and neuropathy (one patient).

All 12 patients treated with more than one cycle of BMS-247550 in combination with EMP have discontinued treatment on the protocol. Reasons for termination of therapy are presented in Table 4. Progressive disease during treatment occurred in five patients while seven (58%) discontinued treatment secondary to toxicity. Of those, six had grade 2 or 3 neuropathy as limiting toxicity. The median duration of treatment was 13 weeks (range 4–16) for patients ceasing treatment due to toxicity and 20 weeks (range 11–27) for patients discontinuing treatment due to disease progression.

Clinical outcomes

Twelve patients were evaluable for antitumor effect (Table 5). A PSA reduction of >50% was seen in 11 patients (92%) [95% con-
All five patients (42%; 95% CI 14% to 70%) with a PSA reduction of >80% also had a PSA normalization (<4 ng/ml). Median time to PSA nadir was 13 weeks (range 3–22) and median time to PSA progression was 19 weeks (range 4–26). In seven patients with measurable disease at baseline, one (14%) had a complete response, three (43%) had a partial response, one (14%) had stable disease and one (14%) had progression of disease. One additional patient had new hepatic metastasis in the setting of PSA decline, a significant reduction in a rectal mass and stable cervical adenopathy after four cycles of therapy. A fine-needle aspiration of the liver revealed adenocarcinoma that was histologically different from his prostate carcinoma with a negative immunostain to PSA. This was felt to represent a second malignancy of gastrointestinal origin. Ten patients had osseous metastasis at baseline. Three patients were not evaluable for bone-scan response, two patients did not have follow-up scans, while another had progressive metastatic disease of non-prostate origin; four patients (40%) had stable/improved scans and three patients (30%) had worsening bone scans, in the setting of PSA decline of >50%, indicating a bone flare reaction.
Three patients have received taxane-based chemotherapy after discontinuation of BMS-247550/EMP. A patient with progressive disease after three cycles of BMS-247550/EMP has achieved a >80% reduction in PSA after receiving paclitaxel/EMP/carboplatin. After six cycles of BMS-247550/EMP, a second patient, treated with docetaxel/EMP, has had a PSA decline of 40%. The third patient has had a >80% reduction of his PSA after receiving docetaxel/EMP. However, this patient did not complete the first cycle of BMS-247550 due to an allergic reaction.

Discussion

The safe dose of BMS-247550 to combine with EMP in patients with castrate-metastatic prostate cancer is 35 mg/m² infused over 3 h every 3 weeks. Myelosuppression observed at higher doses, although transient, was consistent with other trials with BMS-247550. Since ≤50% post-treatment declines in PSA were observed in all patients at 35 mg/m² and experience from the taxanes indicates response proportions do not increase with dose [20], it was decided that the dose should not be escalated to the DLT.

In general, patients treated at 35 mg/m² had tolerable side-effects. An allergic reaction to BMS-247550 was observed in only one patient. Premedication with H1 and H2 receptor anti-histamines proved effective, sparing the use of corticosteroids, which have side-effects and can complicate the interpretation of clinical outcomes in patients with castrate prostate cancer [21–23].

Significant (grade ≥2) neurotoxicity was observed and was the reason for treatment discontinuation in six patients (46%). Given the small number of patients treated on this trial, the incidence of neurotoxicity at the 35 mg/m² dose level and tolerability of prolonged exposure to this agent requires further characterization. Clearly, this information is crucial to establishing the ultimate clinical utility of this regimen and is currently being explored in a large phase II trial. The peripheral neuropathy has resolved in two patients, improved in two patients, and stabilized in two patients after cessation of treatment.

To minimize the neuropathy, the duration of infusion was increased from 1 to 3 h based on a report by Smith et al. [24] demonstrating that less neuropathy occurred with a prolonged infusion of paclitaxel when compared with a shorter infusion. When neuropathy was analyzed by the BMS-247550 infusion duration in the present study, no grade 3 neuropathy was seen in patients treated over 3 h. However, given the limited number of patients and lack of pharmacokinetic data, this relationship between BMS-247550 infusion duration and neuropathy is speculative and requires confirmation. Similarly, while there appeared to be less neuropathy with 35 mg/m² compared with 40 mg/m², the small number of patients treated precludes establishing a significant difference in neurotoxicity between these groups.

Both post-treatment declines in PSA and improvements in measurable disease were noted with this regimen. Ninety-two percent (95% CI 76% to 100%) of patients had a post-therapy PSA decline of >50%; 46% had measurable disease regression and improvement in osseous disease was also documented. However, the median time to PSA progression of 19 weeks was similar to EMP/taxane-based regimens [5, 7, 8]. Notably, patients have responded to EMP/taxane-based regimens, after treatment with

<table>
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<th>Table 5. Clinical outcomes</th>
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<tr>
<td>PSA decline (n = 12)</td>
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<tr>
<td>&lt;50% (stable PSA)</td>
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<td>n = 1 (8%)</td>
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<td>≥50%</td>
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<td>n = 11 (92%; 95% CI 76% to 100%)</td>
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<td>PSA &lt;4.0 ng/ml</td>
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<td>n = 5 (42%; 95% CI (14% to 70%)</td>
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<td>Time to PSA nadir, weeks (range)</td>
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<td>13 (3–22)</td>
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<td>Time to PSA progression, weeks (range)</td>
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<td>19 (4–26)</td>
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<tr>
<td>Measurable disease (n = 7)</td>
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<td>Complete response</td>
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<td>n = 1 (14%)</td>
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<td>Partial response</td>
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<td>n = 3 (43%)</td>
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<td>Stable disease</td>
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<td>n = 1 (14%)</td>
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<td>Progression of disease</td>
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<td>n = 1 (14%)</td>
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<td>Bone metastases (n = 10)</td>
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<td>Stable or improved</td>
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<td>n = 4 (40%)</td>
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<td>Worsening</td>
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<td>n = 3 (30%)</td>
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<td>Not evaluable</td>
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*aComputed tomography scan revealing resolution of retroperitoneal lymphadenopathy and stable lytic bone lesion. Stable findings on bone scan.

*bNew metastatic liver disease of different malignancy.

*cFollow-up bone scans not available or presence of a progressive different malignancy.

CI, confidence interval; PSA, prostate-specific antigen.
BMS-247550/EMP, indicating a possible non-cross-resistant mechanism of action. Although conclusions regarding efficacy are limited by the phase I design and small number of patients, the minimum proportion of patients who achieved a ≥50% post-therapy decline in PSA was 76% (lower limit of CI). This would suggest that further clinical testing is warranted, and this combination has proceeded into a randomized multicenter phase II trial to evaluate the safety and efficacy of BMS-247550 with and without EMP. The randomized portion is not intended to compare the arms but to determine the activity of BMS-247550, and the added benefit and morbidity of EMP, in a larger homogeneous population. This approach will help decrease the inherent single-center patient selection bias, further evaluate the tolerability of BMS-247550, allow us to estimate better the confidence intervals for the clinical outcomes and ultimately expedite the drug development process of BMS-247550 in prostate cancer.

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References