

Introduction to taxane pharmacokinetics and pharmacodynamics

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Objective. To compare the pharmacokinetics and pharmacodynamics of the taxanes, paclitaxel and docetaxel.

Data sources. A MEDLINE search was conducted using docetaxel, dose, drug interactions, liver dysfunction, liver impairment, mechanism of action, paclitaxel, pharmacodynamics, pharmacokinetics, and schedule as search terms. Reference lists, bibliographies of pertinent articles, and abstracts from the American Society of Clinical Oncology and the American Association for Cancer Research annual meetings were also identified and reviewed. Both preclinical and clinical literature were reviewed and analyzed.

Data synthesis. The taxanes, paclitaxel and docetaxel, are a novel class of antineoplastic drugs that provide notable activity, and produce high response rates but minimal side effects. These agents share a similar mechanism of action, but several important pharmacokinetic and pharmacodynamic differences exist. The higher tubulin affinity, slower efflux from cells, triphasic elimina-

tion, and prolonged drug exposure of docetaxel confer pharmacokinetic and pharmacodynamic advantages over paclitaxel. The nonlinear pharmacokinetics of paclitaxel may result in disproportionate increases in plasma concentrations and AUCs; however, several safe and effective paclitaxel regimens are currently used. Because the taxanes are metabolized extensively in the liver by cytochrome P-450 enzymes, patients with hepatic impairment have reduced total body clearance that may result in increased toxicity. Additionally, drugs that induce, inhibit, or compete with microsomal enzymes known to metabolize the taxanes, can result in clinically significant drug interactions. These pharmacokinetic differences should be carefully considered when dosing and scheduling paclitaxel or docetaxel in clinical practice.

J Oncol Pharm Practice (2000) 6, S22–S27.

Key Words: Docetaxel; liver dysfunction; paclitaxel; pharmacodynamics; pharmacokinetics; taxane(s).

INTRODUCTION

The taxanes, paclitaxel and docetaxel, are among the most-used chemotherapy agents for treatment of metastatic breast, non-small cell lung, and head and neck cancers. Both paclitaxel and docetaxel have

similar mechanisms of action; however, important differences exist between their chemical structures (Figure 1). Both taxanes bind to the beta subunits of tubulin, causing stabilization of tubulin polymerization. As a result, cell cycle arrest at the G2/M phase and inhibition of mitosis occur. Docetaxel has greater uptake into the cells and more potent binding to the tubulin subunits than does paclitaxel (Figure 2), probably because of smaller, less lipophilic substitutions of the hydroxyl unit at C-10 and the *tert*-butyl substitution of the phenylpropionate side chain by a carbamate linkage (Figure 1).¹ This more potent binding also results in much slower efflux of docetaxel from the cells (Figure 3),¹ an important distinction —

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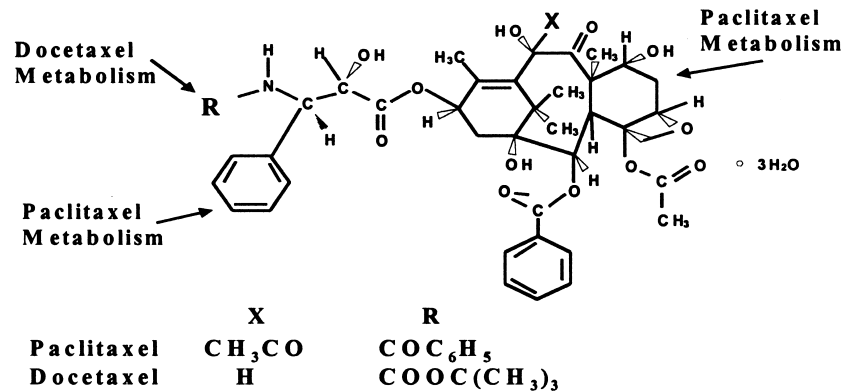


Figure 1. Structure and metabolic sites of the taxanes.

the longer the drug stays in the tumor cells, the greater the chance the cells will reach the mitotic phase while the drug is bound to the tubulin, causing disruption of mitosis and cell death. These pharmacokinetic differences are largely responsible for the pharmacodynamic differences observed and may explain why various dosages and schedules of paclitaxel result in different clinical outcomes.

MECHANISMS OF CYTOTOXICITY

The taxanes have several methods of cytotoxic action. The primary mechanism of action is a direct binding to the beta subunits of tubulin, causing increased tubulin polymer mass, formation of microtubule bundles, and inhibition of microtubule depolymerization. This action prevents reorganization of the microtubule network required for mitosis and cell proliferation.^{2,3} The smaller, less lipophilic substitutions on docetaxel enable greater uptake into the cells and more potent binding to the tubulin subunits compared with paclitaxel (Figure 2).¹ The more potent binding results in docetaxel's much slower efflux from the cells (Figure 3).¹

Another important mechanism of antitumor action is induction of apoptosis. For paclitaxel, the apoptotic

events were primarily coupled with mitotic arrest.⁴ Results of recent studies show that apoptosis induced by low concentrations of paclitaxel or docetaxel may occur without mitotic arrest. In this case, apoptosis may be induced by a p53-independent, gene-directed process of *bcl-2* hyperphosphorylation.^{5,6} The protein *bcl-2* inhibits apoptosis by heterodimerizing with the BAX protein. However, when *bcl-2* is phosphorylated, apoptosis occurs through the disruption of the *bcl-2*-BAX association. Docetaxel is 100-fold more potent *in vitro* in inducing *bcl-2* phosphorylation than is paclitaxel.⁷

PHARMACOKINETICS

Both paclitaxel and docetaxel are metabolized extensively in the liver and excreted primarily through the feces. The molecular sites and the cytochrome P-450-dependent monooxygenases involved in their metabolism differ. The principal site of metabolism for docetaxel is the *tert*-butylpropionate side chain, which undergoes a series of oxidation reactions; paclitaxel hydroxylation occurs at the C-6 position on the taxane ring and the *para*-position on the phenyl ring at the C3' position of the C-13 side chain. Paclitaxel is metabolized primarily by the CYP2C8 and CYP3A4

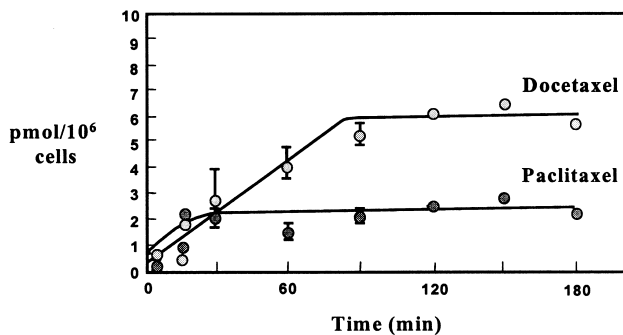


Figure 2. Taxane uptake and binding in a P388 cell line. Adapted from Riou *et al.*¹

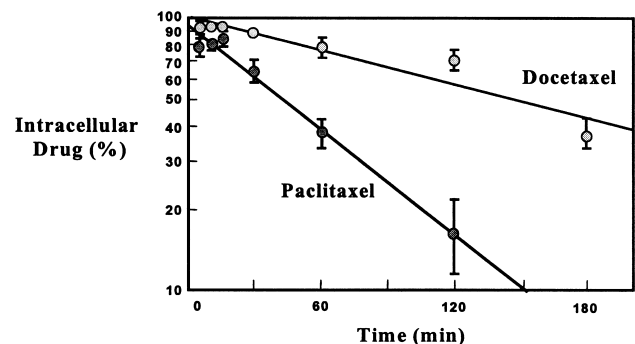


Figure 3. Taxane efflux in a P388 cell line. Adapted from Riou *et al.*¹

hepatic microsomal enzymes, whereas docetaxel is primarily metabolized by the CYP3A enzymes.^{8,9}

These differences in metabolism result in several pharmacokinetic differences. First, docetaxel follows linear pharmacokinetics, whereas paclitaxel demonstrates nonlinear pharmacokinetics.¹⁰ Pharmacokinetic modeling suggest that saturable distribution and elimination processes account for paclitaxel's nonlinear pharmacokinetic profile.^{10,11} Thus, dose escalations of paclitaxel result in disproportionate increases in area under the curve (AUC) values, maximum plasma concentration (C_{\max}) and toxicity, especially with a short infusion of paclitaxel. Dose reductions may have the opposite effect, resulting in disproportionate decreases in AUCs and C_{\max} values, thereby decreasing antitumor activity. A phase III study in ovarian cancer patients compared 3- and 24-hour infusions of paclitaxel 135 and 175 mg/m². Results showed that, at the 24-hour infusion, a dose increase of 30% increased the maximum plasma concentration by 87%, whereas the AUC was only proportionally increased. The same 30% dose increase resulted in a 68% increase in C_{\max} and an 89% increase in AUC after a 3-hour infusion.¹² Conversely, docetaxel exhibits linear kinetics, and its administration times do not vary; therefore, a dosage change results in proportional changes in C_{\max} and AUC.

Docetaxel has a terminal half-life ($t_{1/2}$) of approximately 11 to 13 hours,^{10,13} with plasma concentrations staying for at least 16 to 20 hours above the threshold believed to inhibit tubulin depolymerization. Paclitaxel's half-life depends on the infusion time and varies between 4 and 25 hours.^{14,15} Although the plasma $t_{1/2}$ offers important information about these compounds, tumor cell kill is probably more dependent on the rate of efflux from tumor cells.

LIVER DYSFUNCTION

Pharmacokinetic evaluations show that impaired liver function influences clearance of docetaxel from the body.¹⁶ Docetaxel (100 mg/m²) administration in patients with transaminase levels more than 1.5 times the upper limit of normal and alkaline phosphatase levels greater than 2.5 times the upper limit of normal results in a 27% decrease in total body clearance and a 38% increase in AUC.¹⁷ These results correspond with results observed in phase I and II studies of breast cancer patients who received docetaxel 100 mg/m² every 3 weeks. In the patients with liver dysfunction, significantly more toxic deaths, febrile neutropenia, infections, thrombocytopenia, stomatitis, and skin toxicity occurred than in patients without liver dysfunction.¹⁷ For this reason, the manufacturer

warns that patients with bilirubin levels above the upper limit of normal or the coexistence of transaminase levels more than 1.5 times the upper limit of normal and alkaline phosphatase levels more than 2.5 times the upper limit of normal are at increased risk for grade 4 neutropenia and other docetaxel-related toxicities such as severe stomatitis, severe skin toxicity, and death. Therefore, full doses of docetaxel should not be administered to patients with preexisting liver dysfunction. Based on population pharmacokinetic modeling results, a 25% docetaxel dosage reduction (i.e., 75 mg/m²) is recommended for patients with elevated transaminase levels.¹⁸ This recommendation is only valid within the limits of available data, i.e., for transaminase elevations up to 3.5 times the upper limit of normal and alkaline phosphatase elevations up to five times the upper limit of normal. No data are currently available for patients with elevated total bilirubin levels.¹⁸ The presence of liver metastasis in patients with normal liver function studies, however, does not influence docetaxel's safety profile and should not be cause for dosage adjustment.¹⁹

Similarly, paclitaxel elimination is diminished in patients with impaired liver function, specifically in patients with elevated bilirubin and aspartate aminotransferase levels. Paclitaxel plasma concentrations remained above 0.05 μ mol/L longer in patients with bilirubin levels greater than 1.5 mg/dL than in patients with bilirubin levels less than 1.5 mg/dL, and patients with hepatic dysfunction experienced significantly more myelosuppression than did patients without hepatic dysfunction.²⁰

DRUG INTERACTIONS

Because the taxanes are metabolized by the cytochrome P-450 enzymes, taxane interactions with other drugs metabolized by these enzymes are of concern. Most drug interactions have been observed to occur with paclitaxel. For example, a significant interaction between paclitaxel and doxorubicin, in which doxorubicin inhibits the CYP3A4 metabolism of paclitaxel, has been documented.²¹ Patients receiving the doxorubicin-paclitaxel combination had a higher C_{\max} of the primary paclitaxel metabolite, 6 α -OH-paclitaxel, compared with patients receiving paclitaxel alone.²² This interaction appears to be schedule dependent. When paclitaxel (125 mg/m² over 24 hours) was infused before doxorubicin (48 mg/m² over 48 hours), a 70% increase in peak plasma concentration and a 32% decrease in plasma clearance was observed for doxorubicin.²³ As expected, an increased incidence of neutropenia and

mucositis were observed in patients receiving this combination. These changes in doxorubicin pharmacokinetics and adverse effects were not observed when the two drugs were administered in reverse order. In another study of 18 patients with untreated metastatic breast cancer receiving paclitaxel (200 mg/m² as a 3-hour infusion) followed 15 minutes later by doxorubicin (60 mg/m² iv bolus), doxorubicin's C_{\max} was increased and $t_{1/2}$ was decreased.²² Lower peak concentrations of doxorubicin's major metabolite, doxorubicinol, were also observed. No pharmacokinetic differences were observed when the drugs were administered 24 hours or more apart. A high rate of congestive heart failure (18%) was observed with concurrent administration of doxorubicin and paclitaxel (as a 3-hour infusion) in women with previously untreated metastatic breast cancer.²⁴ No significant pharmacokinetic interaction has been attributed to the doxorubicin and docetaxel combination. One study of 24 patients suggested that docetaxel's AUC was increased by 50% to 70% in the fourth cycle of docetaxel–doxorubicin treatment, indicating a possible effect on the disposition of docetaxel. Two other studies assessing docetaxel and doxorubicin, although of different study design, did not demonstrate a pharmacokinetic interaction between these compounds.¹³

Cremophor EL, the vehicle used for paclitaxel, has been implicated in the paclitaxel–doxorubicin interaction described above, probably through an effect on hepatobiliary excretion. The vehicle for docetaxel is polysorbate 80, which is capable of modifying the hepatobiliary excretion of some compounds *in vitro*; however, no significant pharmacokinetic interactions have been observed clinically. Thus, the choice of vehicle may explain the differences observed in drug interactions between the taxanes.¹³

Anticonvulsants, such as phenobarbital, phenytoin, and carbamazepine, also change the pharmacokinetic profile of paclitaxel, probably because they induce the cytochrome P-450 enzymes involved in paclitaxel metabolism.²⁵ In patients receiving anticonvulsants, the maximally tolerated dose of paclitaxel (as a 3-hour infusion) was increased to 360 mg/m², compared with paclitaxel 240 mg/m² in patients not receiving anticonvulsants; patients receiving concurrent anticonvulsants experienced a dose-limiting toxicity (DLT) of neurotoxicity, whereas patients not receiving anticonvulsants had DLTs of myelosuppression, fatigue, and gastrointestinal toxicity. The major metabolite identified in patients receiving concurrent paclitaxel and anticonvulsants was 3'-P-OH-paclitaxel, and 6 α -OH-paclitaxel was the major metabolite in patients not receiving anticonvulsants, suggesting that the antic-

onvulsants induce CYP3A4-dependent metabolism of paclitaxel, causing more rapid clearance. Formal drug interaction studies with docetaxel and phenytoin or phenobarbital have not been performed; however, it is likely that the clearance of docetaxel will be increased in patients receiving these combinations.¹³

DOSE AND SCHEDULE

Studies of docetaxel have primarily used a single 1-hour infusion, with doses ranging from 60 to 100 mg/m² given every 3 weeks. More recent studies have used weekly 1-hour infusions of 20 to 36 mg/m². The dose and schedules of paclitaxel vary from 135 to 250 mg/m² administered over 1 to 96 hours every 3 weeks. The most common regimen is paclitaxel 135 to 175 mg/m² over 3 or 24 hours every 3 weeks; more recently, a weekly schedule of paclitaxel 100 mg/m² administered over 1 hour has become popular.

As discussed previously, the taxanes induce different intracellular effects depending on the drug concentration achieved. Results of *in vitro* studies show a dose–response effect, which plateaus with higher doses; it appears that the plateau effect varies according to schedule and tumor type, although the most critical determinant is treatment duration.¹⁰ Prolonged exposure to the taxanes generally produces greater cytotoxicity than does increased drug concentration. In one study, an 11-fold increase in the duration of paclitaxel exposure was more cytotoxic than a 100-fold increase in plasma concentration.²⁶ This effect appears to be more pronounced in taxane-resistant cell lines. The taxane concentration at which maximum cell survival curves plateau decreases as the treatment duration increases. Results of several *in vitro* studies show that docetaxel has a median inhibitory concentration much lower than that of paclitaxel, which may be because of docetaxel's higher affinity for the tubulin binding site. The result is that docetaxel produces 2- to 3-fold higher intracellular concentrations and a 3-fold slower efflux rate from the cell than does paclitaxel.³

The optimal dose and schedule of paclitaxel remains under scrutiny. Although 96-hour paclitaxel infusions produce high response rates (RRs) of 48% in women with advanced breast cancer whose disease had progressed during or following treatment with anthracycline-based chemotherapy, this regimen produces more toxicity and is more difficult to deliver than shorter paclitaxel infusions.²⁷ Results of one breast cancer study suggests that the 24-hour paclitaxel schedule should be reserved for patients most likely to attain a cure.^{10,28} In this study, metastatic breast cancer patients who had received no prior chemother-

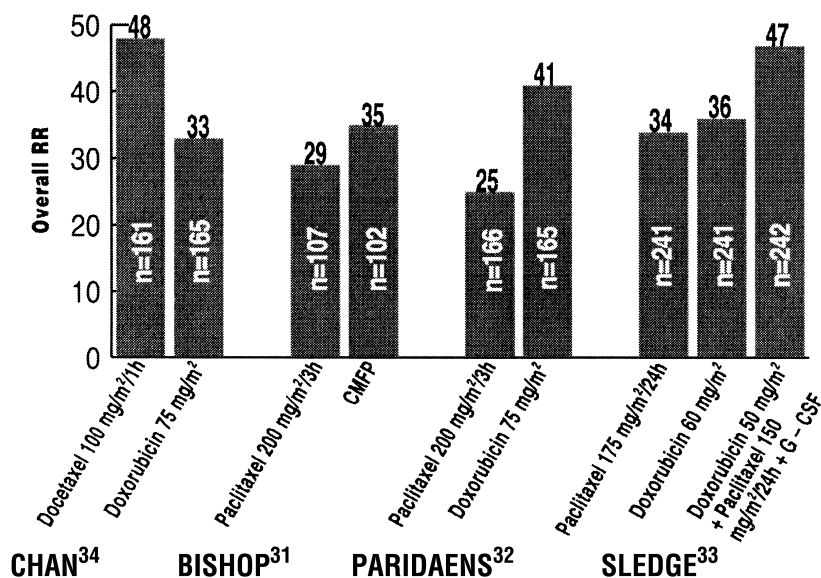


Figure 4. RRs in four separate phase III trials of first-line taxane therapy in metastatic breast cancer.^{31–34} CMFP=cyclophosphamide, methotrexate, fluorouracil, prednisone; G-CSF=granulocyte colony-stimulating factor; RR=response rate.

apy, adjuvant chemotherapy only, or chemotherapy for metastatic disease with or without prior adjuvant therapy were randomized to paclitaxel 175 mg/m² administered over either 3 or 24 hours. When adjusted for prognostic indicators, no significant differences in overall RRs (29% vs 32%), median progression-free survival times (3.8 vs 4.6 months), or overall survival times (9.8 vs 13.4 months) were observed between the two groups.²⁸ However, chemotherapy-naïve patients benefited more from the 24-hour than the 3-hour schedule with RRs of 57% and 34%, respectively, whereas patients receiving prior adjuvant therapy had RRs of 40% vs 36%, and patients receiving both adjuvant and metastatic chemotherapy had RRs of 22% vs 24%.¹⁰ Another study of metastatic breast cancer patients whose disease recurred or progressed following treatment with short schedules of paclitaxel (3-hour) or docetaxel (1-hour) had a 27% RR when treated with paclitaxel (120 to 140 mg/m²) administered over 96 hours.²⁹

Likewise, results of a prospective study of docetaxel reported a RR of 25% in metastatic breast cancer patients whose disease progressed with paclitaxel administered over 1 to 3 hours, but a 0% RR in patients whose disease progressed on paclitaxel administered over 24 hours.³⁰

PHARMACODYNAMICS IN BREAST CANCER PATIENTS

Whether the significant *in vitro* differences between the taxanes are clinically significant remains unknown. Figure 4 shows RRs in four different studies evaluating

the taxanes as first-line therapy for metastatic breast cancer.^{31–34} Although study designs varied, the patient characteristics and the RRs in the anthracycline trials was similar among the studies. These trial results suggest that a 24-hour infusion of paclitaxel produces better RRs than does a 3-hour infusion; however, the highest RR was observed in patients receiving docetaxel. Comparative trials are needed to confirm these observations.

CONCLUSIONS

The taxanes, paclitaxel and docetaxel, are a novel class of antineoplastic drugs that provide notable activity, and produce high RRs but minimal side effects. These agents share a similar mechanism of action, but several important pharmacokinetic and pharmacodynamic differences exist. The higher tubulin affinity, slower efflux from cells, triphasic elimination, and prolonged drug exposure of docetaxel confer pharmacokinetic and pharmacodynamic advantages over paclitaxel. The nonlinear pharmacokinetics of paclitaxel may result in disproportionate increases in plasma concentrations and AUCs; however, several safe and effective paclitaxel regimens are currently used. Because the taxanes are metabolized extensively in the liver by cytochrome P-450 enzymes, patients with hepatic impairment have reduced total body clearance that may result in increased toxicity. Additionally, drugs that induce, inhibit, or compete with microsomal enzymes known to metabolize the taxanes, can result in clinically significant drug interactions. These pharmacokinetic differences should be carefully considered when

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