

Phase I and Pharmacokinetic Study of the New Taxane Analog BMS-184476 Given Weekly in Patients with Advanced Malignancies¹

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ABSTRACT

Purpose: The study was designed to establish the maximum administered dose and maximum tolerated dose (MTD) of BMS-184476, an analogue of paclitaxel, given weekly for 3 consecutive weeks every 28 days, later amended to a regimen of weekly administration for 2 consecutive weeks every 21 days.

Experimental Design: Adult patients with solid tumors received BMS-184476 i.v. on days 1, 8, and 15 without premedication. The trial followed a modified accelerated titration design. Doses of 7, 14, 28, 40, 50, and 60 mg/m²/wk were investigated. Pharmacokinetics of BMS-184476 in plasma and urine were investigated by high-performance liquid chromatography assay.

Results: Fifty-three patients were treated; the maximum administered dose was 60 mg/m²/wk, and the MTD was 50 mg/m²/wk. Dose-limiting neutropenia was the main toxicity. Neutropenia at the higher dose levels frequently prevented administration of the day 15 dose, and a modified schedule at MTD dosing on days 1 and 8 every 21 days was evaluated and found more feasible for Phase II studies. Diarrhea was the main nonhematological toxicity; other toxicities were vomiting, cumulative fatigue, and loss of appetite. Two patients died of neutropenia-related complications.

Antitumor activity was observed in patients with breast and non-small cell lung cancer, with confirmed partial responses in 22% of patients. BMS-184476 was the main spe-

cies found in the plasma with <5% present as paclitaxel or sulfoxide metabolites. The PKs of BMS-184476 appeared to be linear in the dose range of 7–60 mg/m².

Conclusion: The recommended dose and schedule of weekly BMS-184476 is 50 mg/m² on days 1 and 8 every 21 days.

INTRODUCTION

Taxanes were introduced into clinical practice in the 1990s as exciting new antimitotic agents active in a range of tumor types, in particular ovarian, breast, and lung cancers. Paclitaxel was initially isolated in 1971 from the bark and needles of *Taxus brevifolia*, the Pacific Yew tree; docetaxel is an analogue of paclitaxel synthesized from a precursor isolated from the needles of *Taxus baccata*, the European Yew. Both drugs are being incorporated rapidly into the treatment of many of the major solid tumors (1). Taxanes promote and stabilize the assembly of tubulin into microtubules. In the presence of the drug, cells accumulate in the mitotic phase of the cell cycle and undergo apoptosis instead of cell division (2, 3).

The initial development of paclitaxel was halted by the high incidence of hypersensitivity reactions; subsequent investigations discovered that these events could be prevented largely by premedication with steroids and antihistamine. Hypersensitivity has been attributed to the Cremophor EL/ethanol mixture used to prepare paclitaxel (4). One of the principle nonhematological toxicities of paclitaxel is peripheral neuropathy (5), and this problem is also reported with docetaxel (6). In the development of synthetic taxanes efforts have been targeted both at increasing the solubility of the drug, improving its clinical efficacy, and reducing peripheral neuropathy. BMS-184476 is the 7-methylthiomethyl ether of paclitaxel (Fig. 1), which has shown efficacy equal or superior to paclitaxel in a number of *in vitro* and *in vivo* studies in a spectrum of different tumor types sensitive to paclitaxel (7). In addition, BMS-184476 is more soluble in aqueous cosolvents, thus allowing reduction of the amount of Cremophor EL by 65–70% per mg of drug, potentially eliminating the need for premedication.

In preclinical single i.v. dose toxicology studies performed in rats and dogs, a TDL³ was defined at 72 mg/m² and 60 mg/m², respectively (7). Overall, from a qualitative point of

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³ The abbreviations used are: TDL, toxic dose low; MAD, maximum administered dose; MTD, maximum tolerated dose; PK, pharmacokinetic; HPLC, high-performance liquid chromatography; NSCLC, non-small cell lung cancer; CTC, common toxicity criteria; DLT, dose-limiting toxicity; DI, dose intensity; ANC, absolute neutrophil count; Cmax, peak plasma concentration; Tmax, time to reach peak concentration; AUC, area under the plasma concentration-time curve; VSS, volume of distribution at steady state; CLT, total body clearance.

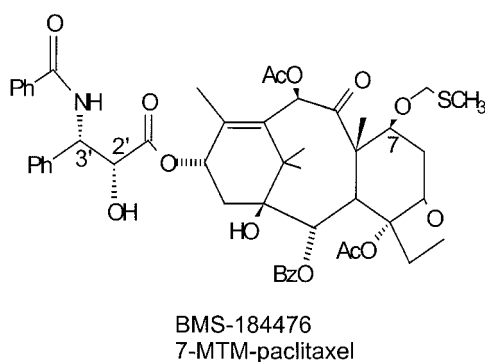


Fig. 1 Structural formula of BMS-184476.

view, the toxicity profile of BMS-184476 was comparable with that of paclitaxel, mainly consisting of dose-related neutropenia, thrombocytopenia, gastrointestinal damage with stool changes, and macroscopic changes of the small and large intestines. Quantitatively, BMS-184476 was somewhat more toxic than paclitaxel, with the exception of neurotoxicity, for which a reduced potential could be inferred from the results of axonal degeneration in peripheral nerves in rats.

In PK studies in mice, rats, and dogs, using HPLC procedures, BMS-184476 showed a mean terminal half-life of 1.5, 7.1, and 11.6 h, respectively, a large VSS and dose-proportional C_{max} , and AUC. In *in vitro* studies with liver S-9 preparations from different species, the major metabolic product was the sulfoxide metabolite BMS-184980, which was also the major metabolite found in rats, dogs, and monkeys; significant conversion to paclitaxel was observed only in mice.

Single, intermittent every 21-day and weekly for 3 consecutive weeks every 28-day schedules were selected for initial Phase I development. Starting doses for the above schedules were 20 mg/m² and 7 mg/m²/week, respectively, corresponding to one-third of the TD_L in dogs.

This paper reports the results of the weekly Phase I study of BMS-184476, carried out jointly at Northern Center for Cancer Treatment, Newcastle Upon Tyne, United Kingdom, and at Oncology Institute of Southern Switzerland, Bellinzona, CH, Switzerland.

PATIENTS AND METHODS

Patients. Patients with advanced nonhematologic malignancies who had progressed on standard therapy or for whom no standard chemotherapy was available were recruited into the study. Before entry each patient underwent assessment with a full history, clinical examination, radiological staging, and laboratory evaluation, informed written consent having been obtained.

Eligibility criteria included histological/cytological confirmation of a nonhematological malignancy; Eastern Cooperative Oncology Group performance status ≤ 2 ; age > 18 years; life expectancy ≥ 3 months; and written informed consent. Patients must have adequate bone marrow (ANC $\geq 2.0 \times 10^9$ /liter, platelet count $\geq 100 \times 10^9$ /liter), hepatic (total bilirubin ≤ 1.5 mg/dl, liver transaminases $\leq 2.5 \times$ upper limit of normal), and

renal (serum creatinine ≤ 1.5 upper limit of normal) function. At least 4 weeks must have elapsed since prior chemotherapy (6 weeks for nitrosoureas, mitomycin C, or carboplatin), immunotherapy, or wide-field radiotherapy. Fertile patients were requested to use effective methods of contraception. Approval from the relevant local ethical committees was obtained for each center before recruitment into the trial.

Major exclusion criteria included any evidence of severe or uncontrolled medical disorder or an active infection, which would impair the ability to receive study medication, including prior known hypersensitivity to Cremophor EL, pre-existing neurological toxicity (\geq grade 2 according to the National Cancer Institute CTC Version 2.0), dementia or altered mental status that would prohibit understanding of the informed consent, active brain metastases including evidence of cerebral edema by computed tomography scan or magnetic resonance imaging, or progression from prior imaging study, clinical symptoms of/from brain metastases, or any requirements for steroids. Pregnant or breastfeeding patients were not recruited.

Study Design. The trial used the modified version 4B of the accelerated titration design to limit the number of patients treated at potentially subtherapeutic doses and, therefore, to reduce the duration of the trial (8). A starting dose of 7 mg/m²/week for 3 consecutive weeks every 28 days was selected.

In the initial accelerated phase, 1 patient per cohort was treated; unless CTC grade 2 toxicity was observed, the dose was doubled between cohorts. The first patient treated at each new dose level had to be on study for at least 28 days before additional patients were entered at that or a higher dose level. On the first instance of grade 2 toxicity 2 additional patients were treated at that dose level. The accelerated phase continued until any 1 patient experienced a DLT any time during treatment or when 2 patients developed any CTC grade 2 or higher toxicity (excluding alopecia) during any course of treatment or in two separate courses of treatment.

In the subsequent standard escalation phase, cohorts of at least 3 patients (6 in case of DLT) were recruited at each dose level with up to 40% dose increments at subsequent levels. Dose escalation was stopped when at least 2 of 6 patients experienced DLT during the first course of treatment; this dose level was defined as the MAD. The dose level immediately below was defined as MTD, and it was planned to expand this level to define its suitability as a recommended Phase II dose.

Inpatient dose escalation was permitted only for patients experiencing CTC $<$ grade 2 toxicity on a previous course. Patients experiencing DLT were permitted to continue on treatment after a dose reduction of a single dose step.

Complete blood cell count with differential was done twice a week, whereas blood biochemistry (including liver function tests, creatinine, electrolytes, and glucose) was repeated before each cycle.

Toxicity was evaluated according to the National Cancer Institute CTC (version 2.0). All of the treated patients were evaluable for baseline and toxicity. Response rate is tabulated for all of the response-evaluable patients with measurable disease at baseline.

DLT were defined as the occurrence of grade 4 neutropenia (lasting ≥ 5 consecutive days or associated with fever $\geq 38^\circ\text{C}$); grade 4 thrombocytopenia or a bleeding episode requiring plate-

let transfusion; \geq grade 3 nausea and/or emesis despite use of maximal antiemetics; \geq grade 3 neurosensory toxicity; \geq grade 2 cardiac, pulmonary, or other neurotoxicity; or any \geq grade 3 nonhematological toxicity except fatigue or transient arthralgia/myalgia. Failure to recover from treatment-related toxicities to baseline or grade 1 by day 42 was also defined as DLT. Hypersensitivity to BMS-184476 was not considered DLT unless the incidence of severe hypersensitivity reactions despite adequate premedication was deemed to impact on the safe administration of the drug.

In patients with measurable or evaluable, disease formal assessment of tumor response was repeated after 2 cycles, and patients showing no evidence of disease progression continued on treatment until withdrawal criteria were met. Tumor response continued to be assessed after alternate cycles using standard response criteria based on Unio Internationale Contra Cancrum/WHO criteria. A complete response was defined as no clinical, radiological, or biochemical evidence of residual lesions for >4 weeks. A partial response was defined as no evidence of disease progression with a $>50\%$ reduction in the sum of the products of the two largest perpendicular diameters of all of the marker measurable lesions maintained for >4 weeks. Progressive disease was defined as the appearance of a new lesion or an increase in $>25\%$ in an existing lesion. Stable disease was defined as neither an objective response nor progression.

Patients with stable disease or tumor response continued treatment with BMS-184476 until tumor progression or unacceptable toxicity, whichever occurred first, whereas patients with progressive disease discontinued the study.

Drug Administration. BMS-184476 was supplied by Bristol-Myers Squibb Company (Wallingford, CT) as a two-vial system: a 75 mg/vial of BMS-184476 injection (15 mg/ml), to be transferred to the diluent vial containing Cremophor EL, 7.5% v/v ethanol in tartrate buffer. The solution was additionally diluted with 5% dextrose to a final drug concentration of 0.1–1.2 mg/ml. The final drug solution was filtered using a Monoject Filter needle and transferred to non-pvc infusion bag for administration.

According to the original protocol, BMS-184476 was given as a 1-h infusion on days 1, 8, and 15 of a 28-day cycle. Doses on days 8 and 15 were omitted if ANC was $<1.0 \times 10^9$ /liter or platelet count $<50 \times 10^9$ /liter, or if nonhematological toxicities $>$ grade 1 were present.

At the higher dose levels it became evident that, because of cumulative neutropenia, doses on day 15 were omitted frequently. A protocol amendment was introduced scheduling treatment on days 1 and 8 of a 21-day cycle to investigate whether such a schedule would improve tolerability while still maintaining an adequate DI.

Premedication for hypersensitivity was not required unless the patient had experienced a prior hypersensitivity reaction to BMS-184476. Routine prophylactic antiemetics were not used unless patients had documented nausea and/or vomiting on a previous cycle.

PKs. Plasma and urine PKs of BMS-184476, and concentrations of its potential metabolites were determined in all of the patients on days 1 and 15 of the first cycle of treatment. Blood samples (5 ml) were collected in K₃EDTA at 0, 0.5, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 24, and 48 h after dosing. Plasma was

separated by centrifugation $1000 \times g$. Urine samples were collected over a period of 24 h after dosing on days 1 and 15 of the first cycle of treatment.

Sample Analysis. Plasma and urine samples were analyzed for BMS-184476, BMS-246178, BMS-246180, and paclitaxel concentrations by a published HPLC method (9). BMS-246178 and BMS-246180 are the individual diastereoisomers of the sulfoxide metabolite BMS-184980 that was quantitated in preclinical species. Briefly, a 0.05-ml aliquot of the internal standard (BMS-183061) was added to 1 ml of plasma, vortexed, and loaded into unendcapped Cyano Bond Elut columns (Varian, Harbor City, CA) that had been conditioned previously with 2×1 ml of 10% methanol in water and 2×1 ml of 5% acetonitrile in water. The analytes and internal standard were eluted with 1 ml of 0.1% formic acid in methanol into tubes. The eluents were evaporated, and the dried residues were reconstituted in 50.5% acetonitrile in water. The reconstituted samples were sonicated for 5 min in a Bransonic 52 ultrasonic bath (Branson Cleaning Equipment Co., Shelton, CT), transferred to WISP vials, and then placed in a randomized manner in a Waters Model 717 autosampler (Waters Associates, Milford, MA) for analysis using HPLC.

One hundred- μ l aliquots from each sample were injected onto the HPLC system, which consisted of a Waters Model 590 solvent pump, a Waters Temperature Control Module, and a Waters 484 Tunable Absorbance Detector. Separation was performed using a Zorbax RX-C18, 5 μ m, 4.6 \times 250 mm column (Hewlett Packard Co., Wilmington, DE), and a mobile phase consisting of 51.5% acetonitrile in water containing 10 mM ammonium acetate (pH titrated to 5.0 with acetic acid) and 10 mM tetramethylammonium hydroxide (pH titrated to 5.0 with acetic acid) at 40°C. The flow rate was 1.0 ml/min. Peak integration and quantitation from resultant chromatograms were performed using a VG Data Systems Multichrom 2 (Fisons, Cheshire, United Kingdom) data collection and processing system. The retention times for BMS-246178, BMS-246180, paclitaxel internal standard, and BMS-184476 were 6.2, 6.5, 8.0, 12.0, and 20.0 min, respectively. The UV absorbance detector was set at 227 nm with a response time of 1.0 s. The 1-V output of the detector was monitored by the chromatography data system. The lower limit of quantitation of the assay is 10 nmol. BMS-184476 standard curves were linear ($R^2 \geq 0.999$) over the concentration range of 10 to 5000 nmol, and the between-run precision and the within-run precision for the BMS-184476 quality control samples were no more than 8 and 4% relative SD with deviations from the nominal concentrations of no more than $\pm 9\%$. These data indicate that the plasma assay method was precise and accurate, and that BMS-184476 was stable in the plasma samples during shipment and storage.

PK Analysis. The plasma concentration-time data for BMS-184476, and metabolites BMS-246178, BMS-246180, and paclitaxel were analyzed by noncompartmental methods using the program MENU/PKMENU. For BMS-184476, the C_{max} and the T_{max} were recorded directly from experimental observations. Using no weighting factor, the slope of the terminal phase of the plasma profile, K, was determined by log-linear regression of at least three data points, which yielded a minimum mean square error. The absolute value

of K was used to estimate the apparent terminal half-life, T-HALF, by $T\text{-HALF} = \ln 2/K$.

The AUC was calculated by trapezoidal and log-trapezoidal summations, and extrapolated to infinity for the determination of AUC(INF). Because BMS-184476 was quantifiable for at least 24 h after dosing for a majority of patients at the lower dose levels of 7 and 28 mg/m², the AUC up to 24 h after dosing [AUC(24 h)], was calculated for all of the patients at all of the dose levels. Although quantifiable levels of BMS-184476 over the entire sampling period of 48 h were obtained consistently in all of the patients only at dose levels >40 mg/m², the AUC extrapolated after the last quantifiable time point was >50% in a majority of patients. Similar observations were made for estimates of the area under the first moment curve (AUMC). Therefore, additional parameter estimates were limited to CLT and VSS at the Phase II dose levels of 50 and 60 mg/m², and were calculated using the following equations:

$$\text{CLT} = \text{Dose}/\text{AUC}(\text{INF})$$

$$\text{VSS} = \left[\frac{\text{AUMC}(\text{INF})}{\text{AUC}(\text{INF})} - T^*/2 \right] \bullet \text{CLT},$$

where T * is the infusion time (1h)

For the metabolites, BMS-246178, BMS-246180, and paclitaxel, C_{max} and T_{max} were determined in the same manner as the parent compound. It should be noted that AUC(24 h) values could not be calculated for the metabolites, because concentrations were not detectable up to the 24 h time point; thus, AUC(0-T) values were determined where T was the last quantifiable time point. In addition, because of the lack of quantifiable metabolite concentrations over the entire sampling interval, T-HALF was not estimated.

The amount of BMS-184476, BMS-246178, BMS-246180, and paclitaxel excreted in the urine during each collection interval was calculated by multiplying the concentration of the intact drug or metabolite in each urine sample by the volume of urine collected over that interval. The total urinary recovery was calculated as the cumulative amount excreted over 24 h, and expressed as a percentage of the administered dose. Because of low and inconsistent urinary concentrations of BMS-184476 and metabolites, renal clearance was not estimated.

RESULTS

Fifty-three patients were recruited into the trial, and a total of 52 were treated; 1 patient with breast carcinoma was treated at a dose of 50 mg/m² on both the three weekly and four weekly schedules. One patient was registered but never treated. Baseline, dosing, and toxicity tables are on all of the treated patients, with the re-enrolled patient represented twice. The characteristics of the 52 patients who received treatment are shown in Table 1. The majority of patients treated were female (64%), reflecting the preponderance of patients with breast carcinoma (34%). Three patients had not received prior chemotherapy, 2 patients with mesothelioma and 1 with a pleural-based tumor. Radiotherapy to drain sites had been given in 2 of these otherwise untreated patients. Thirty-five patients had received two or more prior chemotherapy regimens including taxanes in 3 patients.

A total of 45 patients were treated, and 153 cycles were

Table 1 Patient demographics

	Number
Male:Female	19:33
Median age (range)	54 (25–72)
Performance status	
0–1	50
2	2
Prior chemotherapy (radiotherapy)	48 (29)
No. prior regimens	
None	3 (2)
1	17 (5)
2	18 (12)
≥3	13 (8)
Tumor type	
Breast	17
Colon	5
NSCLC	12
Ovary	4
Unknown primary	3
Gastric	1
Kidney	1
Soft tissue sarcoma	2
Melanoma	1
Mesothelioma	2
Pleura	1
Small cell lung carcinoma	2
Cervix	1

administered on the 28-day schedule; this represented a median number of cycles of 3, ranging from 1 to 8. Table 2 reports the number of cycles administered per dose level, either as first or subsequent cycles.

Inpatient dose escalations were performed in the accelerated phase in 3 patients: the first patient recruited in the study started at 7 mg/m² and then received 14 mg/m², 28 mg/m², and 40 mg/m² on subsequent cycles; the second patient started at 14 mg/m² and then went on to receive 28 mg/m², and the third patient started at 28 mg/m² and then received 40 mg/m². Inpatient dose escalations were also performed in the standard phase in 4 patients who had not developed toxicity >CTC grade 1; 2 patients started at 28 mg/m² and were escalated to 40 mg/m²; 1 patient started at 40 mg/m² and went on to receive 50 mg/m², whereas 1 patient started at 50 and then received 60 mg/m².

CTC grade 2 toxicity (diarrhea) was first observed at 28 mg/m² and the accelerated phase of the study completed; a total of 6 patients were treated at this dose level overall (Table 2). The standard escalation phase of the study was then started with a 40% increment up to the 40 mg/m² dose level followed by 25% and 20% increments to 50 mg/m² and 60 mg/m², respectively. The latter was defined as MAD because of the occurrence of DLT after the first course day 8 dose in 2 of the first 3 patients treated at 60 mg/m², consisting of febrile grade 4 neutropenia associated with severe stomatitis in one case and with severe diarrhea in the other.

Overall, febrile neutropenia and diarrhea were the main DLTs, first observed at 40 mg/m², mostly occurring after the dose on day 8. To better define the dose recommended for Phase II trials, additional patients were recruited at the two dose levels below the MAD, 50 mg/m² and 40 mg/m². Preliminary analysis of the data while the trial was ongoing suggested that 40 mg/m²

Table 2 Number of courses administered by dose level and occurrence of DLT

Dose level	First course	Subsequent courses	Total courses	Day 8 omitted	Day 15 omitted	Courses with omissions ^a	DLT occurrence
7 mg/m ²	1	0	1	0	0	0	—
14 mg/m ²	1	1	2	0	0	0	—
28 mg/m ²	6	12	18	1	4	4 (0)	—
40 mg/m ²	17	49	66	8	25	29 (13)	Diarrhea (1) Diarrhea + febrile neutropenia (1) Febrile neutropenia (1)
50 mg/m ²	18	45	63	12	42	47 (35)	Diarrhea (1) Febrile neutropenia (2)
60 mg/m ²	2	1	3	0	3	3 (3)	Diarrhea + febrile neutropenia (1) Stomatitis + febrile neutropenia (1)
50 mg/m ² (Q3 wks)	8	25	33	2	N/A ^b	2 (2) ^c	Febrile neutropenia (2)

^a In parentheses, number of courses where day 15 dosing was omitted because of neutropenia.

^b N/A, not applicable.

^c Day 8 dosing omitted because of neutropenia.

Table 3 DI achieved in minimally versus heavily pretreated patients

Dose level	Mean dose (mg/m ² /week) ± SD		
	40 mg/m ²	50 mg/m ²	50 mg/m ² (q3 wks)
Minimally pretreated	25.8 ± 4.5	29.4 ± 7.2	29.1 ± 4.2
Heavily pretreated	23.9 ± 5.6	26.5 ± 4.9	27.7 ± 3.3

would be considered the MTD in patients heavily pretreated with chemotherapy and 50 mg/m² in those lightly pretreated or untreated. Heavily pretreated patients had received two or more prior chemotherapy regimens or substantial doses of alkylating agents. Subsequent analysis of DI received did not show a significant difference between the two groups in terms of the achievable dose (Table 3).

However, it appeared that, from the dose level of 40 mg/m² forward, dosing on day 15 could not be given because of an ANC <1.0 × 10⁹/liter in 20% of the cycles at the 40 mg/m², 55% at the 50 mg/m², and 100% at the 60 mg/m² dose levels (Table 2). A modified dosing schedule with dosing on days 1 and 8 repeated every 21 days was then explored for the 50 mg/m² dose level in a total of 8 patients. Over 33 courses, the day 8 dose could not be given because of low ANC in 1 patient on 2 courses. In addition, a new cycle could not be started on time on day 21 in 5 patients (16 cycles) because of lack of hematological recovery in 11 cycles, with a mean delay of 7 days (range, 5–11 days).

Hematological Toxicity

The main hematologic toxicity observed was neutropenia, which was dose-dependent, selective, with no thrombocytopenia, and with a median nadir ANC of 0.70 × 10⁹/liter (range, 0.12–3.5 × 10⁹/liter) at the 50 mg/m² dose level on the 28-day schedule (Table 4).

On the original schedule, grade 4 neutropenia was observed in 3% (2 of 66) of the cycles at the 40 mg/m², 32% (20 of 63) at the 50 mg/m², and 100% (3 of 3) at the 60 mg/m² dose levels, whereas it occurred in 55% (18 of 33) of the cycles with the 21-day schedule. Severity of neutropenia and incidence of febrile neutropenia at 50 mg/m² were comparable between patients

who were heavily (two or more prior chemotherapy regimens) or only minimally pretreated; however, heavily pretreated patients required more frequent omissions of the dose on day 15 on the every 28-day schedule than those who were minimally pretreated [83% (20 of 24) versus 56% (22 of 39)].

The median time to ANC nadir was ~15 days with a median time to recovery of ~1 week. This time pattern of neutropenia, which was similar with both schedules of treatment, led to the adoption of the more feasible 21-day schedule with BMS-184476 given at 50 mg/m² on days 1 and 8 every 21 days, and this regime was eventually the recommended dose and schedule for Phase II studies.

Two toxic deaths occurred on study. One 68-year-old patient with cancer of the ovary pretreated with three prior chemotherapies died of septic shock while neutropenic 9 days after dosing on day 8 at 40 mg/m²; a second toxic death was observed in a 66-year-old patient with breast cancer pretreated with cyclophosphamide, methotrexate, and 5-fluorouracil; epirubicin; and radiotherapy who died because of cardiac complications of neutropenic sepsis 4 days after day 8 dosing at 50 mg/m² (Table 4). Neither of these patients had consented to PK sampling, so there is no data as to whether they exhibited atypical PK parameters.

Nonhematological Toxicity

Diarrhea was the other major toxicity; first observed at 40 mg/m² and present in 60% (38 of 63) of cycles at 50 mg/m² of the 28-day schedule, it was of grade 3 in only 8% of these cycles. With the 21-day schedule, diarrhea was reported in 39% (13 of 33) of the cycles and was of grade 3 in 3% (Table 5). Diarrhea appeared mainly after dosing on day 8, was preceded by abdominal cramps when severe, and was generally controlled with high-dose loperamide. It contributed to the DLT in 4 patients (Table 2).

Overall, treatment given on the 21-day schedule was better tolerated than when given on the 28-day schedule. At the recommended Phase II dose of 50 mg/m² on days 1 and 8 every 21 days, nausea and vomiting, cumulative fatigue, and loss of appetite occurred in 39, 39, and 36% of the cycles, respectively. Nausea and vomiting, and fatigue were of grade 3 in 6 and 15% of the cycles, respectively. Alopecia was also frequent (18 of 28

Table 4 Neutropenia per course by dose level

Dose level	No. of patients ^{a/} courses	CTC grade of neutropaenia				Median nadir, ($\times 10^9$ /liter) (range)	Median time to nadir (days) (range)	Febrile neutropenia
		3		4				
		n/N ^b	%	n/N	%			
7 mg/m ²	1/1					3.40	10	—
14 mg/m ²	2/2					3.27 (3.24–3.30)	17 (17–17)	—
28 mg/m ²	9/17					2.30 (1.2–7.80)	15 (4–22)	—
40 mg/m ²	21/66	10/21	32	2/2	3	1.15 (0.30–7.30)	15 (3–29)	2 ^c
50 mg/m ²	18/63	11/23	37	11/20	32	0.70 (0.12–3.50)	15 (5–29)	2
60 mg/m ²	3/3			3/3	100	0.21 (0.14–0.49)	13 (12–15)	2
50 mg/m ² (q3 wks)	8/33	6/9	27	6/18	55	0.46 (0.15–2.67)	14 (7–19)	1 ^d

^a Total number of patients treated at this dose level for at least one course.

^b n, number of patients developing grade 3 or 4 neutropaenia; N, number of courses at that dose level in which the degree of toxicity was observed; %, percentage of courses compared to total number given where that degree neutropaenia observed.

^c Fatal septic shock during neutropenic period in 1 patient.

^d Neutropenic sepsis, leading to hypotension and to fatal atrial flutter in 1 patient.

Table 5 Nonhaematological toxicity any cause by course

Dose	d1, d8, d15 q 4 weekly			D1, d8 q 3 weekly 50 mg/m ²
	40 mg/m ²	50 mg/m ²	60 mg/m ²	
No. courses given	66	63	3	33
CTC grade	Any (grade 3/4)	Any (grade 3/4)	Any (grade 3/4)	Any (grade 3/4)
Asthenia	37 (3)	46 (3)	0	13 (5)
Nausea/vomiting	25 (2)	33 (6)	1 (0)	13 (2)
Diarrhea	26 (3)	38 (5)	3 (1)	13 (1)
Arthralgia/myalgia	14 (1)	32 (2)	1 (0)	5 (0)
Alopecia	20 (0)	34 (0)	2 (0)	29 (5)
Mucositis	7 (0)	13 (1)	1 (1)	0
Peripheral neuropathy	26 (1)	40 (1)	2 (0)	14 (0)

patients) but was total only after repeated administrations at doses ≥ 50 mg/m² in ~20% of patients. Mucositis was not observed in the 21-day regimen (Table 5). A hypersensitivity reaction was reported in 1 patient, who developed grade 1 skin erythema during the first 2 injections; she was then premedicated with cimetidine and continued study treatment. Peripheral neuropathy was mainly of sensory type and was cumulative; it was of grade 1 and 2 in all but 2 of the cases, and was reported in 42% of cycles of the 50 mg/m², 21-day schedule. One patient treated at 40 mg/m² had a grade 3 paresthesia during the third course, which decreased to grade 1 after reducing the dose to 28 mg/m² from cycle 4 for the three following courses. A second patient treated at 50 mg/m² in the 28-day schedule suffered from grade 3 peripheral neuropathy for a few days. This patient had pre-existing grade 1 peripheral neuropathy at baseline as a result of prior cisplatin treatment.

Antitumor Activity

Only 14 patients (26%) had nonmeasurable disease at baseline. Assessment of antitumor activity was possible in 37 of 39 patients with measurable disease; follow-up measurements were not available in 2 patients. Eight (22%) patients treated at either 40 mg/m² or 50 mg/m² (on both schedules) achieved a confirmed objective response (Table 6). These responses were reported in patients with breast, NSCLC, carcinoma of unknown primary, and a tumor of pleural origin. Overall, among 8 evalu-

able patients with breast cancer, all of them not previously treated with taxanes, 3 achieved a partial response and 3 had stable disease. Among 12 patients with NSCLC, partial responses and stable disease were reported in 3 patients each; these patients were again taxane naive. Stable disease was reported in 2 of 5 patients with colon cancer and in the only patient with gastric cancer entered in the study. The mean duration of stable disease was 53 days (range, 29–79 days). One patient with ovarian cancer, who had responded on two separate occasions to repeated courses of paclitaxel and carboplatin, most recently >6 months before entering the study, achieved a complete radiological remission with normalization of CA-125 after 7 cycles of BMS-184476. The previous treatment with paclitaxel and carboplatin had been associated with severe peripheral neuropathy, which recurred while on BMS-184476 but only of grade 2 and appearing after 7 cycles.

PKs

PK Evaluation. The mean plasma concentration-time data for BMS-184476 in subjects after a 1-h i.v. infusion of 7, 28, 40, 50, and 60 mg/m² on days 1 and 15 are depicted in Fig. 2, and PK parameter values obtained on day 1 are summarized in Table 7. Similar parameter values were obtained on day 15 (data not shown). Within the 28–60 mg/m² dose range, C_{max} and AUC(24 h) values on day 1 increased in ratios that were similar to the dose increment. C_{max} and AUC(24 h) values

Table 6 Antitumor activity

Dose level (mg/m ²)	Tumor type	No. of evaluable patients	No. of responders	Previous treatment	
Days 1, 8, 15 q 28 days	Breast	3	1 PR	Dox ^a × 4, CMF × 6	
		1	1 PR	MIC × 4, ECarboF × 2	
	50	Breast	4	1 PR	Dox × 4, CMF × 6
			1	1 PR	Dox × 4, CMF × 8
		NSCLC	2	1 PR	MIC × 3, MVP × 3
	Pleura	1	1 PR	None	
Days 1, 8 q 21 days	50	Ovary	1	Unconfirmed CR ^b	Carbo/paclitaxel × 6 twice
		NSCLC	3	1 PR	Carbo/VBL × 2, gemcitabine × 2 PNU159548 × 2
				1 PR	Gem/Cis × 2 Gem/Carbo × 1 Intrapericardial thiotepa

^a Dox, doxorubicin; CMF, cyclophosphamide, methotrexate, 5fluorouracil; MIC, mitomycin C, ifosfamide, cisplatin; ECarboF, epirubicin, carboplatin, 5fluorouracil; MVP, mitomycin C, vimblastine, cisplatin; Carbo, carboplatin; Gem, gemcitabine; Cis, cisplatin; and VBL, vimblastine.

^b Confirmatory computed tomography scan not repeated later.

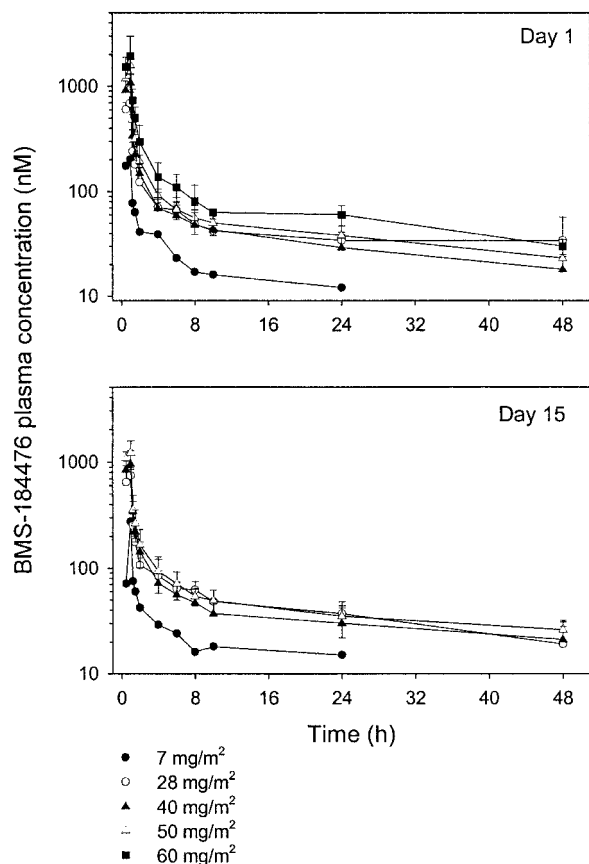


Fig. 2 Mean (SD) plasma concentration versus time profiles of BMS-184476 on days 1 and 15 after i.v. administration of 7, 28, 40, 50, and 60 mg/m² doses of BMS-184476; bars, \pm SD.

obtained on day 15 increased in a dose-related manner. On the basis of data obtained at dose levels of 50 and 60 mg/m² on days 1 and 15, mean terminal T-HALF values ranged from 33.5 to 38.9 h. CLT and VSS values obtained at the 50 and 60 mg/m² dose levels (day 1) appeared to be similar. The mean percentage

of the administered dose values were independent of dose and ranged from 0.39 to 0.80% over the dose range of 7–60 mg/m² on days 1 and 15.

The geometric mean PK parameter values for the metabolites BMS-246178, BMS-246180, and paclitaxel obtained on day 1 are summarized in Table 7. The values obtained on day 15 were not statistically different (data not shown). Plasma concentrations of all of the metabolites were low and quantifiable for only about 2–6 h after a 1-h i.v. infusion of BMS-184476. Plasma concentrations of the metabolites peaked at the end of infusion of BMS-184476 and declined rapidly. The cumulative exposures to the metabolites constituted <10% of the AUC(24 h) of BMS-184476 at the various dose levels. There were increases in exposures (C_{max} and AUC) with increasing dose. Urinary recoveries of the metabolites were low.

DISCUSSION

BMS-184476, the 7-methylthiomethyl derivative of paclitaxel formed through the conversion of the 7-hydroxy group, was brought into clinical development because, in comparison with the parent compound, it had shown similar *in vitro* potency and *in vivo* antitumor activity (7, 10) with a different toxicity profile. In animal studies DLT was gastrointestinal and myelosuppression with less peripheral neuropathy than paclitaxel. However, the most promising feature was the higher solubility of the analogue in aqueous cosolvents, which made it suitable for an improved formulation with reduced content of Cremophor EL, thereby eliminating the need for premedication.

Two Phase I studies, one performed in the United States with a single dose given every 21 days and the other in Europe using a weekly schedule every 21–28 days, have been carried out concomitantly, and have provided comparable results in terms of safety and PKs. Data from the single intermittent 21-day schedule has recently been described elsewhere (9, 11), and preliminary results of the European study have been reported previously (12, 13).

Two distinctive features of the design of the European weekly study, which is subject of the present report, are worth commenting on. The first one is the successful implementation

Table 7 Geometric mean (%CV) pharmacokinetic parameter values for BMS-184476 and its metabolites after administration of a 60-min i.v. infusion of BMS-184476

	7 mg/m ²	28 mg/m ²	40 mg/m ²	50 mg/m ²	60 mg/m ²
C _{max} , nM					
BMS-184476	200	710 (2.1)	1076 (19.9)	1563 (18.0)	1854 (49.1)
BMS-246178	ND ^a	16.4 (31.5)	27.6 (52.3)	32.7 (33.4)	59.6 (27.9)
BMS-246180	ND	13.4 (24.4)	18.3 (43.5)	23.9 (49.8)	34.4 (58.5)
Paclitaxel	ND	ND	18.9 (41.6)	18.3 (25.1)	17.4 (31.4)
T _{max} , h (range)					
BMS-184476	1	1 (0.5, 1)	1 (0.5, 1)	1 (0.5, 1)	0.75 (0.5, 1)
BMS-246178	ND	1.38 (1, 1.5)	1 (1, 1.25)	1 (1, 1.25)	1.25 (1.25, 1.25)
BMS-246180	ND	1 (1, 1.25)	1 (1, 1.25)	1 (1, 1.25)	1.25 (1.25, 1.25)
Paclitaxel	ND	ND	1.5 (1.25, 2)	1.25 (1.25, 1.5)	1.5 (1.5, 1.5)
AUC (24 h) ^b , nM·h					
BMS-184476	625	1722 (10.7)	2063 (19.6)	2760 (10.9)	3712 (31.2)
BMS-246178	ND	17.2 (43.1)	26.7 (83.2)	34.2 (27.7)	96.7 (38.5)
BMS-246180	ND	13.3 (47.2)	19.1 (60.6)	23.6 (18.5)	47.6 (79.6)
Paclitaxel	ND	ND	16.9 (55.7)	17.1 (44.4)	35.2 (95.0)
AUC (INF), nM·h					
BMS-184476	ND	ND	ND	4634 (14.9)	6306 (5.9)
T-HALF, h					
BMS-184476	ND	ND	ND	34.4 (16.4)	33.5 (14.5)
CLT, mL/min/m ²					
BMS-184476	ND	ND	ND	199 (27.8)	172 (12.1)
VSS, liter/m ²					
BMS-184476	ND	ND	ND	379 (161)	350 (223)
%UR					
BMS-184476	ND	0.62 (0.21)	0.78 (0.24)	0.61 (0.20)	0.39 (0.01)
BMS-246178	ND	0.08 (0.03)	0.08 (0.03)	0.06 (0.02)	0.09 (0.01)
BMS-246180	ND	0.06 (0.01)	0.12 (0.21)	0.05 (0.02)	0.06 (0.02)
Paclitaxel	ND	ND	0.20 (0.09)	0.14 (0.05)	0.12 (0.01)

^a ND, not determined as sample collection was incomplete or all of the concentrations were < LLQ.

^b AUC(T) for metabolites where T represents the last detectable timepoint.

of version 4B of the accelerated titration design by Simon *et al.* (8). The accelerated phase covered 3 dose levels, from 7 mg/m² to 28 mg/m², with only 1 patient per dose level; the standard phase was started at the 40 mg/m² dose level, whereas expanded accrual at 28 mg/m² was still ongoing. While the safety of 40 mg/m² was investigated, eligible but heavily pretreated patients were initially recruited at 28 mg/m² with the possibility in inpatient dose escalation.

MAD was defined as 60 mg/m² with first-course DLT in the 2 patients and grade 4 neutropenia observed in all of the patients treated at that dose. Accrual at the two preceding levels of 40 and 50 mg/m² was extended with the same proviso of "assigning" the dose according to the extent of prior treatment and the possibility of inpatient dose escalations from 40 to 50 mg/m². In so doing, an adequate amount of toxicity data at doses suitable for Phase II evaluation became available with a still acceptable overall duration of the study (17 months). This dose-escalation scheme also allowed the majority of the patients on the study to be treated at levels within the therapeutic range and, in part, accounts for the high level of antitumor activity observed.

The second salient feature is the adoption of clear protocol criteria for dose omission on days 8 and 15, which necessitated many missed doses and questioned the safety of such frequent dosing of an agent of which the major toxicity was myelosuppression. Defining specific dose omission criteria highlighted this problem and allowed an effort to be made to establish the optimal duration of treatment given on a weekly regimen. The

observation that ANC nadir occurred at the time of the third weekly dosing on day 15, and that, in case of treatment omission, ANC recovered to baseline the following week, suggested that shortening the duration of treatment from 3 to 2 consecutive weekly administrations followed by 1 week of rest might improve the feasibility of the regimen. This new schedule was then evaluated on a limited number of patients at the MTD of 50 mg/m² on the 28-day schedule.

Overall, the main DLTs of BMS-184476 were diarrhea and selective, short-lasting neutropenia, usually appearing between days 8 and 15, associated with very few neutropenia-related complications. Similar toxicities were observed on the alternative Phase I trial of BMS-184476, where treatment was given once every 21 days (9, 11). In this study the median time to neutrophil nadir was 11 days (range, 8–15). On the multiple dosing schedule the nadir was somewhat later and more profound at a comparable dose of BMS-184476 (Table 4).

Notwithstanding the limited number of patients treated and possible differences in patient selection, it appears that treatment at 50 mg/m² on days 1 and 8 of a 21-day schedule was associated with better tolerability when compared with dosing on days 1, 8, and 15 of a 4-weekly schedule. Patients developed less nonhematological toxicity but also little reported cumulative toxicity, with 6 patients receiving 4 or more courses.

An alternative protocol design could have included the necessity to omit doses because of neutropenia as part of the DLT definition. However, we feel that this would not have altered the dose escalation pattern, because on the 4-weekly

schedule the first course on which a dose was omitted was the second or subsequent cycle of treatment in a substantial proportion of cases (2 of 5 patients at 40 mg/m² and 6 of 15 patients at 50 mg/m²), and dose-defining DLT was applied to the first course only.

The systemic exposure to BMS-184476, after a 1-h i.v. infusion of 7, 28, 40, 50, and 60 mg/m² doses appeared to increase in a ratio that was similar to the dose increment. Plasma concentrations were quantifiable up to 24 h in a majority of patients at the lower dose levels of 7 and 28 mg/m², whereas quantitation up to 48 h was consistently obtained at doses \geq 40 mg/m². These observations were consistent with the dose-related increases in C_{max} and AUC(24 h). Overall, the PKs of BMS-184476 at the clinically relevant doses of 50 and 60 mg/m² appeared to be independent of dose. In addition, the PK parameter values obtained for BMS-184476 and its metabolites were not statistically different on days 1 and 15, indicative of time-independent PKs of BMS-184476 after weekly dosing. The VSS values were greater than total body water (42 liters) suggesting extravascular distribution and tissue binding of BMS-184476 in cancer patients. Overall, the dose- and time-independent PKs of BMS-184476 should result in predictable dose-toxicity and dose-efficacy relationships in the therapeutic dose range. The concentrations of the circulating metabolites were low compared with the concentrations of the parent drug, and the cumulative percentage of dose excreted in the urine as metabolites accounted for <1% of the administered dose. It was interesting to note that the systemic exposure to paclitaxel appeared to be at the lowest extent (compared with BMS-246178 and BMS-246180) thereby indicating negligible contribution of paclitaxel to the activity and toxicity attributed to BMS-184476.

Renal elimination of BMS-184476 and its metabolites were low suggesting extensive biliary excretion. The dose-independent PKs of BMS-184476 suggest lack of saturation of metabolic and biliary elimination pathways in the therapeutic dose range.

Objective responses were reported at both the 40 and 50 mg/m² dose levels in patients with breast cancer (pretreated with anthracyclines but not taxanes) and NSCLC (pretreated with platinum containing combinations but not taxanes). These very preliminary results of activity suggest that doses of 40 and 50 mg/m² could have the same therapeutic potential and could be selected for Phase II studies with BMS-184476 given either as a single agent or in combination, as a salvage or as first-line therapy of paclitaxel-sensitive tumor types.

In the single-dose every 21-day schedule, the MTD, which is also the recommended dose for Phase II, was 60 mg/m² given every 21 days, corresponding to a DI of 20 mg/m²/wk. This is a lower DI than that achieved with the schedule reported in this paper (Table 3). The evaluation of a continuous weekly schedule is currently ongoing at 35 mg/m², and the first available data suggest that a higher DI and an improved tolerability can be achieved with this schedule.

The selection of one schedule for Phase II development is still empirical, and should be also based on patient characteristics (with/without prior treatment) and tumor type, as well as on study design and the treatment regimen being used (single agent or combination). The lack of significant neurotoxicity prompts

the development of combinations with platinum compounds (14), whereas the evaluation of combinations with anthracyclines is supported by the potential of reduced cardiotoxicity because of a lower content of Cremophor EL and by data from myocardial cell studies showing that BMS 184476 causes no increase in the production of cardiotoxic doxorubicin metabolites, unlike paclitaxel or docetaxel (15). The higher incidence of mucositis observed with the single intermittent dosing, and the similar time to nadir for ANC of BMS-184476 and anthracyclines would need to be taken into consideration when designing Phase I combination studies. It is possible that the reduced amount of Cremophor EL used might decrease PK interactions with other agents. The evaluation of these aspects and of their possible implications in taxane-related toxicities is of high priority for a rational development of this derivative of paclitaxel.

The conclusion from this study of a weekly regimen of BMS-184476 is that treatment at 50 mg/m² on days 1 and 8 given every 21 days is associated with better tolerability, as compared with 50 or 40 mg/m² given on days 1, 8, and 15 every 28 days, with comparable mean DI (\pm SD; 50 mg/m² on a 28-day schedule: 28.6 \pm 6.6; 50 mg/m² on a 21-day: 28.6 \pm 3.7; and 40 mg/m² on a 28-day: 24.9 \pm 5.0). Preliminary antitumor activity has also been seen with both schedules.

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