Editorial

On Pushing the *Outer Edge of the Outer Edge* of Paclitaxel's Dosing Envelope

Eric K. Rowinsky[1]

Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, Texas 78229

Thomas Wolfe's account of the space program *The Right Stuff* (1) describes how raw human spirit and determination enabled what would be considered a rather primitive technology, at least by today's standards, to "push the outer edge of the envelope," achieving the seemingly unachievable. In the course of new anticancer drug development for solid malignancies, explorations at the *outer edge* of the dosing envelope, using doses exceeding those that can be administered safely in standard practice along with cytokine support, and even at the *outer edge of the outer edge* of the envelope with hematopoietic stem cell support, have become largely routine and reflexive. In fact, these types of explorations have become embedded in our approach to the development of new agents despite the fact that, although many controlled trials have concluded that "low-dose" therapy is inferior to "standard-dose" therapy, dose-intensive regimens have failed to consistently demonstrate even modest improvements in the therapeutic indices of new cytotoxic agents in nonhematological malignancies. However, although the nihilist would condemn all as yet undeveloped anticancer therapeutics to the same fate, missed opportunities may certainly result if such an approach is broadly adopted.

The collective results of clinical trials to date, which have failed to demonstrate a meaningful impact at the *outer edge* of the dosing envelope, as well as the increased morbidity, mortality, and costs of high-dose therapy mandate the adoption of rational and responsible criteria before selecting agents for dose intensification with cytokine support at the *outer edge* of the dosing envelope and, certainly, before undertaking dose intensification with hematopoietic stem cell support at the *outer edge of the outer edge* of the dosing envelope (2). Before explorations of any new agent at the furthest edges of the envelope are launched, there should be evidence suggesting that the agent possesses the "Right Stuff" to achieve the seemingly unachievable. The dangers inherent in such missions, the costs that might be better spent elsewhere, and the low probability of "real" success based on similar missions undertaken to date mandate clear proof that modest dose intensification with the agent, perhaps with cytokine support, is superior to standard doses in indices that are undisputedly meaningful (*i.e.*, survival, disease-free survival, and quality of life) before lift-off. Furthermore,

these results should be built on a solid mechanistic rationale and a foundation of dose responsiveness established in preclinical models. There is reasonable evidence that paclitaxel does not possess the "Right Stuff" for such explorations. In this issue of *Clinical Cancer Research*, Nieto *et al*. (3) describe a toxicological boundary of *outer edge of the outer edge* of paclitaxel's dosing envelope: acute encephalopathy in six patients following treatment with paclitaxel at doses of ≥ 600 mg/m², culminating in the death of three subjects. The authors' descriptions of these events construct an airtight case for either paclitaxel or one of its diluents being the principal culprit responsible for the encephalopathy. Coupled with the lack of a compelling mechanistic rationale supporting the use of high doses of paclitaxel and the lack of dose responsiveness in both preclinical and clinical studies to date, the report by Nieto *et al.* (3) should be considered the last nail in the coffin of explorations of paclitaxel at the *outer edge of the outer edge* of its dosing envelope.

Paclitaxel induces distinct microtubule and cell cycle effects, all of which are concentration dependent to some extent (4–6). At concentrations that are much lower than those required to increase microtubule mass (<10 nM), paclitaxel induces a sustained mitotic block at the metaphase-anaphase boundary (4). Half-maximal inhibition of cell proliferation and a 50% blockade of mitotic metaphase occur following treatment of HeLa cells with 8 nM paclitaxel, whereas microtubule mass increases half-maximally at 80 nM, with a maximal effect at 300 nM. Distinct underlying mechanisms have also been ascribed to these effects (5). For example, at low paclitaxel concentrations (<9 nM), cell death seems to occur after an aberrant mitosis by a Raf-1-independent pathway, whereas cell death may occur as a result of terminal mitotic arrest by a Raf-1-dependent pathway at higher paclitaxel concentrations (≥ 9 nM). Nevertheless, the range of concentrations required to induce these effects can be maintained in plasma for relatively long periods with paclitaxel dose schedules that do not require either cytokine or hematopoietic stem cell support (7). Furthermore, although predictions about the potential success of various dose schedules are often based on whether biologically active drug concentrations are achieved in human plasma, such extrapolations have potential pitfalls, particularly in situations in which drug concentrations achieved in plasma and peripheral tissues are disparate. For the taxanes, high tissue:plasma drug concentration ratios are achieved in tumors and virtually all tissues, except the brain and testes, which possess active physiological barriers to structurally bulky natural products conferred by the Pgp[2] multidrug transporter (8, 9). Thus, the use of plasma as a window to gauge

---

[2] The abbreviations used are: Pgp, P-glycoprotein; G-CSF, granulocyte colony-stimulating factor; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; CNS, central nervous system.

whether pharmacological conditions that are optimal *in vitro* can be achieved *in vivo* may substantially underestimate drug concentrations and exposures achieved in peripheral tissues and tumors. In essence, the wide tissue distribution, avid tissue binding, and protracted tissue sequestration of paclitaxel further strengthen arguments against explorations at the *outer edge* and, certainly, at *the outer edge of the outer edge* of its dosing envelope.

Although many relevant biological effects of paclitaxel, such as cytotoxicity, formation of microtubule bundles and mitotic asters, increase in tubulin polymer mass, resistance to microtubule depolymerization, apoptosis, and radiosensitization, are concentration dependent to some extent, the duration of drug exposure is the most critical determinant of drug effect *in vitro* (6–8, 10). For example, an 11-fold increase in the duration of paclitaxel exposure is more effective at increasing the cytotoxicity of paclitaxel in an LC8A lymphoma cell line than is an 100-fold increase in drug concentration (6). Similar to the *Vinca* alkaloids, dose responsiveness appears to plateau *in vitro* as paclitaxel concentrations increase (11). In other words, there is a situation of diminishing returns above "plateau" concentrations, the magnitude of which depends on the specific cell line and effect in question. However, the paclitaxel concentrations at which most relevant effects plateau are well within the range of plasma concentrations achieved in the clinic with dose schedules that require neither cytokine nor hematopoietic stem cell support ($\leq$1–10 μM; Ref. 7). The most plausible explanation to account for this behavior is the saturation of paclitaxel binding sites on β-tubulin at dose schedules associated with these plateau concentrations ($\geq$175 mg/m^2 over 3 h and $\geq$200–225 mg/m^2 over 24 h; Ref. 7). An alternate explanation for the situation of diminishing returns noted both *in vitro* and in clinical trials using the current clinical formulation of paclitaxel, which is a mixture of polyoxyethylated castor oil (Cremophor EL; cremophor) and ethanol, is that cremophor may antagonize drug-induced cytotoxicity. Liebmann *et al.* (12) demonstrated that increasing paclitaxel concentrations from 2 to 20 nmol/liter sharply increased cytotoxicity *in vitro*, whereas no additional cytotoxicity occurred with paclitaxel concentrations of >50 nmol/liter, and treatment with very high drug concentrations (>10 μM), paradoxically, resulted in even less cytotoxicity. Furthermore, cremophor, at a concentration of 0.135%, antagonized the cytotoxicity of paclitaxel. The broad implication of these results is that, if the mechanisms responsible for the antitumor activity and toxicity of paclitaxel are disparate, there may be critical plateau drug concentrations *in vivo*, above which the toxicity but not the efficacy increases.

Questions regarding optimal scheduling and dosing in the clinic were addressed even before paclitaxel received regulatory approval in 1992. The cumulative results of these efforts indicate that no single administration schedule clearly portends superior efficacy. Instead, there appear to be "threshold" doses or concentrations, the precise magnitude of which depend upon the specific tumor type and below which only negligible antitumor activity is observed, and plateau doses or concentrations, above which no further antitumor activity, at least of clinical importance, is observed. In clinical practice, paclitaxel doses associated with threshold activity and plateauing of the dose-response curve appear to be inversely related to the duration of

the administration schedule; however, these relationships are less vivid in the clinic than in tissue culture, possibly due to the confounding effects of avid and protracted tissue binding *in vivo*. But, for the most part, comparable antitumor efficacy has been noted with both short and prolonged schedules, as long as equitoxic dosing regimens are used (*i.e.*, higher paclitaxel doses with shorter infusion schedules). Furthermore, the collective results of randomized clinical trials in a variety of settings indicate that plateauing of antitumor efficacy ensues at paclitaxel doses that can be readily administered without cytokine or hematopoietic stem cell support.

In the earliest Phase II studies of paclitaxel on a 24-h schedule in women with recurrent or refractory ovarian cancer, doses ranged from 110 to 300 mg/m^2, with cytokine support generally for doses of $\geq$250 mg/m^2 (13). In individual study reports, each using different patient eligibility criteria to define patient eligibility, response rates were seemingly higher in trials evaluating higher paclitaxel doses (170–300 mg/m^2) compared to those in which patients received lower paclitaxel doses (110–175 mg/m^2; Ref. 13). In buttressing the rationale for trials of paclitaxel at *the outer edge of the outer edge* of its dosing envelope, Nieto *et al.* (3) cite a seemingly impressive response rate of 48% in a Phase II trial of 250 mg/m^2 paclitaxel (24-h schedule) plus G-CSF (14). At first glance, such isolated results might suggest that higher paclitaxel doses are optimal in this and other clinical settings. For example, a simple correlative analysis in trials in women with both advanced breast and ovarian cancers indicated strong positive relationships between paclitaxel dose and response rate (15). However, these nonrandomized trials incorporated patients with a potpourri of demographic and prognostic features. To more appropriately evaluate the effects of dose on outcome, an analysis of individual patient data (meta-analysis) was performed using audited demographic and outcome data from the initial trials of paclitaxel in recurrent or refractory ovarian cancer (16). In this analysis, the probability of achieving a response and the duration of progression-free survival were related to neither paclitaxel dose nor dose intensity, even when the analyses were controlled for individual study, pertinent demographic variables, number of prior regimens, platinum sensitivity, and response to prior therapy. The analysis indicated that there is no clear benefit of increasing paclitaxel doses above 135 mg/m^2, given as a 24-h infusion.

The salient features of randomized clinical trials with paclitaxel that focused on the dose issue are listed in Table 1. Although several randomized trials in women with advanced ovarian cancer and metastatic breast cancer have demonstrated that higher doses may portend "some" increased benefit, the magnitude of this effect is negligible (17, 18). In Ov.9, the NCIC CTG evaluated the effects of two paclitaxel doses (135 *versus* 175 mg/m^2) and two schedules (24 *versus* 3 h) on both response and toxicity (17). With respect to the dosing issue, although the prolongation in progression-free survival in the high-dose arm was statistically significant (19 *versus* 14 weeks), this 5-week difference was inconsequential from a clinical standpoint, and both response rates and survival were similar. The dose-response issue was also assessed in GOG 134, a Gynecologic Oncology Group study, in which a similar group of patients were treated with 24-h infusions of paclitaxel at either 175 or 250 mg/m^2 plus G-CSF (19). There were no differences

Table 1 Clinical trials addressing paclitaxel dosing

Clinical trial	Design	Significant results
Ovary cancer		
BMS 016 (Ov.9)	NCIC CTG study	PFS[a] longer in high-dose arm (19 *vs.* 14 weeks).
	Recurrent or refractory ovarian cancer	No differences in response rates or overall survival
	Bifactoral randomization	
	3 *vs.* 24 h	
	135 *vs.* 175 mg/m^2	
GOG 134	Gynecologic Oncology Group study	Response rate higher in high-dose arm (36% *vs.* 28%)
	Recurrent or refractory ovarian cancer	No difference in PFS or overall survival
	Randomization	
	Initial: 135 *vs.* 175 *vs.* 250 mg/m^2 + G-CSF (24-h schedule)	
	Final: 175 *vs.* 250 mg/m^2 + G-CSF	
Breast cancer		
BMS 048	Metastatic Breast Cancer (adjuvant therapy only, therapy for metastatic cancer only, and therapy in both adjuvant and metastatic settings).	PFS longer in high-dose arm (4.2 *vs.* 3 months)
	Randomization	No difference in response rates or overall survival
	135 *vs.* 175 mg/m^2 over 3 h	
CALGB 9342	Metastatic breast cancer	Incidences or severe myelosuppression and neurotoxicity in moderate- and high-dose arms
	Second line treatment	Borderline correlation between dose and time to treatment failure (3.8, 4.1, and 4.8 months)
	Randomization	No difference in response rates or survival
	175 *vs.* 210 *vs.* 250 mg/m^2 over 3 h	
Lung cancer		
ECOG 5592	Metastatic non-small cell lung carcinoma	Higher response rates in both low- and high-dose paclitaxel arms (26.5 and 32.1%) than etoposide arm (12%).
	Randomization	Longer PFS in both low- and high-dose paclitaxel arms (9.59 and 9.99 months) than etoposide arm (7.69 months)
	Cisplatin/etoposide *vs.* cisplatin/low-dose paclitaxel, 135 mg/m^2 (24-h schedule) *vs.* cisplatin/high-dose paclitaxel, 250 mg/m^2 (24-h schedule) + G-CSF	No differences between paclitaxel arms
		Paclitaxel C_{SS} values different between high-dose and low-dose arms, but no relationships between C_{SS} and response, time to progression, and survival
Head and neck cancer		
ECOG 1393	Advanced head and neck carcinoma	35% response rate in both arms
	Randomization	No differences between high- and low-dose paclitaxel arms
	Cisplatin/low-dose paclitaxel, 135 mg/m^2 (24-h schedule) *vs.* cisplatin/high-dose paclitaxel, 200 mg/m^2 (24-h schedule) + G-CSF	

[a] PFS, progression-free survival.

in either progression-free or overall survival. Although there was a modest differences in the response rates, 36 *versus* 28%, between the 250 mg/m^2 plus G-CSF and 175 mg/m^2 arms, respectively, this difference is hardly of clinical relevance, particularly in this disease setting.

Similar to the situation in ovarian cancer, the relative merits of paclitaxel doses of 135 and 175 mg/m^2 on a 3-h schedule in women with metastatic breast cancer have been assessed (BMS 048; Ref. 18). Again, there were no statistically significant differences in response rates or survival; progression-free survival was statistically longer (4.2 *versus* 3 months), but the clinical significance of this difference is minuscule. Although these results might suggest an element of dose-responsiveness and a lack of a clear plateauing of benefit in the paclitaxel dose range of 135–175 mg/m^2 on a 3-h schedule, possibly arguing for further studies of higher doses, the results

of CALGB 9342 should quell any further attempts (20). In this trial, women with metastatic breast cancer were randomized to treatment with paclitaxel doses of 175, 210, or 250 mg/m^2 on a 3-h schedule without initial cytokine support. As expected, both severe sensory neurotoxicity and myelosuppression were more common in the high- and moderate-dose arms than the lower dose arm. Although there was a borderline correlation between paclitaxel dose and time to treatment failure (3.8, 4.1, and 4.8 months), no statistically significant relationships between paclitaxel dose and either disease response (21, 28, and 22%) or survival (3.8, 4.1, and 4.8 months) were evident. These results indicate that paclitaxel should not be administered in doses of >175 mg/m^2 to women with metastatic breast cancer because higher doses result produce greater toxicity without appreciably improving efficacy or survival.

Diminishing returns have also been noted in patients with

both NSCLC and head and neck cancer treated with paclitaxel doses at the *outer edge* of the dosing envelope. A principal concern during the development of the combination of cisplatin and paclitaxel was that the maximum tolerated dose of paclitaxel (135 mg/m^2) on a 24-h schedule, given in combination with 75 mg/m^2 cisplatin was substantially lower than the paclitaxel dose (250 mg/m^2) that was determined to be active in the earliest Phase II studies in patients with NSCLC and head and neck cancer, and therefore, this low-dose paclitaxel-cisplatin regimen was doomed to fail (21, 22). However, this was not to be the case. In ECOG 5592, chemotherapy-naive stage IIIb–IV NSCLC patients were randomized to treatment with 75 mg/m^2 cisplatin i.v. on day 1 and 100 mg/m^2 etoposide i.v. on days 1–3, or 75 mg/m^2 cisplatin i.v. combined with either a low dose of paclitaxel (135 mg/m^2; 24-h schedule) or a higher dose of paclitaxel (250 mg/m^2; 24-h schedule) with G-CSF (23). Although response rates and survival were superior in the paclitaxel-containing arms (median, 9.9 *versus* 7.6 months; 1 year, 39.9 *versus* 31.8%, $P = 0.048$), there were no differences in response or survival between the two paclitaxel arms. In addition, although there was a difference in paclitaxel C_{ss} between the low- and high-dose paclitaxel arms (0.35 ± 0.16 *versus* 0.94 ± 0.50 μM [$P < 0.001$]), no relationships between paclitaxel C_{ss} and either response, time to disease progression, or survival were apparent (24). These results indicate that neither response nor time to disease progression is influenced by either paclitaxel dose or C_{ss} in chemotherapy-naive NSCLC patients treated with paclitaxel doses ranging from 135 to 250 mg/m^2 (24-h schedule) followed by cisplatin. Nearly identical results were observed in an ECOG randomized Phase II trial (E1193) in patients with advanced head and neck cancer (25). Building on a previous Phase II trial of 250 mg/m^2 paclitaxel (24-h schedule) that produced a 40% response rate, patients with metastatic or locally advanced disease were randomized to treatment with 75 mg/m^2 cisplatin following either 135 mg/m^2 low-dose paclitaxel (24-h schedule) or 200 mg/m^2 high-dose paclitaxel (24-h schedule) plus G-CSF. Response rates were identical in both arms (35%), and there were no differences in survival. These collective results indicate that there is no advantage of using paclitaxel doses of >135 mg/m^2 on a 24-h schedule in combination with cisplatin in patients with advanced NSCLC and head and neck cancer. Taken together, the results of randomized studies in patients with ovarian, breast, NSCLC, and head and neck cancers strongly suggest that increasing the dose of paclitaxel above a certain plateau level, which may vary according to the specific disease setting and administration schedule, is tantamount to a situation of diminishing returns, with minimal or no further benefit ensuing as doses approach the *outer edge* of the dosing envelope.

The discovery of CNS toxicity at the *outer edge of the outer edge* of paclitaxel's dosing envelope would not have been predicted by the vast clinical experience with the agent at standard doses. Although neurons are very rich in tubulin and their microtubules are exquisitely sensitive to paclitaxel *in vitro*, paclitaxel penetrates the intact blood-brain barrier poorly (8, 26, 27). In addition, although CNS penetration is enhanced following disruption of the blood-brain barrier in animals, CNS toxicity has not been evident with paclitaxel in clinical settings that are clearly associated with blood-brain barrier disruption such as

in patients with refractory leukemias and brain tumors and during concurrent treatment with paclitaxel and brain irradiation (27–29). Because overexpression of Pgp, which is responsible for extruding bulky natural products across both plasma membranes and the blood-brain barrier, confers at least two to three orders of magnitude of cross-resistance to paclitaxel, it is unlikely that high-dose paclitaxel, as administered in this report, in which C_{max} values were 3–4-fold higher than those achieved with standard doses, is the sole culprit responsible for the acute encephalopathy described in this report (30).

Given that the encephalopathy reported by Nieto *et al.* (3) occurred in patients with diverse tumor types and concurrent therapies, it is likely that a component of paclitaxel's formulation vehicle—cremophor, ethanol, or both—played a role. The investigators make a compelling case against ethanol as being a contributing factor. Although CNS toxicity in both children and adults receiving paclitaxel has been attributed to the ethanol diluent, the precise nature of the CNS manifestations (*e.g.*, seizures and somnolence) and their temporal nature (*i.e.*, maximal during the infusion) were much more typical of ethanol toxicity than the cases here (31, 32). Furthermore, manifestations related to ethanol accumulation have been exclusively observed following treatment with short (1- and 3-h) infusions of paclitaxel, and, the rate of ethanol coadministration with 24-h infusions of paclitaxel, even at the *outer edge of the outer edge* of its dosing envelope, should not overcome the zero-order kinetics of ethanol and would not be expected to induce CNS toxicity in patients with normal hepatic function (32).

On the other hand, there are many reasons to implicate cremophor as the culprit. Although cremophor is commonly believed to be an inert substance, it has many inherent pharmacological and toxicological properties (33). As discussed by Nieto *et al.* (3), cremophor itself has been demonstrated to reduce cerebral blood flow, induce electroencephalography abnormalities, and affect coagulation factors that may predispose to thromboembolic events. Additionally, it is also not inconceivable that cremophor, by virtue of its ability to modulate Pgp-mediated multidrug resistance *in vitro*, can disrupt blood-brain barrier function, thereby enhancing transport of Pgp substrates, like paclitaxel, into the CNS (33). Webster *et al.* (34) initially determined that cremophor concentrations in plasma of patients receiving paclitaxel are of sufficient magnitude to modulate Pgp-mediated multidrug resistance, and although Sparreboom *et al.* (35) subsequently hypothesized that cremophor is not likely to play a role in reversing Pgp-mediated multidrug resistance in peripheral tissues and tumors *in vivo* because its distribution is limited to the central compartment, the blood-brain barrier may actually be a functional component of cremophor's central compartment (36). If this is the case, then cremophor may enhance the transport of xenobiotics into the CNS, particularly when both cremophor and the xenobiotic are administered concurrently in high doses, as in the study by Nieto et al. (3). Also, when the pharmacokinetics of the xenobiotic are nonlinear, as is the case with paclitaxel formulated in cremophor, the blood-brain barrier is more likely to be overwhelmed (35). Other Pgp-mediated barriers to the entry of xenobiotics, such as the gastrointestinal tract, have been shown to be effectively disrupted by pharmacological modulators of Pgp (37, 38). For example, high systemic availability of oral paclitaxel is

achieved in $mdr1a-/-$ knock-out mice and in both wild-type mice and patients when paclitaxel is administered p.o. in combination with Pgp modulators.

Although we have not yet established the optimal doses of some chemotherapy agents that have been available for 2–4 decades, dosing issues with paclitaxel are rapidly approaching resolution. The reports of devastating CNS toxicity at the *outer edge of the outer edge* of paclitaxel's dosing envelope serve to support the implications of the plateauing of effect and diminishing returns noted with increasing doses and concentrations of paclitaxel in both preclinical and clinical studies in most relevant malignancies. Although paclitaxel undoubtedly possesses the *Right Stuff* as a chemotherapy agent and is a welcome addition to our therapeutic armamentarium, data that have accumulated in a relatively short time indicate that paclitaxel can be added to a rapidly growing heap of agents that should not venture toward the edge of their dosing envelopes, and further missions with paclitaxel to the outermost regions of the dosing galaxy should be scrubbed.

References

1. Wolfe, T. The Right Stuff. New York: Farrar, Strauss & Giroux, Inc., 1983.

2. Savarese, D. M. F., Hsieh, C-C., and Stewart, M. F. Clinical impact of chemotherapy dose escalation in patients with hematologic malignancies and solid tumors. J. Clin. Oncol., *15:* 2981–2995, 1997.

3. Nieto, Y., Cagnoni, P. J., Bearman, S. I., Shpall, E. J., Matthes, S., DeBoom, T., Barón, A., and Jones, R. B. Acute encephalopathy: a new toxicity associated with high-dose paclitaxel. Clin. Cancer Res., *5:* 501–506, 1999.

4. Jordan, M. A., Toso, R. J., Thrower, D., and Wilson, L. Mechanism of mitotic block and inhibition of cell proliferation by Taxol at low concentrations. Proc. Natl. Acad. Sci. USA, *90:* 9552–9556, 1993.

5. Torres, K., and Horwitz, S. B. Mechanisms of Taxol-induced death are concentration-dependent. Cancer Res., *58:* 3620–3626, 1998.

6. Rowinsky, E. K., Donehower, R. C., Jones, R. J., and Tucker, R. W. Microtubule changes and cytotoxicity in leukemic cell lines treated with Taxol. Cancer Res., *48:* 4093–4100, 1988.

7. Rowinsky, E. K. The taxanes: dosing and scheduling considerations. Oncology, *11 (Suppl. 2):* 1–13, 1997.

8. Lesser, G., Grossman, S. A., Eller, S., and Rowinsky, E. K. The neural and extraneural distribution of systemically administered [^{3}H]paclitaxel in rats: a quantitative autoradiographic study. Cancer Chemother. Pharmacol., *34:* 173–178, 1995.

9. Marland, M., Gaillard, C., Sanderink, G., Roberts, S., Jaonnou, P., Facchini, V., Chapelle, P., and Frydman, A. Kinetics, distribution, metabolism, and excretion or radiolabelled Taxotere (^{14}C-RP 56976) in mice and dogs. Proc. Am. Assoc. Cancer Res., *34:* 393, 1993.

10. Georgiadis, M. S., Russell, E., Gazdar, A. F., and Johnson, B. E. Paclitaxel cytotoxicity against human lung cancer cell lines increases with prolonged exposure durations. Clin. Cancer Res., *3:* 449–454, 1997.

11. Jackson, D. V., and Bender, R. A. Cytotoxic thresholds of vincristine in a murine and leukemia cell line *in vitro*. Cancer Res., *39:* 4346–4349, 1979.

12. Liebmann, J. E., Cook, J. A., Lipschultz, C., Teague, D., Fisher, J., and Mitchell, J. B. The influence of Cremophor EL on the cell cycle effects of paclitaxel (Taxol®) in human tumor cell lines. Cancer Chemother. Pharmacol., *33:* 331–339, 1994.

13. Rowinsky, E. K., and Donehower, R. C. Drug therapy: paclitaxel (Taxol). N. Engl. J. Med., *332:* 1004–1114, 1995.

14. Kohn, E. C., Sarosy, G., Bicher, A., Link, C., Christian, M., Steinberg, S. M., Rothenberg, M., Adamo, D. O., Davis, P., Ognibene, F. P., Cunnion, R. E., and Reed, E. Dose-intense Taxol: high response rate in
patients with platinum-resistant recurrent ovarian cancer. J. Natl. Cancer Inst. (Bethesda), *86:* 18–24, 1994.

15. Reed, E., Bitton, R., Sarosy, G., and Kohn, E. Paclitaxel dose intensity. J. Infusional Chemother., *6:* 59–63, 1996.

16. Rowinsky, E. K., Mackey, M. K., and Goodman, S. N. Meta analysis of paclitaxel dose-response and dose-intensity in recurrent or refractory ovarian cancer. Proc. Am. Soc. Clin. Oncol., *15:* 284, 1996.

17. Eisenhauer, E., ten Bokkel Huinink W., Swenerton, K. D., Gianni, L., Myles, J., van der Burg, M. E. L., Kerr, I., Vermorken, J. B., Buser, K., Colombo, N., Bacon, M., Santabarbara, P., Onetto, N., Winograd, B., and Canetta, R. European-Canadian randomized trial of Taxol in relapsed ovarian cancer: high *vs*. low dose and long *vs*. short infusion. J. Clin. Oncol., *12:* 2654–2666, 1994.

18. Nabholtz, J-M., Gelmon, K., Bontenbal, M., Spielmann, M., Catiemel, G., Conte, P., Klaassen, U., Namer, M., Bonneterre, J., Fumoleau, P., and Winograd, B. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J. Clin. Oncol., *14:* 1858–1867, 1996.

19. Omura, G. A., Brady, M. F., Delmore, J. E., Long, H. J., Look, K. Y., Averette, E., Wadler, S., and Spiegel, G. A randomized trial of paclitaxel at 2 dose levels and Filgastrim (G; G-CSF) at 2 dose levels in platinum pretreated epithelial ovarian cancer (OVCA): a Gynecologic Oncology Group, SWOG, NCTTG and ECOG study. Proc. Am. Soc. Clin. Oncol., *15:* 280, 1996.

20. Winer, E., Berry, D., Duggan, D., Henderson, C. I., Cirrincione, C., Cooper, R., and Norton, L. Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer: results from CALGB 9342. Proc. Am. Soc. Clin. Oncol., *17:* 101a, 1997.

21. Rowinsky, E. K., Gilbert, M., McGuire, W. P., Ettinger, D. S., Forastiere, A., Grochow, L. B., Clark, B., Sartorius, S. E., Cornblath, D. R., Hendricks, C. B., and Donehower, R. C. Sequences of Taxol and cisplatin: a Phase I and pharmacologic study. J. Clin. Oncol., *9:* 1692–1703, 1991.

22. Rowinsky, E. K., Chaudhry, V., Forastiere, A. A., Sartorius, S. E., Ettinger, D. S., Grochow, L. B., Lubejko, B. G., Cornblath, D. R., and Donehower, R. C. A Phase I and pharmacologic study of Taxol and cisplatin with granulocyte colony-stimulating factor: neuromuscular toxicity is dose-limiting. J. Clin. Oncol., *11:* 2010–2020, 1993.

23. Bonomi, P., Kim, K., Chang, A., and Johnson, D. Phase III trial comparing etoposide-cisplatin *versus* Taxol with cisplatin-granulocyte-colony-stimulating factor *versus* Taxol-cisplatin in advanced non-small cell lung cancer: an Eastern Cooperative Oncology Group trial. Proc. Am. Soc. Clin. Oncol., *15:* 382, 1996.

24. Rowinsky, E. K., Bonomi, P., Jiroutek, M, Chen, T-L., Johnson, D., and Baker. S. D. Pharmacodynamic studies of paclitaxel in ECOG 5592: a Phase III trial comparing etoposide plus cisplatin *vs* low-dose paclitaxel plus cisplatin *vs* high-dose paclitaxel plus cisplatin plus G-CSF in advanced non-small cell lung cancer. Proc. Am. Soc. Clin. Oncol., *16:* 450, 1997.

25. Forastiere, A. A., Leong, T., Murphy, B., Rowinsky, E., DeConti, R., Karp, D., and Adams, G. A Phase III trial of high dose paclitaxel + cisplatin + G-CSF *versus* low dose paclitaxel + cisplatin in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial. Proc. Am. Soc. Clin. Oncol., *16:* 384, 1997.

26. Rowinsky, E. K., Chaudhry, V., Cornblath, D. R., and Donehower, R. C. Neurotoxicity of Taxol. Monogr. Natl. Cancer Inst., *15:* 107–115, 1993.

27. Heimans, J. J., Vermorken, J. B., Wolber, J. G., Eeltink, C. M., Meijer, O. W., Taphoorn, M. J., and Beijnen, J. H. Paclitaxel (Taxol) concentrations in brain tumor tissue. Ann. Oncol., *5: 951–953, 1994.*

28. Rowinsky, E. K., Burke, P. J, Karp, J. E, Tucker, R. W., Ettinger, D. S., and Donehower, R. D. Phase I and pharmacodynamic study of Taxol in acute adult leukemias. Cancer Res., *49:* 4640–4647, 1989.

29. Fettel, M. R., Grossman, S. A., Fisher, J., Rowinsky, E., Stockel, J., and Piantadosi, S. Pre-irradiation paclitaxel in glioblastoma multiforme

(GBM): efficacy, pharmacology, and drug interactions. J. Clin. Oncol., *15:* 3121–3128, 1997.

30. Horwitz, S. B., Cohen, D., Rao, S., Ringel, I., Shen, H-J., and Yang, C-P. Taxol: mechanisms of action and resistance. Ann. N. Y. Acad. Sci., *466:* 733–744, 1986.

31. Chang, S. M., Kuhn, J. G., Rizzo, J., Robins, I., Schold, S. C., Spence, A. M., Berger, M. S., Mehta, M. P., Bozik, M. E., Pollack, I., Gilbert, M., Fulton, D., Rankin, C., Malec, M., and Prados, M. D. Phase I study of paclitaxel in patients with recurrent malignant glioma: a North American Brain Tumor Consortium report. J. Clin. Oncol., *16:* 2188–2194, 1988.

32. Webster, L. K., Crinis, N. A., Morton, C. G., and Millward, M. J. Plasma alcohol concentrations in patients following paclitaxel infusion. Cancer Chemother. Pharmacol., *37:* 499, 501, 1996.

33. Webster, L. K., Woodcock, D. M., Rischin, D., and Millward, M. J. Cremophor. Pharmacological activity of an "inert" solubiliser. J. Oncol. Pharm. Pract., *3:* 186–192, 1997.

34. Webster, L., Linsenmeyer, M., Millward, M., Morton, C., Bishop, J., and Woodcock, D. Measurement of Cremophor EL following Taxol: plasma levels sufficient to reverse drug exclusion mediated by the multidrug-resistant phenotype. J. Natl. Cancer Inst., *85:* 1685–1690, 1993.

35. Sparreboom, A., Verweij, J., van der Burg, M. E. L., Loos, W. J., Brouwer, E., Vigano, L., Locatelli, A., de Vos, A. I., Stoter, G., and Gianni, L. Disposition of Cremophor EL in humans limits the potential for modulation of the multidrug resistance phenotype *in vivo*. Clin. Cancer Res., *4:* 1937–1942, 1998.

36. Sparreboom, A., van Tellingen, O., Nooijen W. J., and Beijnen, J. H. Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer Res., *56:* 2112–2115, 1996.

37. Sparreboom, A., van Asperen J., Mayer, U., Schinkel, A. H., Smit, J. W., Meuer, D. K. F., Borst, P., Nooijen, W. J., Beijnen, J. H., and van Tellingen, O. Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. Proc. Natl. Acad. Sci. USA, *94:* 2031–2035, 1997.

38. van Asperen, J., van Tellingen, O., van der Valk, M. A., Rozenhart, M., and Beijnen, J. H. Enhanced oral absorption and decreased elimination of paclitaxel in mice cotreated with cyclosporin A. Clin. Cancer Res., *4:* 2293–2297, 1998.

Clinical Cancer Research

On Pushing the *Outer Edge of the Outer Edge* of Paclitaxel's Dosing Envelope

Eric K. Rowinsky

Updated version	Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/5/3/481

Cited articles	This article cites 33 articles, 18 of which you can access for free at: http://clincancerres.aacrjournals.org/content/5/3/481.full#ref-list-1
Citing articles	This article has been cited by 6 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/5/3/481.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/5/3/481. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.