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ORIGINAL ARTICLE

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Preclinical antitumor activity of two novel taxanes

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Abstract *Purpose*: Two taxane analogs, BMS-184476 and -188797, were evaluated for their in vitro cytotoxicity and in vivo antitumor activity, and compared with paclitaxel and occasionally docetaxel (Taxotere). *Methods*: Cytotoxicity was assessed in vitro using a panel of human tumor cell lines. Several different murine and human tumor models were used in vivo to evaluate the taxane analogs. *Results*: Both compounds were found to have cytotoxic potency similar to paclitaxel and to partially overcome two different forms of paclitaxel resistance. BMS-184476 was found to be clearly superior to paclitaxel in three human xenograft tumor models: A2780 ovarian carcinoma; HCT/pk, a moderately paclitaxel-resistant colon carcinoma; and L2987 lung carcinoma. Additionally, in the clinically derived TAXOL-unresponsive ovarian carcinoma, HOC79, BMS-184476 performed slightly better than paclitaxel and Taxotere. BMS-184476 and paclitaxel were inactive in two murine model systems, M5076 sarcoma and the paclitaxel-resistant M109/txlr lung carcinoma. Against the parental M109 tumor, both BMS-184476 and paclitaxel performed comparably. BMS-184476 was never found to be inferior to paclitaxel. The other taxane analog, BMS-188797, displayed efficacy superior to paclitaxel in four in vivo tumor models: HOC79, HCT/pk, M109, and L2987 carcinomas. Like paclitaxel and BMS-184476, BMS-188797 was inactive versus M5076 sarcoma. *Conclusions*: Two new taxane analogs were characterized as superior to paclitaxel or Taxotere in several in vivo tumor models. Both BMS-184476 and -188797 are currently in phase I or II clinical trials.

Key words Taxanes · Antitumor · Anticancer · Taxol · Taxotere

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Introduction

Paclitaxel is the first member of a novel class of cytotoxic drugs with the ability to promote and stabilize the assembly of tubulin into microtubules, the cellular structure that forms mitotic spindles and is required for chromosome segregation. Paclitaxel displays antitumor activity in vivo versus experimental tumor models and is active clinically (i.e., TAXOL) against a broad range of cancers, including ovarian and breast cancer. Unfortunately, not all tumors respond to treatment with taxanes and relapse among responding patients is the usual eventual clinical outcome.

We have been engaged in a paclitaxel analog program that has explored the potential of this chemotype and have identified two second-generation paclitaxel analogs for clinical development based primarily on improved levels of efficacy. A series of presentations regarding these two compounds has been initiated. For example, their respective chemistries were reviewed recently [4], the in vitro characteristics of one of them [6] and preliminary in vivo preclinical efficacy of the other [8] were also presented. We now describe the detailed in vivo antitumor profiles of the two analogs selected for clinical development.

Materials and methods

Compounds

For in vitro cytotoxicity evaluations, BMS-184476, BMS-188797, and paclitaxel were dissolved in dimethyl sulfoxide as a stock solution of 10 mg/ml and stored at –20°C. For in vivo antitumor testing, unless otherwise described, these compounds were

dissolved initially in a 50/50 mixture of Cremophor EL (cremophor) and ethanol. Following dissolution, which may or may not have been facilitated by either sonification or stirring or both, the solutions were diluted 1:4 with sterile distilled water (BMS-184476 and BMS-188797) or sterile 0.9% NaCl (saline) (paclitaxel). The final contribution of each component of the injection vehicle was 10% cremophor/10% ethanol/80% water (or saline). Stock solutions of taxanes in cremophor/ethanol were kept refrigerated upon formation, and for as many as 10 days thereafter (i.e., during the duration of the treatment periods). Prior to each day's required injections, the stock solutions of taxanes were diluted with water (or saline for paclitaxel) and used (generally) within 1 h of preparation. Docetaxel (Taxotere) was dissolved in a 50/50 mixture of Tween 80 and ethanol followed by a 1:9 dilution, within 1 h of use, with 5% dextrose water.

Cell lines

The HCT-116 human colon carcinoma cell line and a multidrug resistant (MDR) variant, HCT-116/MDR, which overexpresses P-glycoprotein 170 (pgp) [5], were maintained in McCoy's 5A media and 10% heat-inactivated fetal bovine serum (Life Technologies). A2780 human ovarian carcinoma cells and A2780/tax cells obtained from Dr. T. Fojo (National Cancer Institute, Bethesda, Md., USA) were maintained in improved minimal essential media (GIBCO) and 10% fetal bovine serum (GIBCO). A2780/tax is a paclitaxel-resistant cell line that does not overexpress pgp but has point mutations in the M40 isotype of β-tubulin [2]. Purified tubulin isolated from these resistant cells is refractory to polymerization by paclitaxel.

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, Ind., USA), were quarantined for approximately 3 weeks prior to 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 and our Bristol-Myers Squibb Company animal care and use guidelines.

Tumors

The following tumors were passaged in the indicated host strain of mouse: murine Madison 109 lung carcinoma (M109) in Balb/c mice; murine M109/txlr, a subline of M109 with developed resistance (pgp MDR-based mechanism of drug resistance) toward paclitaxel, in Balb/c mice; murine M5076 sarcoma in C57Bl/6 mice; and human A2780 and HOC79 ovarian carcinomas, L2987 lung carcinoma, and HCT/pk colon carcinoma (a subline of HCT-116 with a MDR basis, and other possible unknown mechanisms, for partial paclitaxel resistance) in nude mice. With regard to efficacy testing, M109 and M109/txlr tumors were implanted in (Balb/c x DBA/2) F1 hybrid mice, M5076 tumors were implanted in (C57Bl/6 x DBA/2) F1 hybrid mice, and human tumors were implanted in nude mice. All tumor implants for efficacy testing were subcutaneous (s.c.), except HOC79 implants, which were intraperitoneal (i.p.), M109/txlr implants, which were intramuscular (i.m.), and one M109 experiment in which M109 was also implanted i.m. (bilaterally implanted with M109/txlr, i.e., on the opposite leg). A2780 tumors were also implanted s.c. in nude rats for efficacy studies (following passage in nude rats).

In vitro assays

The in vitro cytotoxicity of the taxane derivatives and paclitaxel in human tumor cell lines sensitive and resistant to paclitaxel was assessed using a tetrazolium-based colorimetric assay in which MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) is metabolically converted in live cells to a reduced form that absorbs light at 492 nm [7]. IC50 values, defined as the concentration required to inhibit cell growth by 50% relative to control tumor growth, were determined after 72-h drug exposures. The data presented represent the average of from 3 to 5 experiments per compound.

Antitumor testing

Therapeutic results are presented in terms of: (1) increases in lifespan reflected by the relative median survival time (MST) of treated (T) versus control (C) groups (i.e., %T/C values); (2) cures; and (3) primary tumor growth inhibition determined by calculating the relative median times for T and C mice to grow tumors of a predetermined ''target'' size (1 g for s.c. M109, M5076, and A2780 tumors, 0.5 g for all other s.c. and i.m. tumor models) and expressed as T-C values (in days). The activity criterion for tumor inhibition/reduction was a delay in primary tumor growth consistent with ≥1 gross $\log_{10}$ cell kill (LCK). The absolute T-C value needed to attain this level of efficacy varied from experiment to experiment and depended upon the tumor volume doubling time (TVDT) of the control mice in each study (i.e., LCK = T-C/TVDT × 3.32). When cure rates were ≥50%, they were described in place of LCK. A mouse was considered cured when no mass larger than 35 mg was present at the site of tumor implant after a number of days post treatment had elapsed equivalent to > 10 TVDTs in that experiment. Tumor weights were determined using the formula, Weight in mg = a × $b^2/2$, where ''a'' is the length of a tumor and ''b'' is the width expressed in millimeters. Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test [1] for comparisons of time to reach tumor target size and lifespan profiles, or Fisher's exact test [9] for cure rate comparisons. Statistical significance was declared at $P < 0.05$. The activity criteria for increased lifespan in the i.p. HOC79 and s.c. M5076 models was a T/C of ≥135%, and 125% in the s.c. M109 model. Group sizes typically consisted of eight mice or seven rats. Compounds were typically evaluated at a minimum of three dose levels per experiment.

Treated mice dying prior to having their tumors reach target size were considered to have died from drug toxicity. No control mice died bearing tumors less than target size. Groups of mice with more than one death attributable to drug toxicity were considered to have had excessively toxic treatments and their data were not used in the evaluation of a compound's antitumor efficacy. A maximum tolerated dose (MTD) was defined as one whose toxicity approached but did not attain the degree of lethality just described as being excessive. Therapeutic results were reported at the optimal dose (OD), often, but not always, synonymous with the MTD. Paclitaxel (or Taxotere) was included in each experiment at two or three dose levels intended to approximate the MTD, and administered on a treatment schedule found historically to be very effective, if not optimal, for each particular tumor model.

Results

BMS-184476

Cytotoxicity testing

Evaluation of the in vitro cytotoxicity of BMS-184476 against two human tumor cell lines, HCT-116 and A2780, revealed that this compound was comparable in potency to paclitaxel after a 72-h drug exposure (Table 1). The analog was also evaluated against two paclitaxel-resistant sublines of these tumor cells to determine its ability to overcome two different mechanisms of resistance to paclitaxel (Table 1). The level of

resistance to BMS-184476 displayed by either the pgp170-mediated MDR cell line, HCT/MDR (12-fold resistance), or the altered tubulin-mediated paclitaxel-resistant A2780/tax cell line (5-fold resistance), was less severe than the resistance manifested toward paclitaxel (106- and 14-fold, respectively). Although substantially reduced, the levels of resistance to BMS-184476 remain significant for these resistant cell lines.

Antitumor testing

BMS-184476 was evaluated i.v. in several in vivo tumor models where we have established an extensive database on taxane analogs. It was typically compared relative to one of the clinically approved taxanes, paclitaxel or Taxotere, also administered i.v. A summary of the optimum test results is presented in Table 2.

M109 and M109/txlr murine lung carcinomas

BMS-184476 was evaluated on a qd × 5 treatment schedule, beginning on day 4 post tumor implant with s.c. M109; paclitaxel was included as a reference compound. The novel analog produced a maximum 1.0 LCK at an OD of 13 mg/kg per injection (24 mg/kg per injection was the MTD). Paclitaxel achieved an equivalent 0.9 LCK at its OD of 40 mg/kg per injection. There was no significant difference between lifespan increases achieved with BMS-184476 and paclitaxel (T/C values of 137% and 130%, respectively).

In M109 experiment no. 446, performed in parallel with M109/txlr experiment no. 39, M109 and M109/txlr tumor fragments were implanted i.m. bilaterally in opposing hind legs. Treatment with BMS-184476 and paclitaxel produced identical maximum LCK of 0.7 (marginal effectiveness) in the parental tumor line, but were both inactive (0.1–0.2 LCK) against the M109/txlr tumor.

M5076 murine sarcoma

Neither paclitaxel nor BMS-184476 was active against the paclitaxel-insensitive M5076 murine sarcoma, as demonstrated by the inability of these taxane analogs to achieve 1 LCK and/or %T/C of 135%.

A2780 human ovarian carcinoma

In the initial experiment comparing the activities of BMS-184476 and paclitaxel versus staged s.c. implanted human ovarian A2780 tumors, all treatments were initiated on day 8 post tumor implant when tumors ranged from 100 to 200 mg. BMS-184476 cured all 8 mice at a dose of 30 mg/kg per injection. Paclitaxel was quite active, 6.1 LCK, but no cures were realized. The difference in cure rates is statistically significant ($P < 0.001$). These comparative optimal effects are shown graphically in Fig. 1.

Table 1 In vitro cytotoxicity of taxane analogs and paclitaxel in paclitaxel-resistant tumor cell lines

Compound	IC50 values (nM)[a]			
	HCT-116	HCT/MDR	A2780	A2780/tax
Paclitaxel	3.6	375 (106[b])	4.5	62 (14)
BMS-184476	2.1	25 (12)	3.0	16 (5.3)
BMS-188797	2.3	156 (68)	6.1	35 (5.8)

[a] Cytotoxicity was determined after 72 h exposure. Data shown represent an average of 3–5 experiments per compound
[b] Value in parentheses is fold resistance relative to corresponding parental cell line

Table 2 Summary of selected preclinical antitumor activity of BMS-184476 (*LCK* $\log_{10}$ cell kill, *c*/*t* cures/total, *OD* optimal dose)

Tumor site	BMS-184476				Paclitaxel or Taxotere[d]
	Experiment no.	Schedule	OD[a]	LCK (c/t)	LCK (c/t)
M5076, s.c.	132	q2d × 5;1	25[b]	0.3	0.6
M109, s.c.	444	qd × 5;4	13 (24[b])	1.0	0.9
M109, i.m.	446	qd × 5;4	18[b]	0.7	0.7
M109/txlr, i.m.	39	qd × 5;4	18[b]	0.2	0.1
A2780, s.c.	96-04	q2d × 5;8	30[b]	(8/8)	6.1 (0/8)
	75	q2d × 5;13	20[b]	(6/8)	(4/8)[d]
	82	q2d × 5;14	16 (22[b])	3.2	2.8
	90 rat	q2d × 5;7	10[b]	3.3	2.5
HCT/pk, s.c.	8	q2d × 5;10	24[b]	(6/8)	2.8 (1/8)
	10	q2d × 5;13	20[b]	2.9 (1/8)	1.6 (1/6)
L2987, s.c.	133	q2d × 5;26	22[b]	2.6 (0/7)	1.3 (0/8)
	134	q2d × 5;25	28[b]	4.9 (2/8)	Not done
	134	q4d × 3;25	80[b]	6.7 (0/6)	Not done
	134	q8d × 2;25	80/100	4.3 (0/8)	Not done
HOC 79, i.p.	12	q2d × 5;13	24[b]	293[c]	247[c,d]
	13	q2d × 5;12	20[b]	321[c] (1/7)	273[c]

[a] Optimal dose, expressed in mg/kg per injection, i.v
[b] Maximum tolerated dose (MTD) probably reached
[c] Data shown are median survival time % T/C values
[d] Taxotere, rather than paclitaxel, was used as standard

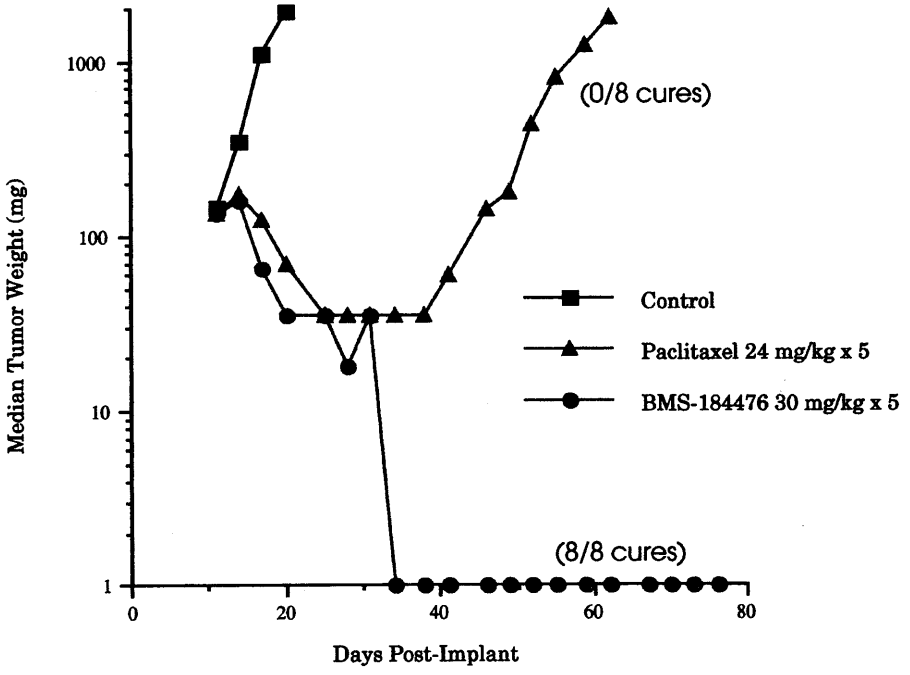

Fig. 1 Optimal antitumor effects of BMS-184476 and paclitaxel versus staged A2780 human ovarian cancer. Both compounds were administered q2d × 5 i.v., beginning on day 8 post tumor implant, at the per injection dose levels indicated. The incidence of cured mice/total is reported on the graph for each compound

A second A2780 tumor experiment (no. 75) was conducted to compare BMS-184476 with Taxotere. In this test, treatment was delayed until day 13 post tumor implantation when most tumors were approximately 250 mg in size, or 1% of the mouse body weight (i.e., larger tumors than in the previous study shown in Fig. 1). Optimal treatment with BMS-184476, 20 mg/kg (q2d × 5), resulted in six of eight cures. Taxotere, at its OD, produced three of eight cures using the identical q2d × 5 schedule, and four of eight cures on a slightly more protracted q4d × 4 schedule. In a third study, no. 82, treatment was delayed until day 14 post tumor implant. Paclitaxel was included as the reference drug and produced a maximum 2.8 LCK, whereas optimal treatment with BMS-184476 yielded 3.2 LCK. No cures were obtained with either compound in producing these effects.

The final A2780 experiment involving BMS-184476 was conducted using nude rats. Treatment with paclitaxel at 8 mg/kg per injection, q2d × 5 i.v., beginning on day 7 post tumor implant yielded a maximum 2.5 LCK. Using the same schedule, but an OD of 10 mg/kg per injection, BMS-184476 produced a slightly greater LCK of 3.3.

HCT/pk human ovarian carcinoma (an MDR tumor model)

BMS-184476 was compared with paclitaxel in the HCT/pk human colon carcinoma model (Fig. 2). HCT/pk was established by exposing parental HCT-116 cells in vitro to concentrations of paclitaxel that mimic clinically achievable plasma levels. This resulted in a MDR tumor model that expresses elevated levels of the mdr-1 gene product, gp 170, and is modestly cross-resistant in vivo and in vitro to several anticancer agents, including paclitaxel (unpublished data). In this experiment, optimal treatment with BMS-184476 (24 mg/kg per injection, i.v. q2d × 5) yielded six of eight cured mice. In comparison, optimal treatment with paclitaxel produced 2.8 LCK with only one of eight mice cured. The difference in cure rates is statistically significant ($P < 0.05$). The parent tumor, HCT-116, does not express the MDR phenotype and is highly sensitive to taxanes.

In a second experiment involving this tumor model, but with treatment initiation delayed until day 13 post tumor implant (i.e., larger tumors at the start of treatment than in the initial HCT/pk study), optimal treatment with BMS-184476 (20 mg/kg per injection, i.v. q2d × 5) resulted in 2.9 LCK with one of eight mice cured. In comparison, optimal treatment with paclitaxel produced 1.6 LCK with one of six mice cured.

L2987 human lung carcinoma

BMS-184476 was also tested in the human lung carcinoma, L2987. In experiment no. 133, the tumors were staged to between 100 and 270 mg and BMS-184476 produced 2.6 LCK (no cures) at a dose of 22 mg/kg per injection, q2d × 5 i.v. Paclitaxel, at its OD, produced only 1.3 LCK and no cures. The difference in maximum LCKs between BMS-184476 and paclitaxel was marginally significant ($P = 0.05$).

A second L2987 experiment no. 134, similar to experiment no. 133 but without paclitaxel included, was performed to evaluate the schedule optimization of i.v. BMS-184476. A maximum dose of 100 mg/kg per injection of the taxane analog was administered safely on a

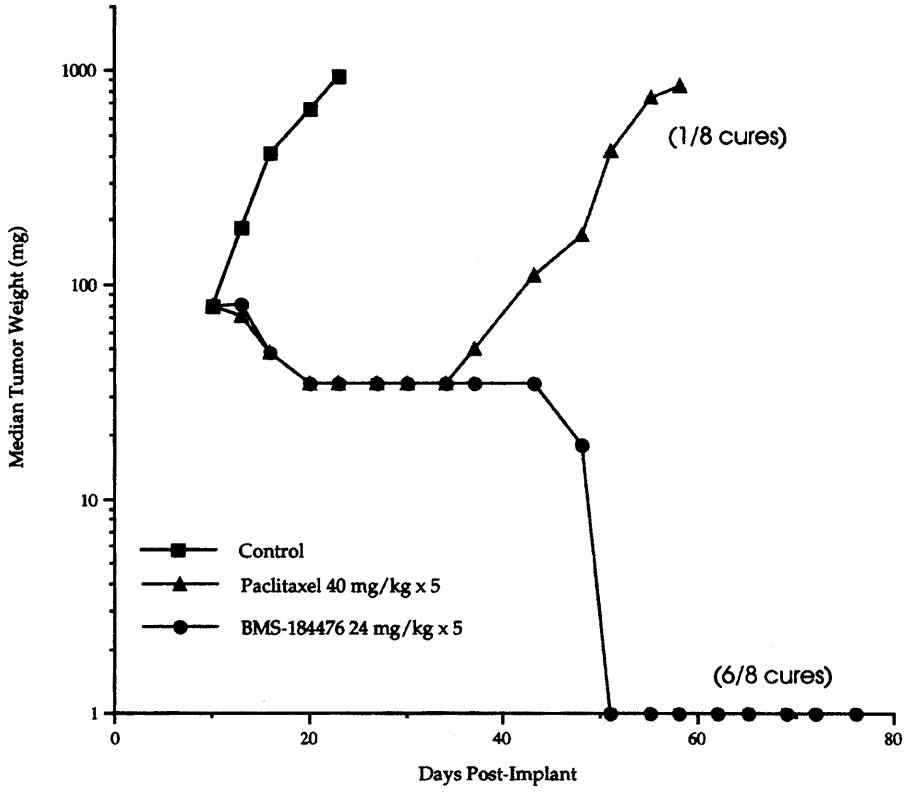

Fig. 2 Optimal antitumor effects of BMS-184476 and paclitaxel versus staged s.c. HCT/pk multidrug resistant human colon carcinoma. BMS-184476 was administered i.v. every other day starting 8 days after tumor implantation

q8d × 2 schedule; further dose escalation was prevented due to solubility constraints. Within this limitation, a dose of 80 mg/kg per injection proved optimal, producing 4.3 LCK with no cures. In comparison, the usually used schedule of treatment, q2d × 5, yielded 4.9 LCK, with two of eight mice cured, at an OD of 28 mg/kg per injection. A better result with regard to LCK, 6.7, but without any cures, was achieved using 80 mg/kg per injection (also a MTD) on a q4d × 3 schedule. The differences in efficacy (cures and LCK considered) obtained using the three schedules were not great and no clear trend in optimal scheduling was apparent. It should be noted however, that the cumulative MTD for BMS-184476 on the q4d × 3 schedule was 240 mg/kg, nearly twice the cumulative MTD of the analog on the q2d × 5 schedule, 140 mg/kg.

HOC79 clinically-derived TAXOL-unresponsive ovarian carcinoma

The HOC79 tumor model was developed from a clinical sample of ovarian carcinoma derived from a woman whose tumor had relapsed following therapy with cisplatin, doxorubicin, and Cytoxan and finally progressed in the face of TAXOL therapy. Compared with other similar clinical specimens of ovarian carcinoma adapted to grow in nude mice during the same time period, we found HOC79 to be the most resistant to paclitaxel treatment.

Optimal treatments with BMS-184476 and Taxotere were compared in HOC 79 experiment no. 12. BMS-184476 produced a maximum T/C of 293%. In comparison, optimal treatment with Taxotere yielded a slightly lower 247% T/C ($P < 0.05$). These two optimum results are shown in Fig. 3. In a second experiment, no. 13, BMS-184476 was compared with paclitaxel. Optimal therapy with BMS-184476 resulted in a maximum T/C of 321%, with 1 of 7 mice cured, slightly better than the T/C of 273% for paclitaxel at its OD ($P < 0.05$).

BMS-188797

In vitro assays

In the in vitro cytotoxicity assays performed (Table 1), the concentration of BMS-188797 needed to inhibit cell growth by 50% was comparable to paclitaxel against the HCT-116 and A2780 cell lines. The level of resistance to BMS-188797 shown by the pgp-mediated MDR cell line, HCT-116/MDR (68-fold), while reduced relative to paclitaxel, was substantial and indicated little likelihood of BMS-188797 circumventing MDR-based resistance. The sixfold resistance found in the altered tubulin-mediated paclitaxel-resistant cell line, A2780/tax, was marginally better than the 14-fold resistance ratio obtained for paclitaxel.

Antitumor testing

BMS-188797 was evaluated in vivo in several tumor models where we have established an extensive database

on taxane analogs. It was compared relative to paclitaxel. A summary of the optimum test results is presented in Table 3.

M5076 murine sarcoma

Neither paclitaxel nor BMS-188797 was active against the paclitaxel-insensitive s.c. implanted M5076 murine sarcoma, as demonstrated by the inability of either taxane to achieve the minimum criteria for antitumor activity (1 LCK or T/C > 135%).

M109 murine lung carcinoma

Against s.c. M109, BMS-188797 evaluated qd × 5 i.v., produced a 2.3 LCK at an OD and MTD of 24 mg/kg per injection. The LCK was superior ($P < 0.01$) to the 1.3 LCK caused by concomitantly evaluated paclitaxel. The MTD of paclitaxel was 30 mg/kg per injection, qd × 5 i.v. There was no statistically significant difference in the percentage T/C values achieved with BMS-188797 (183%) and paclitaxel (T/C 172%).

A2780 human ovarian carcinoma

Neither marketed reference taxane was used in the first experiment (no. 73) in which BMS-188797 demonstrated curative potential in the human A2780 ovarian carcinoma model. Subsequently, in experiment no. 82, using slightly larger tumors than were used in the initial experiment, BMS-188797 was compared with paclitaxel. The analog achieved an optimal effect at its OD (and MTD) of 24 mg/kg per injection that was similar to paclitaxel at its OD (and MTD) of 36 mg/kg per injection, 3.5 LCK versus 2.8 LCK, respectively.

HCT/pk human colon carcinoma

In its first evaluation in this model (experiment no. 9), BMS-188797 produced > 3.1 LCK including three of seven cures. In a subsequent study (no. 11), the analog was compared with paclitaxel. As shown in Fig. 4, optimal treatment with BMS-188797 (24 mg/kg per injection, q2d × 5 i.v.) against staged tumors resulted in 4.6 LCK accompanied by three of seven cures (assessed on day 96 post implant). In comparison, concomitantly evaluated

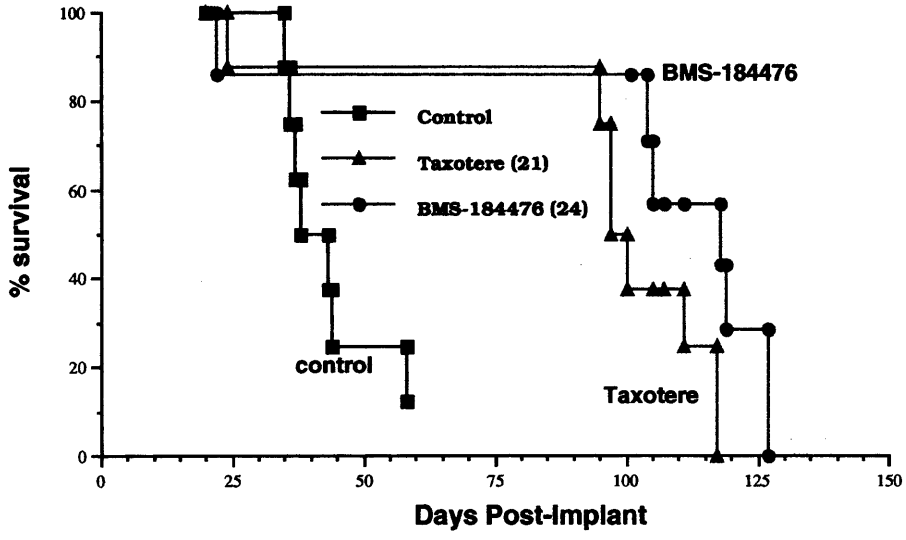

Fig. 3 Optimal antitumor activities of BMS-184476 and Taxotere on the survival of nude mice implanted orthotopically (i.p.) with HOC79 human ovarian carcinoma. All treatments were i.v., every other day for five injections, beginning on day 13 post tumor implant; the optimal dose (in mg/kg per injection) is shown in *parentheses* after the compound name

Table 3 Summary of selected preclinical antitumor activity of BMS-188797[a]

Tumor, site	Experiment no.	BMS-188797			Paclitaxel LCK (c/t)
		Schedule	OD[a]	LCK (c/t)	
M5076, s.c.	136	q2d × 5;1	25[b]	0.5	0.3
M109, s.c.	457	qd × 5;4	24[b]	2.3	1.3
A2780, s.c.	73	q2d × 5;12	25[b]	(4/7)	Not done
	82	q2d × 5;14	24[b]	3.5 (0/7)	2.8 (0/8)
HCT/pk, s.c.	9	q2d × 5;15	25[b]	> 3.1 (3/7)	Not done
	11	q2d × 5;12.	24[b]	4.6 (3/7)	1.7 (0/7)
L2987, s.c.	132	q2d × 5;22	10	2.9 (3/8)	Not done
	135	q2d × 5;23	24[b]	> 5.2 (3/8)	3.6 (1/7)
HOC79, i.p.	15	q2d × 5;11	24[b]	326[c] (1/8)	218[c] (0/8)

[a] Optimal dose, expressed in mg/kg per injection, i.v
[b] MTD probably reached
[c] Data shown are median survival time % T/C values

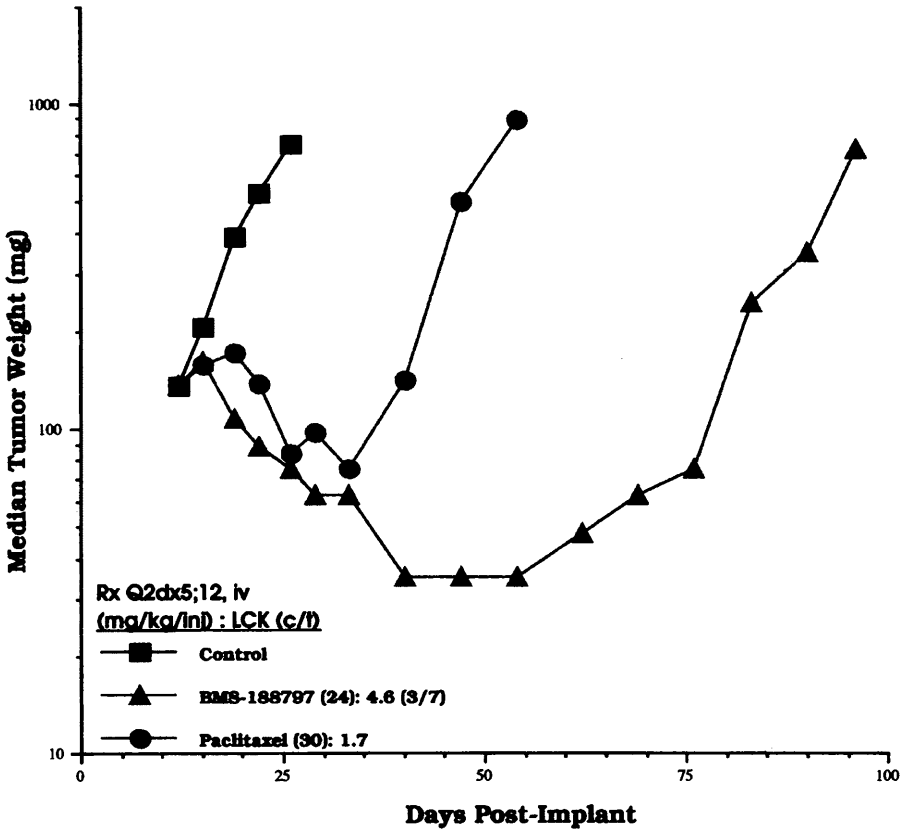

Fig. 4 Optimal antitumor effects of BMS-188797 and paclitaxel versus staged HCT/pk multidrug resistant human colon carcinoma. The optimal dose (in mg/kg per injection) is shown in *parentheses* after the compound name, and the therapeutic effect obtained is presented in terms of gross log cell kill (*LCK*) and any cures (*c*)/total (*t*)

paclitaxel (OD of 30 mg/kg/injection, same regimen) produced 1.7 LCK with no cures. The difference in median time to reach tumor target size (i.e., the basis of LCK determinations) was significant ($P < 0.001$).

L2987 human lung carcinoma

In its first evaluation against the L2987 lung carcinoma (experiment no. 132), BMS-188797 produced 2.9 LCK and three of eight cures. Subsequently, in experiment no. 135, it was compared with paclitaxel. The optimal results obtained using each taxane in that experiment are shown in Fig. 5. Whereas the parent drug achieved a maximum 3.6 LCK with one of seven cures following optimal therapy (20 mg/kg per injection, q2d × 5 i.v.), BMS-188797 produced > 5.2 LCK (nearly statistically significant at $P = 0.08$), with three of eight cures assessed on day 90 post implant, following optimal treatment (24 mg/kg per injection, same regimen). The MTD of paclitaxel in this study was 40 mg/kg per injection, but it was not the OD.

HOC79, a clinically-derived TAXOL-unresponsive ovarian carcinoma

Optimal treatment with BMS-188797 (24 mg/kg per injection, q2d × 5 i.v.) in mice implanted i.p. with HOC79 tumor cells resulted in a T/C of 326%, including one of eight cures determined on day 145 post implant. At the next lower dose, 16 mg/kg per injection, a T/C of 275% with one of eight tumor-bearing (not cured) survivors was obtained. In comparison, optimal treatment with paclitaxel, 20 mg/kg per injection (same regimen) resulted in a T/C of 218% with one of eight tumor-bearing survivors. Due to some early deaths in the optimal BMS-188797 treatment group (perhaps drug-associated, but not possible to determine with certainty), there was not a significant difference between optimal paclitaxel and BMS-188797 treatments; however, there was a significant difference ($P < 0.05$) between optimal paclitaxel treatment and the suboptimal (16 mg/kg per injection) BMS-188797 treatment.

Discussion

Both BMS-184476 and -188797 were selected from a program intent on identifying more-effective taxanes than paclitaxel. The cytotoxic potency of BMS-184476 against two paclitaxel-resistant cell lines in the laboratory (IC50 values of 16–25 nM) may be sufficient to achieve cytotoxic tumor concentrations in patients against similar types of paclitaxel resistance emerging in clinical tumors. This compound also displayed cytotoxic potency comparable to paclitaxel against the parental (paclitaxel-sensitive) cell lines from which the resistant cell lines were derived.

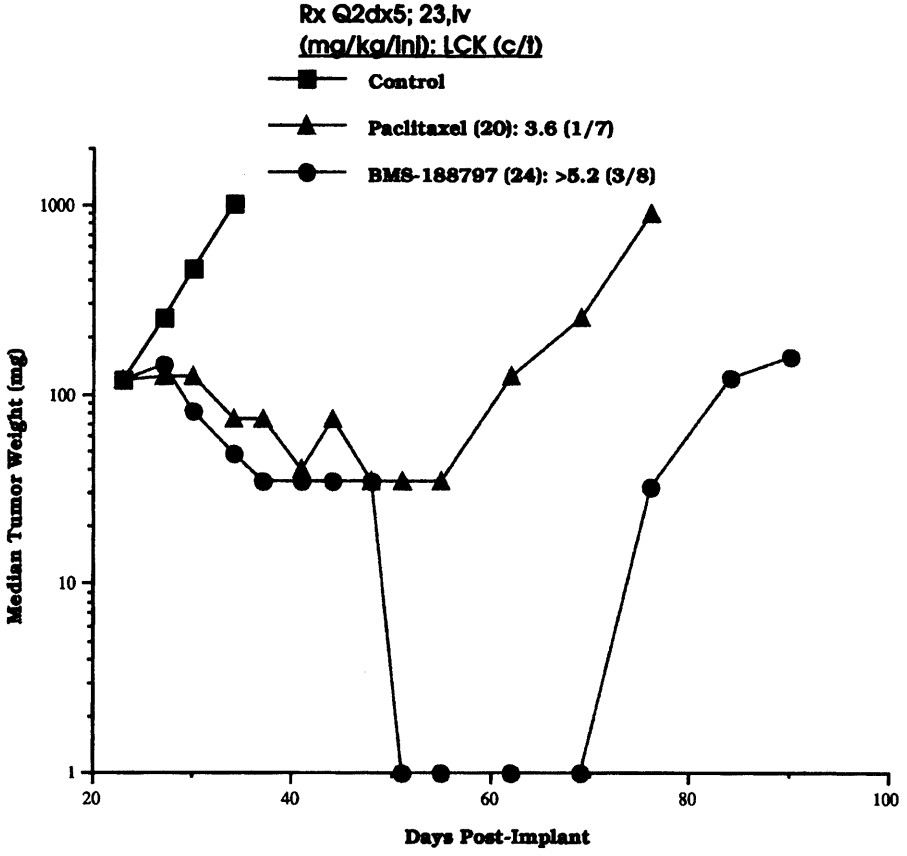

Fig. 5 Optimal antitumor effects of BMS-188797 and paclitaxel versus staged L2987 human lung carcinoma. The optimal dose (in mg/kg per injection) is shown in *parentheses* after the compound name, and the therapeutic effect obtained is presented in terms of gross LCK and any cures (c)/total (t)

BMS-184476 showed efficacy superior to paclitaxel in three in vivo tumor models following i.v. administration. Particularly encouraging is its ability to produce high cure rates (>75%) against moderately staged human tumor xenografts, including a human ovarian tumor and MDR human colon carcinoma tumor model (partially cross-resistant to paclitaxel), results not seen with paclitaxel. The preclinical efficacy data suggest that BMS-184476 has the potential to improve the durability of remissions in paclitaxel-responsive tumors and to possibly increase response rates in paclitaxel-resistant tumors. Although we do not expect to see a broadening of the spectrum of tumors responding to BMS-184476, the superior efficacy observed in the various preclinical tumor models may be a harbinger of newly responsive clinical tumor types.

While the cytotoxic potency of BMS-188797 in vitro was similar to paclitaxel in paclitaxel-sensitive cell lines, considerably higher concentrations (35–156 nM) were required to bring about comparable cytotoxicity against the resistant cells lines, particularly those with an MDR phenotype. In vivo, BMS-188797 displayed efficacy superior to paclitaxel in four tumor models after i.v. administration. Among the models in which a therapeutic advantage has been observed are two human carcinomas (one recently derived from a clinical sample) with partial resistance toward paclitaxel. Based on its activity in the six tumor models used to assess its therapeutic potential, the overall spectrum of tumor types susceptible to BMS-188797 is expected to be similar to paclitaxel.

With regard to potency, BMS-184476 and BMS-188797 are more potent than paclitaxel in mice; their MTDs tends to be about two-thirds that of the parent drug. No appreciable difference in potency compared with paclitaxel was seen in the one experiment conducted using BMS-184476 in rats. Despite the similar potencies of the two new analogs, early data from phase I clinical trials [3] indicate that BMS-184476 is more potent than paclitaxel, as one might have predicted from the mouse data, but the same trend has not been observed for BMS-188797 [11].

Both analogs have entered phase I clinical trials, either singularly [3, 11] or in combination with traditional drugs [10], and will be progressing to phase II trials pending identification of appropriate dosing regimens.

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