A Comparison of the Pharmacokinetics and Pharmacodynamics of Docetaxel between African-American and Caucasian Cancer Patients: CALGB 9871

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Abstract
Purpose: Increased clearance of drugs, such as oral cyclosporine, that are CYP3A and/or ABCB1 (P-gp/MDR1) substrates was reported in African-American compared with Caucasian patients. We hypothesized that the pharmacokinetics and pharmacodynamics of docetaxel, an i.v. administered cytotoxic and substrate for CYP3A4, CYP3A5, and ABCB1, would differ between African-American and Caucasian patients.

Experimental Design: We investigated population pharmacokinetics and pharmacodynamics and the pharmacogenetics of CYP3A4, CYP3A5, and ABCB1 in African-American and Caucasian cancer patients who received docetaxel 75 or 100 mg/m² as a 1-h i.v. infusion. Plasma docetaxel concentrations were measured by high-performance liquid chromatography. Clinical toxicity and absolute neutrophil count (ANC) were monitored on days 8, 15, and 22 postadministration of docetaxel. Using a limited sampling strategy and nonlinear mixed-effects modeling, each patient's docetaxel clearance was estimated. Genotyping for known polymorphisms in CYP3A4, CYP3A5, and ABCB1 was done.

Results: We enrolled 109 patients: 40 African-Americans (26 males; 14 females), with a median age of 61 years (range, 29-73), and 69 Caucasians (43 males; 26 females), with a median age of 63 years (range, 38-81). There was no difference in the geometric mean docetaxel clearance between African-American patients [40.3 L/h; 95% confidence interval (95% CI), 19.3-84.1] and Caucasian patients (41.8 L/h; 95% CI, 22.0-79.7; P = 0.6). We observed no difference between African-American and Caucasian patients in the percentage decrease in ANC nor were docetaxel pharmacokinetic parameters related to the genotypes studied.

Conclusions: Docetaxel clearance and its associated myelosuppression were similar in African-American and Caucasian cancer patients.

Docetaxel (Taxotere) is a semisynthetic taxane derived from an extract of the needles of the European yew tree Taxus baccata L. Currently, docetaxel is approved for the treatment of refractory breast, non–small cell lung and prostate cancer, but it is also active against several other solid tumors, including melanoma, ovarian cancer, and head and neck cancer (1 – 3). Docetaxel is predominantly cleared from humans by hepatic metabolism; ~5% of a docetaxel dose is excreted unchanged in the urine. Docetaxel plasma concentrations measured by high-performance liquid chromatography show a triphasic plasma decay curve with a terminal elimination half-life of ~11 h (2, 4). However, plasma docetaxel measurements using more sensitive liquid chromatography tandem mass spectrometry techniques suggest a terminal elimination half-life of ~30 h (5).
does not exhibit schedule- or dose-dependent pharmacokinetics in the doses and regimens used clinically. In humans, CYP3A4 and 3A5 are the primary enzymes involved in hepatic oxidation of docetaxel to its major metabolite, C-13 hydroxydocetaxel (6, 7). CYP3A4, which is the most abundant CYP450 enzyme found in human liver, catalyzes the metabolism of many structurally diverse endogenous compounds and xenobiotics (8–10).

Prior pharmacokinetic studies with several drugs that are either wholly or predominantly metabolized by CYP3A have suggested a difference in pharmacokinetics between African-American and Caucasian subjects and patients. Initial studies compared the pharmacokinetics of oral cyclosporine, a CYP3A, and ABCB1 substrate in African-American and Caucasian renal transplant patients. The mean oral cyclosporine bioavailability was lower in African-Americans (30.9 ± 12.3%) compared with Caucasians (39.5 ± 16.5%; ref. 11). Several additional studies have reported that oral cyclosporine bioavailability is ~30% lower in African-Americans compared with Caucasians (12–14). Importantly, the reduced oral bioavailability of cyclosporine in African-American renal transplant patients was postulated as one reason that African-American renal transplant patients had an increased incidence of renal graft rejection compared with Caucasian patients. Ethnic differences in apparent oral drug clearance were also suggested by studies of age- and weight-matched African-American and Caucasian healthy volunteer subjects (n = 8, both groups) who received oral triazolam. The mean triazolam area under the plasma concentration versus time curve (AUC) was 4.5 times higher in Caucasian subjects compared with African-American subjects (15). The apparent oral clearance of methylprednisolone in African-American renal transplant patients was also reported to be significantly increased compared with that in Caucasian renal transplant patients (16). In humans, the oral bioavailability and hepatic metabolism and clearance of cyclosporine, triazolam, and methylprednisolone are primarily determined by CYP3A4 activity (17, 18).

Single nucleotide polymorphisms (SNPs) in the genes for proteins involved in drug metabolism and disposition in the liver and gastrointestinal tract (e.g., CYP3A4, CYP3A5, and ABCB1) are hypothesized to play a major role in determining interindividual pharmacokinetic variability. Rebbeck et al. (19) first reported what is now termed as the CYP3A4*1B allele, a SNP in the promoter region of the CYP3A4 gene, in 15 of 94 healthy Caucasian volunteers. The allelic frequency of CYP3A4*1B was reported as 53% in African-American compared with 9% in Caucasian subjects (20). CYP3A5 has a potentially clinically important SNP in intron 3 (21). The CYP3A5*3 allele produces a splice variant with a premature stop codon and no enzyme expression. This polymorphism results in ~50% of African-American subjects and 70–90% of Caucasian subjects not expressing CYP3A5 (21, 22). More than 10 SNPs have been identified in the ATP-binding cassette (ABC) drug transporter protein ABCB1 (also known as P-gp or MDR1; refs. 23–25). The most common SNPs observed at different frequencies among African-Americans and Caucasians are the synonymous SNPs in exon 12 C3435T (allele frequency T in African-Americans = 0.84 and Caucasians = 0.54) and in exon 26 G2677T/A (allele frequency for T in African-Americans = 0.15 and Caucasians = 0.46) and the nonsynonymous SNP in exon 21 C1236T (allele frequency for T in African-Americans = 0.15 and Caucasians = 0.42; refs. 26, 27). Studies with fexofenadine and digoxin reported inconsistent evidence as to whether the exon 26 SNP, either alone or in combination with the other ABCB1 SNPs, was associated with modified ABCB1 expression and, thus, altered drug bioavailability and response (26). However, several studies have suggested that ABCB1 haplotype (mh7) may be more important than single SNPs in determining the level of protein expression and, thus, drug transporter activity (26).

Therefore, we hypothesized that African-American patients would manifest increased metabolic clearance and/or altered disposition of xenobiotics such as docetaxel that are substrates for both CYP3A and ABCB1. The objectives of the current study were (a) to determine whether there is a difference in docetaxel clearance or docetaxel-induced myelosuppression between African-American and Caucasian cancer patients and (b) to undertake a preliminary exploration of the relationships between the known polymorphisms in CYP3A4, CYP3A5, and ABCB1 and the pharmacokinetics and pharmacodynamics of docetaxel.

Materials and Methods

Patients and study design

This was an open-label, prospective, parallel-cohort study to compare the population pharmacokinetics and pharmacodynamics of docetaxel in African-American and Caucasian patients with solid tumors. The study protocol was approved by each local Institutional Review Board. All patients were recruited from oncology clinics participating in Cancer and Leukemia Group B (CALGB) and were entered into the study only after providing written informed consent. Eligible patients received 75 or 100 mg/m² docetaxel infused i.v. over 1 h. Patients underwent timed blood sampling for docetaxel pharmacokinetics on the infusion day (day 1) and were followed up on days 8, 15, and 22 for monitoring of toxicity (specifically hematologic suppression). At the end of cycle 1 (day 22), the patients’ ongoing cytotoxic treatment was at the discretion of the treating oncologist. After the study had begun and 30 patients accrued, the study protocol was amended to add a secondary objective of obtaining blood samples for relevant exploratory pharmacogenetic analyses with appropriate informed consent.

Eligible patients had a histologically proven, unrespectable, non-hematologic malignancy that was suitable for treatment with single-agent docetaxel (commercially available Taxotere from Sanofi-Aventis) and were of either African-American or Caucasian ethnic origin, based on NIH criteria. As the primary study objective related to detecting inter-ethnic differences in pharmacokinetics or toxicity, we limited the study to subjects whose parents and grandparents were all of the same ethnic origin as the patient. Additional eligibility criteria included adequate hematologic function, as evidenced by an absolute neutrophil count >1,500/μL and platelet count >100,000/μL; adequate hepatic function as evidenced by a total bilirubin <1.0 mg/dL and aspartate aminotransferase (AST) < upper limit of normal (ULN); and alkaline phosphatase <2.5 × ULN; adequate renal function as evidenced by a blood urea nitrogen <1.5 × ULN and serum creatinine <1.5 ULN; age ≥18 years; Eastern Cooperative Oncology Group performance status 0 to 2; nonpregnant and non-nursing. Prior treatment restrictions included <2 prior chemotherapy regimens; no prior docetaxel; no prior bone marrow transplant; >2 weeks since prior radiation therapy; >4 weeks since prior chemotherapy except >6 weeks since prior nitrosoureas or mitomycin. Furthermore, patients could not receive known dietary or xenobiotic inducers or inhibitors of CYP3A. Grapefruit juice and ethanol were not permitted for 48 h before and 72 h after docetaxel treatment. Patients were excluded if they had evidence of active infection or an unstable concurrent medical condition,
a history of prior HIV or hepatitis C infection, or a psychiatric condition that would prevent adherence to the study protocol or impairment of the written informed consent process.

All eligible patients received five doses of dexamethasone (8 mg, p.o. every 12 h starting 24 h before and continuing until 24 h after docetaxel treatment). Optional additional premedication consisting of 25 to 50 mg of i.v. diphenhydramine and 50 mg of i.v. ranitidine or 20 mg of i.v. famotidine was offered to patients with a history of mild or moderate allergic reactions to taxanes. The first 30 patients recruited into this study received a single i.v. dose of 100 mg/m² docetaxel administered as a constant infusion over 1 h. Because of concerns of hematologic toxicity at the 100 mg/m² docetaxel dose and the wider acceptance of a lower docetaxel dose by oncologists, the docetaxel dose in the study was reduced to 75 mg/m², which was given to the subsequent 79 study patients. Blood samples for pharmacogenetic analysis were taken before docetaxel treatment. Additional blood samples for docetaxel pharmacokinetics were taken before and after docetaxel administration. Patients were monitored for clinical and hematologic toxicity on days 8, 15, and 22 of their first docetaxel treatment cycle. Docetaxel-related adverse events were graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.

The percentage decrease in ANC was defined as:

\[
\text{( Pretreatment ANC – Nadir ANC/Pretreatment ANC ) \times 100 }
\]

where the pretreatment ANC was the ANC measured before or on day 1 of treatment, and nadir ANC was defined as the lowest ANC measured on days 8, 15, or 22. In addition, we estimated the AUC of neutropenia.

This was quantitated by estimating the area under the ANC versus time curve. The AUC was determined as the area under the line connecting the pretreatment ANC to nadir ANC and nadir ANC to subsequent peak ANC. The AUC was calculated using the trapezoidal rule. The AUC was compared for African-American and Caucasian patients, but to minimize any longitudinal time effects, accrual to the Caucasian cohort was temporarily suspended and was not resumed until after 20 patients had been accrued to the African-American cohort.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were done by CALGB statisticians. As part of the quality assurance program of the CALGB, members of the Data Audit Committee visited all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was done for a subgroup of 46 (42%) of the 109 patients enrolled into this study.

Pharmacokinetic sampling for docetaxel concentrations. Based on a published limited sampling schedule (28), heparinized venous blood samples were obtained before treatment and at 55 min and 6 h after starting the docetaxel infusion. Samples were obtained from the limb contralateral to that into which the docetaxel was infused, and the exact time that each sample was obtained was recorded as were the time of infusion initiation and duration. Within 10 min of sample procurement, blood was centrifuged at 1,000 g for 10 min. The resulting plasma was frozen and stored at -20°C. Plasma samples were shipped on dry ice to the central pharmacokinetic laboratory (A. Miller's Laboratory, Comprehensive Cancer Center of Wake Forest University, Winston Salem, NC), where they were kept frozen at -70°C until analyzed.

Measurement of plasma docetaxel concentrations. The analytic assay used to quantitate docetaxel in plasma was a modification of the published high-performance liquid chromatography methodology to quantitate paclitaxel (29). In our assay, paclitaxel was the internal standard. The lower limit of detection of this assay was 10 ng/mL. The intra- and interday coefficients of variation (CV) for the 100 ng/mL concentration were 10% and 13.2%, respectively. The intra- and interday CV for the 1,000 ng/mL concentration were 6.0% and 7.1%, respectively. The accuracy for the 100 ng/mL and 1,000 ng/mL concentrations varied between 87% to 113% and 94% to 106%, respectively.

Measurement of plasma alpha-1 acid glycoprotein concentration. The plasma obtained from patient blood samples taken just before treatment with docetaxel on study day 1 was also used for measurement of alpha-1 acid glycoprotein (AAG) concentration using an immuno- turbidimetric method. This assay was done using the Roche AAG Diagnostic Kit on a Cobas Integra 800 System (Roche Diagnostics, Almeda, CA). In brief, this is an immunoassay in which anti-AAG antibody binds to AAG and produces a concentration-dependent increase in absorbance at 652 nm. The assay had a limit of detection of 0.016 g/L. The calibration curve was linear over the range of 0.16 to 4.4 g/L. The inter- and intra-day CV of the assay ranged from 1.5% to 2.4% and 0.95% to 1.9%, respectively. AAG measurement was necessary to provide data required for the docetaxel population pharmacokinetic model used in this study.

Docetaxel population pharmacokinetic modeling. A previously published nonlinear mixed-effects model describing docetaxel pharmacokinetics (30) was used to evaluate the sparsely sampled docetaxel concentration versus time data from this study. The majority of the model parameters (fixed and random effects) were fixed to those reported previously (28). Only docetaxel clearance and the interindividual variability in clearance were estimated. Data from this study drove the selection of patient-specific pharmacokinetic parameters within the bounds of interindividual variability and central tendency prespecified by the model. The impact of ethnicity and sex on the post hoc clearance estimates was also evaluated.

Initially, covariate relationships were assessed using the individual maximum a posteriori (post hoc) Bayesian predicted clearances from NONMEM (31; Globoborm Corporation, Hanover, MD) in Excel (Microsoft Corporation, Redmond, WA). Individual deviations of the parameters from the population average clearance were compared with the covariates of interest. Subsequently, unpaired t tests for samples of unequal variance were used to compare the individual clearance estimates between males and females as well as between African-American and Caucasian patients.

Finally, ethnicity and sex covariates were evaluated in the mixed-effects pharmacokinetic model where each covariate was initially assessed individually and then incorporated into the model in a stepwise fashion using forward addition and backward removal. The difference in objective functions (Δ−2LL) was used to compare alternative models. The incorporation of a covariate resulting in an objective function decrease of 7.88 units (Δ−2LL < 0.005; df, 1) was considered significant. This threshold was selected as conservative because the first-order estimation method used occasionally deviates from its approximation of the χ² distribution. Ethnicity and sex were allowed to have an estimated covariate relationship specified as an additive model, with ethnicity and sex having a flag of 0 or 1 that turned additional terms on or off in the model. Mathematically, ethnicity and sex covariates were incorporated into the previously defined definition of clearance as:

\[
\text{TVCL = BSA \times (θ_1 + θ_2 \times \text{AAG} + θ_3 \times \text{Age} + θ_4 \times \text{ALB} + θ_{10} \times \text{Ethnicity} + θ_{11} \times \text{Sex})}
\]

where TVCL is the typical value of clearance (i.e., the population clearance), BSA is the body surface area, and ALB is the albumin.

In each run, the 95% confidence intervals (95% CI) of point estimates were determined from the SE of estimates returned by the covariance step of NONMEM as follows: parameter estimate ± 1.96 × SE. If the covariance step was unsuccessful, the 95% CI was determined by a bootstrapping (sampling with replacement) method (32) that...
consisted of repeatedly fitting the model to 200 bootstrap replicates of the data. The 95% CI of bootstrapped parameter estimates were calculated by taking the 2.5th to 97.5th interpercentile range of parameter estimates.

The apparent volume of distribution at steady state (\(V_{a,s}\)) estimates were calculated from a noncompartmental analysis (using the standard linear trapezoidal rule for the upswing of the infusion and log-linear trapezoidal rule for the decay phase calculation) after simulating each individual’s pharmacokinetic profile from his or her uniquely estimated parameters. Simulations were done using ADVAN6 TRANS1, and noncompartmental calculations were done using WinNonlin 4.0.1.1 (Pharsight, Mountain View, CA).

Genotype determination for CYP3A4, CYP3A5, and ABCB1

Sample collection and handling. Blood samples (4.5 mL) for pharmacogenetic analyses were collected in citrated tubes and then frozen and stored at -20°C. Blood samples were then shipped frozen to the Pharmacogenetics Laboratory at St. Jude Children’s Research Hospital (Memphis, TN), where they were stored at -20°C until analyzed. Samples were thawed in batches, and DNA was isolated using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN) according to the manufacturer’s instructions.

Genotyping. The CYP3A4*1B polymorphism and the CYP3A5*3 (rs776746) polymorphism (G → A at position 22893) were assayed as described previously (33). In the case of ABCB1, genotyping for the common ABCB1 exon 21 G2677T/A and ABCB1 exon 26 C3435T polymorphisms were assayed as described by Kishi et al. (34).

Study sample size and power: projected and actual

For study sample size calculations, we assumed a mean docetaxel clearance of 37.2 L/h and CV of 38%, which is 1.5 times the reported 25% CV (35). In particular, this sample size would give 90% power to detect a significant difference in clearance if the average clearance of one ethnic group differed from the average clearance of the other group by ~30%. Similarly, 35 patients per group would give 80% power to detect a significant ethnicity effect if the average clearance differed by ~20% between ethnic groups. The calculations assumed a two-sample \(t\) test at the two-sided 0.05 level of significance. We expected that nonparametric tests, such as the Wilcoxon rank sum test, would have similar power. We allowed for the possibility that in ≤10% of patients contributing data, their data would not be usable in the analysis, so that our accrual objective was 80 patients (40 patients in each ethnic group).

As the study proceeded, patient accruals to the African-American study arm lagged considerably behind that in the Caucasian study arm. After 20 patients were accrued to the Caucasian arm, further accrual of Caucasian patients was temporarily suspended until accrual numbers in the African-American arm equaled those in the Caucasian study arm. This planned temporary suspension in accrual to the Caucasian arm was intended to minimize any longitudinal time effects on study outcomes. However, it produced almost a complete halt in study accrual for several months. Once the accrual numbers in the African-American arm matched that in the Caucasian arm, the temporary suspension to Caucasian accrual was removed, and both arms of the study were opened. The study then continued accruing patients to both study arms without further interruption until completion. Because accrual to the Caucasian arm of the study continued to be more rapid than accrual to the African-American arm of the study, a total of 69 Caucasian patients were entered into the study by the time the African-American patient accrual reached its predefined goal of 40.

Statistical analysis

To be consistent with the statistical methodology used to determine the study sample size, we initially compared docetaxel pharmacokinetic parameters between African-American and Caucasian patient populations using the two-sample two-sided \(t\) test. Additionally, we then confirmed this analysis using the normal approximation to the two-sample Wilcoxon rank sum test. All analyses included adjustment for docetaxel dose via analysis of covariance or a stratified Wilcoxon-type test (36). We computed the Spearman rank-order correlation coefficients to estimate the relationships between docetaxel and the

Table 1. Demographics of patients enrolled in the study (CALGB 9871)

<table>
<thead>
<tr>
<th></th>
<th>African-American</th>
<th>Caucasian</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>Number of patients enrolled</strong></td>
<td></td>
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<tr>
<td></td>
<td>40</td>
<td>69</td>
<td>109</td>
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<tr>
<td><strong>Median age (y)</strong></td>
<td>60.5 (range, 29-73)</td>
<td>63 (range, 38-81)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male, n (%)</td>
<td>26 (65)</td>
<td>43 (62)</td>
<td>69 (63)</td>
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<tr>
<td>Female, n (%)</td>
<td>14 (35)</td>
<td>26 (38)</td>
<td>40 (37)</td>
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<tr>
<td><strong>Number of prior chemotherapy regimens, n (%)</strong></td>
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<td>21 (19)</td>
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<td>1 (1)</td>
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<tr>
<td><strong>Tumor Types, n (%)</strong></td>
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<tr>
<td>Lung</td>
<td>23 (58)</td>
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<td>72 (66)</td>
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<tr>
<td>Breast</td>
<td>6 (15)</td>
<td>2 (3)</td>
<td>8 (7)</td>
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<td>Gastrointestinal and Pancreas</td>
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<tr>
<td>Head &amp; Neck</td>
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<td>3 (4)</td>
<td>7 (6)</td>
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<tr>
<td>Prostate</td>
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<td>2 (3)</td>
<td>5 (5)</td>
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<td>Other</td>
<td>1 (2)</td>
<td>6 (9)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Docetaxel (100 mg/m²), n (%)</td>
<td>9 (23)</td>
<td>21 (30)</td>
<td>30 (28)</td>
</tr>
<tr>
<td>Docetaxel (75 mg/m²), n (%)</td>
<td>29* (73)</td>
<td>48 (70)</td>
<td>79 (72)</td>
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<tr>
<td><strong>Median baseline WBC (\times 10^3/\mu L), (range)</strong></td>
<td>7.1 (2.5-14.0)</td>
<td>7.2 (2.7-22.8)</td>
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</table>

*Two patients did not receive the study treatment because they withdrew informed consent.
hematologic toxicities of ANC nadir and percentage decrease in ANC and docetaxel clearance. Ethnic differences in the relationship between percentage decrease in ANC and docetaxel AUC were based on a two-way ANOVA to adjust for dose. Relationships between genotypes and docetaxel pharmacokinetic parameters or hematologic toxicity were explored using a Wilcoxon or Kruskal-Wallis test, depending on the number of groups being compared. Analyses of the genotype-docetaxel pharmacokinetic parameter relationships included the adjustment for ethnicity to avoid bias from the population structure. All quoted P values are two sided, and a two-sided P value <0.05 was considered significant. We include the summary data as means with 95% CI or medians with ranges. No adjustment was made for multiple comparisons in this exploratory analysis.

Results

Between September 1998 and August 2003, 109 patients were enrolled into the study. Patient characteristics are shown in Table 1.

Pharmacokinetics. Data from 10 patients were not evaluable for the analysis of the docetaxel pharmacokinetic end points for one of the following reasons: samples thawed during transit (n = 5); patients withdrew consent (n = 3); poor venous access prevented one of the blood draws (n = 1); and samples were drawn from the same arm in which the docetaxel was given (n = 1). Therefore, data from 34 African-American patients and 65 Caucasian patients were analyzed for the primary study end point. A scatterplot of docetaxel clearance for African-American patients and Caucasian patients is shown in Fig. 1. There was no significant difference between the geometric mean docetaxel clearance in African-American patients (40.3 L/h; 95% CI, 19.3-84.1) and that in Caucasian patients (41.8 L/h; 95% CI, 22.0-79.7; two-sample, two-sided t test, P = 0.6). Comparison of the docetaxel clearance data for African-American and Caucasian patients using the Wilcoxon rank sum test, not surprisingly, also revealed no significant difference (P = 0.87). Based on the difference in the log clearance between the ethnic groups, the mean ratio of [(docetaxel clearance in African-Americans)/(docetaxel clearance in Caucasians)] was 0.96 (95% CI, 0.83-1.11).

In addition, there was no significant difference between the docetaxel V_d, in African-American patients (mean 337 L; 95%
Ci, 205-410) and that in Caucasian patients (mean 247 L; 95% CI, 191-304; two-sample, two-sided t test, P = 0.96; ANOVA P = 0.76). We observed neither a sex-related difference in docetaxel clearance or Vd within ethnic groups nor when the data from both ethnic groups was combined to form a single patient population (data not shown). When entered into the nonlinear mixed-effects population pharmacokinetic model, the covariate ethnicity and sex did not result in a significant improvement in model fitness based on the delta -2 log likelihood.

**Pharmacodynamics.** Because four African-American patients had incomplete data for ANC during the treatment cycle, they were excluded from the hematologic toxicity analysis. Pretreatment ANC was similar in both African-American patients (median, 5,395/μL; range, 1,700-18,010) and Caucasian patients (median, 5,080/μL; range, 1,630-12,150; Wilcoxon P = 0.3). There was no significant difference in ANC nadir between ethnic groups when stratified by docetaxel dose (100 or 75 mg/m²; ANOVA P = 0.90; Wilcoxon P > 0.45). There was also no significant difference between the groups in the percentage decrease in ANC, when adjusted for dose (ANOVA P = 0.85). The median percentage decrease in ANC after 75 mg/m² of docetaxel for African-American patients was 77% (range, 25-100; Wilcoxon P = 0.34) and for Caucasian patients was 86% (range, 8-100; Wilcoxon P = 0.34; Fig. 2). Similarly, there was no difference in the decrease in ANC observed in patients from either ethnic group who received 100 mg/m² of docetaxel (Fig. 2). We estimated the AUC of neutropenia caused by docetaxel. As was the case with the percentage decrease in ANC, there were no differences between the ethnic groups treated with either 75 or 100 mg/m² docetaxel (Wilcoxon P = 0.24 and 0.17, respectively; data not shown). Furthermore, there was no discernible relationship between the docetaxel AUC and the percentage decrease in ANC, and the distribution of the data was similar for both ethnic groups (ANOVA P = 0.18; see Fig. 3).

**Pharmacogenomics.** After initiation, the study was amended to include genotyping of patients for CYP3A4*1B, CYP3A5*3, ABCB1 exon 21 2667 and ABCB1 exon 26 3435. A total of 59 out of 109 (54%) patients who enrolled in the study [African-American n = 18:40 (45%); Caucasian n = 41:69 (59.4%)] underwent genotyping for the above polymorphisms. For patients in whom genotype and docetaxel pharmacokinetic and pharmacodynamic data were available, the association between docetaxel pharmacokinetics and genotype within the ethnic groups was explored. There was no discernible relationship between CYP3A4*1B, CYP3A5*3 genotype and docetaxel clearance in either African-American or Caucasian patients (Fig. 4). Similarly, there was no discernible relationship between the ABCB1 genotypes studied and docetaxel clearance in African-American patients and Caucasian patients (data not shown). Because we found no significant difference in docetaxel clearance and Vd between the African-American and Caucasian patient groups, we also explored genotype relationships for the studied polymorphisms and docetaxel pharmacokinetics when the ethnic groups were considered as a single population. These additional analyses again revealed no significant relationship between docetaxel clearance or Vd and the CYP3A4*1B, CYP3A5*3, ABCB1 2667 or 3435 genotype (data not shown). Exploration of potential relationships between the genotypic polymorphisms CYP3A4*1B, CYP3A5*3, or ABCB1 and the docetaxel-related percentage decrease in ANC or AUC of neutropenia revealed no significant relationships (data not shown).

We did not observe any unexpected clinical or laboratory toxicities following docetaxel treatment in either ethnic group (Table 2). One African-American patient died from neutropenic sepsis and acute respiratory distress syndrome. Among the 99 patients for whom docetaxel pharmacokinetic data were available, grade 3 or higher adverse events (National Cancer Institute Common Toxicity Criteria) were reported in 22:34 (65%) African-American patients and 48:65 (74%) Caucasian patients (Table 2). The incidence of grade 4 neutropenia in the patients from both ethnic groups seemed higher in patients treated with 100 mg/m² docetaxel, compared with those treated with 75 mg/m².

**Discussion**

The primary end point of this study was to evaluate a potential difference in docetaxel clearance between African-American and Caucasian cancer patients; however, we observed no significant difference in the estimated docetaxel clearance between these two ethnic groups. The docetaxel clearance we observed for each ethnic group was similar to values reported in the published literature and to those used to define the study

![Fig. 3. Scatterplots of docetaxel AUC versus the percentage decrease in ANC in African-American (n = 30) and Caucasian (n = 65) patients who received a single dose of either 75 or 100 mg/m² of docetaxel. There was no clear relationship between docetaxel AUC and percentage decrease in ANC and the distribution of data for each ethnic group was similar (ANOVA P = 0.18).](http://example.com/fig3)
sample size (3, 4, 35, 37). Furthermore, we found that the docetaxel $V_d$ was not different between the African-American and Caucasian, and that these values were again similar to those previously reported (3, 4, 35). Previous studies that reported differences in drug bioavailability and disposition between African-American and Caucasian patients evaluated orally administered drugs such as cyclosporine, triazolam, and methylprednisolone (10–15). Therefore, our observations with docetaxel would suggest that the reported differences between African-American and Caucasian patients in oral bioavailability of certain drugs that are CYP3A and/or ABCB1 substrates may be due primarily to alterations in the phenotype of processes determining presystemic drug clearance in the gastrointestinal tract. Supporting this interpretation are studies by Stein et al. (38), who reported no significant difference in the pharmacokinetics or pharmacodynamics of oral cyclosporine in a cohort ($n = 9$) of age-matched healthy male African-American and Caucasian subjects studied under strictly controlled dietary conditions. Similarly, Floyd et al. (39) reported no difference in oral midazolam disposition (CYP3A4 substrate) between African-Americans and Caucasians. In contrast, another study comparing African-American ($n = 11$) and Caucasian ($n = 11$) healthy volunteers reported a decreased cyclosporine clearance (∼30%; $P = 0.0001$) in African-Americans following single doses of oral and i.v. cyclosporine (13). The inconsistent findings in these studies suggest that factors other than ethnicity may have an important role in drug disposition. For example, salt was reported to increase presystemic activity of CYP3A, thereby decreasing oral drug bioavailability (40). We considered using the data from our Caucasian and African-American patients to reevaluate the docetaxel population pharmacokinetic model as it was originally generated in European cancer patients (30). However, the sparsity of our docetaxel concentration-time data (2 data points) means that estimating docetaxel pharmacokinetic parameters based on our data would have to use a one-compartment model. This is not appropriate for docetaxel disposition, which is characterized by a three-compartment pharmacokinetic model (2, 30, 37). Therefore, reassessment of the model using our sparse data would not yield valid pharmacokinetic parameters.

Consistent with the lack of inter-ethnic docetaxel pharmacokinetic difference, it was not unexpected that this study did not find a significant difference between African-American and Caucasian patients in myelotoxicity as determined by the percentage decrease in ANC or the AUC of neutropenia. Increased hematologic pharmacodynamic sensitivity to docetaxel with equivalent pharmacokinetic exposure has been reported in elderly compared with the nonelderly lung cancer patients.

![Fig. 4. Scatterplots of docetaxel clearance versus CYP3A4*1B genotype at the -288 position (CYP3A4*1; WT, wild type = AA) and CYP3A5*3 genotype at the base pair 22893 (CYP3A5*3; WT, wild type = GG) in African-American ($n = 18$) and Caucasian ($n = 41$) patients who received a single i.v. dose of 75 or 100 mg/m² of docetaxel. Horizontal bars, median values.](image-url)
patients who received docetaxel combined with cisplatin (41). However, our pharmacodynamic data should be interpreted with some caution. Because the primary objective of the study was pharmacokinetic and the study sample size was calculated on that basis, it is possible that the number of African-American and Caucasian patients studied was insufficient to show a difference in docetaxel-induced myelosuppression. Furthermore, because we only studied a narrow range of the Food and Drug Administration approved docetaxel dosages, which are known to produce significant myelosuppression in most patients, the ability of this study to show inter-ethnic differences in hematologic toxicity may have been limited. Similarly, the narrow range of docetaxel doses employed resulted in a relatively narrow range of docetaxel AUCs, which is a possible explanation for the failure of the current study to show a relationship between docetaxel AUC and neutropenia. At this time, our review of the literature has not revealed previous studies that address inter-ethnic differences in hematopoietic toxicity or hematologic pharmacodynamics. These exploratory data analyses did not reveal any genotype-related differences in docetaxel pharmacokinetics or pharmacodynamics between African-American and Caucasian or any ABCB1 genotype relationships with docetaxel clearance or hematologic pharmacodynamics between ethnic groups or any ABCB1 genotype relationships with docetaxel clearance or hematologic pharmacodynamics in the pooled patient population (data not shown). Interestingly, Bosch et al. (44) studied 92 cancer patients who received docetaxel and found that patients who were homozygous (n = 19) for the ABCB1*8 (C1236T) polymorphism had a 25% reduction in docetaxel clearance compared with wild-type patients (n = 30). In contrast, Tran et al. (45) suggested that patients with the ABCB1 T3435T genotype (n = 10) compared with patients with the C3435C genotype (n = 11) had an increased incidence of grade 3 neutropenia (100% versus 54.5%; P = 0.046). Previous studies that suggested that ABCB1 polymorphisms affect drug pharmacokinetics (e.g., altered oral bioavailability of digoxin, cyclosporine, ritonavir, and fexonadine; ref. 26) have yielded variable and inconsistent results. Furthermore, drug transporter proteins other than ABCB1 (e.g., the multidrug resistance protein 1 gene, ABCG1) may be important in determining docetaxel disposition in vivo (46). It is possible that both our study population (composed of African-Americans and Caucasians) and those of the previously reported docetaxel pharmacokinetic-genotype studies (42, 43) was too small to have adequate power to detect an effect of the polymorphisms studied on docetaxel pharmacokinetics and pharmacodynamics.

In conclusion, the important clinical relevance of the data from this study is that it supports the position that the current Food and Drug Administration recommended range of doses for docetaxel monotherapy, given once every 21 days, do not require adjustment in African-American cancer patients with acceptable physiologic organ function. We have also shown

| Table 2. The most common clinical and laboratory adverse events (grade 3/4/5) in African-American and Caucasian cancer patients who received 75 or 100 mg/m² of docetaxel |
|----------------|-----------------|-----------------|-----------------|
| **Adverse event** | **Dose (mg/m²)** | **African-American (n = 29 at 75 mg/m²; n = 9 at 100 mg/m²)** | **Caucasian (n = 48 at 75 mg/m²; n = 21 at 100 mg/m²)** |
| | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 3** | **Grade 4** | **Grade 5** |
| Total WBC | 100 | 2 (22%) | 5 (56%) | 7 (37%) | 7 (37%) |
| | 75 | 8 (32%) | 3 (12%) | 15 (33%) | 8 (17%) |
| ANC | 100 | 1 (11%) | 6 (67%) | 15 (79%) | 15 (79%) |
| | 75 | 2 (7%) | 8 (32%) | 7 (15%) | 21 (46%) |
| Febrile neutropenia | 100 | 1 (11%) | | | |
| | 75 | 1 (11%) | | | |
| Infection | 100 | 1 (11%) | 1 (4%) | 1 (5%) | 1 (5%) |
| | 75 | | | 1 (2%) | 1 (2%) |
| Fatigue | 100 | 2 (8%) | | | |
| | 75 | 2 (8%) | | | |
| Vomiting | 100 | 2 (10%) | | | |
| | 75 | 1 (5%) | | | |
| Neuropathy; motor | 100 | 2 (8%) | | | |
| | 75 | 1 (5%) | | | |
| Myalgia | 100 | 1 (11%) | | | |
| | 75 | | | | |
| Maximum overall | 100 | 3 (33%) | 6 (67%) | 1 (3%) | 11 (24%) |
| | 75 | 5 (17%) | 7 (28%) | | 22 (46%) |

patients (n = 53) had increased docetaxel clearance (55.2 + 13.2L/h versus 37.3 + 11.7 L/h; P = 0.01). The current literature regarding the effects of CYP3A4*1B and CYP3A5*3 polymorphisms on drug metabolism (20–22, 39, 42–44) seems to be drug and context specific. Our ABCB1 genotyping did not reveal any genotype-related differences in docetaxel clearance or hematologic pharmacodynamics between ethnic groups or any ABCB1 genotype relationships with docetaxel clearance or hematologic pharmacodynamics in the pooled patient population (data not shown). Interestingly, Bosch et al. (44) studied 92 cancer patients who received docetaxel and found that patients who were homozygous (n = 19) for the ABCB1*8 (C1236T) polymorphism had a 25% reduction in docetaxel clearance compared with wild-type patients (n = 30). In contrast, Tran et al. (45) suggested that patients with the ABCB1 T3435T genotype (n = 10) compared with patients with the C3435C genotype (n = 11) had an increased incidence of grade 3 neutropenia (100% versus 54.5%; P = 0.046). Previous studies that suggested that ABCB1 polymorphisms affect drug pharmacokinetics (e.g., altered oral bioavailability of digoxin, cyclosporine, ritonavir, and fexonadine; ref. 26) have yielded variable and inconsistent results. Furthermore, drug transporter proteins other than ABCB1 (e.g., the multidrug resistance protein 1 gene, ABCG1) may be important in determining docetaxel disposition in vivo (46). It is possible that both our study population (composed of African-Americans and Caucasians) and those of the previously reported docetaxel pharmacokinetic-genotype studies (42, 43) was too small to have adequate power to detect an effect of the polymorphisms studied on docetaxel pharmacokinetics and pharmacodynamics.

In conclusion, the important clinical relevance of the data from this study is that it supports the position that the current Food and Drug Administration recommended range of doses for docetaxel monotherapy, given once every 21 days, do not require adjustment in African-American cancer patients with acceptable physiologic organ function. We have also shown
that studies of ethnic comparisons are feasible, but future studies of this nature should consider genotyping of ancestral informative markers.

Appendix A

The following institutions participated in this study:

CALGB Statistical Center, Duke University Medical Center, Durham, NC: Stephen George, Ph.D., supported by CA33601. Duke University Medical Center, Durham, NC: Jeffrey Crawford, M.D., supported by CA47577.

Memorial Sloan-Kettering Cancer Center, New York, NY: Clifford Hudis, M.D., supported by CA77651.

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A Comparison of the Pharmacokinetics and Pharmacodynamics of Docetaxel between African-American and Caucasian Cancer Patients: CALGB 9871

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