A Phase I and Pharmacokinetic Study of Docetaxel Administered in Combination with Continuous Intravenous Infusion of 5-Fluorouracil in Patients with Advanced Solid Tumors

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ABSTRACT

Encouraged by preclinical synergism between docetaxel and 5-fluorouracil (5FU), we conducted a Phase I study of docetaxel in combination with continuous i.v. infusion of 5FU in patients with advanced solid tumors to determine the maximum tolerated dose, the recommended dose for Phase II studies, and the safety and pharmacokinetic profiles of this combination. Forty-two patients with advanced solid tumors, most of whom had been previously treated, received docetaxel on day 1 as a 1-h i.v. infusion, immediately followed by a 5-day continuous i.v. infusion of 5FU, every 3 weeks without hematopoietic growth factor support. All patients were premedicated with methylprednisolone. Dose levels of docetaxel/5FU studied were (daily dose, in mg/m²) 60/300, 75/300, 75/500, 75/750, 85/750, 85/1000, and 75/1000. Forty-one patients were assessable for toxicity. The maximum tolerated dose determined during the first cycle was 1000 mg/m²/day for 5 days of 5FU with either 75 or 85 mg/m² docetaxel. Dose-limiting toxicities at these dose levels were reversible secretory diarrhea (4 of 12 evaluable patients), stomatitis (2 patients), and febrile neutropenia (2 patients). Overall, grade 3/4 neutropenia and febrile neutropenia were seen in 63.4% and 9.8% of the patients, respectively.

Four patients experienced grade 3/4 infection, which led to toxic death in one of them. There were five early deaths: (a) one was clearly treatment related; (b) two others were possibly treatment related or remotely treatment related; and (c) two deaths were not related to the study drugs. Partial responses were documented in 5 of 39 evaluable patients. Pharmacokinetic results of both drugs were consistent with those from single-agent studies. The recommended dose of this combination, which showed acceptable toxicity and antitumoral activity at various dose levels, is 85 mg/m² day of docetaxel given as a 1-h i.v. infusion on day 1 immediately followed by a 5-day continuous i.v. infusion of 5FU (750 mg/m²/day). This study has been extended by adding cisplatin on day 1 of the combination of docetaxel and 5FU.

INTRODUCTION

Docetaxel (Taxotere, RP 56976; Rhône-Poulenc Rorer) is a semisynthetic compound belonging to the taxoid family. Docetaxel is obtained from a precursor (10-deacetyl baccatin III) extracted from the needles of the European yew tree, Taxus baccata. Docetaxel enhances microtubule assembly and inhibits the depolymerization of tubulin, which leads to an accumulation of microtubule bundles in the cell and a subsequent mitotic block in the M-phase of cell division.

In Phase I studies, neutropenia has been shown to be the major DLT of docetaxel (1). Neutropenia, which appeared upon treatment with >50 mg/m² docetaxel and occurred in the majority of patients treated with 100 mg/m² docetaxel, was most often of brief duration, noncumulative, and rarely complicated by fever or infection (1). Other side effects included fluid retention, asthenia, alopecia, hypersensitivity reactions, and skin and nail toxicities. Mucositis was a DLT or at least a significant toxicity only in protracted (i.e., 6- or 24-h) infusion or repeated (day 1–day 5) infusion schedules of docetaxel (1–3). In monotherapy, the recommended docetaxel dose for Phase II trials is 100 mg/m², given as a 1-h i.v. infusion every 3 weeks (1, 3, 4). Docetaxel has been registered in the treatment of breast cancer and is also presently undergoing Phase III evaluation in other tumor types.

5FU is an antimetabolite drug with a broad range of antitumor activity in breast, gastrointestinal, head and neck, and ovarian cancers. When given as a prolonged continuous i.v. infusion, stomatitis and diarrhea are the principal DLTs, whereas myelosuppression is more commonly observed with...
i.v. bolus injections (5). Because 5FU has a demonstrated synergistic interaction with many antineoplastic agents, it is currently most often administered in the setting of combination chemotherapy regimens.

The preclinical cytotoxic effect of docetaxel, the significant laboratory and clinical antitumoral activity of both docetaxel and 5FU in the same type of diseases (breast, gastrointestinal, and head and neck cancers), their synergistic activity in vivo, and the relative lack of overlapping toxicities were the rationale for the design of the present combination.

Here we report the results of a Phase I study in which docetaxel was administered as a 1-h i.v. infusion on day 1, in combination with 5FU given as a continuous i.v. infusion from day 1 to day 5. The primary objectives were to determine the MTD and the recommended dose for Phase II trials. The characterization of the safety and pharmacokinetic profiles and the assessment of any antitumor activity of this combination were secondary objectives of this trial.

MATERIALS AND METHODS

Eligibility. Patients registered in this trial were treated and followed at the Institut Jules Bordet, Brussels, Belgium. To be eligible, patients had to meet the following criteria: (a) histologically or cytologically confirmed diagnosis of solid tumor; (b) advanced disease that had become refractory to conventional effective therapy or for which no standard therapy exists; (c) no chemotherapy or radiotherapy within 4 weeks of study entry (no treatment with nitrosourea, mitomycin C, or carboptatin within 6 weeks of study entry and no treatment with concomitant use of HGF within 8 weeks of study entry); (d) no previous radiotherapy to major bone marrow areas (e.g., >20% of bone marrow); (e) age between 18 and 75 years; (f) complete recovery from toxic effects of previous antitumor therapy; (g) WHO PS ≤ 2; (h) life expectancy of >12 weeks; (i) adequate bone marrow (absolute neutrophil count > 2,000/μl, platelet count > 100,000/μl), hepatic (total bilirubin ≤ 1.25× the upper normal limit, aspartate aminotransferase ≤ 2× the upper normal limit or ≤ 3× the upper normal limit if proven hepatic metastases were present), and renal (serum creatinine < 120 μmol/liter) function; and (j) written informed consent. Exclusion criteria included: (a) brain and leptomeningeal involvement; (b) symptomatic peripheral neuropathy of grade 2 according to the NCI criteria; (c) any coexisting serious medical condition; (d) prior steroid therapy at high dose (≥20 mg of prednisone or an equivalent) for less than 6 months; (e) prior high-dose chemotherapy supported by prophylactic HGF; and (f) prior treatment with docetaxel. This protocol was approved by the local ethics committee.

DLT and MTD. Toxicities were evaluated according to the NCI common toxicity criteria. DLTs were defined as follows: (a) grade 4 neutropenia lasting longer than 7 days; (b) grade 3–4 neutropenia with a grade ≥2 fever lasting >3 days; (c) grade 4 thrombocytopenia; and (d) grade >2 nonhematological toxicity except for vomiting and alopecia. Patients who experienced grade >2 vomiting, diarrhea, or mucositis after the first course were subsequently treated with a prophylactic regimen. Grade >3 nausea/vomiting or grade >2 diarrhea were considered as DLTs only if they were observed despite adequate supportive measures. The MTD was defined as the dose level at which at least three of six patients developed any DLT during the first course.

Drug Administration and Dose Escalation Procedure. Docetaxel was given as a 1-h i.v. infusion on day 1, immediately followed by 5FU, which was given as a 120-h continuous i.v. infusion because of the potentially nonoverlapping toxicity of 5FU using this schedule. Docetaxel was provided as a 2-ml solution containing 40 mg/ml docetaxel in polysorbate 80 and was first mixed with a solvent solution of ethanol 95%. The premix solution was reconstituted in 5% dextrose, the volume of which was adjusted to achieve a final docetaxel concentration of ≤1 mg/ml. Docetaxel was administered through a peristaltic pump as a 1-h i.v. infusion on day 1 every 21 days, starting at 60 mg/m², a dose at which complicated neutropenia is uncommon (6). 5FU was given immediately after the docetaxel infusion as a continuous i.v. infusion for 5 days, every 21 days, at a starting dose of 300 mg/m²/day. At this dose of 5FU, in a combination study with low-dose cisplatin (7), only mild to moderate leukopenia had been observed with occasional thrombocytopenia. 5FU was reconstituted in 2 liters of 5% dextrose and administered through a peristaltic pump. All patients were hospitalized during their first treatment course. If patients showed an acceptable tolerance during the first course, the subsequent cycles on days 2–5 were administered on an outpatient basis. For these patients, 5FU was given as an i.v. continuous infusion through a portable pump (IVAC, Pharmacia, San Diego, CA). When possible, patients were given their treatment through a fully implantable system. Oral prophylactic premedication with methylprednisolone was given to all patients according to the following schedule: 32 mg, 12 h and 3 h before docetaxel and twice daily after docetaxel infusion for 4 days. No other prophylactic treatment (including mouthwashes, antibiotics, antifungal agents, HGF, and antiemetics) was planned during the first course. However, when nausea, vomiting, or mucositis were reported, curative treatment was given, and prophylactic measures were taken for the subsequent cycles. The treatment was repeated every 3 weeks, depending on the toxicities encountered. No intrapatient dose escalation was allowed.

When toxicity occurred, treatment was delayed until recovery to grade <1 (except for anemia and alopecia) and then restarted for the subsequent courses at the same dose level or with dose modification (e.g., a lower dose level) according to the observed toxicity and the physician’s decision. Patients were scheduled to receive at least two cycles of therapy except in cases of disease progression, unacceptable toxicity, or patient refusal. The following dose levels of docetaxel/5FU were investigated (daily dose, mg/m²): (a) 60/300; (b) 75/300; (c) 75/500; (d) 75/750; (e) 85/750; (f) 85/1000; and (g) 75/1000.

Patient Monitoring. The pretreatment patient evaluation included a medical history and physical examination, a complete blood count with differential serum biochemistry, urinalysis (dipstick), electrocardiogram, chest X-rays, and a radiological evaluation of measurable or evaluable disease (by X-rays, computed tomography scan, or ultrasonography). While on treatment, patients were monitored as follows: (a) history and physical examination 10 days after the first cycle and before each subsequent cycle; (b) weekly hematological evaluation (every 2
days in case of grade 4 neutropenia or febrile neutropenia); (c) blood biochemistry on day 21 of each cycle; and (d) urinalysis and chest X-rays every 3 weeks. An electrocardiogram was repeated before each docetaxel infusion. Fluid retention symptoms were recorded as mild, moderate, or severe according to the clinical tolerance and the need for therapeutic intervention. The presence of measurable or evaluable lesions was not required in this study. However, in patients with measurable disease at study entry, assessment of tumoral lesions was performed every two cycles on therapy and every 3 months on follow-up visits for patients who went off-study for reasons other than progressive disease. To be considered evaluable for response, patients had to receive a minimum of two cycles of treatment with at least one follow-up tumor assessment, unless early disease progression was observed. Response was defined according to standardized WHO criteria. After withdrawal from the study, patients were followed until death.

Pharmacokinetics. Pharmacokinetics of docetaxel and 5FU were examined during the first cycle. Blood samples were collected through an indwelling catheter inserted in the arm (in the opposite arm in case of drug administration through peripheral veins). At least one patient per dose level was studied. Five-ml blood samples were collected for docetaxel in heparinized tubes at the following time points: (a) immediately before docetaxel infusion; (b) 30 min after the initiation of docetaxel infusion; (c) 5 min before the end of docetaxel infusion; and (d) 15, 30, 45, 60, and 90 min and 2, 4, 8, 12, 20, 24, and 30 h after the end of docetaxel infusion. For 5FU pharmacokinetics, 5 ml of blood were taken into EDTA tubes at the following time points: (a) immediately before 5FU infusion; (b) 30 and 60 min and 2, 8, 24, 30, 48, 54, 72, 78, 96, and 120 h after the beginning of 5FU infusion; (c) at the end of 5FU infusion; and (d) 15, 30, 45, and 60 min and 2 and 3 h after the end of 5FU infusion. All blood samples were centrifuged within 30 min at 1250 × g for 15 min at 6°C–8°C and stored at −20°C. Additionally, urine was collected by 6-h fractions on day 1 and by 12-h fractions from time 24 h to time 132 h. The total volume was collected, and two aliquots of 10 ml were stored at −20°C in darkness until high-performance liquid chromatography analysis. Docetaxel concentrations in plasma and urine were determined by using the method described by Vergniol et al. (8), with slight modifications. The modifications were mainly done in the solid-phase extraction procedure, which was performed on Bond Elut C18 ethyl columns (100 mg/1 ml; Varian, Harbor City, CA) using a Vac Elut SPS 24 system (Varian). The columns were conditioned with 1 ml of methanol and 1 and 0.5 ml of 0.3% ortho-phosphoric acid. After applying the sample (1 ml of plasma or 2 ml of urine), the columns were rinsed with 1 ml of 0.3% ortho-phosphoric acid and washed with 1 ml of methanol/0.3% ortho-phosphoric acid (50:50, v/v). Docetaxel was eluted with 0.3 ml of methanol/0.3% ortho-phosphoric acid (90:10, v/v), and 0.1-ml aliquots were injected into the high-performance liquid chromatography system consisting of a Model 510 M pump, a Model 717 Plus autosampler, and a 484 spectrophotometer operating at 227 nm (Waters, Milford, MA). The analytical column was a stainless steel Nova Pak C18 cartridge (4 μm; 4.6 × 250 mm, inside diameter) preceded with a Nova Pak C18 Guard-Pak precolumn insert (Waters). The mobile phase consisting of methanol/0.3% ortho-phosphoric acid (670/330, v/v) was delivered at 1 ml/min. The integration of peak heights was performed using the Maxima 820 Baseline program (Waters). The limit of quantitation of the method was 10 ng/ml. The between-day (n = 30) accuracy of quality control samples was 0.6% (for 50 ng/ml) and −1.1% (for 1000 ng/ml). The intraday reproducibility was 8.3% (for 50 ng/ml) and 2.8% (for 1000 ng/ml).

FU concentrations in plasma were determined according to the method of Christophidis et al. (9). The limit of quantitation of the method was 20 ng/ml. The between-day (n = 24) accuracy of quality control samples was 11% (for 50 ng/ml), −4.4% (for 100 ng/ml), and −1.5% (for 1000 ng/ml). The intraday reproducibility was 14.2% (for 50 ng/ml), 7.2% (for 100 ng/ml), and 5.8% (for 1000 ng/ml).

Docetaxel pharmacokinetic parameters were obtained with the ADAPT II program using weighted, iterative, nonlinear least squares regression (10). Parameter estimation was repeated independently 10 times with randomized initial estimates, chosen randomly and independently in the interval 0–2 μ, where μ is the population estimate for that parameter given by Bruno et al. (11). Model discrimination between two- and three-compartment models was done using Akaike’s Information Criterion (12). The 5FU AUC was obtained by the trapezoidal rule. Regression analysis was performed to correlate the pharmacokinetic parameters of docetaxel and 5FU with biological and clinical outcomes.

RESULTS

Patient Characteristics. Forty-two patients were enrolled into the study. Table 1 summarizes characteristics of the 41 evaluable patients. Indeed, one patient (included at dose level 85 mg/m2 docetaxel/1000 mg/m2 5FU) was not evaluated for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of evaluable patients</td>
<td>41*</td>
<td></td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>53 (28–72)</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>18:23</td>
<td></td>
</tr>
<tr>
<td>WHO PS</td>
<td>1 (0–2)</td>
<td></td>
</tr>
<tr>
<td>Prior treatment</td>
<td>34</td>
<td>82.9</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>27</td>
<td>65.9</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1 (1–3)</td>
<td></td>
</tr>
<tr>
<td>Median no. of prior regimens (range)</td>
<td>26</td>
<td>63.4</td>
</tr>
<tr>
<td>Tumor types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>Gynecological tumor (4, cervix; 2, endometrium; 2 ovary)</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>Gastrointestinal tumor (5, esophagus; 2, pancreas, 1 stomach)</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>Head and neck tumor</td>
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<td>14.6</td>
</tr>
<tr>
<td>Carcinoma of unknown origin</td>
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<td>9.8</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>3</td>
<td>7.3</td>
</tr>
<tr>
<td>Non-small cell lung carcinoma</td>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>6</td>
<td>14.6</td>
</tr>
<tr>
<td>Metastatic</td>
<td>32</td>
<td>78.0</td>
</tr>
<tr>
<td>Primary</td>
<td>3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

* One patient was removed from analysis due to loss of follow-up immediately after the first infusion.
safety due to loss to follow-up immediately after the first infusion, after having refused further treatment. The median age was 53 years (range, 28–72 years). As requested before study entry, no patient had a WHO PS > 2 (median PS, 1; range, 0–2). Seventy-eight percent of patients had metastatic disease. The majority (82.9%) of the patients had received prior chemotherapy and/or radiotherapy. The most common tumor types were breast (19.5%), gynecological (19.5%), gastrointestinal (19.5%), and head and neck (14.6%) cancers. Among previously untreated patients, three suffered from an adenocarcinoma of unknown origin, two had advanced pancreatic carcinoma, one had a retroperitoneal sarcoma secondary to radiotherapy, and one presented with a metastatic head and neck squamous cell carcinoma.

**DLTs and MTD after the First Cycle.** The number and type of DLTs that occurred after the first cycle in the 41 patients evaluable for toxicity are illustrated in Table 2 according to each dose level. At level 60 mg/m² docetaxel/300 mg/m² 5FU, one patient experienced DLT that consisted of severe but brief diarrhea and concomitant asthenia. No DLT was observed at level 75 mg/m² docetaxel/300 mg/m² 5FU. At level 75 mg/m² docetaxel/500 mg/m² 5FU, further patient accrual was needed because the first three patients entered were given pre-emptive mouthwashes, despite protocol recommendations. Of the 10 patients treated at this dose level, 2 patients required hospitalization due to grade 3 infection (pneumonia). Given that non-dose-limiting neutropenia predominated and that mucositis was not systematic, the decision was made to increase the 5FU dose to the next dose level while maintaining the docetaxel dose at 75 mg/m². At this level, 75 mg/m² docetaxel/750 mg/m² 5FU, one of six patients experienced febrile neutropenia with concomitant grade 3 stomatitis. At level 85 mg/m² docetaxel/750 mg/m² 5FU, no DLT was observed. Of the seven evaluable patients enrolled at level 85 mg/m² docetaxel/1000 mg/m² 5FU, one had grade 3 diarrhea with concomitant febrile neutropenia, one had grade 3 diarrhea, one had grade 4 diarrhea, and one had grade 3 stomatitis. Given the toxicity profile at 85 mg/m² docetaxel/1000 mg/m² 5FU, it was decided to reduce the dose of docetaxel to 75 mg/m² while maintaining the dose of 5FU at 1000 mg/m².

At level 75 mg/m² docetaxel/1000 mg/m² 5FU, three of five patients experienced DLT. Febrile neutropenia with grade 4 thrombocytopenia was observed in one patient, which led to a dose reduction of 5FU in subsequent courses. The two other patients experienced grade 3 diarrhea and grade 3 stomatitis, respectively. From the above-mentioned toxicities, MTDs were defined as dose levels 75 mg/m² docetaxel/1000 mg/m² 5FU and 85 mg/m² docetaxel/1000 mg/m² 5FU, and the recommended dose level was 85 mg/m² docetaxel/750 mg/m² 5FU.

**Overall Toxicity.** The median number of cycles given per patient was 3 (range, 1–10), with a total of 170 cycles administered throughout the study. Neutropenia was the main hematological toxicity because it was observed in 87.8% of the patients. Grade 4 neutropenia occurred in 53.7% of the patients but was not encountered after the first cycle below dose level 75 mg/m² docetaxel/500 mg/m² 5FU. A cumulative effect of the study drugs on neutropenia was not clearly observed, because no courses of chemotherapy had to be delayed because of slow recovery of neutropenia. However, two patients included at dose levels 75 mg/m² docetaxel/1000 mg/m² 5FU and 85 mg/m² docetaxel/1000 mg/m² 5FU had a dose reduction (from 75 mg/m² docetaxel/1000 mg/m² 5FU to 75 mg/m² docetaxel/750 mg/m² 5FU and 85 mg/m² docetaxel/1000 mg/m² 5FU to 75 mg/m² docetaxel/750 mg/m² 5FU, respectively) after the first cycle because of febrile neutropenia. Overall, febrile neutropenia was observed in 9.8% (4 of 41) of the patients and 2.4% (4 of 170) of the cycles. Brief and noncomplicated grade 4 thrombocytopenia was recorded in two patients. Anemia, which was present in 92.7% of the patients, was graded 3/4 in 19.5% of them. However, 26 (63.4%) patients had grade 1/2 anemia at study entry. Grade 3/4 infection was seen in four patients, three of whom had concomitant grade 4 neutropenia.

The most frequent nonhematological toxicities consisted of stomatitis, asthenia, diarrhea, and nausea. Grade 3 stomatitis, which was first seen with a daily 5FU dose of 750 mg/m² (dose level 75 mg/m² docetaxel/750 mg/m² 5FU), occurred in 14.6% of the patients. However, no grade 4 stomatitis was observed. Asthenia was severe in seven patients. Although it was difficult to differentiate treatment-related asthenia from disease-related

### Table 2 DLTs

<table>
<thead>
<tr>
<th>Dose level (Docetaxel/5FU)</th>
<th>Patients/ cycles</th>
<th>After the first cycle (grade/severity-no. of patients)</th>
<th>After all courses (No. of patients/no. of cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60/300</td>
<td>4/9</td>
<td>Diarrhea (III) and asthenia (severe-1)</td>
<td>Grade 3/4 infection</td>
</tr>
<tr>
<td>75/300</td>
<td>3/18</td>
<td></td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>75/500</td>
<td>10/48</td>
<td>Infection (III-2)</td>
<td>Grade 3/4 stomatitis</td>
</tr>
<tr>
<td>75/750</td>
<td>6/28</td>
<td>Febrile neutropenia and stomatitis (III-1)</td>
<td>Grade 3/4 diarrhea</td>
</tr>
<tr>
<td>85/750</td>
<td>6/30</td>
<td></td>
<td>Severe asthenia</td>
</tr>
<tr>
<td>85/1000</td>
<td>7/22</td>
<td>Febrile neutropenia and diarrhea (III-1)</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 stomatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe asthenia</td>
</tr>
<tr>
<td>75/1000</td>
<td>5/15</td>
<td>Febrile neutropenia and thrombocytopenia (IV-1)</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 stomatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe asthenia</td>
</tr>
</tbody>
</table>

* Fever ≥ grade 2 with concomitant grade 3/4 neutropenia requiring hospitalization and/or i.v. antibiotics.
* Dose reduction for one patient to level 75/750.
* Dose reduction for one patient to level 85/750.
asthenia, that symptom did not lead directly to treatment discontinuation in any of the patients. Among the 41 patients evaluable for overall toxicity, 27 (65.9%) experienced diarrhea. Diarrhea of grade 3/4 occurred at dose level 60 mg/m² docetaxel/300 mg/m² 5FU (one patient), 75 mg/m² docetaxel/1000 mg/m² 5FU (one patient), and 85 mg/m² docetaxel/1000 mg/m² 5FU (three patients). One of these patients, entered at level 85 mg/m² docetaxel/1000 mg/m² 5FU, experienced grade 4 diarrhea that required hospitalization for i.v. hydration and loperamide administration. This episode started on day 8 after drug administration and fully resolved after 7 days of medical support. Concomitant neutropenia was observed from days 9–11. In the four remaining patients, grade 3 diarrhea started within 12 days after initiation of therapy and was concomitant to grade 3/4 neutropenia in three of them. Neutropenic enterocolitis could not be demonstrated in any of the patients who experienced diarrhea.

Grade 3 nausea occurred in 7.3% of the patients. No grade 3 or grade 4 vomiting events were seen. Mild to moderate fluid retention was observed in five (12.2%) patients but did not lead to initiation of a specific treatment or to discontinuation of the study drugs. However, at level 75 mg/m² docetaxel/1000 mg/m² 5FU, the worsening of a preexisting grade 2 neuropathy and concomitant leg edema contributed to the decision to remove a patient with stable disease from the study after two courses. No grade 3/4 skin toxicities were recorded. No significant allergic reactions occurred. The overall incidence of the most important DLT is summarized in Table 2.

Five patients died within 30 days of the last infusion. Pneumonia complicated by a septic syndrome during neutropenia led to toxic death after the third cycle in one patient with recurrent esophageal carcinoma, included at dose level 60 mg/m² docetaxel/300 mg/m² 5FU. One other patient died from pneumonia. In the latter patient, infection was considered to be remotely related to the study drugs because it occurred after recovery from neutropenia. A third patient, who had metastatic cervix carcinoma, was found dead on day 10 of the first course while still hospitalized for fever, positive blood cultures, and antibiotic administration. The autopsy did not allow further clarification of the cause of death (septic shock or cardiac dysrhythmia). No neutropenia had been observed at the last blood cell count performed on day 7. One patient died from disease progression. Tumor lysis syndrome led to death in one patient on cisplatin-based rescue therapy after removal from the study because of disease progression.

There were multiple reasons for therapy discontinuation. Progressive disease was observed in 23 (56.1%) patients. Fourteen (34.1%) patients who had stable disease or PR were withdrawn in the absence of further benefit expected from the treatment. One patient with stable disease was lost to follow-up after the sixth treatment cycle. As described previously, four patients died while on study.

**Antitumor Activity.** Thirty-nine patients were evaluable for response to treatment. Three patients were excluded from the efficacy analysis for the following reasons: (a) loss to follow-up after the first course; (b) early death; and (c) inevaluable liver infiltration. PR was observed in five patients. The response rate is therefore 12.8% (95% confidence interval, 4.3–27.4%). Thirteen patients had stable disease. One partial responder with previously untreated metastatic head and neck carcinoma who entered the study at level 85 mg/m² docetaxel/1000 mg/m² 5FU received a total of eight cycles of the study drugs and experienced a PR of 33+ weeks. A second patient (level 85 mg/m² docetaxel/750 mg/m² 5FU) with metastatic head and neck carcinoma previously managed with surgery and radiotherapy received a total of eight cycles and experienced a PR for 32+ weeks. Partial regression of liver metastasis (duration, 44 weeks) was observed in one additional patient (level 75 mg/m² docetaxel/500 mg/m² 5FU) with heavily pretreated breast carcinoma who received a total of 10 courses. At level 75 mg/m² docetaxel/1000 mg/m² 5FU, a PR was seen in a fourth patient with metastatic esophageal cancer that progressed after 31 weeks. At level 85 mg/m² docetaxel/1000 mg/m² 5FU, one patient with abdominal liposarcoma previously treated with surgery, radiotherapy, and chemotherapy (high-dose Adriamycin), who had progressive disease at study entry, achieved a PR that lasted 37 weeks. Minor responses were seen in two additional patients with metastatic esophageal cancer and metastatic cervix adenocarcinoma, respectively.

**Pharmacokinetics.** Docetaxel and 5FU pharmacokinetics were obtained in the first cycle in 27 and 21 patients, respectively. The major pharmacokinetic parameters are listed in Table 3. The overall clearance of docetaxel across all dose levels (mean ± SD) was 34 ± 12 liters/h/m². Docetaxel clearances show an unusually large interpatient variability over the tested dose levels. Docetaxel clearance seemed to decrease with increasing doses of 5FU (α < 1%, using a Kruskal-Wallis test to determine significant median differences between groups defined by 5FU dose and ignoring the docetaxel dose level here). However, the observed variations of docetaxel clearance were highly correlated (R > 0.93) with variations of the Cₚₑᵃᵏ of docetaxel, and the docetaxel Cₚₑᵃᵏ also seemed to decrease significantly with increasing doses of 5FU, which is unlikely to be related to 5FU, given the sequence of administration. The pharmacokinetic interpatient variability of docetaxel was not ascribed to variable hepatic function within patients because normal or minimally altered liver function tests were an absolute requirement before study entry (13). Accordingly, the docetaxel AUC was not found to be higher in patients with hepatic metastasis. Urine excretion was minimal (<4%), as reported previously for docetaxel in monotherapy (2). The clearance of 5FU across all dose levels (mean ± SD) was 149.2 ± 42.5 liters/h/m². The variation in 5FU clearance over the docetaxel dose levels was not statistically significant (as evaluated by a Kruskal-Wallis test, grouping 5FU clearance values by docetaxel dose level here). A large interpatient variability in 5FU clearance was also observed, but results were within the range usually described (5). A linear correlation was found between 5FU dose and 5FU AUC (R > 0.73). At the highest 5FU doses (1000 mg/m²), mean docetaxel clearance values (mean ± SD, 23.1 ± 9.4 liters/h/m²) were similar to those observed for single-agent docetaxel (6). Pharmacodynamic modeling relating the percentage decrease in absolute neutrophil count and the incidence and severity of mucositis and diarrhea to docetaxel AUC and 5FU AUC was performed, but no significant correlation was seen.


**Table 3: Pharmacokinetic results (mean ± SD; n = 27)**

<table>
<thead>
<tr>
<th>Docetaxel</th>
<th>5FU</th>
<th>AUC_{0-24h}</th>
<th>CLT</th>
<th>AUC_{0-5 days}</th>
<th>CLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg/m²</td>
<td>300 mg/m²</td>
<td>1.6 ± 0.2</td>
<td>21.8 ± 6</td>
<td>3.3 ± 0.6</td>
<td>10.6 ± 1.0</td>
</tr>
<tr>
<td>75 mg/m²</td>
<td>300 mg/m²</td>
<td>2.4 ± 0.3</td>
<td>26.0 ± 4.4</td>
<td>4.4 ± 0.9</td>
<td>17.1 ± 5.3</td>
</tr>
<tr>
<td>85 mg/m²</td>
<td>1000 mg/m²</td>
<td>3.1 ± 0.3</td>
<td>24.0 ± 2.8</td>
<td>3.6 ± 0.4</td>
<td>17.0 ± 5.3</td>
</tr>
</tbody>
</table>

**Notes:**

- \( V_c \): apparent volume of central compartment.
- CLT: clearance.
- CLT: clearance.
- AUC: area under the curve.
- Doses are in mg/m².
- Number of patients for whom pharmacokinetics of docetaxel or 5FU was performed.
- Simulated concentration at the end of a 1-h infusion at the docetaxel dose level received.
- Percentage of the dose administered recovered in the urine during the first 24 h.
- Two patients with unexpectedly high docetaxel concentration.

**DISCUSSION**

Docetaxel has demonstrated activity in breast cancer, non-small cell lung carcinoma, head and neck tumors, gastric carcinoma, ovarian cancer, and pancreatic cancer (1, 14–17). Its unique mechanism of action, its activity in a broad range of tumors, its synergistic interaction with a variety of major cytotoxic drugs, and its predictable toxicity profile make it an attractive compound for combination regimens (18, 19).

Based on our results, the recommended daily doses for Phase II studies of the association of docetaxel (day 1) and 5FU (in continuous i.v. infusion from day 1–5) are 85 mg/m² and 750 mg/m²/day, respectively. DLTs included complicated neutropenia, mucositis, and reversible secretory diarrhea, the latter of which occurred particularly at the highest dose level of 5FU. It is noteworthy that significant diarrhea may occur after 5FU in monotherapy and, to a lesser extent, after docetaxel in monotherapy (5, 20). Diarrhea was also a significant toxicity in two other Phase I trials of docetaxel with 5FU (21, 22). However, in an additional report, diarrhea was not a prominent toxicity, despite the fact that the same MTD of docetaxel and 5FU was reached (23). Diarrhea has also been reported in combination studies of docetaxel and cisplatin (24).

Hematological toxicity was significant but manageable. In particular, at the recommended dose level 85 mg/m² docetaxel/750 mg/m² 5FU, 30 cycles of docetaxel and 5FU could be safely administered despite a high incidence of neutropenia, and no febrile neutropenia was observed. It is doubtful that prophylactic use of HGF would be beneficial after docetaxel and 5FU administration because nonhematological toxicities that are not systematically related to neutropenia have been significant.

No dose-limiting edema, skin toxicity, or neuropathy was observed, even in the 20 patients who received at least four cycles of the study drugs. With stomatitis and diarrhea, asthenia was the most frequent nonhematological toxicity observed. It must be taken into account that the disease progression observed in the majority of our patients could account in part for worsening asthenia, which, by itself, never led to treatment discontinuation.

Results of combinations of docetaxel with other chemotherapy agents have been reported in treatment of various tumor types and with different schedules (24–31). In these studies, the recommended dose of docetaxel ranged from 50–85 mg/m², whereas the recommended dose of 5FU was 300 mg/m²/day in bolus and ranged from 500-1000 mg/m²/day in continuous i.v. infusion (Table 4). As observed in our study, the most frequent DLTs observed were diarrhea, stomatitis, and neutropenia or its complications (21–23, 32).

A large interpatient variability in docetaxel pharmacokinetic parameters was found in this report. This variability could not be explained by parameters such as age, tumor type, renal function, or liver enzyme levels. An apparent decline in docetaxel clearance was noted with increasing doses of 5FU. However, the docetaxel clearance observed at the highest 5FU dose (1000 mg/m²/day) was similar to its clearance in monotherapy, which is a strong argument against any pharmacological influence of 5FU on docetaxel (6). Moreover, because the variability in docetaxel clearance can be ascribed largely to variations of the \( C_{peak} \) and because 5FU infusion follows the
docetaxel infusion, it is unlikely that the decline in docetaxel clearance is related to 5FU in this study. The apparent increase in the third half-life of docetaxel concentration, the most likely to be influenced by 5FU in our design, in parallel with increasing doses of 5FU did not reach a statistically significant level. Pharmacokinetic parameters that we have found for 5FU in combination are in the same range that has been shown for this drug in monotherapy (5). The variation in 5FU clearance over the docetaxel dose levels was not statistically significant. There is no argument in the literature suggesting a possible interaction between docetaxel and 5FU during their respective metabolism (33, 34). Based on these considerations, it is unlikely that there is substantial interaction between docetaxel and 5FU when they are administered as described in this study. This is consistent with the findings of Vernillet et al. (35), who reported the absence of relevant interaction between 5FU and docetaxel in their combination study over the tested dose levels. Furthermore, no relevant pharmacokinetic interactions were reported in combination studies of docetaxel with chemotherapy agents other than 5FU (11).

Responses observed at various dose levels suggest that the combination of docetaxel and 5FU could be of interest in the treatment of several tumor types, particularly head and neck carcinoma. Preliminary results of other studies of docetaxel and 5FU also indicate activity (21, 22, 35).

In the majority of reports in which docetaxel was used in combination regimens, docetaxel-specific toxicities (fluid retention, allergic reactions, and skin and nail changes) were not a clinical issue and did not lead to treatment discontinuation. In most of the combination regimens, as well as in our study, a high dose of docetaxel, which is active in monotherapy, could be administered. This emphasizes the fact that docetaxel has a predictable toxicity profile that supports its use in combination with a variety of active anticancer drugs. Our results prompted us to extend this Phase I study by adding cisplatin on day 1 of the combination of docetaxel and 5FU. This tritherapy is susceptible to be more active, especially in diseases such as head and neck, gastric, and breast cancers (36).

ACKNOWLEDGMENTS

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A Phase I and Pharmacokinetic Study of Docetaxel Administered in Combination with Continuous Intravenous Infusion of 5-Fluorouracil in Patients with Advanced Solid Tumors

Eric Van Den Neste, Dominique de Valeriola, Joseph Kerger, et al.


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