Optimal dosing and scheduling are among the most important issues being addressed in clinical studies of the taxanes. The results to date indicate that there may not be a single administration schedule that produces optimal antitumor efficacy. Instead, the specific doses of the taxanes relative to each schedule and the overall aggressiveness of the dosing schedule should be considered. There appears to be a threshold taxane dose or concentration below which only negligible antitumor activity is observed, as well as a plateau dose or concentration above which no further antitumor activity occurs. The doses at which both threshold effects and plateauing of dose-response curves occur seem to be inversely proportional to the duration of the administration schedule. For paclitaxel (Taxol), it appears that comparable antitumor effects are achieved with both short (1- and 3-hour) and prolonged (24- and 96-hour) schedules as long as equitoxic dosing regimens are used. The majority of clinical studies with docetaxel have used a somewhat aggressive dosing schedule, 100 mg/m² over 1 hour, which marks the outer edge of the dosing envelope, but nonrandomized trial results suggest a dose-response relationship in the 60- to 100-mg/m² dosing range. [ONCOLOGY 11(Suppl):7-19, 1997]

Introduction

The determination of optimal dosing and scheduling has been an important objective during the development of the taxanes. This issue pertains to both paclitaxel (Taxol) and docetaxel (Taxotere). The clinical development of docetaxel has largely involved a single administration schedule (1-hour infusion) and a narrow dosing range (60 to 100 mg/m², with most studies using 100 mg/m² over 1 hour every 3 weeks). The range of paclitaxel doses and schedules, on the other hand, has been broad (ranging from 135 to 250 mg/m² over 1 to 96 hours every 3 weeks).

Impressive antitumor activity has been reported recently for paclitaxel on disparate administration schedules, which leads to the question of whether an optimal dosing schedule truly exists for the taxanes. Fortunately, the results of several prospective randomized studies, in addition to retrospective analyses, may shed light on these questions. This review summarizes pertinent preclinical, pharmacologic, and antitumor results pertaining to optimal taxane dosing and scheduling in clinical practice.

In Vitro Cytotoxicity Studies

The results of in vitro studies designed to evaluate taxane dose-response relationships and optimal taxane scheduling have been reviewed previously.[1,2] Many relevant biologic effects in vitro, such as cytotoxicity, formation of microtubule bundles and mitotic asters, increase in tubulin polymer mass, stabilization of microtubules against depolymerization, apoptosis, radiosensitization, antiangiogenesis, and inhibition of chemotaxis and motility, appear to be directly related to the concentration of the taxanes.[3-14]

The taxanes may induce different intracellular effects, depending on the drug concentration. They inhibit proliferation of cells by inducing a sustained mitotic block at the metaphase/anaphase boundary at concentrations much lower than those required to increase microtubule mass and microtubule bundle formation.[15] Half-maximal inhibition of HeLa cell proliferation and 50% blockade of mitotic metaphase occur at 8 nM of paclitaxel, whereas microtubule mass increases half-maximally at 80 nM of paclitaxel, with maximal effect at 300 nM.[15] At high concentrations, the unique effects of paclitaxel in increasing microtubule mass and microtubule bundles have been associated with growth inhibition.[12,15]

Because these effects have not been noted at the lowest effective concentrations, they could not have accounted for the antiproliferative effects observed at low concentrations. Instead, growth inhibition has been associated with the formation of an incomplete metaphase plate of chromosomes and an arrangement of spindle microtubules resembling the abnormal organization that occurs at
low concentrations of the Vinca alkaloids.[16]

**Plateau and Threshold Concentrations**

As paclitaxel concentrations progressively increase, a plateauing of dose-response effects has been observed in various cell lines.[12,17-22] In other words, a situation of diminishing returns occurs as paclitaxel and docetaxel concentrations are increased above specific plateau concentrations, the magnitude of which appears to vary between cell lines. The broad clinical implication of these results is that there may be a critical plateau concentration, ie, a dose above which toxicity, but not efficacy, increases.

The cumulative results of in vitro studies suggest that the precise concentrations at which plateauing occurs depends on the specific treatment schedule and varies according to tumor type. In addition, there appear to be precise threshold concentrations below which drug effects do not usually occur. Like plateau concentrations, the precise level at which threshold effects take place also varies among cell lines. Threshold concentrations typically are inversely related to the duration of treatment. In essence, these preclinical observations resemble clinical observations to date.

**Treatment Duration**

For both paclitaxel and docetaxel, treatment duration appears to be the most critical determinant of in vitro effect. Prolonging the duration of exposure in vitro generally produces much greater cytotoxicity than increasing drug concentration.[1,2,9,12,14,17,18,20,23-25] For example, an 11-fold increase in the duration of paclitaxel exposure was more effective in increasing the cytotoxic effect of paclitaxel in an LC8A lymphoma cell line than was a 100-fold increase in paclitaxel concentration.[12] Interestingly, this effect appears to be much more pronounced in taxane-resistant cell lines.[24,26-29] The taxane concentrations at which cell survival curves plateau tend to decrease as the treatment durations are prolonged.

For paclitaxel, and probably docetaxel, the effects of increasing microtubule mass are maximal at drug concentrations that are equimolar with tubulin or when the stoichiometry approaches 1 M of paclitaxel per 1 M of polymerized tubulin dimer.[4,30-33] The binding of paclitaxel to polymerized tubulin is reversible with a binding constant of approximately 0.9 μM. Docetaxel, which most likely shares the same tubulin binding site as paclitaxel, has a 1.9-fold higher effective affinity for the site.[4] The assembly of guanosine diphosphate- or guanosine triphosphate-tubulin induced by docetaxel also proceeds with a critical protein concentration that is 2.1-fold lower than that of paclitaxel.[4] In addition, comparative in vitro cellular pharmacologic studies have demonstrated that higher intracellular levels of docetaxel in P388 murine leukemia cells may also be attributed, in part, to its threefold slower efflux rate.[4]

These differences may explain the varying cytotoxic potencies of the taxanes, with median inhibitory concentrations generally much lower for docetaxel.[4,21,22,33-36] The relative potencies may not necessarily translate into a greater therapeutic index for docetaxel, since greater potency may also result in more severe toxicity at identical drug concentrations in vitro. In addition, the taxanes may not be completely cross-resistant, although differences in potency may confound the interpretation of both preclinical and clinical studies regarding cross-resistance.

These schedule-dependent effects have also been documented in studies designed to determine the in vitro interactions of the taxanes with ionizing radiation.[9] In most studies, the radiopotentiating effects of the taxanes have been directly related to the duration of taxane exposure prior to radiation.[9] In one series of studies involving lung cancer cells, a radiosensitizing effect could not be demonstrated for treatment durations of less than 6 hours at any concentration of paclitaxel.[37]

**Preclinical Studies**

In early studies performed by the National Cancer Institute, paclitaxel was administered as a suspension and antitumor evaluations were limited to studies using intraperitoneally (IP) implanted tumors treated with IP drug administration or human tumor xenografts implanted in the subrenal capsule and treated subcutaneously.[38] In mice-bearing IP-implanted P388 leukemia, paclitaxel administered every 3 hours for three doses (pharmacologically simulating a 24-hour infusion schedule) was more effective than other schedules, including those with multiple-drug treatments on days 1, 5, and 9, or daily treatment for 9 consecutive days.[38] However, these studies were constrained due to the limited solubility of paclitaxel in the formulation vehicles used at that time, thereby precluding the design of proper comparative studies of prolonged schedules and single-dosing schedules.

**Lung Cancer Model**

When studies designed to evaluate different schedules were later performed by Bristol-Myers Squibb
in the M109 lung cancer model using polyoxymethylated castor oil (Cremophor EL) or polysorbate 80 formulations, no schedule-dependent differences were observed.[39] However, neither the optimal schedule demonstrated in the P388 leukemia studies (every 3 hours × 8 doses) nor prolonged (eg, 3 24-hour) infusion schedules were evaluated.

The schedule-finding studies in the M109 model indicated that both daily × 5 and daily × 7 schedules were superior to multiple daily dosing for longer intervals (2 or 3 days between injections). Significantly, maximal antitumor activity was achieved at doses that were substantially lower than the maximum tolerated dose (MTD). This was particularly true for the daily × 7-day schedule, in which dosing at the MTD did not result in any therapeutic advantage over an equally effective, but less toxic, lower dose.[40] These results are consistent with the plateau effects noted in the dose-response curves from a variety of cell lines.

**Other Models**
Nevertheless, dose-response effects have been observed in many other preclinical in vitro models. Progressive reductions in vertebral metastases were noted in combined immunodeficient mice inoculated with PC-3 ML prostate cancer cells that were previously incubated with increasing paclitaxel concentrations from 0.1 to 1.0 µM[41] and in mice bearing bladder cancer.[42]

Dose-toxicity relationships have been especially profound. Substantially greater toxicity in both rapidly proliferating (lymphoid, myeloid, gastrointestinal) and nonproliferating (peripheral nerve) tissues has been observed on almost all schedules in mice, rats, and dogs.[43-45] The schedule's effects are more profound in that lower total doses are typically required to induce equivalent toxic effects in animals treated with more intermittent dosing schedules or treatment over more prolonged durations.[38,43]

It is difficult to compare paclitaxel and docetaxel with respect to dose and schedule dependency in preclinical studies in animals due to differences in tumor models, dosing schedules, and the proximity of treatment doses to the MTD. Nevertheless, results of limited studies with docetaxel have indicated clear dose-response relationships, particularly with short- and single-dosing schedules. Although one may conclude that the type of administration schedule appears to have minimal impact on docetaxel's antitumor activity, it should be noted that only limited studies with prolonged schedules have been performed.[5,46,47]

**Pharmacology**
Comprehensive reviews of the clinical pharmacology of paclitaxel and docetaxel have been published previously,[47-51] and only limited pharmacologic aspects relevant to dosing and scheduling issues will be discussed here. Paclitaxel and docetaxel share the following pharmacologic characteristics: large volumes of distribution, rapid and sustained uptake by most tissues, long elimination half-lives, and significant hepatic disposition. The pertinent pharmacokinetic parameters of both agents are summarized in Table 1.

Predictions regarding the potential success of various taxane doses and schedules are often based on whether biologically active drug concentrations can be achieved and maintained in human plasma. Such extrapolations may have several pitfalls, particularly in situations in which drug concentrations achieved in plasma and peripheral tissues (or tumors) may be disparate. For both paclitaxel and docetaxel, plasma concentrations achieved with almost any dosing schedule are capable of inducing relevant biologic and cytotoxic effects in vitro (paclitaxel: more than 0.05 µM with 96-hour infusions, more than 0.3 µM with 24-hour infusions, and more than 5 µM with 1- to 3-hour infusions; docetaxel: more than 3 µM with 1-hour infusions). Despite extensive plasma protein binding, both paclitaxel and docetaxel are readily cleared from plasma. More important, the volumes of distribution of the taxanes are very large, which is most likely attributable to avid and ubiquitous drug binding to tubulin. Tissue distribution studies in animals using radiolabeled drug have revealed high tissue/plasma concentration ratios in virtually all tissues except brain and testes, which are generally considered tumor sanctuary sites.[52-55] In fact, docetaxel concentrations in mice have been demonstrated to be substantially higher in the implanted tumor tissue than in plasma.[6] Not only are high taxane concentrations achieved in almost all peripheral tissues, but biologically relevant concentrations are maintained for relatively long periods.[6] In both animals and humans, the results of radiolabeled drug distribution studies suggest that there is substantial sequestration of the taxanes in peripheral tissues.[47-55] Approximately 20% of an administered dose is recovered as either parent compound or metabolites from bile and feces collected for 24 hours after treatment. Most of the total administered radioactivity is recovered from feces collected for 1 week following treatment.[52-58] Renal
clearance is insignificant for both taxanes, whereas hepatic P450 mixed-function oxidative metabolism, biliary excretion, fecal elimination, and tissue binding are responsible for the bulk of systemic clearance.[47-58]

These pharmacologic characteristics, particularly wide total body distribution, avid tissue binding, and tissue sequestration, indicate that plasma concentrations may underestimate drug concentrations and pharmacologic exposure in peripheral tissues and tumors. This behavior also suggests that short infusion schedules may be as effective as prolonged schedules in saturating peripheral tissues and tumors. The maintenance of effective tissue saturation may also depend on other factors, including the duration of plasma concentrations maintained above a critical threshold, the duration of the infusion, and the total dose of drug, particularly in situations in which tissue binding may not be avid.

**Linear vs Nonlinear Pharmacokinetics**

The pharmacokinetic behavior of paclitaxel appeared linear in early studies of prolonged administration schedules. However, the results of pharmacokinetic studies accompanying a National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) pivotal bifactoral randomized trial (BMS 016 or Ov.9) demonstrated that the pharmacokinetic behavior of paclitaxel is nonlinear.[48,49] The NCIC-CTG study observed the effects of paclitaxel (135 vs 175 mg/m², 3 vs 24 hours with premedication) in women with recurrent or refractory carcinoma of the ovary. Pharmacokinetic data from subsequent studies that were performed in both children and adults have confirmed these results.[48,49]

As with all drugs with nonlinear pharmacokinetic profiles, nonlinear or saturable behavior is accentuated on shorter infusion schedules. Both plasma concentrations and drug exposure increase disproportionately with increasing doses on shorter schedules. In addition, the pharmacokinetics of drugs like paclitaxel, which truly exhibit a nonlinear pharmacokinetic behavior at higher plasma concentrations, are more likely to appear linear with prolonged infusion schedules that yield low plasma concentrations.

When plasma levels are much lower than $K_m$ (the Michaelis-Menten constant), elimination or distribution processes are not saturated and pharmacokinetics appear linear (first-order). Conversely, nonlinear (zero-order) pharmacokinetics become more apparent with shorter infusion schedules, which result in higher plasma concentrations that approach or exceed the $K_m$ of the saturable processes.

Pharmacokinetic modeling of paclitaxel plasma concentration data indicates that both saturable distribution and elimination processes account for paclitaxel's nonlinear pharmacokinetic behavior.[48, 49] Physiologically, nonlinear drug elimination is most likely due to saturable hepatic P450 metabolic processes and/or excretion, which accounts for a principal component of drug disposition. Saturable drug distribution, on the other hand, is much more difficult to explain. Two pharmacokinetic models have been used successfully to describe nonlinear drug distribution. One model assumes that the drug transfer process into peripheral tissues is saturable, resulting in $K_m$ distribution kinetics. An alternate, more physiologic model assumes that there is a limited (therefore, saturable) number of drug-binding sites in the peripheral compartment. This model displays a rate constant for transfer of drug to the peripheral compartment, varying directly with the number of unoccupied binding sites in the peripheral compartment.[E.K. Rowinsky, MD, unpublished results] For paclitaxel, the limited number of binding sites may represent binding sites on beta-tubulin.

**Clinical Implications**

Paclitaxel's nonlinear pharmacokinetic profile may have several clinical implications. For example, dose escalations, especially on shorter administration schedules, may result in disproportionate increases in both area under the concentration-time curve (AUC) and peak plasma concentration (Cpeak), as well as disproportionate increases in toxicity. Dose reductions may have the opposite effect, resulting in disproportionate decreases in AUC and/or Cpeak, thereby possibly decreasing antitumor activity. In addition, these models predict that tissue sites are effectively saturated at relatively low paclitaxel concentrations (achieved with paclitaxel doses less than 175 mg/m² on a 3-hour schedule), whereas elimination processes are effectively saturated at higher doses (achieved with paclitaxel doses (3 175 mg/m² on a 3-hour schedule).

To characterize tissue saturation as a function of paclitaxel dose, model simulations have been performed using actual plasma concentration data and both types of tissue distribution models, taking saturable elimination processes into account.[E.K. Rowinsky, md, unpublished results] The simulations have demonstrated that the peak drug contents in tissues do not change significantly when paclitaxel doses are increased from 135 to 250 mg/m² on both 3- and 24-hour schedules. In
addition, these simulations indicate that tissue saturation is greater with shorter administration schedules for all paclitaxel doses, and the rate that tissues become saturated is also greater with shorter infusion schedules. Based on this model, peak drug content is approximately 70% of the theoretical maximum at a dose of 135 mg/m², 85% at a dose of 175 mg/m², and greater than 90% at a dose of 250 mg/m² when paclitaxel is administered over 3 hours. Respective tissue saturation values are approximately 35%, 45%, and 55% when paclitaxel is administered over 24 hours. These results suggest that increasing drug content in peripheral tissues and tumors by increasing paclitaxel dose or dose intensity within a clinically relevant dosing range may be tantamount to a situation of diminishing limiting returns as tissue binding sites become progressively saturated. It should be pointed out, however, that the precise levels of tissue saturation that result in maximal cytocidal or toxicologic effects are not known. There may also be other important determinants of drug effect, such as the duration that any specific degree of tissue saturation is maintained. In other words, a maximal effect may occur with any degree of tissue saturation. In addition, it may be important to consider the duration that any specific degree of tissue saturation is maintained. Therefore, direct comparisons between prolonged and short treatment schedules with respect to the effect of different degrees of tissue saturation on outcome (ie, cytotoxicity, toxicity) cannot be adequately performed until other critical determinants of effect are characterized. However, the notion of a “threshold concentration” or a “threshold dose” due to saturable pharmacokinetic processes may account for the plateauing dose- or concentration-response relationships that have been observed in vitro and in clinical practice.

**Dose and Schedule in Clinical Trials**

A broad range of dosing schedules has been evaluated for paclitaxel, whereas most clinical trials with docetaxel have used a single-dosing schedule (100 mg/m² over 1 hour). Evaluations of paclitaxel were initially limited to the 24-hour schedule because of the high incidence of major hypersensitivity reactions in patients receiving short schedules without premedication, and the 24-hour schedule was the first to be approved for women with recurrent or refractory ovarian cancer. Most available information about paclitaxel in various disease settings thus pertains to the 24-hour schedule. However, prominent antitumor activity has also been observed with 1- and 3-hour schedules of paclitaxel in women with recurrent or refractory breast and ovarian cancers. This activity has also been apparent in both chemotherapy-naive and previously treated patients with non-small-cell lung cancer and other tumor types. The results of the NCIC-CTG's pivotal Ov.9 (or BMS 016) trial that addressed the relative merits of administration schedule and premedication led to the regulatory approval of the 3-hour schedule in women with recurrent or refractory ovarian cancer, and it stimulated broader interest in exploring alternate doses and schedules.[59] The equivalence of both the 3- and 24-hour schedules of paclitaxel in this setting, in which the overall basal response rate is low and large numbers of patients are required to detect small differences, does not necessarily imply that both schedules are equivalent in other tumor types and settings, particularly when equivalent doses are used. Intriguing results, consisting of some of the highest response rates achieved with paclitaxel, have been noted on more prolonged schedules (particularly the 96-hour infusion) in women with recurrent or refractory breast cancer.[60,61] Impressive antitumor activity has been observed in patients with both chemotherapy-naive and previously treated non-small-cell lung cancer treated with paclitaxel on an even shorter 1-hour schedule.[62] However, it should also be noted that the impressive results with both schedules occurred with doses that resulted in a level of neutropenia comparable to that observed in initial pivotal trials using the 24-hour schedule.

**Paclitaxel at its MTD**

A concern during the early development of paclitaxel was that its limited supply would preclude the scope and number of phase II evaluations.[63,64] Because heavily pretreated women with advanced ovarian cancer were able to tolerate substantially lower paclitaxel doses than untreated or minimally pretreated patients, investigators initially opted to perform most phase II evaluations of paclitaxel at its MTD with granulocyte colony-stimulating factor (G-CSF [Neupogen]) support, as well as limited phase II trials at lower paclitaxel doses without G-CSF. In several clinical situations, such as in untreated or minimally pretreated women with advanced breast cancer, phase II studies using high doses of paclitaxel and occasional G-CSF were performed from the outset. In essence, the decision to evaluate paclitaxel at its MTD with G-CSF support was based on the...
possibility that the demonstration of unimpressive activity at higher paclitaxel doses would obviate the need to perform additional phase II trials of paclitaxel at lower doses. It was similarly felt that the demonstration of negligible activity at submaximal doses would not conclusively prove that paclitaxel was inactive across its entire dosing spectrum, and additional studies evaluating higher drug doses might be required.

In studies of paclitaxel at its MTD, negligible activity was demonstrated in patients with advanced melanoma and colorectal, renal, and gastric cancers,[63,64] which argued strongly against performing additional phase II trials of lower doses in these tumor types. A similar reasoning was subsequently used during the development of docetaxel in that broad phase II evaluations were performed using an MTD schedule (100 mg/m² over 1 hour).[51,65] This approach results in unequivocally negative conclusions regarding activity when high-dose phase II studies are negative. The potential benefits of this approach are offset by the dilemma that often arises when significant antitumor activity is observed in nonrandomized phase II studies employing maximal drug doses with or without hematopoietic colony-stimulating factor support. In this situation—as was the case for paclitaxel in phase II trials in lymphoma and carcinomas of the breast, lung, cervix, and head and neck—further clinical investigations may focus solely on the most intensive dosing schedule, in which lower, less toxic doses and/or dose intensity may also produce substantial antitumor activity.

Clinical Doses

In clinical practice, paclitaxel is usually administered at a dose of 175 mg/m² over 3 hours or 135 to 175 mg/m² over 24 hours every 3 weeks. These dosing schedules may result in optimal therapeutic indices in many disease settings, such as in palliating patients with refractory or recurrent advanced ovarian and breast cancers. It may, however, be more appropriate to use alternate dosing schedules in other tumor types and settings, particularly in less heavily pretreated patients and when prolongation of survival is a tangible objective.

A broad range of paclitaxel doses has been evaluated on almost all schedules, and the most appropriate dose for any schedule is currently being studied in randomized trials in ovarian, breast, and non-small-cell lung cancers. Although several administration schedules for docetaxel have been studied in phase I evaluations, the agent is most commonly administered at a dose of 100 mg/m² as a 1-hour infusion every 3 weeks. Lower doses (60 to 75 mg/m²) on a 1-hour schedule may be associated with a lower incidence of both hematologic and nonhematologic toxicities; however, the relative therapeutic advantages of high vs low doses are not clear.

Ovarian Cancer

In the initial five phase II studies of paclitaxel on a 24-hour schedule in women with recurrent or refractory ovarian cancer, which were used for registration of the agent in the United States, doses ranged from 110 to 300 mg/m².[66-70] Individual study reports used somewhat different criteria to define patient eligibility and evaluability for response. In these reports, response rates were seemingly higher (36% to 48%) in trials evaluating higher paclitaxel doses (170 to 300 mg/m²) and dose intensity than in trials in which most patients were treated with lower paclitaxel doses (response rates, 30% to 37%; 110 to 175 mg/m²) or higher doses, albeit administered in a less dose-intensive regimen (response rate, 20%; 250 mg/m² with treatment delays).[66-70] G-CSF support was also used from the outset to ameliorate severe neutropenia and maintain dose intensity in trials that employed high paclitaxel doses or dose intensity.[68-70] Nonhematologic toxicities, particularly neurotoxicity, occurred more frequently than in those trials that evaluated lower paclitaxel doses or dose intensity.[66,67] At first glance, such observations may suggest that higher paclitaxel doses and dose intensity are optimal in this and other settings. For example, using the correlative methods of Hrynick and Levin, Reed et al retrospectively analyzed the relationships between paclitaxel dose intensity and antitumor activity in women with advanced ovarian and breast cancers.[71] They demonstrated strong positive relationships in both settings (P = .022 and .004, respectively). It should be stressed that these trials were nonrandomized and incorporated diverse patient populations with respect to pertinent demographic and prognostic variables.

Results of a Meta-analysis

To more appropriately evaluate the effects of paclitaxel dose and dose intensity on the antitumor activity and survival of patients with refractory or recurrent advanced ovarian cancer, a pooled analysis of individual patient data (meta-analysis) was performed.[72] The database was derived from the initial five studies that were used for registration of paclitaxel in the United States for recurrent or refractory disease. It audited demographic, categorical response, and successive tumor
measurement data from 191 ovarian cancer patients who were treated with paclitaxel on a 24-hour schedule every 3 weeks.

In this analysis, the probability of achieving a partial or complete response was not related to the average paclitaxel dose (odds ratio, 1.0 per 10 mg/m²; P = .60). In fact, the probability of responding appeared to decrease with increasing dose intensity (odds ratio, -0.77 per 10 mg/m²/wk; P = .06). A strong negative relationship between the maximum percent reduction in tumor size and dose intensity was also apparent (odds ratio, -6.1% per 10 mg/m²/wk; P = .007). Not only was a negative effect demonstrated in the logistic regression analysis of the data from all studies but also a negative effect was found in each individual study.

With respect to overall survival, the analysis suggested a negative relationship between average paclitaxel dose and survival (hazard ratio, 1.06 per 10 mg/m²; P = .0001). There was also a strong negative relationship between dose intensity and survival (hazard ratio, 1.3 per 10 mg/m²/wk; P = .0001). Similar relationships were demonstrated between paclitaxel dose, dose intensity, and progression-free survival. These relationships were minimally affected when the analyses were controlled for individual study, performance status, number of prior regimens, platinum sensitivity, and response to prior therapy. These results indicate no clear benefit of increasing paclitaxel doses above 135 mg/m² when the drug is administered as a 24-hour infusion every 3 weeks to women with recurrent or refractory advanced ovarian cancer. This is supported by the known saturable pharmacologic behavior of paclitaxel.

Possible Explanations

There are several possible explanations that may account for the lack of an effect of higher paclitaxel doses on both the categorical response and percentage reduction in measurable disease (such as tissue saturation, as discussed previously). It is difficult, however, to propose reasonably strong biologic or pharmacologic explanations for why antineoplastic activity might decrease with higher paclitaxel dose intensity.

Liebmann et al reported a negative relationship between paclitaxel concentration and cytotoxicity in a panel of eight human tumor cell lines that were treated for 24 hours.[20] Increasing paclitaxel concentrations from 2 to 20 nM/L sharply increased cytotoxicity. No additional cytotoxicity occurred with paclitaxel concentrations above 50 nM/L, and treatment with very high drug concentrations (more than 10 µM) resulted in even less cytotoxicity. Furthermore, the principal constituent of paclitaxel's clinical formulation vehicle, polyoxyethylated castor oil, at a concentration of 0.135%, antagonized the cytotoxic effects of paclitaxel. Even in light of these experimental data, the potentially negative effects of paclitaxel dose intensity on antitumor activity and survival in the meta-analysis must be interpreted with considerable caution and awaits confirmation in larger prospective studies.

These results argue strongly against the possibility that increasing paclitaxel dose above 135 mg/m² on a 24-hour schedule or dose intensity might enhance clinical antitumor activity. The analysis suggests that the optimal paclitaxel dose intensity for similar patients is at the lower end of the range of dose intensity used in these investigations, ie, 45 mg/m²/wk (or 135 mg/m² every 3 weeks) as a 24-hour infusion. At this juncture, however, it is not known whether these results can be generalized to describe paclitaxel dose and dose-intensity relationships using other dosing schedules (eg, 3- or 96-hour schedules) and in other disease settings.

Two Randomized Trials

To date, the effect of paclitaxel dose on clinical response in women with refractory or recurrent ovarian cancer has been evaluated prospectively in two randomized trials.[59,73] The salient features of randomized clinical trials of the taxanes that focused on dosing and scheduling issues in ovarian and other neoplasms are listed in Table 2.

In Ov.9 (BMS 016), the NCIC-CTG evaluated the effects of two different paclitaxel doses (135 vs 175 mg/m²) and two different schedules (24 vs 3 hours) on both response and toxicity.[59] With respect to the dosing issue, progression-free survival was significantly, albeit not profoundly, longer in the high-dose arm (19 vs 14 weeks, P = .02), but response rates and survival were similar. Nevertheless, the two paclitaxel doses were not very disparate, and the study design and patient numbers precluded comparisons between each of the four individual treatment arms, so that patients treated with both schedules were analyzed together. It is possible the patients receiving paclitaxel on the 3-hour schedule, and not the 24-hour schedule, contributed to the significant difference between the two doses.

The dose-response issue has also been assessed in an intergroup study in which a similar group of patients were treated with 24-hour infusions of paclitaxel at one of three doses: 135, 175, and 250 mg/m² plus G-CSF. However, the lowest dose arm was terminated after the regulatory approval of
paclitaxel, which resulted in reduced patient accrual.[73] A preliminary analysis of the results of the study indicates only modest differences in response rates. Response rates were 36% vs 28% in the 250-mg/m²-plus-G-CSF and 175 mg/m²-arms, respectively, but there were no differences in either progression-free or overall survival.[73]

Based on the results of nonrandomized trials, meta-analyses, and the limited randomized trials to date, there is no compelling reason to administer paclitaxel as a 24-hour infusion in women with recurrent or refractory ovarian cancer at doses above 135 to 175 mg/m². The cumulative results indicate that paclitaxel doses above 135 mg/m² result in either little or no further benefit with respect to obtaining categorical responses and certainly do not prolong disease-free and overall survival times.

In the Ov.9 study, myelosuppression was substantially more severe in patients receiving identical doses of paclitaxel over 24 hours compared with 3 hours, probably due to longer drug exposure above a critical threshold concentration. Toxicologically, the results suggest that the precise paclitaxel dose capable of inducing any given effect depends on the specific administration schedule.

These findings preclude extrapolation of the relationships between dose and effect (ie, toxicity, disease activity) from one dosing schedule to another. The limited availability of comparable data with shorter (eg, 3-hour) schedules in this disease setting, particularly at paclitaxel doses above 175 mg/m², preclude making similar recommendations. Study results in this and other disease settings nonetheless indicate that paclitaxel doses below 175 mg/m² on short schedules may be suboptimal.

For docetaxel in this disease setting, there are sufficient impressive results available only for 100 mg/m² over a 1-hour dosing schedule [51,65].

Breast Cancer

As in the case of ovarian cancer, the determination of optimal taxane dosing and scheduling has been the principal goal of several clinical trials in breast cancer. To date, it appears that dose may be a critical determinant of response for both paclitaxel and docetaxel administered on short schedules (eg, paclitaxel over 3 hours and docetaxel over 1 hour).

Paclitaxel Dosing

The results of a randomized trial (BMS 48) of paclitaxel doses of 135 vs 175 mg/m² on a 3-hour schedule in women with metastatic breast cancer who had previously been treated with adjuvant chemotherapy only, chemotherapy for metastatic disease only, or chemotherapy in both adjuvant and metastatic settings, revealed no differences in response rates (29% [high dose] vs 22% [low dose]) or in median survival (11.7 [high dose] vs 10.5 months [low dose]). Progression-free survival was longer, however, with the higher dose (4.2 vs 3 months; P = .02).[74] Severe neutropenia was not common with either dose; the incidences of grade 4 neutropenia were 19% and 28% in patients treated with paclitaxel 135 and 175 mg/m², respectively. Although this trial used nondisparate paclitaxel doses, these results indicate that neutropenia and antitumor activity may be congruent indices of drug effect.

These results led to the regulatory approval of paclitaxel 175 mg/m² (3-hour schedule) in women with metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant therapy. The Cancer and Leukemia Group B is currently evaluating whether higher paclitaxel doses achieve greater activity in women with metastatic breast cancer. In this trial (CALGB 9342), patients are being randomized to treatment with paclitaxel doses of 175, 210, or 250 mg/m² on a 3-hour schedule.

Docetaxel Dosing

There has been a paucity of studies addressing optimal dosing with docetaxel. This is because the agent has been evaluated almost exclusively at a dose of 100 mg/m² over 1 hour, which induces severe neutropenia in most patients. Although substantial activity with less toxicity has been noted at lower docetaxel doses (60 to 75 mg/m²), the results of nonrandomized studies indicate that there may be a positive dose-response relationship with docetaxel given on a 1-hour schedule at doses ranging from 60 to 100 mg/m². In women with metastatic breast cancer who have progressed on anthracycline-based chemotherapy, response rates with docetaxel on a 1-hour schedule have averaged 35% and 47% at doses of 60 and 100 mg/m², respectively.[51,65,75-77] Respective response rates have averaged approximately 55% and 48% in patients who have not received chemotherapy in the metastatic setting.[78-81] A multicenter randomized trial, in which women with metastatic breast cancer are receiving docetaxel doses of either 75 or 100 mg/m² on a 1-hour schedule, is ongoing.
Paclitaxel Scheduling

Optimal paclitaxel scheduling was studied in a randomized trial (BMS 71) in which women with metastatic breast cancer were treated with paclitaxel 175 mg/m² infused over either 3 or 24 hours.[82,83] Women who had received no prior chemotherapy, adjuvant chemotherapy only, or chemotherapy for metastatic disease with or without prior adjuvant therapy were eligible. Paclitaxel dose escalations to 200 and 225 mg/m², as well as dose reductions to 135 mg/m², were permitted, depending on the degree of myelosuppression during the previous course.

There were no differences in cumulative response rates (29% vs 31%), median progression-free survival (3.5 vs 4.6 months), or survival (9.8 vs 13.4 months) between the 3- and 24-hour groups, respectively. However, it was apparent that the starting doses were not equitoxic, which is demonstrated by the fact that 30% and 79% of women in the 3- and 24-hour groups, respectively, developed grade 4 neutropenia. In the 3-hour group, paclitaxel doses were increased on one or two occasions in 65% of patients, whereas dose reductions were required in only 5% of patients. In contrast, 34% of patients in the 24-hour group required dose reductions, and paclitaxel doses were escalated in 36% of patients.

It is also important to note that responses rates in patients receiving paclitaxel over 3- and 24-hour schedules were more disparate in women who had no prior therapy (34% vs 57%) compared with those who had adjuvant therapy only (36% vs 40%) or chemotherapy in both adjuvant and metastatic settings (24% vs 22%). These results suggest that the more aggressive 24-hour schedule does not result in a significant improvement in outcome in the palliative setting. However, more aggressive dosing schedules should be considered for patients with earlier stages of disease. This does not necessarily imply that the 24-hour or more prolonged schedules are superior and should be used exclusively. Instead, alternate aggressive dosing schedules, as gauged by their potential to induce a degree of toxicity similar to paclitaxel 175 mg/m² over 24 hours, might suffice. For example, paclitaxel doses ranging from 200 to 250 mg/m² on a 3-hour schedule appear to be equivalent toxicologically to paclitaxel, 175 mg/m² on a 24-hour schedule.

Sigmoid curves that describe the relationships between paclitaxel effect (eg, the percentage decrement in absolute neutrophil counts) as a function of the duration of drug exposure above a critical threshold concentration on 1-, 3-, and 24-hour paclitaxel schedules are depicted in Figure 1. It should be noted that the magnitude of the effects induced by all three dosing schedules converge. For the percentage decrements in neutrophil counts, convergence occurs in the 225- to 250-mg/m² dosing range.

It seems reasonable that clinical evaluations of optimal taxane scheduling should be performed using equitoxic regimens (ie, 1- to 24-hour schedules using doses at or near the point of convergence). The design of an ongoing National Surgical Adjuvant Breast and Bowel Project study (NSABP B26) may be better suited than BMS 71 to discern whether an optimal paclitaxel schedule truly exists. In this study, women with metastatic or locally advanced breast cancer are being randomized to treatment with paclitaxel, 250 mg/m² given over either 3 or 24 hours with G-CSF. These dosing schedules are much more likely to be equitoxic compared with those employed in BMS 71, minimizing potential confounding variables.

Prolonged Paclitaxel Schedules

Much attention has been paid to more prolonged (96-hour) paclitaxel dosing schedules since Wilson et al reported an impressive response rate of 48% in women with advanced breast cancer who had either progressed during or following treatment with anthracycline-based chemotherapy.[60] Most patients, however, were treated with paclitaxel at its MTD on this prolonged schedule (140 mg/m² over 96 hours), and patients often required G-CSF support.

Building on this experience, Seidman et al demonstrated that 7 (25%) of 28 women with metastatic breast cancer who developed recurrent or progressive disease following treatment with short schedules of either paclitaxel or docetaxel responded to paclitaxel, 140 mg/m² over 96 hours with G-CSF support, if necessary.[61] Both hematologic and nonhematologic toxicities were substantial in this study, and the range of taxane doses that the responding patients had previously received was not reported. However, it is likely that most patients received prior treatment with paclitaxel, 175 mg/m² over 3 hours, a dosing schedule that produces substantially less toxicity than does 140 mg/m² over 96 hours.

Although these results are provocative, they do not necessarily indicate that the 96-hour schedule is superior to shorter taxane schedules, and it is likely that the aggressiveness of the dosing schedule itself may have accounted for this impressive activity. Indeed, such an effect might have been achieved with shorter taxane schedules, albeit at higher doses. Similar caution should be used in interpreting the preliminary reports of responses in women with heavily pretreated metastatic breast...
cancer who are treated with docetaxel on an aggressive dosing schedule (eg, 100 mg/m² over 1 hour) after developing progressive disease during or after treatment with less aggressive taxane dosing schedules (eg, paclitaxel, 135 to 175 mg/m² over 3 hours).[84]

Ongoing Trials
Clinical trials designed to compare the intrinsic antitumor efficacy of the various taxanes should use equitoxic regimens. An ongoing phase III multicenter trial (NCI T93-0165) being conducted at Memorial Sloan-Kettering Cancer Center, the M. D. Anderson Cancer Center, Swedish Tumor Institute, and British Columbia Cancer Agency is more appropriately designed to address the scheduling issue. In this trial, women with metastatic breast cancer are randomized to treatment with equitoxic paclitaxel dosing schedules at two extremes, 140 mg/m² over 96 hours and 250 mg/m² over 3 hours.

In contrast, an ongoing randomized phase III trial (RPR 56976-311) that is designed to determine whether paclitaxel or docetaxel possesses superior activity in women with metastatic breast cancer who have received prior chemotherapy in the metastatic setting does not use equitoxic regimens. In this study, patients are being randomized to treatment with either docetaxel, 100 mg/m² on a 1-hour schedule, or paclitaxel, 175 mg/m² on a 3-hour schedule. The paclitaxel dosing schedule is substantially less aggressive in terms of its potential to induce myelosuppression, and possibly, its antitumor activity; therefore, this may be an unfair comparison.

Lung Cancer
Early phase II trials of paclitaxel and docetaxel in patients with both non-small-cell and small-cell lung cancers, as well as in other tumor types, were performed using relatively aggressive dosing regimens (paclitaxel, 200 to 250 mg/m² over 24 hours, and docetaxel, 100 mg/m² over 1 hour). There have been only limited attempts to rigorously address questions regarding optimal dosing and scheduling using randomized trial designs in these tumor types. For both paclitaxel and docetaxel, comparisons of the results of phase II studies involving patients with similar relevant demographic characteristics suggest that there may be dose-response relationships that parallel dose-toxicity relationships, particularly on short taxane schedules.

For example, response rates in chemotherapy-naive patients with non-small-cell lung cancer treated with docetaxel, 60, 75, and 100 mg/m² on a 1-hour schedule, were 23%, 25%, and 31%, respectively.[85] For paclitaxel given on a 1-hour schedule to both previously treated and chemotherapy-naive patients with non-small-cell lung cancer, negligible toxicity and anti-tumor activity (2 responses in 17 patients [12%]) were reported at the 135-mg/m² dose level. A dose of 200 mg/m² resulted in much greater toxicity and antitumor activity (11 responses in 36 patients [31%]).[62]

A major concern during the development of the cisplatin (Platinol)/paclitaxel regimen was that the MTD of paclitaxel on a 24-hour schedule in combination with cisplatin (135 mg/m²) was significantly lower than the paclitaxel dose (250 mg/m²) that was determined to be active in early phase II studies in untreated patients with non-small-cell lung cancer. Since neutropenia was the principal toxicity of paclitaxel combined with cisplatin, phase I studies of the regimen subsequently focused on using G-CSF to enable further dose escalation of paclitaxel combined with cisplatin. In these trials, peripheral neurotoxicity precluded repetitive administration of paclitaxel doses above 250 mg/m² (day 1) on a 24-hour schedule followed by cisplatin 75 mg/m² (day 2) and G-CSF.

Randomized Trial
In view of the acceptable toxicity profile demonstrated for cisplatin (75 mg/m²) combined with higher doses of paclitaxel (250 mg/m²) plus G-CSF, the Eastern Cooperative Oncology Group (ECOG 5592) conducted a randomized trial of chemotherapy-naive patients with metastatic non-small-cell lung cancer. Patients received either standard therapy, consisting of etoposide (VePesid), 100 mg/m² on days 1 to 3, and cisplatin, 75 mg/m² on day 1; or cisplatin, 75 mg/m², combined with either low doses of paclitaxel, 135 mg/m² on a 24-hour schedule, or high doses of paclitaxel, 250 mg/m² 24-hour schedule, plus G-CSF.[86]

Response rates in both the high- and low-dose paclitaxel arms (26.5% and 32.1%, respectively) were superior (P less than .001) to the rate in the etoposide arm (12%). Median survival times with high- and low-dose paclitaxel (9.56 and 9.99 months, respectively) also were significantly longer (P less than .001) than with etoposide (7.69 months). Despite similar rates of severe neutropenia, fever, and infection in both paclitaxel arms, the overall impact of high-dose paclitaxel with G-CSF support in this disease setting was negligible.

In accompanying pharmacodynamic studies, steady-state paclitaxel concentrations (Css) in plasma
were measured in courses 1 and 2 in both paclitaxel arms, and Css was related to outcome.\cite{87}
Although there was a significant difference in Css between the low- and high-dose paclitaxel arms (mean ± SD, 0.35 ± 0.16 µM vs 0.94 ± 0.50 µM; P less than .001), no significant pharmacodynamic relationships were evident between Css and both response and time to disease progression. These results indicated that neither response nor time to disease progression is influenced by either paclitaxel Css or dose in chemotherapy-naive patients with non-small-cell lung cancer who are treated with paclitaxel doses ranging from 135 to 250 mg/m² (24-hour schedule) followed by cisplatin. Collectively, these results in non-small-cell lung cancer indicate that the relationship between taxane dose and response plateaus at lower taxane doses with progressively longer infusion schedules, which is similar to the situation demonstrated in ovarian cancer.

**Head and Neck Cancer and Other Tumor Types**

As in the use of taxanes in patients with advanced non-small-cell lung cancer, in which early phase II trials of paclitaxel and docetaxel were performed using relatively aggressive dosing regimens, there has been a paucity of clinical studies designed to rigorously explore dosing and scheduling issues in patients with advanced head and neck cancer and other tumor types. Perhaps the only attempt to date is a phase III trial (ECOG 1393) that evaluated the optimal dosing of paclitaxel on a 24-hour schedule in combination with cisplatin in patients with advanced squamous cell carcinoma of the head and neck.\cite{88} A previous phase II trial of paclitaxel, 250 mg/m² on a 24-hour schedule, produced a 40% response rate. Building on these data, Forastiere et al randomized patients with metastatic or locally advanced disease who had not previously received chemotherapy for recurrent disease to treatment with cisplatin (75 mg/m²) following either low-dose paclitaxel (135 mg/m² on a 24-hour schedule) or high-dose paclitaxel (200 mg/m² on a 24-hour schedule) plus G-CSF. A preliminary analysis demonstrated that response rates were identical in both arms (35%) and there were no differences in survival parameters. In addition, there appeared to be no significant differences in rates of both severe hematologic and nonhematologic toxicities. The results of an accompanying pharmacodynamic study, which is similar to that performed in the ECOG 5592 trial in non-small-cell lung cancer, is undergoing analysis. As is the case with non-small-cell lung cancer, these clinical results indicate that there is no advantage to using paclitaxel doses above 135 mg/m² on a 24-hour schedule in combination with cisplatin in patients with advanced head and neck cancer.

**Conclusions**

Based on the current cumulative results of nonrandomized and randomized trials of the taxanes in cancers of breast, ovary, lung, and head and neck, there does not appear to be a single dosing schedule that produces a vastly superior clinical outcome. Although there are reports of both impressive and unimpressive antitumor activity with some paclitaxel schedules in several disease settings in nonrandomized studies, the overall aggressiveness of the treatment regimen itself must be taken into account. In both tissue culture and clinical trials, there appears to be a threshold paclitaxel dose or concentration, below which only negligible antitumor activity is observed, and a plateau dose or concentration, above which minimal, if any, further antitumor effects occur. The doses at which both threshold and plateau effects occur appear to be inversely related to the duration of the administration schedule used in clinical practice.

For paclitaxel, it appears that comparable antitumor effects can be achieved with either short (1- and 3-hour) or prolonged (24- and 96-hour) schedules as long as equitoxic dosing regimens are used (ie, higher paclitaxel doses with short infusion schedules). For docetaxel, although there are insufficient data available for the gamut of possible dosing schedules relative to paclitaxel, the impressive results and toxicities noted with the most common dosing schedule, 100 mg/m² over 1 hour, indicate that both plateau and threshold effects are being achieved. It may not, therefore, be necessary to evaluate alternate administration schedules. However, lower docetaxel doses on the 1-hour schedule may result in vastly different toxicity profiles and therapeutic indices. In disease settings in which the principal therapeutic goal is palliation (eg, women with recurrent or refractory breast and ovarian cancers), there appears to be little difference in outcome between various dosing schedules as long as a minimal plateau paclitaxel dose is exceeded (ie, 3 175 mg/m² on a 24-hour schedule or 3 175 mg/m² on a 3-hour schedule). However, the use of higher doses on


shorter administration (ie, more than 200 mg/m² on 1- or 3-hour schedules) may be necessary to achieve a maximal therapeutic outcome in situations in which prolongation of survival is a reasonable expectation.

References:


77. Rhone-Poulenc Rorer: Data on file.


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