Preclinical Pharmacology of BMS-275183, an Orally Active Taxane

William C. Rose,1 Byron H. Long, Craig R. Fairchild, Francis Y. F. Lee, and John F. Kadow

ABSTRACT
BMS-275183 is a taxane, the mechanism of action of which is like other known taxanes, and is the polymerization of tubulin. BMS-275183 given p.o. was as effective as i.v. paclitaxel in five tumor models [murine M109 lung and C3H mammary 16/C; and human A2780 ovarian (grown in mice and rats) and HCT/pk colon]. It was active in one other tumor model (human HCT-116 colon) but inferior to parenteral paclitaxel. BMS-275183 given p.o. was active in a human, hormone-dependent, prostate tumor model, CWR-22, and just as effective as anti-androgen chemotherapy. In a schedule dependency study, increasing the interval of time between oral administrations resulted in greater cumulative dose tolerance and improved therapeutic outcome. Oral BMS-275183 was evaluated as a combination therapy in conjunction with i.v. paclitaxel. Therapeutic advantages were evident for tumor-bearing mice that received the oral taxane either after induction chemotherapy or between courses of such treatment. BMS-275183 is currently in Phase I clinical trials at multiple sites.

INTRODUCTION
Paclitaxel, the active ingredient in Taxol, is a schedule-dependent drug that provides its benefits, traditionally, from prolonged tumor exposure times (1). Clinically, i.v. infusions of Taxol for 1–3 h are typically used and efficacious (2–5). Clinical utility has also been demonstrated recently using repetitive, once-weekly administrations of moderate (i.e., other than maximally tolerated) doses of Taxol or the other marketed taxane, Taxotere (2, 5–10). An oral taxane would be ideal for such low (11–13), and neither it nor Taxotere have oral efficacy in preclinical models (14, 15). Poor passive absorption and active efflux (because of P-glycoprotein) are considered to be the major barriers to oral bioavailability (12). A p.o.-administered effective taxane would offer both an attractive alternative from the parenteral format of current clinical taxane usage and a potential therapeutic advantage because of the many avenues of scheduling yet to be investigated.

The goal of our oral taxane analogue program had been to identify and develop a compound with good oral bioavailability, having activity at least comparable with i.v. administered paclitaxel, and possessing no unmanageable toxicities. BMS-275183 is the culmination of many years of research to achieve the aforementioned goals. We describe herein the preclinical pharmacology pertaining to its tubulin binding, cytotoxicity, and antitumor activity.

MATERIALS AND METHODS
Cell Lines. The following cell lines were used: HCT-116 human colon carcinoma; a MDR2 variant, HCT-116/MDR, which overexpresses p170 glycoprotein (16); A2780 human ovarian carcinoma; and A2780/tax cells (obtained from Dr. T. Fojo, National Cancer Institute, Bethesda, MD). A2780/tax is a paclitaxel-resistant cell line that does not overexpress p170 glycoprotein but has point mutations in the M40 isotype of β-tubulin (17). Purified tubulin isolated from these resistant cells is refractory to polymerization by paclitaxel. The cell lines were maintained as described previously (18).

Compounds. For in vitro cytotoxicity evaluations, BMS-275183 and paclitaxel were dissolved in DMSO as a stock solution of 10 mg/ml and stored at −20°C. For all in vivo antitumor testing except that described as a “schedule optimization study,” these compounds were dissolved initially in a 50:50 mixture of Cremophor EL (cremophor) and ethanol, followed by aqueous dilution as described previously. In the schedule optimization study, BMS-275183 was dissolved in 75% polyethylene glycol and 25% Tween 80. Casodex was suspended in 80% polyethylene glycol and 20% Tween 80. Compounds were administered in volumes based on 0.01 ml (mice) or 0.005 ml (rats/g of body weight).

Animals. Conventional and athymic (“nude”) mice, 5–6 weeks of age, and nude rats, 4–6 weeks of age, purchased from Harlan Sprague Dawley (Indianapolis, IN), were quarantined for ~3 weeks before their use for tumor propagation and drug efficacy testing. They were fed food and water ad libitum. All studies involving these animals were conducted in accordance with NIH (Bethesda, MD) and Bristol-Myers Squibb Company animal care and use guidelines.

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2 The abbreviations used are: MDR, multidrug resistant; IC50, the concentration required to inhibit cell growth by 50% relative to control tumor growth; LCK, gross log10 cell kill; MTD, maximum tolerated dose; OD, optimal dose; T, drug-treated group; C, control group.
Tumors. The following tumors were maintained in the indicated host strain of mouse: murine Mad109 lung carcinoma (M109) in BALB/c mice; murine Mammary 16/C breast carcinoma (Mam 16/C) in C3H mice; human A2780 ovarian carcinoma, CWR-22, a human, androgen-dependent, prostate carcinoma, and both HCT-116 and HCT/pk colon carcinomas (a subline of HCT-116 with a MDR basis, and other possible unknown mechanisms, for partial paclitaxel resistance) in nude mice. For efficacy testing, M109 tumors were implanted in (BALB/c × DBA/2)F1 hybrid mice, Mam 16/C tumors were implanted in C3H mice, and human tumors were implanted in nude mice. All tumor implants for efficacy testing were s.c. A2780 tumors were also implanted s.c. in nude rats for efficacy studies (after passage in nude rats).

In Vitro Assays. The in vitro cytotoxicity of BMS-275183 and paclitaxel in human tumor cell lines sensitive and resistant to paclitaxel was assessed using a tetrazolium-based colorimetric assay (19). The concentration of a compound required to inhibit cell growth by 50% relative to control tumor growth (IC_{50}) was determined after 72 h of drug exposure. In a study designed to determine the effect of varying times of drug exposure on IC_{50}s, A2780 cells were treated for 72, 6, or 2 h with paclitaxel or BMS-275183. After drug exposure for 6 or 2 h, cells were washed and put into drug-free medium until 72 h elapsed, at which time the IC_{50} was determined.

For the in vitro tubulin polymerization assay, calf brain tubulin was prepared following the procedure of Williams and Lee (20). Quantification of tubulin polymerization potency was accomplished following a modified procedure of Swindell et al. (21).

Antitumor Testing. A detailed description of the methods used to assess antitumor effects has been provided previously (18). Briefly, therapeutic results are presented in terms of either cures and/or primary tumor growth inhibition determined by calculating the relative median times for drug-treated (T) and control (C) groups of mice to grow tumors of a predetermined “target” size and expressed as T-C values (in days). For acute treatment regimens (10 days duration or shorter), the delays in tumor growth are presented in terms of LCK. Statistical evaluations of data were performed using Gehan’s generalized Wilcoxon test for comparisons of time to reach tumor target size or Fisher’s exact test for cure rate comparisons. Statistical significance was declared at P < 0.05. Group sizes typically consisted of seven or eight mice or seven rats.

Definitions of MTD and OD have been published previously (18). Therapeutic results were reported at the OD, i.e., that yielding the best effect without exceeding the MTD. OD was often, but not always, synonymous with the MTD.

RESULTS

Mechanism of Action. BMS-275183 was evaluated for its ability to polymerize tubulin. The concentrations of the analogue and paclitaxel required to achieve the common end point used in this assay were compared. BMS-275183 had the ability to polymerize tubulin with a potency similar (0.5-fold) to that of paclitaxel (data not shown).

In Vitro Cytotoxicity. BMS-275183 and paclitaxel were evaluated for its cytotoxicity against HCT-116 human colon carcinoma cells, a MDR subline, HCT-116/MDR, A2780 human ovarian carcinoma cells, and a subline, A2780/txl, with a non-MDR, altered tubulin basis for its resistance toward paclitaxel. These data are summarized in Table 1. The potency of the analogue in the HCT-116 and A2780 cell lines was similar (within 2-fold) to paclitaxel.

In the two paclitaxel-resistant sublines, significantly reduced resistance toward BMS-275183 was found compared with that observed for paclitaxel, suggesting that the analogue may be effective against resistant tumors in vivo. For example, in the HCT-116/MDR cell line, the IC_{50} of BMS-275183 was only 3.9-fold higher than against the parental line. In comparison, paclitaxel showed a loss in potency of >69-fold.

The time that a cell is exposed to paclitaxel is critical for its ultimate cell killing potency both in vitro and in vivo. Therefore, the effect of exposure time on in vitro cytotoxicity was examined in the A2780 cell line (Table 1). Compared with a 72-h drug exposure, shorter exposures of 6- and 2-h durations resulted in similar increases in IC_{50}s (loss of potency) for both paclitaxel and BMS-275183.

In Vivo Antitumor Activity. The optimal antitumor test results (i.e., best outcomes without exceeding the MTD) for BMS-275183 and concomitantly evaluated paclitaxel are shown in Table 2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>HCT-116 IC_{50}</th>
<th>HCT-116/MDR R:S ratio</th>
<th>A2780 IC_{50}</th>
<th>A2780/txl R:S ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>0.0017</td>
<td>&gt;69</td>
<td>0.0028</td>
<td>16.3</td>
</tr>
<tr>
<td>BMS-275183</td>
<td>0.0018</td>
<td>3.9</td>
<td>0.0028</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0890 (32)</td>
<td>Not done</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1877 (67)</td>
<td>0.0046</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not done</td>
<td>0.1497 (48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not done</td>
<td>0.2593 (84)</td>
</tr>
</tbody>
</table>

*c* Drug concentration (μM) that inhibited cell growth by 50% was determined after 72 h of exposure unless indicated otherwise within the A2780 column.

*b* HCT-116/MDR R:S ratio, IC_{50} versus HCT-116/MDR cells divided by IC_{50} versus HCT-116 cells.

£ A2780/txl R:S ratio, IC_{50} versus A2780/txl cells divided by IC_{50} versus A2780 cells.

Values in parentheses are the fold loss in potency for 6- or 2-h exposures relative to 72-h exposure. The results are the average of three separate experiments.
Table 2  Comparative preclinical antitumor activity of BMS-275183 versus concomitantly evaluated paclitaxel

<table>
<thead>
<tr>
<th>Tumor, s.c.</th>
<th>Optimal treatment for BMS-275183a</th>
<th>Gross log cell kill (cures/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schedule, Route</td>
<td>Dose (mg/kg/administration)</td>
</tr>
<tr>
<td>M109</td>
<td>q2d×5; 4, p.o.</td>
<td>25b</td>
</tr>
<tr>
<td>Mam 16/C</td>
<td>q2d×5; 4, i.v.</td>
<td>13 (20b)</td>
</tr>
<tr>
<td>HCT-116</td>
<td>q2d×5; 5, p.o.</td>
<td>16b</td>
</tr>
<tr>
<td></td>
<td>q2d×5; 13, p.o.</td>
<td>45b</td>
</tr>
<tr>
<td></td>
<td>q2d×5; 14, p.o.</td>
<td>60b</td>
</tr>
<tr>
<td></td>
<td>q×9; 14, p.o.</td>
<td>32b</td>
</tr>
<tr>
<td>HCT/pk</td>
<td>q2d×5; 15, p.o.</td>
<td>45b</td>
</tr>
<tr>
<td>A2780</td>
<td>q2d×5; 13, p.o.</td>
<td>65b</td>
</tr>
<tr>
<td></td>
<td>q2d×5; 13, i.v.</td>
<td>36b</td>
</tr>
<tr>
<td></td>
<td>q×9; 14, p.o.</td>
<td>36b</td>
</tr>
<tr>
<td></td>
<td>q4d×3 10, p.o.</td>
<td>6.5b</td>
</tr>
<tr>
<td></td>
<td>q8d×2; 13, p.o.</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>q8d×2; 13, p.o.</td>
<td>12</td>
</tr>
</tbody>
</table>

a OD expressed in mg/kg/administration. Schedule of, e.g., qd×5 = one administration given daily consecutively for a total of five treatments or q2d×5 = every other day administration for five treatments. The number following the semicolon signifies the day of treatment initiation after tumor implant. There were usually seven or eight animals per treatment and control groups. Paclitaxel was administered i.v. either qd (M109), qd×5 (Mam 16/C), q2d×5 (HCT-116), q2d×5 (A2780), q×9 (HCT/pk), q4d×3 (rat A2780), or q2d×5 (all other models).

b MTD reached (may be distinct from OD).

c Smaller (n = 4) than the typical group size used because of a lab error.

BMS-275183 was evaluated p.o. and i.v. in the same M109 experiment. (Note: additional test results in this model are described in the “schedule optimization” experiment, see below). Comparable results were obtained for both p.o.- and i.v.-administered BMS-275183 and i.v. paclitaxel.

BMS-275183 was evaluated p.o. in the Mam 16/C breast carcinoma model. Both the analogue and i.v.-administered paclitaxel achieved similar maximum effects of 2.4 and 3.1 LCK, respectively.

BMS-275183 was administered p.o. to mice bearing the HCT-116 tumor. It was evaluated twice in this tumor model, using two different treatment schedules in one of those studies, and each time produced an active result that was inferior to that of i.v. paclitaxel.

BMS-275183 was evaluated p.o. to mice bearing the A2780 tumor. In the first of two experiments, using an every other day times five (q2d×5) treatment schedule, the therapeutic outcome obtained compared well with the optimal therapy using i.v. paclitaxel. In a second experiment, BMS-275183 was administered p.o. on a consecutive daily schedule of qd×9. Both it and i.v. paclitaxel produced similar cure rates at their ODs.

BMS-275183 was also evaluated i.v. on an intermittent injection schedule in mice implanted with A2780 tumors. At the highest dose evaluated, 36 mg/kg/injection, which was not associated with any deaths and only caused a minimal 1 g of body weight loss (i.e., probably not an MTD), BMS-275183 produced 4.2 LCK, including one of seven cures. Concomitantly tested i.v. paclitaxel produced five of seven cures.

BMS-275183 was evaluated in a paclitaxel-resistant subline of HCT-116, HCT-116/pk. At their respective ODs, both paclitaxel, i.v., and BMS-275183, p.o., produced similar maximum effects.

BMS-275183 was also evaluated p.o. in rats bearing A2780 ovarian carcinoma. In the initial experiment, a q4d×3 dosing regimen was used, which had proven very effective for i.v. paclitaxel. At its MTD, p.o., BMS-275183 produced only a modest effect, whereas i.v. paclitaxel was quite active. In subsequent experiments in this model, BMS-275183 was administered on a q8d×2, p.o., treatment schedule. The analogue cured 100% of the treated rats, but because of a lab accident in the pilot study, only four rats remained in the treatment group. Upon retest, BMS-275183 was again very effective and compared favorably with i.v. paclitaxel.

BMS-275183 given p.o. was as effective as i.v. paclitaxel in five tumor models [murine M109 lung and Mam 16/C breast, and human A2780 ovarian (grown in mice and rats) and HCT/pk colon]. It was active in one other tumor model (human HCT-116 colon) but inferior to parenteral paclitaxel.

BMS-275183 was also given p.o. to mice bearing staged CWR-22 human, androgen-dependent prostate carcinoma. Treatment was given every other day for 11 administrations (q2d×11). Other groups of tumor-bearing mice in the experiment were either castrated or given Casodex. Treatment with Casodex p.o. daily for 30 consecutive days (q2d×30) was as effective (T-C of 29.5 days) as treatment (q2d×11) with the oral taxane (T-C of 42 days), but neither therapy was as efficacious as castration (Fig. 1).

Schedule Optimization Study. BMS-275183 was administered p.o. on several different treatment schedules to mice bearing s.c. M109. A summary of the optimal effects obtained is shown in Table 3. For each schedule, the total duration of therapy was 7 days.

As the interval between oral administrations of BMS-275183 increased, so did the cumulative MTD. In parallel, improved antitumor activity was observed as the interval be-
Cumulative doses that were ineffective (0.1–0.4 LCK) when administered on a daily or twice daily basis, e.g., 56–70 mg/kg, produced >0.6 LCK when administered on q2d or q3d schedule. The best effect was observed using the q6d schedule; a MTD of 90 mg/kg/administration produced 0.9 LCK. This outcome was significantly better ($P < 0.01$) than the 0.1 LCK obtained using the 2qd×7 schedule (but not when compared with the optimum results from any other schedules). With the more effective intermittent schedules, the levels of activity obtained did not vary greatly between the cumulative MTD to half, or slightly less than half, that amount of BMS-275183 (i.e., the slopes of the dose-response curves were gradual on the more effective schedules).

**Combination Therapy with i.v. Paclitaxel.** Two experiments, referred to as A and B, were performed to evaluate the potential utility of administering BMS-275183 in combination with paclitaxel. In experiment A, the oral taxane was administered between courses of induction chemotherapy using i.v. paclitaxel. Mice bearing staged s.c. C3H Mam 16/C tumors received either i.v. paclitaxel alone (qd×5; d.10, d.32) or i.v. paclitaxel plus an additional course of p.o. BMS-275183 initiated 1 week after the end of the first course of i.v. paclitaxel (i.e., paclitaxel qd×5; d.10, d.32 + BMS-275183 qd×5; d.21). Dose response titrations were performed using each treatment approach.

A summary of the outcomes obtained with selected treatment regimens is shown in Table 4. The optimal effect obtained with paclitaxel alone (40.5 days T-C, including two of eight cures) was obtained at a MTD regimen; lesser amounts of paclitaxel on either or both courses of therapy resulted in diminished efficacy. In comparison, when p.o. BMS-275183 was added to certain i.v. paclitaxel courses of treatment, an improvement in overall efficacy was observed, but the results were not statistically different compared with the optimal i.v. paclitaxel regimen. Whereas optimal treatment with paclitaxel alone resulted in some tumor regrowth during the interval between courses of therapy (days 15–32 after tumor implant), the administration of oral taxane between paclitaxel courses suppressed (and even slightly diminished) the median tumor size of this combination treatment group.

In experiment B, the oral taxane was offered as sequential therapy after a single course of induction therapy using i.v. paclitaxel. A summary of the various treatments and outcomes is shown in Table 5. For mice receiving only i.v. paclitaxel, the two top doses evaluated yielded nearly identical therapeutic outcomes (14.3–14.5 days T-C). For groups of mice that re-

![Image](https://clincancerres.aacrjournals.org)
received the induction chemotherapy using paclitaxel but then received one of two different regimens using oral taxane BMS-275183, the benefits of an extra 4 weeks (approximately) of oral taxane therapy are evident. The most effective of the oral taxane therapies did more than prevent tumor progression; they managed to further reduce the tumor burden.

There was a definite dose response associated with the oral taxane treatments such that doses much below the MTD were not capable of adequately suppressing tumor growth. Although these lower doses may have delayed the median time to reach a 1-g tumor, the delay was less than the duration of therapy administered (i.e., the tumor grew in the face of treatment, and the tumor grew in the face of treatment, and the tumor grew in the face of treatment). Similarly, in rats, the use of an every 8th day schedule was much more effective than an every 4th day schedule. Several different administration of schedule effects were conducted, the data indicated in one murine tumor model in which the most careful exami-

DISCUSSION

Paclitaxel (e.g., Taxol) is a major weapon in the modern arsenal against cancer, but it is poorly absorbed p.o. (13). Issues of compliance and reimbursement notwithstanding, there is an interest, by patients and clinicians alike for the identification and development of safe and effective oral chemotherapeutics. The administration of oral chemotherapeutics offers several potential advantages that have formed the basis for the long-standing interest in their development. Where efficacy is not compromised (compared with parenteral alternatives) and safety margins are adequate, these factors should combine to yield good compliance in an educated and monitored patient population with a life-threatening disease (22). Certainly, when faced with a choice among equally safe and efficacious delivery forms, patients have indicated their overwhelming preference for oral versus i.v. chemotherapy (23).

The preclinical efficacy data presented for the oral taxane, BMS-275183, establishes its comparability to paclitaxel. Additional reports concerning its pharmacokinetics, metabolism, and toxicology will be forthcoming.

Results of in vitro experiments with an MDR-overexpressing cell line, HCT/MDR, showed a reduced loss of potency for BMS-275183 compared with paclitaxel. If susceptibility to a P-glycoprotein efflux pump is considered to be a major cause of the lack of oral efficacy and bioavailability (12, 13) of paclitaxel, the relatively modest loss of potency for BMS-275183 in the MDR-overexpressing cell line is consistent with BMS-275183 being active when administered p.o. Shortening the exposure time of cells to BMS-275183 produced a loss in cytotoxic potency similar to that observed for paclitaxel. These results would suggest the advantage of a sustained time of exposure for the analogue.

BMS-275183 was as effective as parenteral paclitaxel in nearly all of the in vivo antitumor assays performed. In mice, good results were obtained using consecutive daily or every other day administration protocols in certain tumor models. But in one murine tumor model in which the most careful examination of schedule effects were conducted, the data indicated that intermittent administrations of BMS-275183 were optimal. Similarly, in rats, the use of an every 8th day schedule was much more effective than an every 4th day schedule. Several different

![Fig. 2](image-url) Effect of BMS-275183 sequential therapy after induction chemotherapy with paclitaxel in mice bearing staged s.c. mammary 16/C carcinoma (experiment B).
treatment schedules will need to be explored in Phase I clinical investigations.

The addition of an oral taxane, BMS-275183, to effective parenteral induction chemotherapy using paclitaxel i.v. resulted in an improvement in the time to reach tumor target size. The increases in time to progression were occasionally greater than the duration of the combination therapy regimens, indicating a further reduction in tumor burden achieved with the combination therapy (or a perturbation in the cytokinetics of the remaining tumor population). It is not known if the mechanism of the antitumor effect caused by BMS-275183 was cytotoxicity toward tumor cells, or antiangiogenesis (24), or both. To make maximum use of effective combination treatments, some reduction in monochemotherapy dose levels may be necessary. For i.v. paclitaxel preclinically, this sacrifice was not detrimental, possibly because of the gradual slope of the dose-response near the MTD (a gradual asymptote). Additionally, there was a dose-response associated with BMS-275183 therapy; as the oral taxane dosage was reduced below its MTD level, antitumor benefits waned. No predominant advantage was seen for either of the two oral taxane regimens (q2d and q4d) evaluated, but the greater latitude in dose selection and slightly superior effects were seen using the more intermittent treatment schedule. The oral taxane BMS-275183 provided therapeutic advantages when applied as combination therapy either between courses of induction chemotherapy or after induction chemotherapy.

Although the preclinical efficacy data support the clinical evaluation of BMS-275183 in all of the therapeutic roles currently established for parenteral taxanes, the efficacy of BMS-275183 when given p.o. provides a basis for nontraditional applications (25). The availability of an oral taxane permits one to assess the benefits of chronic treatment regimens, whether these be daily or weekly, or some variation that nevertheless requires long-term administration schedules. BMS-275183 is currently enrolled in several Phase I clinical trials worldwide with the intent of establishing a safe, effective dose level while investigating several treatment regimens.

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