Influence of Amifostine on the Toxicity and Pharmacokinetics of Docetaxel in Metastatic Breast Cancer Patients: A Pilot Study

Gilles Freyer, Philippe Hennebert, Ahmad Awada, Thierry Gil, Joseph Kerger, Jean Selleslags, Christiane Brassinne, Martine Piccart, and Dominique de Valeriola


ABSTRACT

Preclinical studies suggest that amifostine could protect against toxicities induced by taxoids. We conducted a clinical and pharmacokinetic pilot study to assess the feasibility and toxicity of the docetaxel plus amifostine combination and the absence of influence of amifostine on docetaxel pharmacokinetics. We included 18 previously treated women with metastatic breast cancer (median age, 58.5 years; range, 34–74) in this single-center study. They were to receive a first course of docetaxel at 100 mg/m² i.v. as a 1-h infusion, then subsequent courses of docetaxel at 100 mg/m² preceded by amifostine at 910 mg/m² given as a 15-min i.v. infusion. Treatment was given every 3 weeks until disease progression or occurrence of unacceptable toxicity. We focused on neutrophils nadir (NN), time to nadir occurrence, and time to recovery of a neutrophil count ≥2 × 10⁹/liter, means of which were compared between cycle 1 and each of the other cycles by paired Student’s t test.

The total number of administered cycles was 84 (median number/patient, 4; range, 1–8). One patient received only the first course of docetaxel and was therefore not evaluable for amifostine effect. Neutropenia grade ≥2 occurred in 16 patients and was febrile in only 1. Other hematological and nonhematological toxicities were mild and manageable. Amifostine had no obvious influence on docetaxel-induced myelotoxicity as expressed by NN, time to nadir occurrence, and time to recovery. The mean NN (1 × 10⁹/liter) was 345 (18 patients) for cycle 1, then 318 (17 patients), 330 (13 patients), 340 (11 patients), 470 (8 patients), 200 (8 patients), 680 (5 patients), and 545 (4 patients) for cycles 2, 3, 4, 5, 6, 7, and 8, respectively (P > 0.2). Individual pharmacokinetic (PK) parameters of docetaxel estimated in 11 patients undergoing blood sampling showed no influence of amifostine on the PK profile of docetaxel. Mean clearances (liter/h/m²) and peak concentration (Cₚₑᵃᵏ; ng/ml) were 29.9 at cycle 1 versus 32.8 at cycle 2 (not significant) and 2849.9 at cycle 1 versus 2542.5 at cycle 2 (not significant), respectively. The population analysis including those 11 patients and 49 additional patients receiving docetaxel in other studies confirmed those findings.

This study does not support evidence for amifostine cytoprotection against docetaxel-induced myelosuppression and shows that there is no major influence of amifostine on docetaxel PK parameters. For the other toxicities, which are usually cumulative, the present study has design limitations and further comparative trials are warranted.

INTRODUCTION

Docetaxel (Taxotere; Aventis, Antony, France) is a semisynthetic compound belonging to the taxoid family, mainly developed for the treatment of advanced breast carcinoma and non-small cell lung carcinoma. Its beneficial activity in patients with such tumors has been well established in large, multicenter trials (1–4). It is a broad-spectrum cytotoxic agent, the major toxicity of which is grade 3–4 neutropenia at the recommended dose of 100 or even 75 mg/m² every 21 days. This toxicity is increased when docetaxel is combined with other myelosuppressive agents, such as anthracyclines. Other side effects include alopecia, asthenia, fluid retention, hypersensitivity reactions, skin and nail toxicity, and sensitive peripheral polyneuropathy (5).

Amifostine (Ethyol; Schering-Plough, Bedford, Ohio), S-[(3-aminopropyl)aminoethyl] dihydrogen phosphorothioate, is an organic thiophosphate compound that has been shown to protect normal tissues against the toxicity induced by alkylating agents, while still preserving their antitumor activity. This cytoprotective treatment may now be used in the prevention of chemotherapy-induced febrile neutropenia and nephrotoxicity attributable to cisplatin (6).

Preclinical studies suggest that amifostine could also protect from toxicities induced by taxoids (7, 8). In those studies, the authors suggested that amifostine could protect the hematological progenitors through a mechanism of cell rescue. Preliminary clinical data on its efficacy in association with paclitaxel are currently available (9), but the docetaxel plus amifostine combination remains unexplored. At the time our study began, data concerning the paclitaxel plus amifostine combination were not available.

In this pilot study, 18 metastatic breast cancer patients were treated with docetaxel alone for the first chemotherapy cycle, followed by docetaxel and amifostine for the subsequent cycles. Our aims were as follows: (a) to test the feasibility of the amifostine-docetaxel combination; (b) to assess its toxicity pro-
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PATIENTS AND METHODS

Eligibility. Patients registered in this trial were to receive treatment and follow-up at the Institut Jules Bordet, Brussels, Belgium. To be eligible, patients had to meet the following criteria: (a) histologically or cytologically proven breast cancer; (b) progressive, locally advanced (not amenable to surgery and/or radiotherapy) and/or metastatic breast cancer; (c) presence of a \( \geq 1 \text{ cm} \) bidimensionally measurable lesion; (d) age between 18 and 75 years; (e) WHO-Eastern Cooperative Oncology Group (ECOG) PS \( \leq 2 \); or, 1, or 2; (f) life expectancy \( \geq 3 \) months; (g) adequate bone marrow reserve as evidenced by neutrophils \( \geq 2 \times 10^{9}/\text{liter} \) and platelets \( \geq 1 \times 10^{11}/\text{liter} \) within 1 week before protocol entry; (h) serum creatinine \( \leq 1.5 \text{-fold above the UNL} \); (i) serum bilirubin within normal limit. Aspartate aminotransferase and/or alanine aminotransferase \( \leq 1.5 \text{-fold above the UNL} \) and alkaline phosphatase \( \leq 2.5 \text{-fold above the UNL} \); (j) prior adjuvant and/or adjuvant combination polychemotherapy was allowed; and (k) written informed consent from the patient. One prior chemotherapy regimen, with or without anthracycline, was required for advanced or metastatic disease, unless the patient experienced a relapse during an adjuvant/neoadjuvant regimen containing an anthracycline. No prior treatment with taxoids was permitted. A minimum of 4 weeks had to elapse since the last chemotherapy course.

Exclusion criteria were as follows: (a) male patients; (b) symptomatic peripheral neuropathy grade >2 according to the NCI criteria (11); (c) any coexisting serious medical condition; (d) prior steroid therapy at high doses (\( \geq 20 \text{ mg/day of prednisone or equivalent} \)) or for <6 months; (e) prior dose-intensification regimens with autologous bone marrow transplantation or peripheral blood progenitor cells; and (f) brain and/or leptomeningeal disease.

This protocol was approved by the local ethics committee.

Treatment. Patients received 100 mg/m\(^2\) of docetaxel alone for the first cycle, followed by 100 mg/m\(^2\) of docetaxel plus 910 mg/m\(^2\) of amifostine for all consecutive cycles. Docetaxel was given as a 1-h i.v. infusion through a pump with a constant dose rate on day 1 and every 21 days after adequate corticoid and antiemetic premedication (8 mg of ondansetron and 1 mg of lorazepam as i.v. short infusion). To avoid any potential pharmacokinetic interference, the same antiemetic treatment was given for cycle 1 and for each subsequent cycle; it was always given at least 30 min before amifostine. Additional oral methylprednisolone (32 mg/day) was given on days 2 and 3. Amifostine (910 mg/m\(^2\)) was added to normal saline to obtain a total volume of 50 ml and administered by pump over 15 min as a continuous i.v. infusion, ending 15 min before the start of docetaxel infusion. Blood pressure was measured immediately before, every 5 min during, and 5 min after the infusion. Adequate procedures were recommended in case of hypotension induced by amifostine: Trendelenburg’s position, rapid infusion of normal saline, and close monitoring of blood pressure; amifostine infusion was restarted only if blood pressure returned or was above the baseline value within 5 min after stopping.

A reduction of 25% of the docetaxel dose was planned in case of severe toxicity: neutropenia and thrombopenia grade 4 lasting >7 days and/or with febrile neutropenia, cutaneous reaction grade 3, peripheral neuropathy grade 2, uncontrolled diarrhea, nausea, or vomiting despite preventive and/or curative medications, increase of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase values >3-fold above UNL). However, in the case of neutropenia grade 4 lasting >7 days or febrile neutropenia after the first cycle, the docetaxel dose remained unchanged (100 mg/m\(^2\)) at the second cycle with the addition of amifostine as a cytoprotective agent. For the subsequent cycles, dose reductions were planned as indicated above. Treatment was delayed in the case of incomplete hematological recovery on day 21 for a maximum of 2 weeks, after which time the patients were taken off the protocol. The prophylactic administration of G-CSF was allowed only in patients presenting with febrile neutropenia after their second cycle, despite a reduced docetaxel dose and amifostine administration.

Treatment was administered until disease progression, unacceptable toxicity, or patient refusal.

Patient Monitoring. The pretreatment evaluation included the following: a medical history and physical examination, including a complete neurological examination by a neurologist; a complete blood count with differential, serum biochemistry; electrocardiogram; chest X-ray; and a radiological assessment of measurable and evaluable lesions performed within 2 weeks before study entry (by X-rays, computed tomography scan, magnetic resonance imaging, or ultrasonography). While on treatment, patients were monitored as follows: (a) history and physical examinations before each chemotherapy cycle and a neurological examination before the third and after the last cycle; (b) toxicity notation according to the NCI Common Toxicity Criteria grading system (11); (c) complete blood count on days 1, 8, 10, 12, 15, and 22 of the first 2 cycles, then on days 1, 8, 12, and 22 for the subsequent cycles; (d) biochemistry analysis before each cycle; and (e) tumor measurements repeated every 9 weeks by the same methods throughout the study. Response was defined according to standardized WHO criteria (10). To be evaluable for response, patients had to receive a minimum of 2 cycles of treatment with at least one follow-up tumor assessment, unless early disease progression was observed.

Patients were seen 1 month after discontinuation of protocol therapy, then visits were planned every 3 months thereafter.

Assessment of the Cytoprotective Effect of Amifostine. An exploratory analysis of toxicities between cycles 1 and 2 was performed to detect any potential protective effect of amifostine against docetaxel-induced neutropenia. In each patient, the neutrophils nadir, time to nadir occurrence (time elapsed between chemotherapy administration and nadir occurrence), and time to complete neutrophil recovery (neutrophil count >2 \times 10^{9}/\text{liter})
were measured. Median, mean, and SD were calculated for each of those parameters. Paired Student’s *t* tests were used to assess statistical significance of observed differences between the first cycle and each subsequent cycle.

**Pharmacokinetics**

**Individual Analysis.** The pharmacokinetics of docetaxel were examined during the first cycle (patients receiving docetaxel alone) and the second cycle (patients receiving docetaxel plus amifostine), to compare the main pharmacokinetic parameters of docetaxel in each patient with or without amifostine. Blood samples were collected through an indwelling catheter inserted in the arm (in the opposite arm in case of drug administration through the peripheral veins). Blood samples (5 ml) were collected at each cycle in heparinized tubes at the following points: immediately before the beginning of docetaxel infusion (*t*0), then 30 min; 55 min; 1 h, 5 min; 1 h, 10 min; 1 h, 20 min; 2 h, 3 h, 5 h, 7 h, 11 h, 25 h, and 37 h after the beginning of docetaxel infusion. All blood samples were centrifuged within 30 min at 1250 g for 15 min at 6–8°C and stored at −20°C. Docetaxel concentrations in plasma were determined by using the method described by Vergniol et al. (12) with slight modifications. Those modifications were mainly performed in the solid-phase extraction procedure, which was performed on Bond Elut C8 ethyl columns (100 mg/ml; Varian, Harbor City, CA) with 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% of orthophosphoric acid. After applying the sample (1 ml of plasma), we rinsed the columns with 1 ml of 0.3% orthophosphoric acid and washed them with 1 ml of methanol and 0.3% orthophosphoric acid (50:50, v/v). Docetaxel was eluted with 0.3 ml of methanol and 0.3% orthophosphoric 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; inside diameter, 4.6 × 250 mm) preceded with a Nova Pak C18 Guard Pak precolumn insert (Waters). The mobile phase consisting of methanol and 0.3% orthophosphoric acid (670:330, v/v) was delivered at 1 ml/min. The integration of peak heights was performed with 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 interrun reproducibility was 8.3% (for 50 ng/ml) and 2.8% (for 1000 ng/ml).

Docetaxel individual pharmacokinetic parameters were obtained at each cycle with the ADAPT II program using weighted, iterative, nonlinear least squares regression (13). Parameter estimation was independently repeated 10 times with 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. (14). Model discrimination between 2- and 3-compartment models was performed with Akaike’s Information Criterion (15). Student’s *t* test was used to compare the means of the individual pharmacokinetic parameters for cycles 1 and 2 and, hence, to detect a potential effect of amifostine on docetaxel pharmacokinetics.

**Population Pharmacokinetic Analysis.** Individual docetaxel concentration data were pooled with other data coming from 33 metastatic cancer patients receiving docetaxel plus 5-FU, 13 patients receiving docetaxel alone at days 1 and 8, and 3 patients receiving 14C-radiolabeled docetaxel in two Phase I trials (16, 17) and a pilot study, respectively (18). In the docetaxel plus 5-FU study, patients received i.v. 1-h 60–100 mg/m² of docetaxel on day 1 plus 300–1000 mg/m² of 5-FU by continuous infusion on days 1 to 5, every 21 days. The characteristics of those patients were as follows: 18 males and 15 females; median age, 55 years (range, 32–72 years); median weight, 65 kg (range, 47–94 kg); median height, 169 cm (range, 151–183 cm); PS 0, 12 patients; PS 1, 18 patients; PS 2, 3 patients; head and neck carcinoma, 9 patients; carcinoma of the esophagus, 5 patients; carcinoma of unknown origin, 4 patients; breast carcinoma, 3 patients; carcinoma of the cervix uteri, 3 patients; non-small cell carcinoma of the lung, 2 patients; soft tissue sarcoma, 2 patients; ovarian carcinoma, 1 patient; pancreatic carcinoma, 1 patient; carcinoma of the parotid gland, 1 patient; carcinoma of the bladder, 1 patient; and carcinoma of the endometrium, 1 patient. The administration of 5-FU had no obvious influence on the pharmacokinetics of docetaxel (16, 19).

In the other Phase I trial (17), patients received docetaxel as a single agent at a dose ranging from 10 to 100 mg/m², given as a 1-h infusion on days 1 and 8 every 21 days. The characteristics of those 13 patients were as follows: 5 males and 8 females; median age, 49 years (29–65 years); median weight, 57 kg (46–84 kg); median height, 169 cm (155–180 cm); PS 0, 6 patients; PS 1, 5 patients; PS 2, 1 patient; PS 3, 1 patient; ovarian carcinoma, 4 patients; breast carcinoma, 2 patients; colon carcinoma, 3 patients; osteosarcoma, 2 patients; carcinoma of unknown origin, 1 patient; malignant mesothelioma, 1 patient.

In the pilot study (18), three patients received 14C-radiolabeled docetaxel at 100 mg/m² during only one course. There were two metastatic breast cancer patients (46 years and 53 of age; PS 1 and PS 0, respectively) and one male patient presenting with metastatic Ewing’s sarcoma (20 years of age; PS 0).

The methodology of blood sampling, centrifugation, and assays was similar to the one described in the previous section. Time points for blood sampling, however, were slightly different: immediately before the beginning of docetaxel infusion (*t*0), then 30 min; 55 min, 1 h, 15 min; 1 h, 30 min; 1 h, 45 min; 2 h, 2 h, 30 min; 3 h; 5 h; 9 h; 13 h; 21 h; 25 h; and 31 h after the beginning of docetaxel infusion. Here only pharmacokinetic data from the first cycle of these studies were used.

All concentration data were analyzed with the NONMEM program (Ver. 5; University of California, San Francisco, CA) to simultaneously estimate the population pharmacokinetic parameters: clearance (*CL*), volume of distribution (*Vd*), transfer rate constants (*kij*), and area under the curve (*AUC*) of docetaxel to assess the interpatient variability given by the CV of *CL* and the effect of the comedication with the amifostine covariate on the estimated pharmacokinetic parameters of the population. More details about this methodology have been published elsewhere (20). In our study, 2- and 3-compartment models have been tested both graphically (individually predicted versus observed concentrations of docetaxel) and by comparing the val-
Amifostine: Influence on Docetaxel Toxicity and Pharmacokinetics

Overall Toxicity and Cytoprotective Effect of Amifostine. The median number of cycles given per patient was 4 (range, 1–8), with a total of 84 cycles administered throughout the study. Neutropenia grade >2 was the main hematological toxicity, which occurred in 16 patients (89%). Table 2 gives the main characteristics (value of the nadir, time to occurrence of the nadir, and time to obtain a complete recovery defined by neutrophil count >2 × 10^9/liter) of the neutropenia induced by docetaxel at each cycle. We observed no significant difference between the first cycle without amifostine and the others, which included an infusion of amifostine. The evolution of the mean nadir for all cycles is shown in Fig. 1.

Febrile neutropenia was diagnosed in one patient during cycle 2 with an uncomplicated recovery within 1 week. G-CSF was never used in this study.

Other hematological toxicities were mild: anemia grade 3 was observed in one patient and the most severe thrombocytopenia was grade 2 in one patient.

Among nonhematological toxicities, presented in Table 3, alopecia and asthenia grades 2–3 were the most frequent. The neurological toxicity of docetaxel was mild: peripheral neuropathy grade 1 was observed in 4 patients and grade 2 in only one. Moderate fluid retention, including peripheral edema and/or pleural or pericardial effusion and/or unexplained weight gain occurred in 6 patients. One patient experienced severe peripher edema located in the legs and this side effect contributed to the decision to stop treatment after the 8th cycle. Severe hypotension induced by amifostine and requiring infusion stopping was never encountered.

There were multiple reasons for therapy discontinuation: progressive disease (five patients), stable disease/investigator’s decision (five patients), partial response with absence of further benefit expected from the treatment (five patients), excess of toxicity (two patients), and lack of follow-up (one patient). No patient died during treatment in this study.

Antitumor Efficacy and Survival. Only 17 patients were evaluable for efficacy. Six partial responses (35%), six stabilizations (35%), and five progressions (30%) were observed. With a median follow-up of 2 years, the median overall survival in the studied population was 338 days, according to Kaplan-Meier estimation.

Pharmacokinetics

Individual Analysis. Docetaxel pharmacokinetics were obtained in the first two cycles in 11 patients. The other 7 patients refused to be included in the pharmacokinetic study, which had no affect on their treatment. The major pharmacokinetic parameters are listed in Table 4. Docetaxel CL was ~30 liters/h/m^2 at each cycle. The interpatient variability (CV) was 30% for cycle 1 and 44% for cycle 2.

We did not observe any significant difference between the parameters of cycle 1 and cycle 2, which indicates no major influence of amifostine on the docetaxel pharmacokinetics.

Population Analysis. The previously described subpopulation of 11 patients was included into the larger population described in the “Patients and Methods” section. The total number of patients was 60. The best model we obtained with NONMEM for concentration data fit was a three-compartment model with linear elimination using first-order methods. An

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yr (range)</td>
<td>58.5 (34–74)</td>
</tr>
<tr>
<td>Weight, median kg (range)</td>
<td>65 (47–91)</td>
</tr>
<tr>
<td>Height, median cm (range)</td>
<td>160.5 (154–175)</td>
</tr>
<tr>
<td>ECOG, PS 0/1/2</td>
<td>5/9/4</td>
</tr>
<tr>
<td>Menopausal status (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>9</td>
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<tr>
<td>Postmenopausal</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Hormone receptors (no. of patients)</td>
<td></td>
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<tr>
<td>ER +, PGR +</td>
<td>4</td>
</tr>
<tr>
<td>ER +, PGR –</td>
<td>1</td>
</tr>
<tr>
<td>ER –, PGR +</td>
<td>2</td>
</tr>
<tr>
<td>ER –, PGR –</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
</tr>
<tr>
<td>Time to first relapse, median mo (range)</td>
<td>32 (7–112)</td>
</tr>
<tr>
<td>No. of metastatic sites per patient</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Prior adjuvant radiotherapy (no. of patients)</td>
<td>16</td>
</tr>
<tr>
<td>Prior hormone therapy (no. of patients)</td>
<td>15</td>
</tr>
<tr>
<td>Prior chemotherapy (no. of patients)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>9</td>
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<tr>
<td>Metastatic</td>
<td>6</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
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<tr>
<td>Progression under an anthracycline-containing regimen (no. of patients)</td>
<td>4</td>
</tr>
<tr>
<td>Metastatic sites (no. of patients)</td>
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<tr>
<td>Skin/soft tissues</td>
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</tr>
<tr>
<td>Bone</td>
<td>9</td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>9</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>3</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>7</td>
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</tbody>
</table>

* ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PGR, progesterone receptor.
exponential model to describe interpatient variability on CL, Vd, and \( k_{ij} \) values was used. The residual error model was mixed, proportional, and additive. The accuracy of the prediction (individually predicted concentration values versus observed ones) is shown in Fig. 2. The population pharmacokinetic parameters are presented in Table 4. We did not detect any major impact of amifostine administration on the main pharmacokinetic parameters of docetaxel. As shown in Fig. 3, the individual docetaxel clearances obtained with the individual conditional estimation step obtained after a First Order population estimation option of NONMEM in the patients included in the docetaxel plus amifostine study were within the range of the overall population and were not different between cycle 1 and cycle 2. Overall interpatient variability was 29.5% on CL and 36.5% on Vd. Interpatient variability was not ascribed to variable hepatic function within patients because normal or minimally altered liver function tests were an requirement before study entry. The residual error was 34.06% for the proportional term and 3.61 ng/ml for the additive term. Among the individual covariates studied, such as age, sex, weight, height, serum creatinine, and presence of liver metastases, none had any significant influence on the population pharmacokinetic parameters of docetaxel.

**DISCUSSION**

Docetaxel has demonstrated activity in various tumor types (5, 21). Recently, controlled trials have demonstrated the superiority of this agent over doxorubicin in first-line metastatic breast cancer and over reference combinations after anthracycline failure (1, 2). It also seems to be a promising agent when used in the preoperative setting in patients with locally advanced tumors (22). In advanced non-small cell lung cancer, docetaxel has proved to be the only drug that produces a survival benefit over best supportive care after cisplatin failure (3, 4). The usual dose for monochemotherapy is 100 mg/m² (75 mg/m² for salvage therapy in advanced lung cancer), and this dose must be reduced when docetaxel is given in combination with other agents, mainly because neutropenia becomes the main limiting toxicity. It is therefore worthwhile to look for means of decreasing docetaxel toxicities, e.g., mainly but not only neutropenia which can also be prevented by the use of G-CSF. This goal could be achieved by cytoprotective agents and amifostine remains the most one extensively studied to date. Indeed, it was shown to protect patients against neutropenia induced by alkylating agents (including cisplatin) and against nephrotoxicity due to cisplatin, in randomized controlled trials (23, 24). The American Society of Clinical Oncology recently recommended to consider the use of amifostine in combination with those cytotoxic agents and also emphasized that hematopoietic growth factors could be an alternative to the use of amifostine for hematoprotection (6).

**Table 2** Characteristics of docetaxel-induced neutropenia for each cycle

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>Cycle 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>18</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Median nadir (1 × 10⁹/liter)</td>
<td>345</td>
<td>318</td>
<td>330</td>
<td>340</td>
<td>470</td>
<td>200</td>
<td>680</td>
<td>545</td>
</tr>
<tr>
<td>Median time to nadir (days)</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Median time to recoverya (days)</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>8.5</td>
<td>11.5</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

*Time elapsed between nadir and neutrophil count > 2 × 10⁹/liter.

**Fig. 1** Mean values and SDs of the neutrophil count nadir for each chemotherapy cycle.
paclitaxel 250 mg/m² every 21 days with or without amifostine 910 mg/m². No difference was seen for any toxicity between the two arms. Moreover, amifostine induced more nausea and hypotenstion in the experimental arm. The authors concluded that paclitaxel toxicity is not amenable to amifostine cytoprotection. In our study, we did not detect any obvious difference concerning nausea and vomiting with or without amifostine, but the antiemetic premedication combining a setron, a corticosteroid, and an anxiolytic was maximal.

The focus of our study was docetaxel-induced neutropenia because we expected a lower incidence of other side effects; in particular, docetaxel is less neurotoxic than paclitaxel, which was confirmed in this study where only one patient experienced grade >1 peripheral neuropathy.

The clinical results of our study do not support evidence for amifostine cytoprotection against docetaxel-induced neutropenia. The value of the nadir, the time to nadir occurrence, and the duration of the hematological recovery period did not seem to be influenced by amifostine administration. Grade 4 neutropenia was observed in the vast majority of patients at each cycle. The most interesting comparisons between cycles involved cycles 1, 2, and 3 because a low proportion of patients received >3 cycles; they revealed no significant difference. Even from cycle 4 on, where the remaining patients were selected by their more favorable prognosis, no obvious improvement in hematological toxicity parameters was seen. Time points for nadir assessment (complete blood count) seemed to be a priori well defined and there were <10% missing data.

Anemia and thrombocytopenia were rarely severe and no conclusion can be formulated about a possible effect of amifostine.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overall toxicities (other than neutropenia) according to the NCI-CTC grading system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorest toxicity (per patient)</td>
<td>No. of patients (percentage of the study population)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 1 7 (39%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 1 4 (22%)</td>
</tr>
<tr>
<td>Fever/infection without neutropenia</td>
<td>Grade 1 3 (17%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Grade 1 1 (6%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 1 6 (33%)</td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>Grade 1 4 (22%)</td>
</tr>
<tr>
<td>Skin toxicity/Onycholysis</td>
<td>Grade 1 3 (17%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Grade 1 3 (17%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Grade 1 4 (22%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 1 3 (17%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 1 5 (28%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Grade 1 4 (22%)</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Grade 1 3 (17%)</td>
</tr>
</tbody>
</table>

* NCI-CTC, Common Toxicity Criteria.

Table 4 Individual and population pharmacokinetic parameters from patients receiving docetaxel (cycle 1), and docetaxel + amifostine (cycle 2) (n = 11 patients; 22 cycles).

<table>
<thead>
<tr>
<th>Cycle</th>
<th>C peak (ng/ml)*</th>
<th>Vd (liter/m²)*</th>
<th>Transfer rate of docetaxel (h⁻¹)</th>
<th>CL (liter/h/m²)</th>
<th>AUC0−24 h (ng/h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2849.9 3.7</td>
<td>8.8 2.2 0.7 1.8 1.2</td>
<td>29.9 3462.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2542.5 (NS) 8.2 (NS)</td>
<td>7.2 (NS) 2.4 (NS) 1.4 (NS) 1.4 (NS) 0.6 (NS)</td>
<td>32.8 (NS) 3156.1 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation (SD)</td>
<td>8.2 (NS)</td>
<td>5.7 (NS) 1.9 (NS) 1.0 (NS) 1.3 (NS) 0.2 (NS)</td>
<td>30.7 3249.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of amifostine</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Simulated concentration at the end of the 1-h infusion of docetaxel.

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Nonhematological toxicities were mild and the overall toxicity profile was as expected with docetaxel: significant asthenia, arthralgia/myalgia, and skin toxicity/onycholysis were observed in 30% of patients. No grade 4 toxicity was observed. We cannot suggest a possible protective role of amifostine on non-hematological toxicities because this pilot study was not designed to compare the chronic and cumulative toxicities induced by docetaxel, with or without amifostine.

We did not observe any major side effect attributable to amifostine alone, such as severe hypotension requiring infusion stopping. This can be considered surprising because amifostine-induced hypotension is usually regarded as frequent and could be attributable to the relatively low number of patients included in our study or perhaps to the dexamethasone premedication.

The individual pharmacokinetic study revealed no major influence of amifostine on docetaxel pharmacokinetic parameters because no difference was observed between cycles 1 and 2 in the 11 patients studied. The observed results are consistent with those obtained in our previous study (16) on docetaxel used in combination with 5-FU: \( CL \) ranged between 24.0 and 42.9 liters/h/m\(^2\), peak concentration \( (C_{\text{peak}}) \) between 1400 and 3700 ng/ml, and \( Vd \) between 2.9 and 6.4 liters/m\(^2\). They are also comparable with the data found in the literature (14, 19). Nevertheless, intraindividual, intercourse variability of docetaxel parameters from cycle 1 to cycle 2 was not distinguishable from a possible effect of amifostine in the individual analysis.

To make the pharmacokinetic analysis more exhaustive, we also performed a population analysis with the NONMEM program to simultaneously estimate the docetaxel pharmacokinetic parameters and their variance in our patients with and without amifostine and in other “control” patients receiving docetaxel with or without 5-FU. It is noteworthy that the concomitant administration of 5-FU had no influence on the pharmacokinetics of docetaxel (16, 19). Similarly, we observed no influence of amifostine on docetaxel \( CL \) or \( Vd \). The variance parameters, as well as the residual error attributable to assay error and model inaccuracies, were close to those observed in population studies on docetaxel and many other cytotoxic agents, using one-stage parametric methods (14).

In conclusion, our results do not provide evidence for amifostine cytoprotection against acute toxicities induced by docetaxel, particularly neutropenia. However, overall toxicities and, interestingly enough, neurotoxicity, appeared relatively mild in this small population of patients in contrast to previous reports and to our own experience. From a clinical point of view, more data from comparative, randomized studies seem necessary. On the other hand, we believe this study provides sufficient evidence in favor of the lack of any significant influence of amifostine on the pharmacokinetics of docetaxel.

ACKNOWLEDGMENTS

We thank the “Bourse Michel Clavel” committee, Lyon, France, for supporting the research fellowship of Gilles Freyer.

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Amifostine: Influence on Docetaxel Toxicity and Pharmacokinetics


Influence of Amifostine on the Toxicity and Pharmacokinetics of Docetaxel in Metastatic Breast Cancer Patients: A Pilot Study

Gilles Freyer, Philippe Hennebert, Ahmad Awada, et al.


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