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Preclinical antitumor activity of water-soluble paclitaxel derivatives

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Abstract *Purpose*: Five water-soluble paclitaxel derivatives were extensively evaluated for their antitumor activities relative to the parent drug. *Methods*: Both subcutaneous (s.c.) murine (M109 lung) and human (A2780 ovarian, L2987 lung) tumor models were used for this purpose. *Results*: Consecutive daily intravenous (i.v.) paclitaxel therapy of mice bearing s.c. M109, beginning on day 4 or 5 posttumor implant and continuing for 5 days, resulted in a range of maximum gross log cell kill (LCK) values (reflective of delays in tumor growth) and maximum relative median survival time (%T/C) values (reflective of increases in lifespan) of 1.0–2.1 and 132–162% (and one outlying result of 235%), respectively. Against the same tumor model, using the same treatment schedule, each of the water-soluble derivatives was active, with maximum LCK of 1.3–2.5 and T/C of 124–254%. These LCK and %T/C values were always within 0.5 LCK and 15%, respectively, of the concomitantly obtained maximum effects of paclitaxel. When tested in several experiments against staged (50–100 mg) s.c. A2780 tumors, using various i.v. treatment schedules, the water-soluble derivatives achieved a maximum LCK of 1.4–3.8. Evaluated in parallel, paclitaxel achieved a maximum LCK of 2.1–4.5 following every other day × 5 i.v. therapy. When paclitaxel was assayed in several experiments using the staged (50–100 mg) s.c. L2987 tumor model, maximum LCK of 0.9–>4.1 were produced following every other day × 5 i.v. therapy. Concomitant testing of the water-soluble derivatives, using the same i.v. treatment schedule, resulted in maximum LCK of 0.2–>4.1. In each of the tumor models used, the consistently active, and usually the most active, water-soluble derivative was BMS-185660. The levels of activity observed were comparable (within 1 LCK) to those achieved concomitantly using paclitaxel, and its potency was only slightly inferior to the parent drug. *Conclusions*: Based on the evaluations performed in three distal site tumor models, we conclude that BMS-185660 is a water-soluble paclitaxel derivative with preclinical antitumor activity comparable to that of the parent drug.

Key words Taxol · Taxanes · Anticancer

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Introduction

The clinical activity of Taxol (paclitaxel) has been well established in several neoplastic disease situations [3, 5, 14]. The drug is administered in a vehicle containing both ethanol and cremophor and is typically given in conjunction with other agents intended to mitigate or circumvent the otherwise often-observed hypersensitivity reactions [10, 18]. Taxotere, a paclitaxel derivative undergoing clinical trial in which some incidence of hypersensitivity reactions is observed, also is administered in a vehicle containing ethanol and derivatized castor oils, i.e. Tween 80 [2]. It may be advantageous to provide a derivative of paclitaxel that could be administered clinically without excipients associated with provoking untoward reactions. A compound that could, for example, be administered in an aqueous vehicle and yet possess the antitumor activity of paclitaxel would be worthy of consideration for clinical development.

The aqueous solubility of paclitaxel is only approximately 0.25 μg/ml [1]. Several investigators [4, 8, 9, 15, 19] have described their attempts to improve its solubility by synthesizing ester derivatives which serve as

paclitaxel prodrugs, but while some of these derivatives are biologically active, few possess adequate antitumor activity [4, 8, 9, 19]. An attempt to improve the solubility of paclitaxel by introducing phosphate groups at C-2′ and C-7 has likewise proved unsuccessful [17]. Recently, however, modifications to the aforementioned approach have resulted in the synthesis of water-soluble paclitaxel prodrugs with potentially useful antitumor activity, including several compounds which have proved to be as active as paclitaxel in preliminary studies [7, 16]. Further testing of the best of these derivatives appears to be clearly warranted.

In the studies described herein, we subjected several water-soluble paclitaxel derivatives to extensive preclinical antitumor evaluations using both murine and human distal site established tumor models. On the basis of its activity in the stringent assays described herein, one derivative in particular, BMS-185660, may be described as having antitumor activity comparable to that of the parent drug.

Materials and methods

Mice

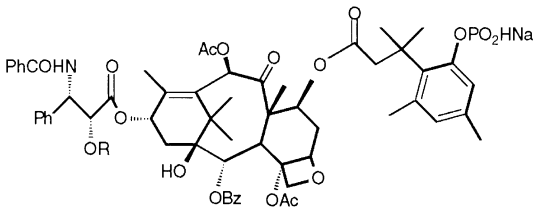
Balb/c and (Balb/c × DBA/2)F_1 hybrid (CDF_1) conventional mice and Balb/c-background athymic ("nude") mice, 16–20 g, were purchased from Harlan Spague-Dawley Co. (Indianapolis, Ind.). They were provided with food and water *ad libitum*. All studies involving these animals were conducted in accordance with Bristol-Myers Squibb Company (BMS) and NIH animal care and use guidelines.

Tumors

The murine lung carcinoma, M109, was passaged subcutaneously (s.c.) biweekly in Balb/c mice and implanted s.c. into CDF_1 mice for antitumor evaluations. The human A2780 ovarian and L2987 lung carcinomas were grown s.c. in athymic mice for both passage (every 2–3 weeks) and therapy experiments.

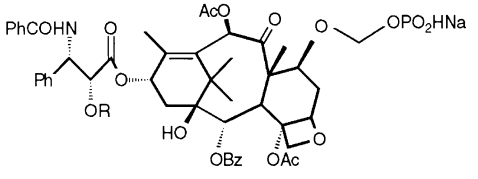
Compounds

Paclitaxel was nearly always dissolved in cremophor/ethanol (50%/50%) and further diluted with saline, within 30 min of use, to a final vehicle proportion of cremophor (10%)/ethanol (10%)/saline (80%). The five water-soluble paclitaxel derivatives, BMS-180820, -182178, -184481, -185218 and -185660 (Fig. 1), each as a sodium phosphate salt of >98% purity, were administered in water within 30–60 min of their preparation. Additionally, BMS-185660 and -184481 were also provided as triethanolamine (TEA) salts, >98% pure, and identically handled and administered. BMS-181681 (Fig. 1), also >98% pure but an insoluble paclitaxel derivative, and the intermediate metabolite of BMS-185660 (on the path toward conversion to paclitaxel), was dissolved in dimethylsulfoxide (DMSO) and diluted with water not more than 10 min before its i.v. administration. Compounds were administered i.v. in a volume of 0.01 or 0.02 ml/g body weight. The derivatives described in Fig. 1 were prepared in the Antitumor Chemistry Department, BMS, Wallingford, Ct.



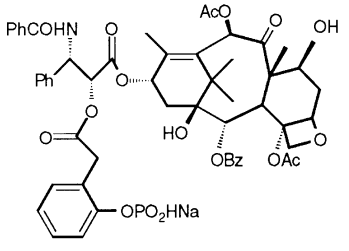
BMS 180820 R = H

BMS 182178 R = COOEt

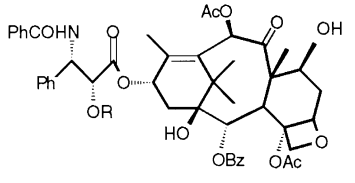


BMS 184481 R = H

BMS 185660 R = COOEt



BMS 185218



Paclitaxel R = H

BMS 181681 R = COOEt

Fig. 1 Structure of paclitaxel and derivatives evaluated in vivo

With regard to the five aforementioned water-soluble derivatives, their true water solubility ranged from 0.5 to 1.0 mg/ml (M. Kaplan, unpublished data). At concentrations between 1 and 3 mg/ml, apparent (but not true) solutions (actually, ultramicrocolloidal suspensions) of each compound were formed which were capable of passing through a 0.22-μm nylon filter without loss of concentration as determined by high-pressure liquid chromatography but were birefringent in polarized light (M. Kaplan, unpublished data).

Assessment of antitumor activity

Detailed descriptions of the basic assay and evaluation procedures used for the tumor models and experiments contained herein have been reported previously [11, 13]. Briefly, therapeutic results are presented in terms of: (a) increases in lifespan reflected by the relative median survival time (MST) of treated (T) versus control (C) groups (i.e. %T/C values) in the M109 experiments, and any long-term survivors (typically determined on day 60 for s.c. M109 experiments and days 60–93 for human tumor xenograft studies); and (b) 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 M109 and A2780 tumors, 0.5 g for L2987 tumors) and expressed as T − C values (in days). Individual mice bearing A2780 or L2987 tumors were sacrificed soon after having grown tumors to the aforementioned target sizes. The dose of a compound which yielded the maximum therapeutic effect was termed the optimal dose (OD). When more than one therapeutic endpoint was determined (as in M109 experiments), it was possible to derive more than one OD value. Tumor weights were determined using a previously described procedure [11, 13]. Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test [6]. Additionally, complete tumor regressions which were observed following treatment are reported when notable. The activity criterion for increased lifespan in the s.c. M109 tumor model was a T/C of $\geq 125\%$. 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).

Groups typically consisted of eight or nine mice. The treatment regimen for the s.c. M109 tumor tests was always five consecutive once-daily administrations beginning on day 4 or 5 posttumor implant. For the human tumor xenograft tests, compounds were given once daily, either every other day for four or five administrations, or consecutively for 7 days, beginning when the tumors were staged between 50 and 150 mg (note: in any single experiment, tumor sizes usually spanned a range of no more than 50 mg). These treatment schedules were selected based upon previously reported data describing them as optimal for paclitaxel in the same or comparable tumor models [12]. 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. Operationally, when a particular dose of a compound caused excessive lethality, the MTD would be typically assigned the nearest concomitantly evaluated lower dose which was not excessively lethal. The MTD was often synonymous with the OD. Compounds were evaluated at a minimum of three dose levels per experiment.

Results

M109 murine lung carcinoma

The five water-soluble paclitaxel derivatives were assayed in the staged s.c. M109 tumor model in several experiments, with two of the derivatives evaluated on more than one occasion. Paclitaxel was included in each study. The control tumor growth rates were quite similar in all experiments except one, no. 234, where the TVDT of 5.0 days was greater than usually observed (i.e. 2–3.5 days). Nevertheless, the response to paclitaxel, when considered on a LCK basis, was consistent in all these experiments, (1.0–2.1 LCK) and the maximum %T/C values ranged from 132 to 167% except for one outlying result in experiment no. 234, 235% T/C. The OD of paclitaxel in the eight experiments varied from 18 to 48 mg/kg per injection, and the dose-response curves were often flat over the several dose levels evaluated in each experiment. A summary of the maximum effects of paclitaxel and each water-soluble derivative is shown in Table 1.

Using a daily × 5 i.v. treatment schedule against s.c. M109, each of the five derivatives achieved a maximum delay in primary tumor growth reflected by 1.3 to 2.5 LCK. Additionally, these delays in tumor growth were very similar (within 0.5 LCK) to those obtained concomitantly with paclitaxel administered on the same treatment schedule. The maximum lifespan increases caused by the derivatives, 124–254% T/C, were almost

Table 1 Maximum effects of i.v. administered water-soluble paclitaxel derivatives against staged s.c. M109 lung carcinoma

Expt. no.	Derivative		Derivative			Paclitaxel		
	BMS no.	Optimum dose (mg/kg per injection)[a]	T − C		LCK	T − C		LCK
			%T/C	(days)		%T/C	(days)	
234	180820	36	254	34.8	2.1	235	28.5	1.7
232	182178	40	138	18.0	1.5*	133	12.3	1.0
239	184481	45	131	14.0	2.1	134	14.0	2.1
257	184481	36	124	10.5	1.3	139	13.3	1.6
241	185218	51/34[b]	142	16.5	1.7	152	15.8	1.6
245	185660	24	160	18.8	2.5	151	15.0	2.0
249	185660	36	155	19.0	1.6	132	13.0	1.1
254	185660	48	170	17.0	1.7	167	14.0	1.4
278	185660	30/45[b]	149	17.3	2.1*	138	13.5	1.6

*$P < 0.05$ versus maximum effect of concomitantly tested paclitaxel

[a] All treatments were daily days 4 to 8, except for BMS-185660 in expt. no. 245 which was daily days 5 to 9

[b] First dose indicated was associated with the best increase in lifespan; second dose indicated yielded the maximum delay in tumor growth

always within the threshold required for activity in this model, and were always similar (i.e. <15% apart) to those found in parallel using paclitaxel. BMS-184481 and BMS-185660 were evaluated twice and four times, respectively, and they yielded reasonably consistent maximum effects with regard to both lifespan increases and delays in primary tumor growth. The last three experiments conducted using BMS-185660, and the last experiment conducted with BMS-184481, involved the use of TEA salts.

The nonwater-soluble paclitaxel derivative, BMS-181681, the intermediate in the conversion of BMS-185660 to paclitaxel, was also evaluated in two separate s.c. M109 experiments (data not included in Table 1). In the first study, at an OD of 30 mg/kg per injection it produced a maximum T/C of 168% and at 20 mg/kg per injection the derivative caused a maximum delay in tumor growth (T − C) of 16.0 days. Paclitaxel, evaluated in parallel, achieved a maximum T/C of also 168% and maximum T − C value of 15.3 days. The effects of BMS-181681 and paclitaxel, in terms of LCK, were nearly identical, 1.1 and 1.0, respectively. In a confirmatory experiment, BMS-181681 and paclitaxel both achieved a maximum LCK of 1.6.

A2780 human ovarian carcinoma

A summary of the optimal therapeutic effects obtained in the s.c. A2780 tumor model is shown in Table 2.

In the first experiment performed no. 40, each of the five water-soluble derivatives and paclitaxel was evaluated using an every 2 days × 5 i.v. treatment schedule. A MTD level was attained for each compound and each was active. The two most effective derivatives were BMS-180820 and -185660. At an OD of 75 mg/kg per injection, BMS-180820 caused a 28.8-day delay in primary tumor growth, or 2.9 LCK considering the TVDT of 3.0 days in this experiment. BMS-185660 achieved a T − C of 37.8 days at its OD of 48 mg/kg per injection, a delay reflected by 3.8 LCK. In comparison, paclitaxel at an OD of 36 mg/kg per injection, produced a 44.8 day T − C or 4.5 LCK.

A second A2780 experiment, no. 41, was initiated to confirm the activities of BMS-180820 and -185660. Two slightly different treatment schedules were used, an every-other-day injection schedule and one involving consecutive daily injections, but the total durations of therapy were identical. Paclitaxel was included as a reference drug using only the intermittent injection schedule. BMS-180820 administered on the consecutive daily 7-day i.v. injection schedule produced a maximum T − C of 19.0 days at an OD of 40 mg/kg per injection. This delay in tumor growth was reflected by a 1.9 LCK given the 3.0-day TVDT. On the every-other-day × 4 i.v. treatment schedule, an OD of 66 mg/kg per injection of BMS-180820 caused a 27.8 day T − C, or 2.8 LCK. Consecutive daily i.v. injections of BMS-185660 at an OD of 20 mg/kg per injection resulted in a 24.5 day T − C, or 2.5 LCK. This was a slightly greater therapeutic effect than the 18.5-day T − C, or 1.9 LCK, achieved at an OD of 36 mg/kg per injection of BMS-185660 every other day × 4 i.v. In comparison, optimal therapy with paclitaxel, 24 mg/kg per injection i.v. resulted in a 20.5-day T − C, or 2.1 LCK. On their most advantageous treatment schedules, both water-soluble paclitaxel derivatives produced therapeutic effects in mice bearing s.c. A2780 tumors that were comparable to that of the parent drug.

In the final A2780 experiment performed, no. 42, BMS-185660 was again compared directly with paclitaxel. Both agents were administered i.v. on an every

Table 2 Maximum effects of i.v. administered water-soluble paclitaxel derivatives against staged s.c. A2780 human ovarian carcinoma xenografts

Expt. no.	Derivative		Derivative		Paclitaxel	
	BMS no.	Optimum dose i.v. (mg/kg per injection)	T − C(days)	LCK	T − C(days)	LCK
40	180820	75[a]	28.8	2.9	44.8[a]	4.5
	182178	48[a]	18.8	1.9		
	184481	36[a]	14.8	1.5*		
	185218	32[a]	19.8	2.0		
	185660	48[a]	37.8	3.8		
41	180820	66[b]	27.8	2.8	20.5[b]	2.1
		40[c]	19.0	1.9		
	185660	36[b]	18.5	1.9		
		20[c]	24.5	2.5		
42	180820	48[a]	25.5	1.4*	>62[a]	>3.5
	184481	24[a]	35.3	2.0		
	185660	24[a]	≥49	≥2.8		

*$P < 0.05$ versus maximum effect of concomitantly tested paclitaxel
[a] Treatment was every other day × 5 beginning on day 11 in expt. no. 40 and day 14 in expt. no. 42
[b] Treatment was every other day × 4 beginning day 10
[c] Treatment was daily × 7 beginning day 10

other day × 5 injection schedule. At an OD of 36 mg/kg per injection, BMS-185660 caused a T − C of ≥ 49 days, reflected by ≥ 2.8 LCK considering the 5.3 day TVDT. In comparison, paclitaxel, at an OD of 24 mg/kg per injection, produced a T − C of > 62 days, or > 3.5 LCK. There were several tumor-free mice in each OD treatment group and the experiment was terminated (on day 89) without either group having had the majority of its mice achieve the tumor target size of 1 g. BMS-180820 and -181481 were included in this study, but their performance at MTD levels was inferior to that of paclitaxel.

L2987 human lung carcinoma

A summary of the optimal results obtained in several experiments involving the L2987 tumor model is shown in Table 3.

In the initial L2987 experiment (no. 67), BMS-180820 administered every other day × 5 i.v. at a MTD of 48 mg/kg per injection, produced a 4.0-day T − C, equivalent to only 0.3 LCK given the 4.0 day TVDT. The inactivity seen with this derivative was also found with BMS-182178, the only other water-soluble compound included in this study. It produced a T − C of 3.5 days at a MTD of 48 mg/kg per injection every other day × 5 i.v. With paclitaxel, however, on the same treatment schedule, a borderline active result of 0.9 LCK, associated with a 12.5-day T − C, was obtained at a dose of 24 mg/kg per injection, i.v.

In the next L2987 experiment performed, no. 68, the remaining three water-soluble derivatives were evaluated in comparison with paclitaxel. BMS-184481 achieved a T − C of 21.5 days at 48 mg/kg per injection every other day × 5 i.v., an effect equivalent to 1.0 LCK considering the TVDT of 6.2 days in this experiment. There were also three of eight mice whose tumors underwent transient but complete regressions following the therapy. BMS-185218, at an MTD of 21 mg/kg per injection, on the same treatment regimen, produced only a 4.0-day T − C (0.2 LCK), an inactive result. BMS-185660 was excessively toxic at all the dose levels tested and had to be rescheduled. Paclitaxel, at an OD of 24 mg/kg per injection, every other day × 5 i.v. achieved a T − C of 22.5 days, or 1.1 LCK, accompanied by four of nine mice undergoing complete (albeit transient) regressions of their tumors. Thus, of the two derivatives evaluable in this study, only BMS-184481 produced a therapeutic result comparable to that of paclitaxel at tolerated doses.

In L2987 expt. no. 70, we re-evaluated BMS-180820 because of its activity in the other two tumor models, and BMS-185660 because of its toxicity in the previous experiment. BMS-180820 achieved a maximum T − C of 16.5 days at a dose of 48 mg/kg per injection, every other day × 5 i.v. This effect was equivalent to 1.7 LCK considering the TVDT of 3.0 days in this study. The inconsistency of results pertaining to BMS-180820 (in this experiment compared to expt no. 67) was noted but unresolved (except to comment that beginning with expt no. 70, L2987 began to display an increased susceptibility to paclitaxel). BMS-185660, also at 48 mg/kg per injection, on the same regimen, produced a T − C of 36.5 days or 3.7 LCK. In comparison, paclitaxel at its OD of 24 mg/kg per injection, yielded a maximum T − C of 31.0 days or 3.1 LCK.

In the final L2987 experiment performed, no. 72, we wished to confirm the activity of BMS-185660 observed in expt. no. 70, and to re-evaluate the activities of two other previously tested derivatives. At an OD of 36 mg/kg per injection, every other day × 5 i.v., BMS-185660 caused a T − C of > 68 days, or > 4.1 LCK given the 5.0-day TVDT; at the termination of the experiment on day 93, there were four of eight mice tumor-free. BMS-180820, found previously to have

Table 3 Maximum effects of i.v. administered water-soluble paclitaxel derivatives versus s.c. staged human L2987 lung carcinoma xenografts

Expt. no.	Derivative		Derivative		Paclitaxel	
	BMS no.	Optimum dose i.v. (mg/kg per injection)[a]	T − C (days)	LCK	T − C (days)	LCK
67	180820	48	4.0	0.3*	12.5	0.9
	182178	48	3.5	0.3*		
68	184481	48	21.5	1.0	22.5	1.1
	185218	21	4.0	0.2*		
70	180820	48	16.5	1.7*	31.0	3.1
	185660	48	36.5	3.7		
72	180820	48	17.3	1.0*	> 68	> 4.1
	184481	36	24.0	1.4		
	185660	36	> 68	> 4.1		

*$P < 0.05$ (or $P = 0.05$ for BMS-180820 in expt. no. 72) versus concomitantly tested paclitaxel

[a] Or maximum tolerated dose if inactive. Treatment was every other day × 5 beginning on either day 13 (expt. nos. 67 and 70) or day 15 (expt. nos. 68 and 72)

produced inconsistent activity in this model, was retested and achieved a minimally active 1.0 LCK (T − C of 17.3 days) at its OD of 48 mg/kg per injection, on the same treatment regimen. BMS-184481 was similarly retested and at 36 mg/kg per injection produced a 24.0-day T − C, equivalent to 1.4 LCK. The OD of paclitaxel in this experiment, 36 mg/kg per injection, produced a maximum T − C of >68 days, including three of eight cured mice. Thus, paclitaxel and BMS-185660 achieved comparable levels of antitumor activity in this experiment and in relation to this tumor model.

Discussion

Because of the extreme aqueous insolubility of paclitaxel, effectively 0.25 μg/ml [1], both ethanol and cremophor are used in clinical formulations. Since these excipients have been associated with untoward hypersensitivity reactions in some patients receiving Taxol [3, 5, 14], it is of potential benefit to develop a water-soluble paclitaxel derivative. Such a derivative should be at least as efficacious as paclitaxel and certainly no more toxic. Investigators at Bristol-Myers Squibb Company and elsewhere have been addressing the solubility issue and have described several derivatives (including prodrugs) with varying degrees of antitumor activity [4, 7–9, 15–17, 19]. From those efforts, a few compounds have been identified as being worthy of more intensive preclinical antitumor evaluation.

Five water-soluble paclitaxel derivatives were subjected to a series of antitumor tests involving distal site solid tumor models of both murine and human origin. Against the murine tumor, M109 lung carcinoma, each compound was as active as the parent drug. These results marked the first time we had seen such activity with water-soluble paclitaxel derivatives. Subsequent testing of the compounds against two human tumor xenografts led to results which both broadened the spectrum of activity of each of them and differentiated the degrees of activity between them. One of the derivatives, BMS-185660, was found in each of the models used to be consistently active, and usually the most active of the group, with activity levels comparable (within 1 LCK) to those of concomitantly tested paclitaxel. BMS-185660 administered i.v. was as active as paclitaxel in four s.c. M109 experiments, three s.c. A2780 human ovarian carcinoma experiments, and two s.c. L2987 human lung carcinoma experiments. This water-soluble paclitaxel derivative was therefore shown to possess a broad spectrum antitumor activity profile with levels of potency and activity akin to those of the parent drug.

With regard to the issue of water solubility, each of the derivatives described as water soluble is known to have a true solubility in the 0.5–1.0 mg/ml range, representing a 2000–4000-fold improvement in water solubility compared with paclitaxel. The virtual solubility of BMS-185660, approximately 3 mg/ml, represents a 10 000-fold improvement in water solubility compared with the parent drug.

We sought to identify a water-soluble paclitaxel derivative with antitumor efficacy rivaling that of the parent drug. We believe BMS-185660 represents such an entity based upon its 2000–10 000-fold improvement in water solubility, and the reproducible, broad spectrum activity profile obtained in stringent distal site solid tumor models.

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References

1. Adams JD, Flora KP, Goldspiel BR, Wilson JW, Arbuck SG, Finley R (1993) Taxol: a history of pharmaceutical development and current pharmaceutical concerns. Monogr Natl Canc Inst 15:141
2. Burris H, Irvin R, Kuhn J, Kalter S, Smith L, Shaffter D, Fields S, Weiss G, Eckardt J, Rodriguez G, Rinaldi D, Wall J, Cook G, Smith S, Vreeland F, Bayssas M, LeBail N, Von Hoff D (1993) Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. J Clin Oncol 11:950
3. Chabner BA (1991) Taxol. Cancer: Principles and Practice of Oncology Updates. 5:1
4. Deutsch HM, Glinski JA, Hernandez M, Haugwitz RD, Narayanan VL, Suffness M, Zalkow LH (1989) Synthesis of congeners and prodrugs. 3. Water-soluble prodrugs of taxol with potent antitumor activity. J Med Chem 32:788
5. Einzig AI, Wienik PH, Schwartz EL (1992) Taxol: a new agent active in melanoma and ovarian cancer. In: Muggia FM (ed) New drugs, concepts and results in cancer chemotherapy. Kluwer Academic Publishers, Boston, p 89
6. Gehan EA (1985) A generalized Wilcoxon test for comparing arbitrarily singlycensored samples. Biometrika 52:203
7. Golik J, Wong HSL, Chen SH, Doyle TW, Wright JJK, Knipe J, Rose WC, Casazza AM, Vyas DM (1996) Synthesis and antitumor evaluation of paclitaxel phosphonooxymethyl ethers: a novel class of water soluble paclitaxel pro-drugs. Bioorg Med Chem Lett 6:1837
8. Guéritte-Voegelein F, Guénard D, Lavelle F, Le Goff M-T, Mangatal L, Potier p (1991) Relationships between the structure of taxol analogues and their antimitotic activity J Med Chem 34:992
9. Magri NF, Kingston DGI (1988) Modified taxols: 4. Synthesis and biological activity of taxols modified in the side chain. J Nat Prod 51:298
10. Peereboom DM, Donehower RC, Eisenhauer EA, McGuire WP, Onetto N, Hubbard JL, Piccart M, Giani L, Rowinsky EK (1993) Successful re-treatment with taxol after major hypersensitivity reactions. J Clin Oncol 11:885
11. Rose WC (1981) Evaluation of Madison 109 lung carcinoma as a model for screening antitumor drugs. Cancer Treat Rep 65:299
12. Rose WC (1995) Preclinical antitumor activity of taxanes. In: Suffness M (ed) Taxol: science and applications, CRC Press, Boca Raton, p 209

13. Rose WC, Basler GA (1990) In vivo model development of cisplatin-resistant and sensitive A2780 human ovarain carcinomas. In Vivo 4 : 391
14. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82 : 1247
15. Swindell CS, Krauss NE, Horwitz SB, Ringel I (1991) Bio logically active taxol analogues with deleted A-ring side chain substituents and variable C-2′ configurations. J Med Chem 34 : 1176
16. Ueda Y, Mikkilineni AB Knipe JO, Rose WC, Casazza AM, Vyas DM (1993) Novel water soluble phosphate prodrugs of taxol possessing in vivo antitumor activity. Bioorg Med Chem Lett 3 : 1761
17. Vyas DM, Wong H, Crosswell AR, Casazza AM, Knipe JO, Mamber SW, Doyle TW (1993) Synthesis and antitumor evaluation of water soluble taxol phosphates. Bioorg Med Chem Lett 3 : 1357
18. Weiss RB, Donehower RC, Wiernik DH, Ohnuma T, Gralla RJ, Trump DL, Baker JR Jr, Van Echo DA, Von Hoff DD, Leyland-Jones B (1990) Hypersensitivity reactions from taxol. J Clin Oncol 8 : 1263
19. Zhao Z, Kingston DGI, Crosswell AR (1991) Modified taxols 6. Preparation of water-soluble prodrugs of taxol. J Nat Prod 54 : 1607