Phase I Clinical and Pharmacokinetic Study of BMS-247550, a Novel Derivative of Epothilone B, in Solid Tumors

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ABSTRACT

Purpose: The purpose of this study was to determine the maximum tolerated dose, toxicity, and pharmacokinetics of BMS-247550 administered as a 1-h i.v. infusion every 3 weeks.

Experimental Design: Patients with advanced solid malignancies were premedicated and treated with escalating doses of BMS-247550. Blood sampling was performed to characterize the pharmacodynamics and pharmacokinetics of BMS-247550.

Results: Twenty-five patients were treated at six dose levels ranging from 7.4 to 59.2 mg/m². At 50 mg/m², 4 of 9 patients (44.4%) had dose-limiting toxicity (neutropenia, abdominal pain/nausea). At 40 mg/m² (the recommended Phase II dose), 2 of 12 patients (16.7%) had dose-limiting neutropenia. Overall, the most common nonhematological toxicity was fatigue/generalized weakness (grade 3–4 seen in 9.0% of patients), followed by neurosensory deficits manifested as peripheral neuropathy and by gastrointestinal discomfort. At 40 mg/m², the incidence of grade 3 fatigue, abdominal pain, diarrhea, and neuropathy was 7.7%. Grade 1–2 neuropathy was observed in all patients enrolled and treated at 40 mg/m². Two patients with paclitaxel-refractory ovarian cancer, one patient with taxane-naïve breast cancer, and another patient with docetaxel-refractory breast cancer had objective partial responses (lasting 6.0, 5.3, 3.0, and 4.5 months, respectively). The mean pharmacokinetic parameter values during course 1 for clearance, volume of distribution, and apparent terminal elimination half-life at the 40 mg/m² (recommended Phase II dose) dose level were 21 liters/h/m², 826 liters/m², and 35 h (excluding one outlier of 516 h), respectively. Values during course 1 and course 2 were similar.

Conclusions: The recommended dose for Phase II evaluation of BMS-247550 is 40 mg/m², although more long-term observations are needed. BMS-247550 has advantages over taxanes in relation to drug resistance and warrants further study.

INTRODUCTION

Microtubules are an established target for antitumor drug development. Paclitaxel, the prototypical microtubule-stabilizing agent, has an established role in the treatment of solid tumors; however, its efficacy is limited by the development of drug resistance (1, 2). Although taxane analogs are being evaluated in the clinic, non-taxane natural products may be effective alternatives (3). The best-characterized non-taxane compounds are the epothilones, originally derived from a fermentation broth of the soil myxobacterium, Sorangium cellulosum (4). Total biosynthesis of a number of epothilones has been accomplished (5–7).

Epothilone B is a potent antiproliferative agent with in vivo antitumor activity in paclitaxel-resistant tumor models. The drug is currently in clinical trials (8, 9). BMS-247550 (Bristol-Myers Squibb, Wallingford, CT; Fig. 1) is a semisynthetic analog of epothilone B that is metabolically more stable than its parent compound due in part to the substitution of the epothilone B lactone with a lactam, thereby reducing its metabolism by carboxylesterase. BMS-247550 produces tumor regressions in a variety of human xenografts and syngeneic mouse models including ones that are paclitaxel resistant (10, 11). Preclinical toxicology revealed that BMS-247550 caused myelosuppression and neuropathy, as expected for a microtubule-interacting drug. Preclinical evidence of in vivo efficacy in various human tumor models demonstrated greater log cell kill using less frequent dosing schedules (e.g., every 2 days ×5 versus every 4 days ×3; Ref. 10). Furthermore, experience with microtubule-stabilizing drugs (e.g., docetaxel and paclitaxel) suggested that 1-h infusion schedules were practical and well tolerated (11). Therefore, the decision was made to administer the drug in this initial Phase I trial as a 1-h i.v. infusion every 3 weeks.

The aims of this study were to determine the maximum tolerated dose (MTD), the recommended Phase II dose (RPTD), and the toxicities associated with BMS-247550 administered as
a 1-h i.v. infusion every 3 weeks to patients with advanced solid tumors. Because peripheral neuropathy was observed in preclinical models, noninvasive instruments were used to quantitatively characterize peripheral (median) nerve function. In addition, we have characterized the pharmacological profile of the parent compound and described preliminary evidence of antitumor activity in taxane-refractory human tumors.

PATIENTS AND METHODS

Eligibility. Patients included adults $\geq$18 years with histological evidence of advanced solid tumors that were clinically refractory to conventional treatment or for which there was no standard treatment. Other criteria included an Eastern Cooperative Oncology Group performance status of 0-2; chemotherapy or radiation at least 3 weeks before study entry; adequate hematopoietic reserves defined by absolute neutrophil count (ANC) $\geq$ 1,500/$\mu$L, platelet count $\geq$ 100,000/$\mu$L, and hemoglobin $\geq$ 9 g/dl; total bilirubin within institutional normal limits; aspartate aminotransferase and alanine aminotransferase $\leq$ 3.0x the upper limit of institutional normal; and creatinine $\leq$ 2.0 mg/dl. Patients were excluded from study entry if they had received more than three prior chemotherapy regimens for metastatic disease, had evidence of grade 1 neuropathy or tumor metastases to the brain, or had recently exacerbated or uncontrollable medical or surgical illness. Patients were excluded if they were pregnant or nursing a child or demonstrated a history of allergy or hypersensitivity to paclitaxel or other therapies containing polyoxyethylated castor oil or intolerance to premedication. Before beginning therapy, all patients gave written informed consent for study participation according to federal and institutional guidelines.

Dosage and Drug Administration. BMS-247550 for injection (10 mg/vial lyophilized cake) was supplied by Bristol-Myers Squibb and provided by the National Cancer Institute (Bethesda, MD). BMS-247550 was diluted in an ethanol USP + polyoxyethylated castor oil mixture (1:1 by volume) to achieve a final concentration of approximately 2 mg/ml. The appropriate volume was withdrawn by syringe and mixed with Lactated Ringer’s Injection to produce the final desired concentration of BMS-247550. To minimize patient exposure to di-(2-ethylhexyl) phthalate, which may be leached from polyvinyl chloride infusion bags, diluted BMS-247550 solutions were stored in bottles (glass or polypropylene) or plastic bags (polypropylene or polylefin) and administered through polyethylene lines.

BMS-247550 was administered i.v. over 1 h at a starting dose of 7.4 mg/m² (representing one-tenth the 10% severe toxic dose in rats and a tolerable dose in dogs) with hypersensitivity prophylaxis repeated every 21 days (one course). Hypersensitivity prophylaxis consisted of dexamethasone (20 mg) administered orally (or its equivalent), 12 and 6 h before BMS-247550; diphenhydramine (50 mg, i.v.) or its equivalent; and cimetidine (300 mg, i.v.) or ranitidine (50 mg, i.v.) 30 min before BMS-247550 administration. The total dose delivered was rounded to the nearest milligram. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. The National Cancer Institute’s accelerated titration design with intrapatient dose escalation (design 4B) was used initially to accrue patients into the dose cohorts (12). At any dose level, the last patient entered was observed for at least 3 weeks before new patients were entered on the next dose level. Retreatment in subsequent courses was initiated only after the ANC recovered to at least 1,500/$\mu$L, the platelet count recovered to at least 100,000/$\mu$L, and all other toxicities had resolved to either pretreatment grade or grade 1 or less. A modification of the published dose increments described in design 4B is shown in Table 1 (12). This deviation from the published version of design 4B was based on evolving data from other Phase I studies of BMS-247550 that described a narrow therapeutic index and a steep dose-toxicity relationship near the MTD (13).

The MTD was defined as the dose level at which at least 33% of six patients experienced dose-limiting toxicity (DLT) in the first course. The recommended Phase II dose was defined as one dose level below the MTD. Patients who experienced DLT could continue to receive BMS-247550 after dose reduction by one level. DLT was defined as grade 3 or greater neuropathy that did not resolve before initiation of the next cycle of therapy; grade 3 or greater nausea and/or vomiting that occurred despite maximal antiemetic therapy; grade 3 or greater diarrhea that did not resolve before initiation of the next cycle of therapy; grade 3 or greater febrile neutropenia, sepsis with neutropenia, or recurrent grade 1 neuropathy.

Pretreatment and Follow-Up Studies. History, physical examination, and routine laboratory tests including complete blood counts were performed before treatment and weekly once treatment began. A standard serum chemistry panel including lactate dehydrogenase, transaminases (aspartate aminotransferase and alanine aminotransferase), bilirubin and kidney function (blood urea nitrogen and creatinine) tests were obtained pretreatment and on day 14 of each treatment cycle. Pretreatment studies also included chest radiographs and computed tomography scans to evaluate all sites of disease. Computed tomography scans were repeated every 6 weeks (or after two courses of therapy) to assess response. Patients were able to continue treatment if they did not have progressive disease. Objective antitumor response assessments were ascertained.
using previously published criteria (14). Toxicity assessments were performed weekly in the clinic.

**Neurological Assessments.** Vibration perception threshold (VPT), distal motor latency (DML), and F-wave latency values were obtained at baseline and at the end of every two courses of therapy until disease progression or onset of intolerable toxicity. The same measurements were also obtained at 8 weeks after the discontinuation of drug. VPT is an assessment of the strength and quality of the vibration sense and is measured in the upper extremities by an instrument capable of altering vibration frequencies. The lowest vibration frequency sensed accurately by the patient is termed the VPT (15). DML is the interval between the stimulus and the onset of the compound muscle action potential in the thenar muscles. F-wave latency is the median interval between the stimulus and the onset of an action potential in the thenar muscle resulting from antidromic activation of motor neurons in the spinal cord. These parameters were measured in the median nerve using NC-Stat (Neurometrix, Inc., Boston, MA), which has a 90% sensitivity and specificity in detecting median nerve entrapment or systemic neuropathies. NC-Stat is noninvasive and requires less than 5 min to set up and use (16–21). Detailed neurological assessments using these techniques have been reported in other studies of peripheral neuropathy (15–26).

**Plasma Sampling and Analytical Assay.** Whole blood (7 ml) was obtained before the start of drug infusion and at 0.5, 1 (just before the end of infusion), 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 24, 48, and 72 h after the start of infusion. Within 30 min of collection, plasma was separated by centrifugation at 2000 × g for 5 min at 0°C–5°C. Plasma samples were stored at −80°C until analysis. Concentrations of BMS-247550, BMS-326412 (an inactive chemical degradant of BMS-247550 formed in solution), and BMS-249798 (an intermediate in the degradation of BMS-247550 to BMS-326412) were measured by a validated assay at Bristol-Myers Squibb (New Brunswick, NJ). After addition of an internal standard (BMS-212188) to 0.2 ml of each study sample, calibration standard, and quality control sample, the samples were precipitated with acetone. The supernatant was extracted with 1-chlorobutane, and the organic layer was removed and evaporated to dryness. The residue was reconstituted and injected into a YMC ODS-AQ column (4.6 × 50 mm; YMC, Wilmington, NC). Chromatographic separation was achieved isocratically at a flow rate of 0.3 ml/min with detection by electrospray tandem mass spectrometry using a Quattro LC mass spectrometer (Micromass, Beverly, NJ). The mobile phase contained acetonitrile:0.01 M ammonium acetate (pH 5.0: 65:35). The retention times were 2.2 min for BMS-326412, 2.5 min for BMS-249798, 2.9 min for BMS-247550, and 4.2 min for the internal standard. The standard curve, which ranged from 2 to 500 ng/ml for all analytes, was fitted to a 1/x weighted quadratic regression model. The within-run coefficients of variation of quality control samples for BMS-247550, BMS-326412, and BMS-249798 were within 10%, 11%, and 15%, respectively. The between-run coefficients of variation for quality control samples were within 10% for all compounds. Deviations of the predicted concentrations from nominal values for quality control samples were within 7% for all compounds.

**Pharmacokinetic and Pharmacodynamic Analyses.** Plasma concentration-time data of BMS-247550, BMS-249798 (Fig. 2A), and BMS-326412 (Fig. 2B; the latter two are inactive degradation products; Ref. 11) were analyzed by noncompartmental methods (25) using the PKMENUS application written in

![Fig. 2](https://clincancerres.aacrjournals.org/) Chemical structures of (A) BMS-249798 and (B) BMS-326412.
SAS version 6.12 (SAS, Cary, NC). The peak plasma concentration ($C_{\text{max}}$) and the time to reach maximal concentration ($T_{\text{max}}$) represent observed values. The area under the concentration-versus-time curve from time zero to the time of the last quantifiable concentration ($\text{AUC}_{\text{last}}$) was calculated using a combination of linear and log trapezoidal summations. The terminal phase slope of the plasma profile, $k$, was determined using unweighted log-linear regression of at least three data points. The AUC$_{0-t}$ was extrapolated to infinity ($\text{AUC}_{0-\infty}$) by dividing the last measurable concentration by the absolute value of $k$. The absolute value of $k$ was used to estimate the apparent terminal elimination half-life, $t_{1/2} = \ln 2/\text{absolute value of } k$. The total body clearance (Cl) was determined by dividing dose by AUC$_{0-\infty}$. The volume of distribution at steady-state ($V_{\text{ss}}$) was calculated using standard noncompartmental methods for an i.v. infusion (25). The relative extent of exposure to BMS-249798 or BMS-326412 was estimated as AUC$_{0-\infty}$ decomposition product/ AUC$_{0-\infty}$ BMS-247550 $\times$ 100%.

Simple linear regression analysis determined the relationship between renal function (BUN and serum creatinine), liver function (bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), and drug clearance. Intraindividual and interindividual kinetic variability was assessed with Wilcoxon matched pairs signed-rank test and the coefficient of variance, respectively. Statistical analysis was performed by the Analyze-it for Microsoft Excel statistical program (Analyze-it Software, Ltd., Leeds, United Kingdom). Relationships between measures of systemic exposure and toxicity (percentage change in neutrophil count from baseline and presence or absence of DLT) were evaluated using the nonlinear least squares regression program (GraphPad Prism Version 3.00). The relative hematological toxicity was calculated as follows: percentage of decrease in blood counts = (100% $\times$ [pretreatment count – nadir count]/pretreatment count). The nonparametric Mann-Whitney $U$ and the Kruskal-Wallis tests were used to compare pharmacokinetic parameters in patients with varying grades of toxicity.

RESULTS

General. Twenty-six patients were registered in this study (Tables 1 and 2). One patient withdrew consent and did not receive the study drug. Twenty-five patients (Table 1) were treated with 85 courses of BMS-247550 across 6 dose levels. The majority of patients were elderly with either breast or ovarian cancer and had good performance status on trial entry. All patients had received prior chemotherapy; 11 patients received prior taxane-based treatments; and 4 patients received concurrent radiation therapy. The median number of courses administered per patient was 4 (range, 1–8).

The dose escalation initially followed the accelerated titration scheme (design 4B) as proposed by Simon et al. (Table 1; Ref. 12). However, at a dose of 59.2 mg/m$^2$, one patient died, presumably due to sepsis on day 11, after receiving the first treatment. This, together with data presented from a trial also using the same every-3-week schedule (13), suggested that intolerable toxicities were being observed at a dose of 60 mg/m$^2$. Therefore, nine patients (eight heavily pretreated patients and one minimally pretreated patient) were enrolled at a dose of 50 mg/m$^2$. At this dose, four DLTs (two patients each with grade 4 neutropenia lasting $>5$ days, one patient with febrile neutropenia, and one patient with grade 3 abdominal pain/nausea and vomiting) were observed in course 1. A dose of 40 mg/m$^2$ was chosen because there were no major toxicities observed at 29.6 mg/m$^2$. Three patients were entered at 40 mg/m$^2$, and one patient had grade 4 neutropenia lasting $>5$ days as DLT in course 1, which resulted in expansion of this dose level to six patients. Only one of six patients (16.7%) treated at 40 mg/m$^2$ had a DLT during course 1, and, therefore, this dose level was considered the RPTD. To further assess toxicities at the RPTD, 6 additional patients were treated, bringing the total treated at 40 mg/m$^2$ to 12 patients. Only 2 of 12 patients (16.7%) experienced course 1 DLTs (grade 4 neutropenia lasting $>5$ days), and this dose was confirmed as the RPTD for future studies.

Six patients were treated at more than one dose level (Table 1). Two patients initially treated at 40 mg/m$^2$ were reduced to a dose level of 29.6 mg/m$^2$ due to DLT in course 2. Four patients initially treated at 50 mg/m$^2$ were reduced to a dose level of 29.6 mg/m$^2$ (three patients) and 40 mg/m$^2$ (one patient), respectively, due to DLT in course 2. Two of these four patients again received doses of 50 mg/m$^2$ in courses 3 and 4. Both patients also received G-CSF (filgastrim) with such treatment. Treatment delays by 5–10 days were experienced by three patients in course 2 (two patients) and course 3 (one patient).

Of the three deaths on study, one patient with metastatic endometrial cancer, who had previously received three chemotherapy regimens and whole pelvis radiation, received a BMS-247550 dose of 59.2 mg/m$^2$ as described previously. This patient had grade 2 fatigue, grade 1 nausea, vomiting, and diarrhea

<table>
<thead>
<tr>
<th>Table 2 Patient characteristics</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age (yrs)</td>
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<td>Range</td>
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<td>ECOG performance status</td>
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<td>Previous treatment</td>
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<td>Tumor type$^b$</td>
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</table>

$^a$ One patient registered to be treated at the 40 mg/m$^2$ dose level subsequently withdrew consent and did not receive drug treatment.

$^b$ ECOG, Eastern Cooperative Oncology Group.

$^c$ Adenocarcinoma unless otherwise stated.

$^d$ Includes one each of the following: nonfunctioning pancreatic islet cell tumor, melanoma, and uterine leiomyosarcoma.
Table 3 Hematological toxicity

A. Hematological toxicity: neutropenia

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients (courses)</th>
<th>ANC nadir (µl)</th>
<th>No. of patients with neutropenia (courses)</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 4 lasting &gt;5 days</th>
<th>Grade 4 with fever</th>
<th>DLT*</th>
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<tbody>
<tr>
<td>7.4</td>
<td>1 (2)</td>
<td>4210³</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14.8</td>
<td>1 (1)</td>
<td>2468²</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>29.6</td>
<td>6 (20)</td>
<td>1980</td>
<td>644–4769</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>59.2</td>
<td>1 (1)</td>
<td>1072²</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>50.0</td>
<td>9 (21)</td>
<td>2190</td>
<td>200–7104</td>
<td>0</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>40.0</td>
<td>13 (40)</td>
<td>2538</td>
<td>458–4200</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (2)</td>
<td>2</td>
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- *Dose-limiting toxicity (DLT) events summed for all courses administered.
- *Mean of cycle 1 and 2.
- *N/A, not applicable.
- *Cycle 1 nadir value. The 40 mg/m² dose cohort in this table includes the one patient enrolled but not treated with study drug.

on day 7 of the first course and subsequently died suddenly on day 11. The cause of death was listed as an acute pulmonary event or pneumonia. The other patient with metastatic pancreatic cancer who had received prior abdominal radiation therapy and three prior chemotherapy regimens received a BMS-247550 dose of 50 mg/m². On day 4 of course 1, this patient was admitted with neutropenic sepsis (grade 4 neutropenia, fever, and positive blood cultures) and died on day 7 due to sepsis. The third patient, who had metastatic breast cancer and had a chest wall minor response lasting 3 months on BMS-247550, was dosed at 40 mg/m² but slipped and fell at home and suffered a hip and lower leg fracture. This was then complicated by a presumed stroke 28 days after her last dose of BMS-247550. Subsequently, this patient suffered a grade 5 cardiac ventricular arrhythmia while recuperating in a nursing home. The cause of death was attributed to postfracture complications in the elderly and was unlikely to be due to the drug.

Hematological Toxicity. Myelosuppression, specifically neutropenia, was the principal DLT of BMS-247550 administered as a 1-h infusion every 3 weeks. At the MTD (50 mg/m²), three of four DLTs were related to neutropenia. Three patients had grade 4 neutropenia, and in two patients, neutropenia persisted for more than 5 days. The third patient with grade 4 neutropenia had a fever complicating the neutropenia that lasted <5 days, albeit with G-CSF support. At 40 mg/m², three and two patients had grade 3 and grade 4 neutropenia, respectively. However, two patients had neutropenic fever in course 1, and this constituted a DLT. The onset of neutropenia typically occurred between 10 and 14 days after treatment; the median time to nadir and recovery of neutrophil count (ANC > 1500/µl) was 14 (range, 3–28) days and 7 (range, 1–18) days, respectively. Due to rapid recovery of neutrophils, delays in treatment due to persistent neutropenia were infrequent. Neutropenia is clearly related to dose (Table 3), as demonstrated by a progressive decrease in the nadir neutrophil counts with an increase in the dose of BMS-247550 from 7.4 to 50 mg/m². Three courses delivered at 50 mg/m² were administered with G-CSF and excluded from the analysis.

Thrombocytopenia was a less frequent hematological toxicity. At the MTD (50 mg/m²), two patients (2 courses) who had grade 3 thrombocytopenia but did not require platelet transfusions recovered spontaneously. There were no bleeding episodes associated with thrombocytopenia. The onset of thrombocytopenia typically occurred between 10 and 14 days after treatment; the median time to nadir was ~14 days, and recovery (platelets > 100,000/ml) usually occurred within 7 days. Thrombocytopenia was less clearly associated with dose; however, in dose cohorts of 40 (n = 7 over 17 cycles) and 50 mg/m² (n = 11 over 21 cycles), the median platelet nadir was lower for the higher dose (Table 3B). The effects of BMS-247550 on the RBC count and hemoglobin content were minor. There was only one grade 3 and no grade 4 episodes of anemia, and no patients required blood transfusions.

Nonhematological Toxicity. Fatigue, “feeling drained,” or lethargy, the most common toxicity present in 14 (73.7%) patients, most often occurred within the first and second week of each treatment course. This toxicity usually resolved by the next treatment course within 21 days, except in two patients (50 mg/m² dose level) who required dose delays for up to 2 weeks for persistent grade 2 fatigue. Progressive fatigue developed in three patients (treated at the 40 and 50 mg/m² dose level) over 5 courses, suggesting that fatigue may be a cumulative toxicity
abdominal surgery was treated at 40 mg/m² and had bowel intestinal discomfort in course 1. One patient who had had prior treatment in course 3. Another patient treated at 50 mg/m² had grade 3 nausea/vomiting. Further treatment was not given due to disease progression; however, grade 3 toxicity persisted for 2 weeks off treatment, after which this patient was lost to follow-up. Interestingly, the median nerve DML increased progressively from baseline (3.9) to end of cycle 2 (4.2), and the VPT increased 2.3-fold from 2.0 units to 4.6 units at the end of study assessment. There was no change in the F-wave latency of the median nerve in this patient. In another patient, grade 1 neuropathy was documented after six courses of therapy. However, the VPT score increased from baseline (3.9) to end of cycle 2 (4.2), and the VPT increased 2.3-fold from 2.0 units to 4.6 units at the end of study assessment. There was no apparent increase in electrophysiological parameters from baseline overall, findings appeared to predict onset of clinical neuropathy in the following two patients. One patient, treated at 50 mg/m², manifested symptoms of neuropathy with each course of treatment. This patient had grade 1 neuropathy at baseline, which persisted in course 1, and grade 1 neuropathy was documented after six courses of therapy. The treatment was discontinued due to disease progression; however, grade 3 toxicity persisted for 2 weeks off treatment, after which this patient was lost to follow-up. Interestingly, the median nerve DML increased progressively from baseline (3.9) to end of cycle 2 (4.2), and the VPT increased 2.3-fold from 2.0 units to 4.6 units at the end of study assessment. There was no change in the F-wave latency of the median nerve in this patient. In another patient, grade 1 neuropathy was documented after six courses of treatment with no change in either median nerve DML or F-wave latency. However, the VPT score progressively increased 2.7-fold from baseline (0.9 unit) to a peak level at the end of cycle 4 (2.5 units) and remained elevated through course 6 (2.0 units).

**Peripheral Neuropathy.** Neurosensory deficits were characterized as paresthesia or dysesthesia and typically manifested in a symmetric, glove-and-stocking distribution. This occurred in 16 (64%) patients over 26 courses. In two courses, progressive grade 3 neuropathy resulted in termination of drug therapy. In two patients, neuropathy also included pain in the fingertips. Fifteen of the 16 patients (93.8%) had previously been treated with a chemotherapy agent known to be associated with peripheral neuropathy. Furthermore, 50% of these patients were either diabetic or had known glucose intolerance. Whereas the protocol excluded patients with > clinical grade 1 neuropathy, virtually all had described a “pins-and-needle” sensation associated with prior therapy.

Twenty-one patients had baseline electrophysiological assessments (four patients refused these tests). In patients who received ≥2 courses of therapy (n = 20), 12, 16, and 16 patients had baseline and course 2 F-wave latency, DML, and VPT scores available, respectively. There was no difference between baseline and course 2 F-wave (two-tailed P = 0.13), DML (P = 0.52), and VPT (P = 0.18). In patients who received ≥4 courses of therapy (n = 10), only six patients completed ≥4 course measurements. In these patients, there was no significant increase in either F-wave latency, DML or VPT.

Whereas there was no apparent increase in electrophysiological parameters from baseline overall, findings appeared to predict onset of clinical neuropathy in the following two patients. One patient, treated at 50 mg/m², manifested symptoms of neuropathy with each course of treatment. This patient had grade 1 neuropathy at baseline, which persisted in course 1, and in the third week of course 2 developed grade 2 neuropathy that escalated to grade 3 toxicity within 10 days. The treatment was discontinued due to disease progression; however, grade 3 toxicity persisted for 2 weeks off treatment, after which this patient was lost to follow-up. Interestingly, the median nerve DML increased progressively from baseline (3.9) to end of cycle 2 (4.2), and the VPT increased 2.3-fold from 2.0 units to 4.6 units at the end of study assessment. There was no change in the F-wave latency of the median nerve in this patient. In another patient, grade 1 neuropathy was documented after six courses of treatment with no change in either median nerve DML or F-wave latency. However, the VPT score progressively increased 2.7-fold from baseline (0.9 unit) to a peak level at the end of cycle 4 (2.5 units) and remained elevated through course 6 (2.0 units).

**Antitumor Activity.** Objective evidence of antitumor activity was observed in four patients. Two patients had minor responses. One patient, who had progressive metastatic melanoma documented while receiving biochemotherapy, had a minor response (20% overall tumor shrinkage; 70% shrinkage in in-transit lower extremity metastases) while receiving 40 mg/m²

### Table 4 Nonhematological toxicities of BMS-247550

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients (courses)</th>
<th>Fatigue/generalized weakness&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Neurotoxicity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>GI discomfort&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>1 (2)</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
<tr>
<td>14.1</td>
<td>1 (1)</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
<tr>
<td>29.6</td>
<td>6 (20)</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
<tr>
<td>59.2</td>
<td>1 (1)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
<tr>
<td>50.0</td>
<td>9 (21)</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
<tr>
<td>40.0</td>
<td>13 (40)</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
<td>Grade 1–2: 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reported weakness of a generalized nature or as evidenced by reduced performance status.

<sup>b</sup> Peripheral neuropathy.

<sup>c</sup> Complaints of distension, queasiness with or without diaphoresis, anorexia with or without nausea, vomiting, constipation or altered bowel movements characterized as “not normal”, abdominal cramping, or symptoms of gastrointestinal reflux (burning or distension); GI, gastrointestinal.

<sup>d</sup> Death (grade 5 toxicity) presumed due to pneumonia during cycle 1 of therapy.
BMS-247550. This patient’s response lasted for 6.0 months. Another patient with paclitaxel-refractory breast cancer had a minor response in the chest wall lesion while receiving 40 mg/m² BMS-247550. This patient’s response lasted for 3.0 months. A 53-year-old female with prior docetaxel-refractory (progression documented while receiving weekly docetaxel treatments at a dose of 40 mg/m²/week) breast cancer manifested as clinical chest wall and axillary lymph node involvement had a partial response lasting 4.5 months. She was treated with seven courses of BMS-247550 at 50 mg/m². Another patient with locally advanced breast cancer, who did not respond adequately with neoadjuvant doxorubicin and cyclophosphamide, had a partial response lasting 3 months on BMS-247550. A 73-year-old patient with metastatic ovarian cancer had previously responded to paclitaxel (175 mg/m²) and carboplatin (AUC = 5). However, the tumor recurred less than 6 months after discontinuing therapy. She received topotecan but developed progressive disease while on treatment and subsequently received doxil plus gemcitabine. After an initial response (as determined by a fall in CA-125 levels), she developed progressive disease, at which time she entered this trial. On BMS-247550, she had a partial response (pelvic soft-tissue tumor reduction > 60%) that lasted ~5.3 months. She received nine courses of treatment; however, course 1 was complicated by dose-limiting neutropenia, and the subsequent two courses were dosed at 29.6 mg/m². The same patient was given a dose escalation to 50 mg/m² plus G-CSF, but the onset of severe neutropenia necessitated reduction of her dose to 29.6 mg/m² for the remainder of her treatment course. Her CA-125 continued to progressively decline from a pretreatment value of 596 milliunits/ml to a nadir value of 49 milliunits/ml in course 8 of treatment. At recurrence, computed tomography scans documented new pulmonary nodules, and her CA-125 had risen to 244.9 milliunits/ml. Another patient with paclitaxel-responsive ovarian cancer, but who later developed resistance to paclitaxel, had a partial response on BMS-247550 lasting 6 months.

**Pharmacological Studies.** Plasma samples were obtained from 22 patients during the first course of treatment and from 16 patients during the second course of treatment. Samples were not obtained from three patients during the first course and nine patients during the second course of treatment due to patient refusal and withdrawal of consent for blood procurement. Table 5 lists the pharmacokinetic parameters derived by noncompartmental methods. Inspection of individual plasma concentration data sets indicates that the drug disposition is multiexponential and that concentrations of BMS-247550 decrease to <10% of peak concentration by 8 h from the start of the hour-long infusion (Fig. 3). Both $C_{\text{max}}$ and AUC values appeared to increase in a proportion related to the increase in dose level (Table 5). However, only one patient was entered at four of the six dose levels studied. Therefore, the linearity of the pharmacokinetics of BMS-247550 cannot be assessed by this study. There was an equivalent correlation of dose (in mg) with AUC ($r^2 = 0.51$) when compared with dose normalized to body surface area (mg/m²) with AUC ($r^2 = 0.42$). $C_{\text{max}}$ was poorly related to dose, due in part to variations in infusion duration (actual infusion times varied between 0.97 and 1.6 h) and to late collection of end-of-infusion blood samples in 6 of 38 cycles. Clearance was not significantly different between the various...
dose levels explored (P = 0.48). At the MTD and RPTD of 50 (n = 7) and 40 mg/m² (n = 11) during course 1, interpatient kinetic variability in AUC₀₋₅₉₅, Cl, and Vₑ was moderate, with coefficients of variation of 37%, 43%, and 48% and 46%, 38%, and 87%, respectively. Intrapatient pharmacokinetic variability (n = 16) was minimal, without significant differences in any parameter studied. The decomposition products of BMS-247550, BMS-249798, and BMS-326412 were quantifiable in all patients treated at 50 mg/m². The relative extent of exposure was ≤2%.

There was no apparent relationship between BMS-247550 exposure (AUC₀₋₅₉₅) and the percentage decrease in ANC from baseline during course 1 (r² = 0.16). However, the mean ± SD AUC₀₋₅₉₅ was significantly higher in those patients experiencing course 1 DLT compared with those not experiencing DLT [2047 ± 1005 (n = 6) versus 599 ± 407 ng·h/ml (n = 11); P = 0.02]. Mean Cmax values were also higher, but the difference was not statistically significant [477 ± 172 versus 428 ± 351 ng·h/ml; P = 0.08]. The propensity for development of severe toxicities was not related to exposure to either BMS-247978 or BMS-326412.

**DISCUSSION**

BMS-247550 is a metabolically stable derivative of epothilone B with major preclinical activity in both taxane-sensitive and -resistant human tumor xenograft models. The drug has more favorable toxicological and pharmacological properties than conventional taxanes (10). This Phase I study has demonstrated that the MTD of BMS-247550 is 50 mg/m² given i.v. over 1 h every 3 weeks, and the RPTD is 40 mg/m². Major hematological toxicity at both the 50 and 40 mg/m² doses included grade 3–4 neutropenia (24%), febrile neutropenia (6%), and grade 3 thrombocytopenia (6%); whereas grade 3–4 nonhematological toxicity included fatigue, weakness, neuropathy (6%), and gastrointestinal discomfort (6%). There were no systemic paclitaxel-like hypersensitivity reactions observed. There were two drug-related deaths due to neutropenic sepsis and pulmonary embolus/acute pneumonia.

Because only 12 patients were entered at 40 mg/m², a complete understanding of the true incidence of myelosuppression and other toxicities such as fatigue would require a cautious Phase II evaluation in the clinic. The incidence of neuropathy at 50 mg/m² (n = 11) was 36.3%, with only one of eight patients entered at this dose level experiencing grade 3 or 4 toxicity. At 40 mg/m² (n = 13), all patients had grade 1 neuropathy, whereas the incidence of grade 2 symptoms was 67%, and only one patient (8%) exhibited grade 3 or greater neuropathy. In two patients, significant elevations in VPT scores were observed before documentation of clinical neuropathy. This observation generated the hypothesis that VPT scores may predict for occurrence of neuropathy. This hypothesis is currently being tested in ongoing Phase II studies.

The Vₑ of BMS-247550 is especially large (>1000 liters/m²), which may reflect more avid tissue binding. The long t₁/₂ for BMS-247550 most likely reflects the release of parent drug from deep tissue compartments rather than the actual rate of its metabolism or excretion. The shorter t₁/₂ observed in the single patient at the 7.4 mg/m² dose level may result from lack of quantifiable concentrations at the 48 and 72 h time points. Plasma concentrations were determined over a time period that was only approximately twice the t₁/₂, and the extrapolated portion of AUC was often >15% of AUC₀₋₅₉₅, resulting in an increased possibility of error (27). A future study will measure concentration values over 168 h to address this imprecision. In addition, further population-based pharmacokinetics would be required to accurately calculate true exposure and elimination rates of the drug. There remains significant pharmacokinetic variability, reflected also by pharmacodynamic variability at clinically relevant doses. This suggests that inherent variations (e.g., genetic, drug-induced, and so forth) in metabolism and/or elimination can influence BMS-247550 pharmacokinetics-pharmacodynamics (28). Because BMS-247550 is a known CYP3A4 substrate, additional studies are needed to delineate these relationships (29, 30).

Our recommendation of 40 mg/m² must also be viewed with caution because it is based only on 12 patients treated at this dose level. The observed DLT rate (16.7%) for a small sample size yields large 95% Wilson quadratic confidence limits (31). Another important limitation of accelerated design is that there are insufficient numbers of patients treated at lower doses or lack of a “smoother” dose range on which pharmacokinetic assessments can be performed. Hence, with limited data sets, it is impossible to accurately define dose-pharmacokinetic relationships or pharmacokinetic-pharmacodynamic relationships. Finally, because these designs with intrapatient dose escalations are frequently used with limited cohort numbers, a true relationship between dose and chronic toxicity is also difficult to define. To better define toxicities at 40 mg/m², we have planned an expansion study in common solid tumors (i.e., breast and gynecological malignancies).

In our study, the rate of neuropathy is considerably lower at the MTD than in a similar study published as an abstract (13). To lower the incidence of neuropathy, an empirical decision was made by the National Cancer Institute and Bristol-Myers Squibb to consider conducting Phase II studies as a 3-h infusion rather than a 1-h infusion. In part, this decision was based on the belief that Cmax may correlate with acute neuropathy, as observed for other drugs such as oxaliplatin. Cmax is also known to correlate with unusual side effects such as anthracycline-induced cardiotoxicity (32, 33). Phase II trials incorporating the 3-h, every-3-week infusion schedule are ongoing in melanoma, sarcoma, breast cancer, non-small cell lung cancer, colorectal cancer, and gastric cancer (34–36). Given the observation that with taxanes (e.g., docetaxel), other schedules (e.g., weekly) may be less toxic than the every-3-week schedules (37), additional Phase I studies have been initiated that include two every-3-week schedules, two weekly schedules, and one daily × 5-day schedule (24, 29, 38–40). Preliminary data from these ongoing Phase I studies indicate that BMS-247550 has activity in non-small cell lung cancer, breast cancer, ovarian cancer, melanoma, vulvar cancer, and colon cancer (24, 29, 38–40). These data suggest that BMS-247550 has activity in tumor types not classically recognized as taxane sensitive (e.g., melanoma, sarcoma, and colon cancer). In addition, patients treated in this study, who were clearly refractory to taxanes
by standard criteria, showed tumor response. Therefore, it is possible that BMS-247550 may possess useful clinical activity in taxane-inactive or -refractory settings. Clearly, BMS-247550 is an active antineoplastic drug, and its toxicity profile compares favorably with that of paclitaxel and docetaxel. Further study of this drug using different schedules aimed at lowering the incidence of toxicities such as peripheral neuropathy and myelosuppression are warranted and ongoing (39, 40).

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Clinical Cancer Research

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Sridhar Mani, Hayley McDaid, Anne Hamilton, et al.


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