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A phase I study of flavopiridol and docetaxel

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Summary

Background. Flavopiridol is a cyclin dependent kinase inhibitor. Preclinical models suggest a sequence dependent synergy between flavopiridol and taxanes. The primary objective of this study was to determine the maximum tolerated dose (MTD) of flavopiridol and docetaxel and the influence of flavopiridol on the pharmacokinetics of docetaxel. *Methods:* The major eligibility criteria included: a diagnosis of non-hematologic cancer with no conventional effective therapy, normal organ function, and ECOG performance status of 0-2. Patients were treated with docetaxel followed 24 h later by flavopiridol given via continuous intravenous infusion over a 24-h period. The starting doses of docetaxel and flavopiridol were 60 and 60 mg/m^2, respectively. Cycles were repeated every 21 days. All patients received diarrhea prophylaxis consisting of bismuth subsalicylate. *Results:* Ten patients (M:F 4:6; median age 56 years) were treated. The median number of cycles per patient was 2 (range 1–6). Two of the three patients on dose level 1 developed dose-limiting toxicities consisting of neutropenia and fever. Seven patients were subsequently enrolled on dose level −1 (docetaxel 60 mg/m^2, flavopiridol 50 mg/m^2). One episode of grade 3 diarrhea was reported at dose level −1. *Conclusions:* Neutropenia complicated by infection was the major dose-limiting toxicity. The recommended doses of flavopiridol and docetaxel for phase II trials are 50 and 60 mg/m^2 every three weeks, respectively.

Introduction

Abnormalities in cell cycle regulation are a hallmark of malignant cells [1]. Progression through the cell cycle is controlled by a series of enzymes known as cyclin dependent kinases (CDKs) [2]. Aberrant cell cycle control contributes to the resistance of tumor cells to chemotherapy [3]. Therefore, CDKs are rational targets for new drug development in cancer.

Flavopiridol [5,7-dihydroxy-8-(-4-N-methyl-2-hydroxypyridol)-6′-chloro-flavone hydro-chloride] is a synthetic flavone, which inhibits several phosphokinases [4]. Flavopiridol is a pan-CDK inhibitor with an IC50 of 100-400 nM [5]. Flavopiridol also inhibits the transcription of cyclin D1, which further contributes to the inhibition of the CDKs 4 and 6 [6]. Other effects of flavopiridol include inhibition of epidermal growth factor receptor kinase activity and protein kinase C with IC 50s of 10 μM or greater [5]. Flavopiridol has potent growth-inhibitory activity against a number of human tumor cell lines, both *in vitro* and in xenograft models [7, 8]. Preclinical models suggest a sequence dependent synergy between flavopiridol and docetaxel [9]. Cells treated with taxanes are temporarily arrested at the G2-M phase. Flavopiridol induces a rapid decrease in cyclin B/cdc-2 kinase activity enhancing the exit of taxane treated cells from mitotic arrest to undergo apoptosis [9, 10]. Furthermore, a 24 h exposure to flavopiridol was sufficient to potentiate the pro-apoptotic effects of taxanes [10].

Flavopiridol by continuous intravenous infusion over 72 h has undergone two phase I trials [11, 12]. The dose limiting toxicity was secretory diarrhea at a dose of 62.5 mg/m^2/day [12]. When diarrhea prophylaxis was administered, the maximal tolerated dose was 78 mg/m^2/day [11]. A subsequent phase I trial of paclitaxel followed by a 24-h continuous venous infusion of flavopiridol reported neutropenia and pulmonary toxicity as the dose limiting toxicities [13]. The maximal tolerated dose for paclitaxel and flavopiridol were 175 , and 70 mg/m^{2}day, respectively.

Docetaxel has a broad spectrum of anti-tumor activity [14]. As with paclitaxel, docetaxel disrupts microtubular networks arresting cells in the M-phase of the cell cycle [14]. *In vivo* human tumor models suggest a higher activity for docetaxel as compared to paclitaxel [15–17]. Based on the encouraging preclinical data, we conducted a phase I trial evaluating docetaxel on day 1 followed by flavopiridol by 24-h infusion on day 2. A secondary objec-

tive of this study was to determine the effect of flavopiridol on the pharmacokinetics of docetaxel.

Materials and methods

(a) *Patient eligibility*: Patients were eligible for the study if they had a confirmed pathologic diagnosis of a non-hematologic malignancy for which no standard curative or palliative therapy was available. Patients were also required to have a Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2, a life expectancy of at least 12 weeks, and adequate hematologic, renal and hepatic function defined by the following parameters: neutrophil count $\geq$1,500/ μL, platelet count $\geq$ 100,000/μL, serum creatinine $\leq$1.5 mg/dL, total serum bilirubin within the institution's normal limits and serum aminotransferases less than 2.5 times upper limit of the institutional normal range. Patients were required to have bidimesionally measurable disease. Irradiated tumors with no evidence of progression after radiation therapy were not considered measurable. Prior chemotherapy, surgery, or radiation therapy was permitted as long as the patients had recovered adequately from these procedures. At least 6 months must have elapsed from completion of prior taxane-based therapy to be eligible for the study. Female patients of childbearing potential must have had a negative serum pregnancy test prior to enrolment, and all fertile patients must have agreed to use contraception during the study. All patients provided a signed informed consent in accordance with the Wayne State University Human Investigation Committee guidelines prior to enrolment on the study.

Patients were excluded from study participation if they had uncontrolled brain metastases. Other exclusion criteria included uncontrolled intercurrent illness such as active infection, symptomatic congestive heart failure, or unstable angina.

(b) *Drug administration and dose escalation*: Dose limiting toxicity (DLT) was defined as (1) grade 3 or 4 non-hematologic toxicity excluding alopecia. (2) Nausea and vomiting grades 3 or 4 despite optimal anti-emetic therapy, (3) grade 4 thrombocytopenia, or (4) grade 4 neutropenia complicated by either fever or treatment delay of more than 1 week.

A minimum of three patients was entered onto each dose level. If one DLT occurred, three additional patients were entered on that dose level. Dose escalation would stop when two or more DLTs were observed. Three more patients were entered at the next lower dose level to better define the maximal tolerated dose (MTD). The MTD recommended for phase II trials was defined as the dose level at which one or less of six patients developed a DLT.

Docetaxel (Taxotere®, Aventis, Bridgewater, NJ) was infused intravenously over 60 min on day 1. Flavopiridol (Provided by the CTEP Cancer Therapy Evaluation Program at the National Cancer Institute, Bethesda, MD) was administered by a 24-h infusion starting 24 h after docetaxel administration. Cycles were repeated every 21 days.

Patients were premedicated with oral dexamethasone 8 mg twice daily starting the day prior to docetaxel administration and continuing for a total of 3 days (6 doses). Ondansetron 16 mg p.o. was given 30–60 min prior to docetaxel. Patients received 1,048 mg of bismuth subsalicylate one hour prior to flavopiridol followed by 524 mg every 6 h until 1 day after flavopiridol administration. If diarrhea occurred, loperamide was initiated orally at a dose of 2 mg every 2 h while awake and every 4 h during sleep until diarrhea resolved for 12 h. If grade $\geq$ 3 diarrhea occurred during a cycle than diarrhea prophylaxis for subsequent cycles included loperamide with or without cholestyramine.

The starting doses for docetaxel and flavopiridol were 60 mg/m^2 and 60 mg/m^2/day, respectively. Table 1 summarizes the dose escalation schedule. No dose escalations were allowed within an individual patient.

(c) *On-study evaluation*: Baseline evaluation included a complete history and physical examination, EKG, complete blood and differential counts, serum electrolytes, total serum bilirubin, serum ALT, serum AST, prothrombin time, partial thromboplastin time, and urinalysis. Toxicity was graded by the Common Toxicity Criteria Version 2. Evaluation for toxicity was undertaken after each treatment cycle. Response was measured according to the RESICT criteria. Radiological evaluation for response was performed every six weeks or at the time of clinical disease progression.

(d) *d. Docetaxel Pharmacokinetics*:Plasma levels of docetaxel were determined in the six patients treated at the MTD level. Docetaxel pharmacokinetics were determined during the first two cycles of therapy using a limited sampling method. Blood samples (5 mL) were collected before docetaxel infusion, and at 15, 45 min

Table 1. Dose escalation schema of flavopiridol and docetaxel. Dose level 1 was the starting dose level of the study. Docetaxel was administered I.V. on day 1 followed by flavopiridol on day 2 of a 21 day cycle

Dose level	Docetaxel dose (mg/m^2) Over 1 h on day 1	Flavopiridol dose (mg/m^2) Over 24 h on day 2
−2	50	50
−1	60	50
1*	60	60
2	75	60

*Starting dose level.

and 2, 5.15, and 23 h postinfusion. Blood samples were immediately centrifuged and plasma was coded and stored at −20°C until analysis.

Docetaxel concentration in plasma was quantified using a modified reversed phase HPLC method of Lee et al. [18] One mL volume of frozen heparinized plasma was spiked with 20 μL of paclitaxel solution (100 μg/mL) as the internal standard. One mL of 0.2 M ammonium acetate was added, vortexed and loaded on to a Sep-Pak C18 cartridge preconditioned with 2 mL methanol and 2 mL 0.2 M ammonium acetate solution. The cartridge was washed with 3 mL water and then eluted with 1 mL acetonitrile. The acetonitrile extract was evaporated at approximately 45°C under a gentle stream of nitrogen. The residue was reconstituted in 150 μL of mobile phase and 100 μL were injected into the HPLC system. A Waters Nova-Pak C18 4 μm (3.9 × 300 mm) column maintained at 25°C was used in the analysis. The mobile phase was 50% acetonitrile in 0.1% phosphoric acid in water at a flow rate of 1.0 mL/min and the analytes were detected at 200 nm. The retention times for docetaxel and paclitaxel were 6.9 and 7.9 min respectively. Linearity was obtained in the range of 0.05–10 mg/mL of docetaxel ($r^2 > 0.99$) with an intra/inter day coefficient of variation <11%. The measured plasma concentration-time data was subjected to PK analysis employing a two-compartmental model using WinNonlin® 4.0.1 software (Pharsight Corporation, CA).

Results

Patients: A total of 10 patients were enrolled on the study. All patients had received prior cytotoxic therapy. Table 2 summarizes the patient characteristics. Nine patients were evaluable for toxicity. One patient on dose level 1 was found to have a platelet count of 65,000 after enrolment and was considered ineligible and hence did not receive the study drug. A total of 20 cycles of chemotherapy were administered with a median of 2 cycles per patient (range 1–6).

Dose escalation and toxicity: Two of the three patients at the starting dose level developed DLTs after the first cycle of therapy. The first patient developed neutropenia (ANC of 300/μl and platelet count 211,000/μl) with fever but no documented source of infection. The patient had a history of lung cancer and was previously treated with gemcitabine and cisplatin (3 cycles), gefitinib, and CI-1040. The second patient developed fever with grade 3 neutropenia (ANC of 900/mL and platelet count 176,000/μl). The patient had a history of breast cancer previously treated with doxorubicin, 5-fluorouracil, and docetaxel (6 cycles) followed by surgery and radiation to the breast and had a relapse in the brain treated by whole brain radiation. Subsequently, seven patients were entered to dose level −1. Table 3 summarizes all the observed toxicities. Four of ten patients developed diarrhea. The only episode of grade 3 diarrhea was observed on dose level −1.

Table 2. Characteristics of the 10 patients treated with flavopiridol and docetaxel

	Number
Age	
Median	56 years
Race	
Caucasian	9
African american	1
Sex	
Male	4
Female	6
Performance status	
0/1	9
2	1
Primary tumor site	
Lung	3
Pancreas	2
Beast	1
Melanoma	1
Ampulla of Vater	1
Laryngeal cancer	1
Unknown primary	1
Disease sites	
Liver	4
Lung	5
Bone	2
Other	2
Prior cytotoxic therapy	
One regimen	5
Two regimens	1
>2 regimens	4
Prior Radiation therapy	3

Five patients required hospitalization while on study; two patients for neutropenic fever, one patient for infection of an indwelling venous catheter, one for hemorrhagic pleural and pericardial effusions, secondary to disease progression, and one patient was hospitalised for uncontrolled tumor related pain.

Objective response: One patient with ampullary cancer had stable disease that lasted 4 months. All other patients had disease progression on therapy.

Pharmacokinetics of docetaxel: The time course of mean plasma concentrations of docetaxel following 60 mg/m^2 one hour infusion in cycles 1 and 2 are shown in Figure 1. The mean pharmokinetic parameters are summarized in Table 4. The plasma levels of docetaxel exhibited a biexponential decline and adhered to a two compartmental model. No significant differences in the plasma concentrations of docetaxel were observed between cycles 1 and 2 indicating that flavopiridol administered in cycle 1 had no significant effect

Table 3. The occurrence of treatment related toxicities in 10 patients treated with flavopiridol and docetaxel. Toxicity was assessed by the NCI-CTC version 2

	Grade 1		Grade 2		Grade 3		Grade 4	
	Dose 1	Dose −1	Dose 1	Dose −1	Dose 1	Dose −1	Dose 1	Dose −1
Neutropenia	0	1	0	1	1	0	1*	0
Fever	0	0	0	1	1*	0	0	0
Thrombocytopenia	1	0	0	1	0	1	0	0
Anemia	0	2	0	1	0	1	0	0
Diarrhea	1	0	1	1	0	1*	0	0
Nausea	0	2	2	0	0	0	0	0
Fatigue	1	3	0	1	1	0	0	0

*Associated with dose limiting toxicity.

on docetaxel disposition in cycle 2. Similarly, none of the PK parameters of docetaxel was significantly affected due to flavopiridol treatment.

Discussion

Flavopiridol has already undergone two phase I trials as a 72-hour continuous venous infusion every 14 days [11, 12]. The MTD based on these studies was defined as 50 and 78 mg/m^2 without and with diarrhea prophylaxis, respectively. The toxicity profile for the 24- and 72-h infusion schedules of single agent flavopiridol appear to be distinctly different [11, 13]. The 24-h infusion schedule is more tolerable with the absence of venous thrombosis, and diarrhea facilitating its combination with chemotherapeutic agents. Subsequent phase II trials conducted in patients with advanced malignancies including gastric, [19] renal, [20] and lung cancer [21] failed to demonstrate any activity for flavopiridol as a single agent. The main observed toxicities in these studies were diarrhea, venous thromboses and sudden death.

Preclinical models suggested that flavopiridol can potentiate the pro-apoptotic effects of several classes of chemotherapeutic drugs including the taxanes [9, 10]. This interaction was highly sequence dependent and required a 24-h exposure to flavopiridol starting at least several hours after exposure to taxanes [9]. With the absence of activity as single agent and the encouraging preclinical models, combinations of flavopiridol with cytotoxic chemotherapeutic drugs were designed. A phase I trial evaluating paclitaxel and flavopiridol as a 24-h infusion was conducted [13]. The dose limiting toxicities were neutropenia and pulmonary toxicity. The recommended phase II doses for paclitaxel and flavopiridol were 175 and 70 mg/m^2, respectively. Clinical activity was observed in nine patients with esophageal, lung, prostate, pancreatic, gastric, neuroendocrine tumors and sarcoma.

In this phase I trial, the MTD for docetaxel followed by a 24-h infusion of flavopiridol were 60 mg/m^2, and 50 mg/m^2, respectively. The DLT observed was neutropenia with fever. The grade 3 or 4 neutropenia observed with the flavopiridol and docetaxel combinations was higher than expected for single agent docetaxel at a dose of 60 mg/m^2 [22]. The myelotoxicity of docetaxel is dependent on the systemic exposure to the drug [23]. It was therefore of interest to determine the possibility of an increase in the AUC of docetaxel as a cause for increased myelotoxicity. The PK profile of docetaxel in this study demonstrated that the postinfusion kinetics were biphasic with an AUC of 3.05μg · h/ml and a serum half-life of 5.05 h. Previous studies have shown that docetaxel at a 100 mg/m^2 dose achieved an AUC of 3.1 ug · h/ml [24]. Similarly, Extra et.al. reported an AUC of 4.1 μg · h/ml with a docetaxel dose of 85 mg/m^2 [23]. The AUC achieved in this study at the dose of 60 mg/m^2 appears to be within the AUC range observed at doses of 80 to 100 mg/m^2. Similarly, historical data shows a half-life

Table 4. Pharmacokinetic parameters (mean ± SD) of docetaxel 60 mg/m^2 administered I.V. over 1 h in 6 patients. Flavopiridol 50 mg/m^2 was administered as a 24 h I.V. infusion after the completion of docetaxel infusion

Parameter	Cycle 1		Cycle 2	
	Mean	SD	Mean	SD
C_{max} (μg/mL)	1.67	1.05	2.09	0.36
AUC (μg · h/mL)	3.05	1.70	2.81	0.34
T1/2 alpha (min)	5.05	1.03	5.50	1.69
T1/2 beta (h)	5.04	3.18	3.31	1.15
CL (L/h/m^2)	14.41	6.98	21.57	2.59
V_{ss} (L/m^2)	105.49	71.20	37.72	22.53

C_{max}: maximum plasma concentration, AUC: area under the curve, T1/2: plasma half-life, CL: clearance from plasma, V_{ss}: volume of distribution at steady state.

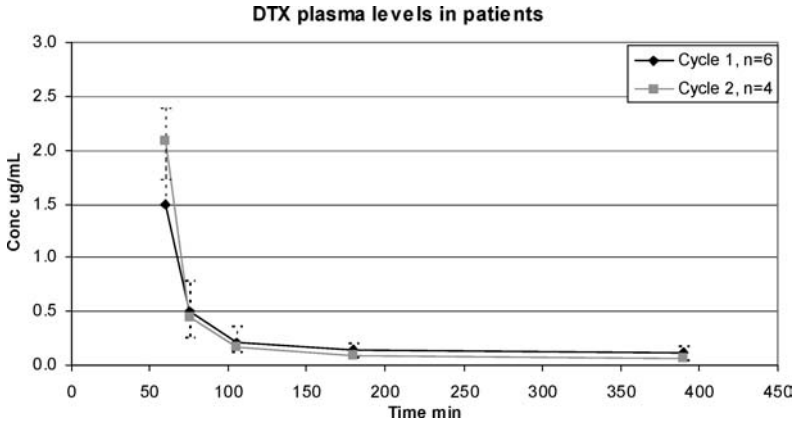

Figure 1. Time course of plasma levels of docetaxel following 60 mg/m^2 one hour infusion in phase I patients.

of docetaxel administered as a 1-h infusion of 2.5 to 4.1 h [23, 25]. This apparent increase in AUC of docetaxel in this population of patients may have contributed to the increased myelotoxicity observed in this study. There was no appreciable increase in AUC of docetaxel with the second cycle of docetaxel. Some reduction of AUC and increased clearance of docetaxel was noted.

Another factor contributing to the high incidence of neutropenia observed in this study may be the schedule of flavopiridol administration. Myelosuppression was the dose limiting toxicity of flavopiridol as a single agent when administered as a 1-h infusion while no significant myelotoxicity was observed with the 72-h infusion schedule. No phase I trial has been conducted with single agent flavopiridol as a 24-h infusion. In preclinical models, significant myelotoxicity was observed with higher concentrations of flavopiridol. Therefore, the increased neutropenia observed in this study could be related to an effect of the combination on the hematopoietic system rather than an alteration of the pharmacokinetics of docetaxel. In conclusion, results of this study show that flavopiridol and docetaxel can be administered in combination at a dose of 50 and 60 mg/m^2, respectively. The dose limiting toxicity of this combination is neutropenia.

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References

1. Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100(1):57–70, 2000
2. Morgan DO: Cyclin-dependent kinases: Engines, clocks, and microprocessors. Annu Rev Cell Dev Biol 13:261–291, 1997
3. Shah MA, Schwartz GK: Cell cycle-mediated drug resistance: An emerging concept in cancer therapy. Clin Cancer Res 7(8):2168–2181, 2001
4. Senderowicz AM, Sausville EA: Preclinical and clinical development of cyclin-dependent kinase modulators. J Natl Cancer Inst 92(5):376–387, 2000
5. Sedlacek HH: Mechanisms of action of flavopiridol. Crit Rev Oncol Hematol 38(2):139–170, 2001
6. Carlson B, Lahusen T, Singh S, Loaiza-Perez A, Worland PJ, Pestell R, Albanese C, Sausville EA, Senderowicz: Down-regulation of cyclin D1 by transcriptional repression in MCF-7 human breast carcinoma cells induced by flavopiridol. Cancer Res 59(18):4634–4641, 1999
7. Li Y, Bhuiyan M, Alhasan S, Senderowicz AM, Sarkar FH: Induction of apoptosis and inhibition of c-erbB-2 in breast cancer cells by flavopiridol. Clin Cancer Res 6(1):223–229, 2000
8. Carlson BA, Dubay MM, Sausville EA, Brizuela L, Worland PJ: Flavopiridol induces G1 arrest with inhibition of cyclin-dependent kinase (CDK) 2 and CDK4 in human breast carcinoma cells. Cancer Res 56(13):2973–2978, 1996
9. Motwani M, Rizzo C, Sirotnak F, She Y, Schwartz GK: Flavopiridol enhances the effects of docetaxel *in vitro* and in vivo in human gastric cancer cells. Mol Cancer Ther 2(6):549–555, 2003
10. Motwani M, Delohery TM, Schwartz GK: Sequential dependent enhancement of caspase activation and apoptosis by flavopiridol on paclitaxel-treated human gastric and breast cancer cells. Clin Cancer Res 5(7):1876–1883, 1999
11. Senderowicz AM, Headlee D, Stinson SF, Lush RM, Kalil N, Villalba L, Hill K, Steinberg SM, Figg WD, Tompkins A, Arbuck SG, Sausville EA: Phase I trial of continuous infusion flavopiridol, a novel cyclin-dependent kinase inhibitor, in patients with refractory neoplasms. J Clin Oncol 16(9):2986–2999, 1998
12. Thomas JP, Tutsch KD, Cleary JF, Bailey HH, Arzoomanian R, Alberti D, Simon K, Feierabend C, Binger K, Marnocha R, Dresen A, Wilding G : Phase I clinical and pharmacokinetic trial of the cyclin-dependent kinase inhibitor flavopiridol. Cancer Chemother Pharmacol 50(6):465–472, 2002
13. Schwartz GK, O'Reilly E, Ilson D, Saltz L, Sharma S, Tong W, Maslak P, Stoltz M, Eden L, Perkins P, Endres S, Barazzoul J, Spriggs D, Kelsen D: Phase I study of the cyclin-dependent kinase inhibitor flavopiridol in combination with paclitaxel in patients with advanced solid tumors. J Clin Oncol 20(8):2157–2170, 2002
14. Huizing MT, Misser VH, Pieters RC, ten Bokkel Huinink WW, Veenhof CH, Vermorken JB, Pinedo HM, Beijnen JH: Taxanes: A new class of antitumor agents. Cancer Invest 13(4):381–404, 1995
15. Grant DS, Williams TL, Zahaczewsky M, Dicker AP: Comparison of antiangiogenic activities using paclitaxel (taxol) and docetaxel (taxotere). Int J Cancer 104(1):121–129, 2003

16. Crown J: Docetaxel: Overview of an active drug for breast cancer. Oncologist 6(Suppl 3):1–4, 2001
17. Leahy M, Howell A: Docetaxel. Br J Hosp Med 57(4):141–144, 1997
18. Lee SH, Yoo SD, Lee KH: Rapid and sensitive determination of paclitaxel in mouse plasma by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 724(2):357–363, 1999
19. Schwartz GK, Ilson D, Saltz L, O'Reilly E, Tong W, Maslak P, Werner J, Perkins P, Stoltz M, Kelsen D: Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma. J Clin Oncol 19(7):1985–1992, 2001
20. Stadler WM, Vogelzang NJ, Amato R, Sosman J, Taber D, Liebowitz D, Vokes EE: Flavopiridol, a novel cyclin-dependent kinase inhibitor, in metastatic renal cancer: A University of Chicago Phase II Consortium study. J Clin Oncol 18(2):371–375, 2000
21. Shapiro GI, Supko JG, Patterson A, A phase II trial of the cyclin-dependent kinase inhibitor flavopiridol in patients with previously untreated stage IV non-small cell lung cancer. Clin Cancer Res 7(6):1590–1599, 2001
22. Clarke SJ, Rivory LP: Clinical pharmackokinetics of docetaxel. Clin Pharmacokinetics 36(2):99-114, 1999
23. Extra JM, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M: Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 53(5):1037–1042, 1993
24. Rosing H, Lustig V, van Warmerdam LJ, Huizing MT, ten Bokkel Huinink WW, Schellens JH, Rodenhuis S, Bult A, Beijnene JH: Pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion. Cancer Chemother Pharmacol 45(3):213–218, 2000
25. Bruno R, Riva A, Hille D, Lebecq A, Thomas L: Pharmacokinetic and pharmacodynamic properties of docetaxel: Results of phase I and phase II trials. Am J Health Syst Pharm 54(24 Suppl 2):S16–S19, 1997

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