Phase I and Pharmacokinetic Study of Escalating Dose of Docetaxel Administered with Granulocyte Colony-stimulating Factor Support in Adult Advanced Solid Tumors

Anthony Gonçalves,1 Frederic Viret, Joseph Ciccolini, Dominique Genre, Gwenaelle Gravis, Marc Giovannini, Jacques Camerlo, Jacques Catalin, Dominique Maraninchi, and Patrice Viens

Department of Medicine, Institut Paoli-Calmettes, 13273 Marseille, France [A. G., F. V., D. G., G. G., M. G., J. Cam., D. M., P. V.]; Pharmacokinetic and Toxicokinetic Laboratory, School of Pharmacy, Marseille, France [J. Ci., J. Cat.]; and Université Méditerranée, IFR57 Marseille, France [J. Cat., D. M., P. V.]

ABSTRACT

Purpose: The purpose of our study was to assess the feasibility, toxicity, and pharmacokinetics of an escalating dose of docetaxel when administered with granulocyte colony-stimulating factor (G-CSF) support every 3 weeks.

Experimental Design: Patients with advanced solid malignancies were treated with escalating doses of docetaxel as a 1-h infusion every 3 weeks, supported by s.c. administration of human recombinant glycosilated G-CSF Granocyte (lenogastim), 5 µg/kg/day (from day 4 until neutrophil count >0.5-10⁶/liter for two consecutive days). Plasma sampling was performed to characterize the pharmacokinetics of docetaxel at the new recommended high-dose level.

Results: Forty-seven patients were treated with 116 courses of docetaxel at eight dose levels ranging from 100–185 mg/m². Dose-limiting toxicities were nonhematologic and included mucositis and dermatitis. Severe skin toxicity observed at 185 mg/m² led to discontinuing the study, and 175 mg/m² was selected as the recommended dose of docetaxel + G-CSF for future Phase II studies. Analysis of multiple courses revealed dermatitis, mucositis, arthralgia/myalgia, and neuropathy as the main dose-related toxic events. At 175 mg/m² mean ± SD values for docetaxel plasmatic peak, area under the curve, clearance, volume of distribution, and terminal half-life were 6.7 ± 1.7 µg/ml, 9.7 ± 4 µg·h/ml, 34.2 ± 12 liters/h, and 122.7 ± 124 liters, respectively. Of the 16 patients treated at 175 mg/m², 8 patients responded (7 breast cancer and 1 lung cancer patients) including one complete response (1 breast cancer patient).

Conclusions: Using G-CSF support allows substantial dose escalation of docetaxel. Whether such a dose increase improves the response rate warrants further investigation. At the highest dose level studied, pharmacokinetic parameters seem to maintain a linear profile.

INTRODUCTION

During the past 10 years, taxoids have generated great interest and hope in cancer treatment. These compounds bind to the β-subunit of tubulin and strongly alter the dynamic behavior of the microtubule network. They promote tubulin assembly into microtubules and prevent depolymerization of the formed polymers, leading ultimately to apoptotic cell death (1). Docetaxel is a hemisynthetic compound obtained from a nontoxic Taxol precursor, 10-deacetyl baccatin III, extracted from the needles of the European yew tree, Taxus baccata (2). In clinical studies, docetaxel has displayed promising results in several malignancies, especially in advanced breast cancer, where, as a single agent, impressive response rates have been achieved, even in poor prognosis patients such as those with liver metastasis or disease refractory to anthracyclines. In combination with anthracyclines, docetaxel, as well as paclitaxel, represent probably the best first-line chemotherapy in metastatic breast cancer, and both drugs are under intense investigation in the adjuvant setting. Promising results have also been recorded for docetaxel in other human cancers such as ovarian, non-small cell lung, and head and neck cancers (3–5).

Several Phase I studies (6–10) have established the currently recommended schedule of administration of docetaxel as a single agent: 100 mg/m² as a 1-h i.v. infusion every 3 weeks. At this dose level, the major toxicity is neutropenia, which affects nearly 80% of patients. Neutropenia is often brief and most frequently uncomplicated. Usual nonhematologic toxicities such as mucositis, emesis, diarrhea, neurotoxicity, and cardiac toxicity are mild. Specific docetaxel-induced toxicities including acute hypersensitivity reactions, skin toxicity, and fluid retention, have also been noted but are not acutely dose limiting. However, fluid retention is clearly dose limiting with chronic administration of docetaxel. Numerous Phase II studies have confirmed this toxicity profile (3).

By considering the antitumor activity of docetaxel in these Phase I/II studies, there is some evidence suggesting a dose-response relationship for this drug. First, responses observed in Phase I studies occurred generally at the highest dose levels investigated (i.e., between 100 and 115 mg/m²). Second, taken together, published objective response rates in Phase II studies, using three different initial doses of docetaxel as first-line therapy for advanced breast cancer (i.e., 100, 75, and 60 mg/m²), seem to show an actual dose-dependent antitumor effect with...
response rates ranging between 38% and 70% at 100 mg/m², 40% and 50% at 75 mg/m², and 42% and 44% at 60 mg/m² (11).

Because clinical studies have clearly demonstrated that neutropenia is the only dose-limiting toxicity of docetaxel when administered as a short i.v. infusion of 100 mg/m², it can be speculated that hematopoietic growth factor may allow this dose threshold to be overcome and, potentially, optimize the response rate.

We report here the results of a Phase I study investigating a dose escalation of docetaxel as a 1-h i.v. infusion every 3 weeks, associated with lenograstim (Granoctye; 5 µg/kg) administered s.c. between courses. Our objectives were: (a) to define the MTD of docetaxel when given with hematopoietic growth factor support and, therefore, to provide a new recommended dose for Phase II trials; and (b) to investigate the pharmacokinetics of docetaxel when given at the highest tolerable dose level.

PATIENTS AND METHODS

Patients. The protocol was approved by an independent ethics committee. Before entry, all patients provided a complete history and underwent physical examination: height, weight, body area, Karnofsky index, blood pressure, pulse rate, and temperature were recorded, and clinical tumor measurements were made where possible. Routine laboratory studies were performed, including complete blood cell counts with differential and serum chemistry for renal and hepatic function. Cardiac function was assessed by chest X-ray, electrocardiogram, and echocardiographic or isotopic left ejection fraction. Radiological tumor measurements were obtained by appropriate means within 30 days before inclusion.

Patients were eligible for entry into the study if they met the following criteria: (a) histological or cytological confirmed diagnosis of a solid tumor or a non-Hodgkin’s lymphoma; (b) age between 18 and 70 years; (c) life expectancy ≥3 months; (d) WHO performance status <3; (e) no more than two prior chemotherapy regimens and/or prior radiation therapy to less than 50% of the bone marrow; (f) adequate bone marrow function (WBC, ≥3×10⁹/liter; granulocytes, ≥1.5×10⁹/liter; hemoglobin, ≥9 g/dl; platelets, ≥100×10⁹/liter), renal function (creatinine ≤1.25 times the upper limits of normal), and hepatic function (bilirubin within normal range of the institution, aspartate aminotransferase, and alkaline phosphatase ≤2.5 times the upper normal limit, regardless of presence of liver metastases); and (g) written informed consent according to all required guidelines.

Exclusion criteria included (a) previous anticancer treatment before inclusion: less than 4 weeks previously for chemotherapy (6 weeks for a nitrosourea or mitomycin), less than 6 and 8 weeks previously for radiation therapy and immunotherapy, respectively; (b) other simultaneous anticancer treatment and any other investigational agent given within the 4 weeks before inclusion; (c) previous taxanes treatment (paclitaxel or docetaxel); (d) brain or meningeal metastases; (e) peripheral neuropathy higher or equal to National Cancer Institute grade 2; (f) active infection or wound, uncontrolled diabetes or any conditions preventing corticosteroid administration; (g) active heart disease including coronary or conduction disorders and cardiac failure (Sokolov index ≥40 or ejection fraction less than 50%); (h) pregnancy (negative pregnancy test for all women before inclusion and effective contraceptive method during treatment were required); (i) history of other cancers (except in situ cervical cancer or cutaneous epithelioma that had been given curative treatment); and (j) history of hypersensitivity to Tween 80 or G-CSF; 11°/social, geographic or psychological conditions preventing full medical follow-up.

Dose-Escalation Procedures. The eight dose levels investigated with G-CSF support were predefined and were 100 mg/m², 115 mg/m², 130 mg/m², 140 mg/m², 150 mg/m², 165 mg/m², 175 mg/m², and 185 mg/m². The starting dose of docetaxel was 100 mg/m² without G-CSF, selected as a reference representing the currently recommended dose in clinical practice. The second dose level (100 mg/m² with G-CSF) was selected to investigate the ability of docetaxel to collect peripheral blood stem cells, and the results of this study will be reported later.

At each dose level, the inclusion of three consecutive patients was planned. Whatever the toxicities recorded at the first two dose levels (100 mg/m² without and with G-CSF support), dose escalation was performed after inclusion of three patients. For the following dose levels, a first patient was treated and observed for at least 2 weeks. If no DLT occurred, two additional patients were treated again at the same dose level and were observed for at least 2 weeks. If no DLT was recorded among the three patients treated at this dose level, the next dose level was investigated. If one patient experienced a DLT, three additional patients were entered at the same dose level. DLT was defined as a nonhematologic grade 3 or 4 toxicity (except alopecia, nausea, and vomiting) or a grade 4 neutropenia associated with fever >38.5°C lasting more than 4 days, despite i.v. antibiotic therapy. Patients experiencing a DLT were allowed to continue docetaxel treatment at the conventional dose if a clinical benefit was observed. The MTD was initially defined as the dose level causing DLTs in at least 50% of patients (i.e., two or more of three patients or three of six patients) and had to be assessed on the first course. The recommended dose was defined as the dose level immediately preceding the MTD. However, recorded toxicities at the last dose level investigated (185 mg/m²), as well as data published in a concomitant pediatric study (12), led us to discontinue dose escalation and to determine MTD without matching those initial criteria, as explained in “Results.” High-dose docetaxel was administered for a maximum of three courses. In case of clinical benefit, patients were allowed to continue with conventional dosing of docetaxel.

Drug Administration. Docetaxel was provided by Aventis as a concentrated 2-ml sterile solution of 40 mg/ml in polysorbate 80. Before use, each vial was diluted in 6 ml of a 13% solution of ethanol in water, and an appropriate amount of drug was further diluted in 250 ml of 5% dextrose. The drug was administered as a 1-h infusion every 21 days, for three courses. To prevent hypersensitivity reactions, skin toxicity, or peripheral edema, premedication with corticosteroids (methylpred-
nisolone p.o.) was systematically administered before each infusion (40 mg at 13 h, 7 h, and 1 h before) and was continued (40 mg every 12 hours) for 3 days.

According to observed toxicity, dose reduction and/or delayed administration were planned. Patients were treated on day 22 if they had a neutrophil count $\geq 1.5 \times 10^9$/liter and a platelet count $\geq 100 \times 10^9$/liter. In case these criteria were not matched on day 22, treatment was delayed by 1-week intervals until bone marrow recovery occurred. If nonrecovery lasted more than 1 week, further courses were performed at 100 mg/m$^2$. In case of grade 3 or 4 nonhematologic recovery (except alopecia), treatment was delayed by a maximum of 2 weeks until recovery of a grade $\leq 1$, and subsequent courses were also performed at 100 mg/m$^2$.

Human recombinant glycosilated G-CSF lenograstim (Granocyte) was provided by Aventis and was administered s.c. after all courses at a dose of 5 $\mu$g/kg/day from day 4 until granulocyte reached $0.5 \times 10^9$/liter for two consecutive days.

**Follow-Up and Treatment Evaluation.** During the study, all patients were seen once weekly and before each administration for patient history and physical examinations including Karnofsky index assessment, weight, and vital signs. Complete blood count and differential were obtained three times a week and on day 22. Other laboratory studies, noted previously, were also performed before each administration.

All patients receiving at least one administration of docetaxel were assessable for toxic reactions. The toxic effects of the drug were graded using the Common Toxicity Criteria of the National Cancer Institute (13).

All patients with measurable disease were assessed for response if they had received at least two administrations. Tumor assessments were performed 4–6 weeks after the last course, by identical means used for initial evaluation. Standard response criteria as defined by the WHO were used.

**Pharmacokinetics.** Thirteen patients were enrolled at the recommended dose-level to explore pharmacokinetics of high-dose docetaxel, and 11 patients were fully assessable. Blood samples were withdrawn before docetaxel administration and 30, 45, 60, 70, 80, and 90 min and 2, 3, 4, 6, 8, 12, 18, 24, and 36 h after the beginning of the infusion.

Whole blood samples were collected into heparinized tubes, placed at 4°C, and then centrifuged within 2 h after collection. Resulting plasma was stored at $-80^\circ$C until assayed.

Samples were assayed by high-performance liquid chromatography, as described previously with paclitaxel as internal standard (14). Briefly, plasma samples were subjected to liquid-liquid extraction using diethyl ether and ammonium acetate buffer (pH 5). Tubes were mixed by vibration for 45 s and then centrifuged at 3500 $\times$ g at 4°C for 5 min. An organic layer was next dried under nitrogen, reconstituted with the mobile phase, and injected into the system.

The high-performance liquid chromatography apparatus consisted of a Waters 600 system coupled with a Kontron UV detector set at 227 nm. Separation of docetaxel from endogenous compounds and internal standard was achieved using a Nucleosil C18 column (Macherey-Nagel). The mobile phase pumped at a flow rate of 1.8 ml/min consisted of acetonitrile/ammonium acetate buffer (32 mm, pH 5)/tetrahydrofuran (45:50:5). All samples were analyzed at room temperature. The limit of quantification for docetaxel in plasma was 12.5 ng/ml.

The docetaxel concentration versus time curves were fitted using Apis 4.1 software (Miips, Marseille, France). The best fit was obtained using a three-compartment model. Fitted parameters (coefficients and exponents of exponential equations) permitted the computation of the following parameters: half-life, AUC, total plasma clearance, and volume of distribution.

**RESULTS**

Between October 1997 and May 2000, 47 patients were treated with docetaxel in this Phase I study, including 13 patients treated at the recommended dose (175 mg/m$^2$), with pharmacokinetic analysis for 11 of them. Patient characteristics are listed in Table 1. The median performance status was 1 with 43 patients classified 0–1 at the inclusion. All but one patient had received prior therapy. Forty-four patients were female, and a large number ($n = 34$) had advanced breast cancer.

A total number of 116 courses were given and fully assessable for toxicity. The number of patients and courses per dose level are listed in Table 2.

**DLTs and Recommended Dose.** As shown in Table 3, no DLTs were observed until 140 mg/m$^2$. At this dose level, two grade 4 mucositis were recorded in six patients. The next DLT was observed on the third patient treated at 185 mg/m$^2$ and was a grade 4 dermatitis. This patient experienced a very severe erythematous desquamating skin rash, complicated by fever and requiring hospitalization for 14 days. Four additional patients were enrolled at this dose level, and three mild skin toxicities (grade 1/2) were further observed. In addition, a patient with previously known liver metastasis developed grade 3 liver toxicity at 185 mg/m$^2$. As shown in Table 4, skin toxicity severity was clearly dose related because grade 3/4 toxicity was only observed at doses $\geq 165$ mg/m$^2$. The occurrence of an additional grade 3 dermatitis in another patient receiving a second cycle at 185 mg/m$^2$ led us to discontinue dose escalation at this dose level. This decision...
Hematological toxicity was strengthened by the recent report of a pediatric study describing similar and severe dose-limiting skin toxicity above 185 mg/m² of docetaxel (12). Therefore, 175 mg/m² was selected as the recommended dose for future Phase II studies evaluating high-dose docetaxel with G-CSF support. However, of the 16 patients treated at 175 mg/m² in the second part of the study, only 7 completed three courses at this dose level, the remaining patients being treated at a standard dose or discontinuing treatment, mostly due to unacceptable nonhematological toxicity (Table 5). Eleven DLTs (mainly myalgia, mucositis, dermatitis, and peripheral neuropathy) were observed of the 35 to 47 total patients treated at the recommended dose (175 mg/m²) were recorded during the study. Interestingly, no grade 4 and only one grade 3 thrombocytopenia was recorded during the first cycle. Neutropenia was shown to be the primary dose-limiting toxicity in this study, and this rate did not seem to correlate with the docetaxel dose. One-third to half of patients experienced grade 4 neutropenia, which was not dose limiting irrespectively of the investigated dose. Only five of 11 patients (mean, 9.7 h). The mean maximal plasma concentration was 6.7 µg/ml. Plasma clearance was 34.2 (±12 liter/h) with a volume of distribution ranging from 25–378 liter (mean, 122 liter). Pharmacokinetics were available for the two patients who died on therapy. Docetaxel maximal plasma concentration and AUC was among the highest of the population for the first patient (massive inhalation and progressive disease), but was not different of the mean of the population for the second one (cardiovascular collapse).

**DISCUSSION**

As demonstrated for the first time in adult patients, using G-CSF allowed substantial escalation of docetaxel from the conventional dose of 100 mg/m² to 175 mg/m² (+75%). Neutropenia was shown to be the primary dose-limiting adverse event associated with docetaxel at conventional dose. It has been reported in >90% of patients (grade 4 in approximately 70% of patients) receiving docetaxel 100 mg/m² as a 1-h infusion every 3 weeks. In our study, neutropenia was easily overcome: the absolute neutrophil count nadir was almost always superior to 0.1×10⁹/liter, and febrile neutropenia were very

### Table 2 Entry per dose level

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>No. of patients</th>
<th>Total no. of courses³</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/m²</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>100 mg/m² + G-CSF</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>115 mg/m² + G-CSF</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>130 mg/m² + G-CSF</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>140 mg/m² + G-CSF</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>150 mg/m² + G-CSF</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>165 mg/m² + G-CSF</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>175 mg/m² + G-CSF</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>185 mg/m² + G-CSF</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>175 mg/m² + G-CSF/pharmacokinetics⁶</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>116</td>
</tr>
</tbody>
</table>

³ Patients experiencing DLT could receive subsequent docetaxel at the starting dose. These courses are not included in the analysis.

⁴ Thirteen additional patients were treated at the dose level immediately below the MTD, and a pharmacokinetic study was performed in 11 patients.

**Non-DLTs.** As shown in Table 3, hematological toxicity was not dose limiting irrespectively of the investigated dose. One-third to half of patients experienced grade 4 neutropenia, and this rate did not seem to correlate with the docetaxel dose. Median absolute neutrophil count nadir was on day 7 and was superior to 0.1×10⁹/liter at all dose levels. Median duration of grade 4 neutropenia after the first cycle was 1 day (range, 1–6), and febrile neutropenia was observed in only one-third of patients even at the highest dose levels investigated. No febrile neutropenia lasted more than 4 days after the first cycle. Overall, the interval between the first and the second cycle was 22 days (range, 19–30). Median duration of G-CSF administration was 9 days.

Nonhematological non-DLTs were relatively common and included grade 1/2 diarrhea, arthralgia, bone pain, and myalgia that seemed dose related. Mild nausea and vomiting, and constipation as well as severe asthenia were also recorded.

**Multiple Exposure Toxicities.** After multiple courses, the profile of hematological toxicities was not significantly altered, as shown in Table 4. Overall, febrile neutropenia lasting more than 4 days was recorded during only 3 of 116 delivered cycles (all at 175 mg/m², after the second or the third cycle). Grade 3 or 4 anemia was not uncommon (13 cycles of 116). Interestingly, no grade 4 and only one grade 3 thrombocytopenia (at 185 mg/m²) were recorded during the study.

The analysis of nonhematological toxicities following multiple high-dose docetaxel courses indicates that dermatitis, mucositis, and arthralgia/myalgia were the main severe and dose-related toxic events. Neuropathy was observed in more than half of patients at the highest dose levels investigated, and its severity increased after multiple exposure. Neither serious hypersensitivity nor major weight gain were observed, and no significant cardiac toxicity was recorded. A cohort of 13 additional patients was treated at the recommended dose (175 mg/m²) to study pharmacokinetics. The recorded toxicities were similar to those identified during the dose-finding part of the study, including mucositis, dermatitis, and arthralgia/myalgia.

Of note, two deaths occurred following the first cycle in this cohort. The first patient, a 50-year-old woman, was treated for a peritoneal relapse of an ovarian carcinoma and was hospitalized on day 5 for aggravation of a prior partial bowel obstruction and subsequent neutropenic fever. She recovered from neutropenia and fever but died on day 8 after massive inhalation following vomiting. The death was mainly related to a progression of the peritoneal disease. The second patient, a 58-year-old woman with relapsing ovarian carcinoma, was hospitalized on day 5 for diffuse myalgia and died on day 7 after experiencing thoracic pain, convulsion, and brutal cardiovascular collapse. The cause of death was unknown, but a docetaxel implication was not ruled out.

**Response.** Eighteen of 35 evaluable patients experienced an objective response. Responses were observed in breast (n = 15), head and neck (n = 2), and lung (n = 1) cancer patients. A complete response was registered at 175 mg/m² in a 63-year-old woman with a cutaneous metastasis from breast cancer. Among the patients treated at the recommended dose, 8 (7 breast and 1 lung cancer patients) of the 10 evaluable patients responded to therapy.

**Pharmacokinetics.** Eleven patients treated at the recommended dose level (175 mg/m²) for future Phase II studies were subjected to and assessable for pharmacokinetic analysis following the first cycle. The main pharmacokinetic parameters best fitted a three-compartment model and are listed in Table 6. There was a significant interpatient pharmacokinetic variability. The total docetaxel AUC ranged from 5.46–18.3 µg·h/ml (mean, 9.7 µg·h/ml). The mean terminal half-life was 13.4 (±15 h). The mean maximal plasma concentration was 6.7 µg/ml. Plasma clearance was 34.2 (±12 liter/h) with a volume of distribution ranging from 25–378 liter (mean, 122 liter). Pharmacokinetics were available for the two patients who died on therapy. Docetaxel maximal plasma concentration and AUC was among the highest of the population for the first patient (massive inhalation and progressive disease), but was not different of the mean of the population for the second one (cardiovascular collapse).
rarely severe. Interestingly, no severe thrombopenia was observed, whatever the dose level investigated, suggesting a particular resistance of the megacaryocyte lineage to docetaxel. Such a lack of severe platelet toxicity was also described in a recent study investigating high-dose paclitaxel with hematopoietic support, suggesting that it may relate to specific features of microtubule-stabilizing agents (15).

As expected, DLTs were nonhematologic. Dose escalation

### Table 3 Toxicities following first course of docetaxel

<table>
<thead>
<tr>
<th>Dose level (no. of patients)</th>
<th>100 (3)</th>
<th>100 (3)</th>
<th>115 (3)</th>
<th>130 (3)</th>
<th>140 (6)</th>
<th>150 (3)</th>
<th>165 (3)</th>
<th>175 (3)</th>
<th>185 (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2a</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥4 days</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a The first two dose levels included six patients receiving 100 mg/m² docetaxel with or without G-CSF.
b Only patients participating in MTD determination are considered.
c No. of patients with specified grade of toxicity.

### Table 4 Toxicities following all courses of docetaxel

<table>
<thead>
<tr>
<th>Dose level (no. of courses)</th>
<th>100 (7)</th>
<th>100 (9)</th>
<th>115 (9)</th>
<th>130 (9)</th>
<th>140 (15)</th>
<th>150 (9)</th>
<th>165 (7)</th>
<th>175 (4)</th>
<th>185 (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0b</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (1)</td>
<td>2 (0)</td>
<td>5 (3)</td>
<td>4 (0)</td>
<td>6 (2)</td>
<td>3 (3)</td>
<td>0</td>
<td>17 (6)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

a All patients treated at this dose level were considered, including 13 patients treated after MTD determination.
b No. of courses with specified grade of toxicity.
c F, febrile grade 4 neutropenia.
patients. At 185 mg/m² in the present study grade 3
toxicological adverse events were observed in less than 10% of (16). However, they were rarely severe: grade 3 and 4 derma-
ular lesions, swelling, burning, and desquamation) have been
tion. Dermatological effects (including erythema, dry skin, mac-
including a grade 4 dermatitis requiring prolonged hospitaliza-
was stopped at 185 mg/m² after observation of skin toxicities,
including a grade 4 dermatitis requiring prolonged hospitalization.
Dermatological effects (including erythema, dry skin, mac-
ular lesions, swelling, burning, and desquamation) have been
observed after administration of docetaxel at conventional doses (16). However, they were rarely severe: grade 3 and 4 derma-
tological adverse events were observed in less than 10% of
patients. At 185 mg/m² in the present study grade 3–4 derma-
titis was noted in about 20% of cycles.
Other DLTs included mucositis and also seemed to corre-
late with docetaxel dose. All these side effects have been fre-
quently reported at conventional doses but were almost always
moderate and nondose limiting.
Interestingly, such a toxicity profile was similarly de-
scribed in a recent pediatric study investigating dose escalation of
docetaxel with hematopoietic growth factor administration (12). This report determined 185 mg/m² as the MTD of do-
cetaxel with G-CSF support and, consistent with our results,
reported severe dermatitis as the main DLT. It is particularly
unusual and noteworthy that adult and pediatric Phase I trials of
doctaxel pharmacokinetics, even though they were not likely to
have a significant impact at the dose and administration schedule
used in routine clinical practice. They also suggested that in the
case of docetaxel dose escalation, such nonlinear processes might
contribute to an unexpected increase in patients systemic exposure
and thereby unexpected toxicities. As shown in Fig. 1, our results
suggest that at 175 mg/m² pharmacokinetics parameters remain
linear. Indeed, drug AUC, peak plasma, and plasma clearance
values were found to increase proportionally to dose escalation, as
compared with values previously published at doses ≥70 mg/m².
However, this conclusion is based on a retrospective comparison
between different studies and probably different patient popula-
tions. For instance, the large number of females in the present study
may lead to a slightly different pharmacokinetic profile than the
more sex-balanced initial Phase I studies. In our study, pharma-
kinetic analysis at intermediate dose levels would have been valu-

### Table 5  Multicycle exposure at the recommended (175 mg/m²)
docetaxel dose level

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Docetaxel dose course 1 (mg/m²)</th>
<th>Docetaxel dose course 2 (mg/m²)</th>
<th>Docetaxel dose course 3 (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>2</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>4</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>5</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>6</td>
<td>175</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>8</td>
<td>175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>175</td>
<td>175</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>11</td>
<td>175</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>14</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>15</td>
<td>175</td>
<td>175</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>175</td>
<td>175</td>
<td>175</td>
</tr>
</tbody>
</table>

### Table 6  Pharmacokinetics of 175 mg/m² docetaxel

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (µg/ml)</td>
<td>6.7</td>
<td>1.7</td>
<td>4.2–10.5</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>13.4</td>
<td>15</td>
<td>1.9–46.9</td>
</tr>
<tr>
<td>AUC (µg·h/ml)</td>
<td>9.7</td>
<td>4</td>
<td>5.4–18.3</td>
</tr>
<tr>
<td>Cl (l/h)</td>
<td>34.2</td>
<td>12</td>
<td>15.8–54</td>
</tr>
<tr>
<td>Vd (l)</td>
<td>122.7</td>
<td>124</td>
<td>24.7–378.4</td>
</tr>
</tbody>
</table>

* T½, terminal half-life; Cl, clearance; Vd, volume of distribution.

Fluid retention did not seem to increase significantly, even at the
highest dose level investigated and even in patients receiving
multiple cycles at full dose.

Clearly, the definition of hematologic DLT we selected (fever
and grade 4 neutropenia lasting more than 4 days) was rather
aggressive compared with common criteria (grade 4 neutropenia
without fever lasting more than 4 days or any febrile neutropenia).
However, we were in a clinical trial of high-dose chemotherapy,
and we considered acceptable the risk of febrile neutropenia easily
manageable by an antibiotic therapy of short duration.

Similarly, nonhematologic toxicities observed after multi-
ple exposure may strongly limit the use of this strategy in a
routine setting. Nevertheless, it might be interesting to evaluate
in future Phase II/III studies a strategy including a short induc-
tion of two or three cycles of 165–175 mg/m² docetaxel, fol-
lowed by 100 mg/m² on a more chronic basis. Of course, such
an approach should be reserved to a very selected population
with good performance status and no extensive prior treatment.

Pharmacokinetics of high-dose docetaxel was investigated for
the first time in this study. At conventional doses, there is clear
evidence that the disposition of docetaxel is linear with dose (8, 17–19). This contrasts with the nonlinear pharmacokinetic profile
of paclitaxel (20). As expected, such a nonlinear profile (i.e., a
disproportionate increase in AUC in relation to increased dose) was
also observed after high-dose paclitaxel. In Phase I dose-finding
studies, the pharmacokinetics profile of docetaxel at doses
≥70 mg/m² was consistent with a three-compartment model, with
peak plasma and AUC values being proportional to dose. Data
from McLeod et al. (21), using a nonlinear three-compartment
model, suggested that nonlinear processes may be involved in
doctaxel pharmacokinetics, even though they were not likely to
have a significant impact at the dose and administration schedule
used in routine clinical practice. They also suggested that in the
case of docetaxel dose escalation, such nonlinear processes might
contribute to an unexpected increase in patients systemic exposure
and thereby unexpected toxicities. As shown in Fig. 1, our results
suggest that at 175 mg/m² pharmacokinetics parameters remain
linear. Indeed, drug AUC, peak plasma, and plasma clearance
values were found to increase proportionally to dose escalation, as
compared with values previously published at doses ≥110 mg/m².
However, this conclusion is based on a retrospective comparison
between different studies and probably different patient popula-
tions. For instance, the large number of females in the present study
may lead to a slightly different pharmacokinetic profile than the
more sex-balanced initial Phase I studies. In our study, pharma-
kinetic analysis at intermediate dose levels would have been valu-

![Fig. 1](image-url)
able, especially to confirm the apparent linear behavior we observed. Unfortunately, it was not scheduled in the initial trial design. Thus, confirmatory studies are needed.

At the preclinical and biological levels, there is a debate regarding the dose response of taxanes beyond a plateau concentration (22). Alteration of microtubule-dependent processes, especially mitotic microtubule dynamics, have been found to represent the main biological substratum of the potent antiproliferative activity of docetaxel as well as other antimicrotubule agents (23). In most cancer cell lines, these effects are observed when cells are treated at docetaxel concentration of 10–500 nM, a plasma concentration that is easily reached in patients when docetaxel is administered at conventional doses. However, several other cellular effects, not clearly or directly related to the antimicrotubule properties, including gene activation or mitochondria-dependent proapoptotic processes have been described in vitro following treatment with taxanes (24–26). These effects were observed at substantially higher concentration (several micromolars), suggesting that an increase in the docetaxel dose (and thereby in the plasma concentration) may result in activating alternative apoptotic pathways, resulting in optimizing antitumor effects.

As demonstrated in several Phase II studies involving breast cancer patients (4), docetaxel monotherapy at a conventional dose (100 mg/m²) was able to induce an impressive response rate (ranging from 55–70%). However, the complete response rate still remained relatively low, ranging from 5–15%. In this study, we demonstrated that an increase in dose by a factor 1.75 is feasible. Such an increase may be considered as moderate but may be sufficient to activate nonclassical apoptotic pathways and overcome drug resistance in cancer cells and ultimately improve the complete response rate. Because the complete response rate represents the most critical prognostic factor for survival in cancer treatment, this hypothesis deserves to be tested in future Phase II/III studies.

REFERENCES

Phase I and Pharmacokinetic Study of Escalating Dose of Docetaxel Administered with Granulocyte Colony-stimulating Factor Support in Adult Advanced Solid Tumors


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/9/1/102

Cited articles
This article cites 25 articles, 10 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/9/1/102.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/9/1/102.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.