Influence of Garlic (*Allium sativum*) on the Pharmacokinetics of Docetaxel

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Abstract

Purpose: The herbal supplement garlic (*Allium sativum*) is commonly used by cancer patients. Preclinical studies have shown that allicin, a major component of garlic, may affect cytochrome *P*450 3A4 (CYP3A4) activity. This study examines the influence of garlic supplementation on the pharmacokinetics of docetaxel, a CYP3A4 substrate.

Experimental Design: Women with metastatic breast cancer were treated with docetaxel (30 mg/m^2) given weekly for 3 of 4 weeks. Three days after the initial dose of docetaxel, patients received 600 mg of garlic twice daily for 12 consecutive days. Docetaxel pharmacokinetics were assessed during the first three administrations.

Results: In 10 evaluable patients, the mean baseline clearance of docetaxel was 30.8 L/h/m^2 [95% confidence intervals (95% CI), 16.7-44.9]. Coadministration of garlic reduced mean clearance of docetaxel to 23.7 L/h/m^2 (95% CI, 15.5-31.8) and 20.0 L/h/m^2 (95% CI, 13.3-26.7) on days 8 and 15, respectively ($P = 0.17$). Additional pharmacokinetic variables of docetaxel, including peak concentration ($P = 0.79$), area under the curve ($P = 0.36$), volume of distribution ($P = 0.84$), and half-life ($P = 0.36$), were also not statistically significantly different. The mean area under the curve ratio between day 15 and day 1 was 3.74 in three individuals with the *CYP3A5*1A/*1A* genotype (all African American) compared with 1.02 in six individuals with the *CYP3A5*3C/*3C* genotype (all Caucasian).

Conclusions: This study indicates that garlic does not significantly affect the disposition of docetaxel. However, it cannot be excluded that garlic decreases the clearance of docetaxel in patients carrying a *CYP3A5*1A* allele.

Passage of the Dietary Supplement Health and Education Act in 1994 made herbal dietary supplements readily available to U.S. consumers. A study has shown that 42% of the U.S. population uses complementary and alternative medicine (CAM), with 13% reporting the use of herbal products (1). With the widespread use of herbal supplements, the risk of herb-drug interactions is a growing medical concern. This is particularly important because nearly 20% of adults who reported regularly taking prescription drugs also reported simultaneous use of either a herbal product or high dose vitamin (1). Reports indicate that between 7-64% of adult cancer patients use at least one kind of CAM (2), and 13-63% of these patients have reported the use of herbal products (3). More recently, it was reported that ~50% of patients with breast or gynecologic malignancies use complementary and alternative medicine, and as much as 5% of this population takes the herbal supplement, garlic (4).

Garlic (*Allium sativum*) has been used since time immemorial as a culinary spice and medicinal herb. Its use in China was first mentioned in A.D. 510, and Louis Pasteur first studied the antibacterial action of garlic in 1858. Whereas earlier trials suggest it may mildly lower cholesterol and triglyceride levels in the blood (5), more recent evaluations found garlic to have minimal activity in this regard (6).

The active ingredient of garlic is the sulfur compound allicin, produced by crushing or chewing fresh garlic or by taking powdered garlic products with allicin potential, which in turn produces other sulfur compounds, including ajoene, allyl sulfides, and vinyldithiins (7). Garlic has been shown to potentially modulate the activity of transferases and cytochrome *P*450 isozymes, both *in vitro* and *in vivo* (8). If these effects occur in patients treated for malignancy, then garlic has the potential to impair the metabolism of many clinically important agents, including the CYP3A4 substrate drug docetaxel (Fig. 1; ref. 9). This could have clinical ramifications of decreased docetaxel clearance such as neutropenia and sepsis

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(10). In addition, the area under the curve (AUC) of docetaxel is a significant predictor of time to tumor progression in non–small-cell lung cancer (11) and under dosing (i.e., a lower docetaxel AUC) could be associated with a worse time to progression and time to death (12). Docetaxel has shown a dose-response relationship in the second line management of metastatic breast cancer (13). Against this background, we prospectively evaluated the influence of garlic supplementation on the pharmacokinetics of docetaxel in women with metastatic breast cancer.

Because of the genetic diversity in the genes encoding the main enzymes involved in docetaxel metabolism (i.e., CYP3A4 and CYP3A5), it has been proposed that genotyping for clinically important *CYP3A4* and *CYP3A5* polymorphisms may be useful for prediction of the extent of interaction between an inhibitor and substrate. In the present study, we therefore also included an analysis of two common variants in the *CYP3A4* and *CYP3A5* genes to exclude the possibility that genetic heterogeneity in drug metabolism was confounding our results.

Patients and Methods

Eligibility criteria. Patients were eligible for enrollment if they had metastatic or incurable, localized, histologically confirmed adenocarcinoma of the breast for which treatment with single-agent, weekly docetaxel was considered appropriate. Additional inclusion criteria included age ≥18 years; an Eastern Cooperative Oncology Group performance status ≤2; at least 12 weeks life expectancy; and adequate end-organ function (absolute neutrophil count >1,200 × 10^6 cells/L; platelets >100 × 10^9 cells/L; serum creatinine <1.2 g/dL; and liver transaminases within reference ranges). Patients requiring medications known to affect the function of CYP3A4 were excluded, as were patients who had received immunotherapy, chemotherapy, and/or radiotherapy within 3 weeks of enrollment, or hormonal therapy less than 2 weeks before enrollment. Concurrent administration of investigational agents, or within 30 days or 5 half-lives of such agents, was not allowed. Additional exclusion criteria included clinical signs or symptoms of brain and/or leptomingeal metastasis in patients who have not undergone definitive therapy or who require corticosteroid treatment; uncontrolled intercurrent illness, or concurrent medical problems that would limit full compliance with the study or put the patient at extreme risk; and known gastrointestinal problems (e.g., chronic diarrhea or delayed gastric emptying). Patients of childbearing potential were required to practice adequate contraception, and patients who were pregnant or lactating were excluded.

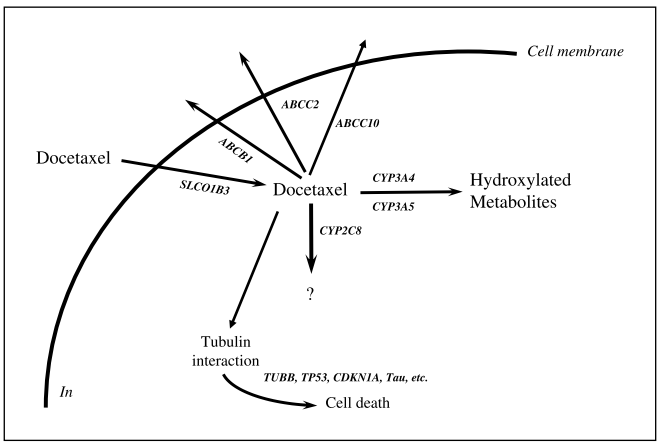

Fig. 1. Schematic diagram of docetaxel metabolism and transport. CYP2C8, CYP3A4, CYP3A5, cytochrome *P*450 isoforms 2C8, 3A4, and 3A5; ABCB1, ATP-binding cassette transporter B1 (P-glycoprotein); ABCC2, ATP binding cassette transporter C2 (MRP2, cMOAT); ABCC10, ATP-binding cassette transporter C10 (MRP7); OATP1B3, organic anion transporting polypeptide 1B3 (OATP8, LST-2).

Study design and treatment. This was a prospective pharmacokinetic study, in which patients acted as their own controls, during the first cycle of weekly docetaxel coadministered with a commonly used garlic supplement. Docetaxel was administered as a 1-hour i.v. infusion once every week for 3 consecutive weeks (days 1, 8, and 15), with cycles repeated every 4 weeks, at a dose of 30 mg/m^2. All patients received oral premedication with dexamethasone, 8 mg every 12 hours for three doses, starting 12 hours before docetaxel infusion; ondansetron 8 mg; ranitidine 150 mg; and diphenhydramine 25 mg, 30 minutes before docetaxel. Starting on day 5 and continuing through day 17, patients took 600-mg garlic tablets (GarliPure Maximum Allicin Formula, Natrol, Chatsworth, CA; containing 3,600 μg allicin per tablet) twice a day, orally. All tablets were from the same production lot (#2004938). Compliance with garlic dosing and drug restrictions were assessed by pill count and patient questioning.

No patients required breakthrough antiemetics. Colony-stimulating factors were allowed, with the exception of pegfilgrastim. Megesterol acetate or oral tetrahydrocannabinol was not permitted for malnutrition during the first cycle. The use of trastuzumab was allowed following the first cycle, if appropriate. Provided toxic effects were not prohibitive, patients were eligible to continue treatment with weekly docetaxel given with or without garlic supplementation, at the discretion of the patient, until there was evidence of progressive disease.

The Institutional Review Board of the National Cancer Institute (Bethesda, MD) approved this study and patients were required to provide written informed consent before starting treatment. The study was conducted according to the most recent version of the Declaration of Helsinki and applicable regulations and guidelines.

Blood sampling and analysis. On days 1, 8, and 15 of cycle one, blood samples were obtained for pharmacokinetic analysis before docetaxel infusion; 5 minutes before the end of infusion; 5, 15, and 30 minutes after the end of infusion; and 1, 2, 4, 8, 12, and 24 hours after the end of docetaxel infusion. Blood samples were centrifuged and the resulting plasma was placed in polypropylene tubes, and then stored frozen at −70°C until analysis. Determination of docetaxel concentrations in plasma was done by liquid chromatography with tandem mass spectrometric detection using a previously published method with modifications (14).

Pharmacokinetic data analysis. Plasma concentration versus time data following docetaxel administration were analyzed using noncompartmental methods as implemented in WinNonLin (Version 5.0, Pharsight Corporation, Mountain View, CA). Calculated pharmacokinetic variables included peak concentration, AUC extrapolated to infinity (hereafter referred to as AUC), clearance (defined as the ratio of dose administered in mg/m^2 and AUC), the rate constant of the terminal disposition phase (k), and the half-life of the terminal disposition phase (defined as ln 2/k).

Genotype analysis. DNA was isolated from whole blood samples using the TRIzol method (Invitrogen, Carlsbad, CA) per instructions of the manufacturer. The *CYP3A4*1B* and *CYP3A5*3C* genotypes were determined by direct nucleotide sequencing as described elsewhere (15).

Statistical considerations. The mean clearance for docetaxel used in the sample size calculation was 23.99 L/h/m^2, estimated from a group of 56 cancer patients treated with docetaxel and that had sampling for pharmacokinetic analysis on at least two occasions.[6] Because we intended to conduct a trial with paired continuous data, the SD of the differences of the two measurements was required (denoted s_d), with

[6] Unpublished data.

the sample size calculation using the standardized effect size (defined as $d = d/s_d$, where d is the effect size). The value for s_d was calculated as $s_d = s_w \times \sqrt{2}$, where s_w denotes the intrasubject SD. The s_w was estimated from the same group of 56 cancer patients as the average SD of the clearance difference between courses in the same patient. This was done under the assumption of log-normal variable distribution. In this group of patients, $s_w = 3.46$ and $s_d = 3.46 \times \sqrt{2} = 4.89$ (16). In the planned trial, we assumed that the interval between treatments was an adequate washout period so that there was no carryover and no period effect. The trial was designed to detect an effect size of 25%; thus, $23.99 \times 25/100 = 6.00$. In a pairwise (two-sided) analysis, this resulted in a sample size of at least 9 for the prospective evaluation, with a conservative significance level of 0.025 (2.5%) and a statistical power of 0.80 (80%). This analysis was done in the SISA-Binomial program (D.G. Uitenbroek, Hilversum, the Netherlands, 1997).[7]

All pharmacokinetic data are presented as mean values with 95% confidence intervals (95% CI), unless stated otherwise. Differences in docetaxel pharmacokinetic variables as a function of garlic administration and treatment period were evaluated by repeated-measures ANOVA. The associations between the *CYP3A4*1B* or *CYP3A5*3C* genotypes and the AUC ratios on days 15 and 1 were assessed with the Mann-Whitney test. Statistical calculations were done with the NCSS software package (Version 2001; J. Hintze, Number Cruncher Statistical Systems, Kaysville, UT).

Results

Patient characteristics. Eleven patients were enrolled between January 2004 and September 2005. Ten of 11 patients completed the first cycle of docetaxel and were evaluable for pharmacokinetic analysis. Patient characteristics are described in Table 1. One patient was taken off the study following the second week of therapy for rapidly progressive disease and was not included in the final analysis. All patients reported that they ingested all prescribed doses of garlic.

Effect of garlic on docetaxel pharmacokinetics. The mean clearance of docetaxel in the absence of garlic of 30.8 L/h/m^2 (95% CI, 16.7-44.9) was reduced on days 8 and 15, with mean values of 23.7 L/h/m^2 (95% CI, 15.5-31.8) and 20.0 L/h/m^2 (95% CI, 13.3-26.7), respectively ($P = 0.17$). Statistical significance was also not observed when comparing directly the mean clearance on day 15 and day 1 ($P = 0.13$, Mann-Whitney t test). Garlic supplementation had no statistically significant effects on the pharmacokinetic profile of docetaxel when administered over the short term (4 days) or long term (12 days). Additional pharmacokinetic variables of docetaxel, including peak concentration and AUC (Fig. 2), were also not statistically significantly different (Table 2). Consequently, the plasma concentration versus time profiles were very similar among the three study periods (Fig. 3).

Variant genotypes. Two single-nucleotide polymorphisms were analyzed in two genes of putative relevance for docetaxel disposition. For the *CYP3A4*1B* polymorphism, two homozygous variants were observed, whereas eight patients had the wild-type sequence. For *CYP3A5*3C*, six homozygous variants were observed (all Caucasian), three patients carried the wild-type sequence (all African American), and a sample from one patient did not show PCR amplification. The docetaxel AUC ratio on day 15 compared with day 1 was unaffected by the *CYP3A4*1B* genotype ($P = 0.99$). However, this ratio was substantially increased in the three individuals, all African Americans, with the *CYP3A5*1A/*1A* genotype (mean ratio, 3.74; 95% CI, −7.31-14.8) as compared with the six individuals carrying the *CYP3A5*3C/*3C* genotype (mean ratio, 1.02; 95% CI, 0.788-1.25), although this difference was not statistically significant ($P = 0.38$).

Table 1. Baseline patient characteristics

Characteristic	Value
Baseline screening	
Total enrolled	11
Age (y)	53 (40-66)
Sex, female	11
Race	
Caucasian	6
African American	3
Middle Eastern	1
Body surface area (m^2)	1.91 (1.54-2.37)
Metastatic disease sites	
Lung	3 (27%)
Liver	4 (36%)
Bone	6 (54%)
Other	7 (63%)
No. prior metastatic chemotherapy regimens	4 (0-8)
ECOG performance status	1 (0-1)
Pretherapy chemistry	
Alanine aminotransferase (units/L)	22 (11-49)
Aspartate aminotransferase (units/L)	21 (12-41)
Total bilirubin (mg/dL)	0.48 (0.2-1.1)
Serum creatinine (mg/dL)	0.78 (0.6-1.1)

NOTE: ECOG, Eastern Cooperative Oncology Group. Continuous data are given as median with range in parentheses, and categorical data as number of patients with percentage of the total population in parentheses.

Discussion

In the present study, we showed that the coadministration of garlic with docetaxel does not significantly influence the pharmacokinetics of the anticancer drug in women with metastatic breast cancer. A wealth of preclinical studies has suggested that garlic constituents can modulate the activity of various drug-metabolizing enzymes. Fresh garlic extracts and commercially available garlic products were shown to inhibit cytochrome P450 isoforms 2C9*1, 2C19, 3A4, 3A5, and 3A during metabolism of a marker substrate (17). However, garlic oil and its three allyl sulfide components administered for 6 weeks have been shown to lead to enhanced activity and increased expression of CYP3A1, 2B1, and 1A1 in the hepatic detoxification system of rats (18). Similarly, *in vitro* and *in vivo* animal models have indicated that various garlic constituents used at very high concentrations can induce the activity of the rodent orthologue of CYP3A4 (19).

Recent investigations have also shown that garlic supplements taken for prolonged periods at commonly used doses have a profound effect on the systemic exposure to oral saquinavir, a CYP3A4 substrate, in healthy volunteers with trough levels decreasing by 49% and the AUC decreasing by

[7] Available at http://home.clara.net/sisa/samsize.htm.

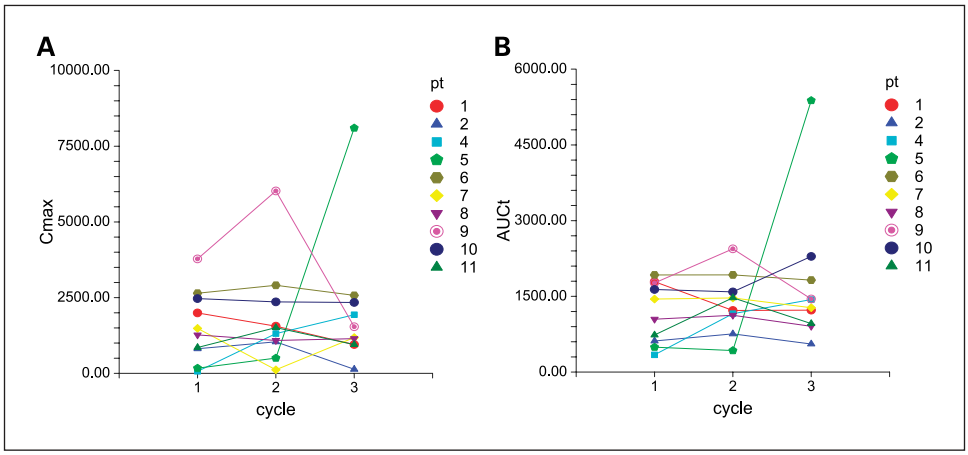

Fig. 2. Comparison of individual docetaxel pharmacokinetic variables obtained before garlic administration (period 1) and 4 days (period 2) and 12 days (period 3) after start of garlic intake. C_{max}, peak plasma concentration (in units of ng/mL); AUC, area under the docetaxel plasma concentration versus time curve extrapolated to infinity (in units of ng h/mL).

51% (20). In contrast, acute dosing of garlic supplements over 4 days had no significant effect on the pharmacokinetics of another CYP3A4 substrate, ritonavir (21), suggesting that more prolonged dosing may be required to affect CYP3A4 activity in humans. We designed our study as a hybrid between these two prior studies to allow accurate assessment of both short-term and long-term exposure to garlic constituents in patients receiving docetaxel. As previously observed with the other drugs metabolized by CYP3A4 such as alprazolam (22) and midazolam (23, 24), no statistically significant differences were observed in the pharmacokinetic profile of i.v. docetaxel in the presence and absence of garlic supplementation. However, it cannot be entirely excluded based on the current study that intake of garlic for longer than 12 days might alter activity of the CYP3A subfamily members. Alternatively, it is possible that patients still can efficiently eliminate docetaxel following prolonged exposure to CYP3A4-inhibitory components present in garlic through compensatory mechanisms, including elimination via other enzymes or through hepatobiliary excretory pathways. Although direct evidence for this hypothesis is lacking, this possibility is supported by a recent observation that docetaxel, like the related compound paclitaxel, can also be metabolized via CYP2C8 (25), the function of which is not known to be affected by garlic constituents. Collectively, this suggests that the potential for garlic supplementation to affect the pharmacokinetics of CYP3A4 substrates is drug specific and possibly also dependent on the route of administration.

Another reason for the lack of a significant effect of garlic on docetaxel pharmacokinetics may be secondary to poor bioavailability of allicin, as well as the general lack of standardization in herbal supplements. Without this standardization, garlic products can have highly variable bioavailability and/or pharmaceutical properties (26). We have tried to eliminate this bias by using all tablets from the same manufacturing lot, and a

Table 2. Summary of docetaxel pharmacokinetic variable estimates

Parameter	Day 1	Day 8	Day 15	*P*
C_{max} (μg/mL)				
Mean	1.55 ± 1.17	1.84 ± 1.68	2.08 ± 2.23	0.79
95% CI	0.714-2.39	0.641-3.04	0.487-3.68	
Range	0.066-3.78	0.117-6.02	0.134-8.10	
AUC (μg h/mL)				
Mean	1.34 ± 0.704	1.51 ± 0.613	1.96 ± 1.36	0.36
95% CI	0.837-1.84	1.07-1.95	0.981-2.93	
Range	0.412-2.35	0.615-2.51	0.796-5.59	
CL (L/h/m^2)				
Mean	30.8 ± 19.7	23.7 ± 11.4	20.0 ± 9.35	0.17
95% CI	16.7-44.9	15.5-31.8	13.3-26.7	
Range	12.8-72.8	12.0-48.8	5.36-37.7	
V_{ss} (L)				
Mean	417 ± 448	323 ± 291	403 ± 399	0.84
95% CI	96.4-737	115-531	117-689	
Range	64.0-1,549	64.0-1,062	33.0-1,155	
$T_{1/2,z}$ (h)				
Mean	11.9 ± 8.21	11.2 ± 7.68	15.4 ± 9.22	0.36
95% CI	6.01-17.8	5.66-16.7	8.58-22.0	
Range	4.87-27.9	5.05-32.1	4.52-32.9	

NOTE: Pharmacokinetic data are given as mean ± SD, 95% CI, and range, and were obtained on day 1 (docetaxel alone), day 8 (4 days after start of garlic), and day 15 (12 days after start of garlic). *P* values were obtained from a repeated-measures ANOVA model.
Abbreviations: C_{max}, peak plasma concentration; CL, clearance; V_{ss}, volume of distribution at steady state; $T_{1/2,z}$, half-life of the terminal disposition phase.

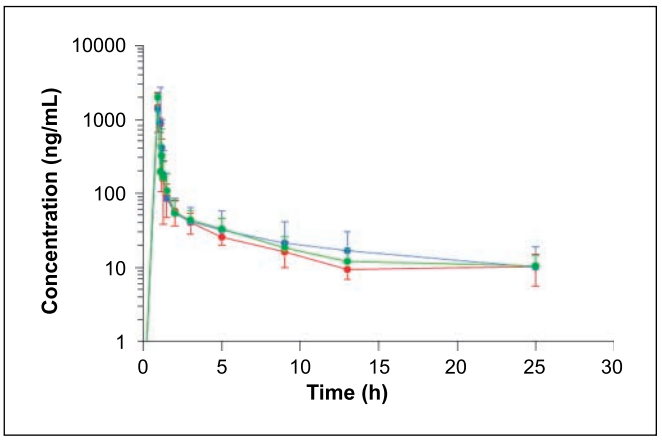

Fig. 3. Plasma concentration time profiles of docetaxel obtained in 10 patients before garlic administration (*red symbols*) and 4 days (*blue symbols*) and 12 days (*green symbols*) after the start of garlic intake. Points, mean; bars, SD.

similar product to that previously used in the study with saquinavir (20), and by pill counting. Finally, it should be pointed out that the present study was not randomized for treatment period. Specifically, a separate control group of patients receiving a placebo instead of garlic supplementation could have provided additional information on potential changes in the elimination pathways after repeated exposure to docetaxel alone.

The patients in this study that did not carry a variant *CYP3A5*3C* allele exhibited an aberrant docetaxel pharmacokinetic profile in the presence of garlic, with a profound inhibition of drug clearance on day 15 compared with day 1. This was particularly evident in one African American female showing 89% reduced clearance of docetaxel on day 15. Although this genotype-dependent effect was not statistically significant, presumably because of the small sample size, this observation is of particular interest. *CYP3A5*3C* is an intronic splice variant that introduces a frameshift during translation and results in a truncated, nonfunctional protein (27). In contrast, in individuals carrying at least one *CYP3A5*1A* allele, CYP3A5 protein expression may contribute to >50% of total CYP3A protein in the liver (27). In view of the fact that the affinity of CYP3A5 for docetaxel is substantially lower than that of CYP3A4 (28), it is plausible that CYP3A4-metabolizing capability becomes more rapidly saturated through chronic inhibition in individuals that express functional CYP3A5. Additional investigation is clearly required to further resolve this issue and assess its clinical implications.

In conclusion, this report indicates that garlic supplementation does not significantly affect the disposition of the CYP3A4 substrate drug docetaxel. However, on average, over a 12-day period, garlic decreased the clearance of docetaxel in patients carrying a *CYP3A5*1A* allele. This suggests that genotyping of drug-metabolizing enzymes that exhibit clinically important polymorphisms should become an integral part of herb-drug interaction studies.

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