Phase I and Pharmacokinetic Study of Weekly Docetaxel, Cisplatin, and Daily Capcitabine in Patients with Advanced Solid Tumors

Marwan G. Fakih,1,2 Patrick J. Creaven,1,2 Nithya Ramnath,1,2 Donald Trump,1,2 Milind Javle,1,2 Sandra Strychor,3 Trisha V.W. Repinski,3 Beth A. Zamboni,4 James K. Schwarz,1,2 Renee A. French,1 and William C. Zamboni3,5,6

Abstract  
**Purpose:** Docetaxel, cisplatin, and capecitabine are three active chemotherapeutic agents with different mechanisms of action. This phase I study investigated the feasibility and pharmacokinetics of this combination given on a weekly schedule.

**Experimental Design:** Docetaxel and cisplatin were given i.v. over 30 minutes on days 1 and 8 and capecitabine was given orally bid on days 1 to 14 (every 21 days). Escalation occurred in cohorts of three patients until the maximum tolerated dose was defined. Pharmacokinetics studies of docetaxel and total and ultrafiltrate platinum after cisplatin administration were done on cycle 1 (with capecitabine) and cycle 2 (without capecitabine).

**Results:** Twenty-five patients were enrolled. Two of six patients at dose level 5 had a dose-limiting infection and diarrhea. One of six evaluable patients at dose level 4 (27 mg/m² docetaxel, 27 mg/m² cisplatin, 825 mg/m² capecitabine) had a dose-limiting hypomagnesemia. Pharmacokinetics of docetaxel were similar on cycles 1 and 2. Area under the plasma concentrations versus time curves of total platinum was significantly greater in cycle 2 compared with cycle 1 ($P = 0.001$). There was no difference in the disposition of docetaxel on cycles 1 and 2.

**Conclusions:** The recommended docetaxel, cisplatin, and capecitabine dose for phase II studies is 27/27/825 mg/m². The alteration in total and ultrafiltrate platinum disposition on cycle 2 compared with cycle 1 may be inherent to sequential cisplatin administration; however, prior treatment with capecitabine cannot be ruled out as a factor.

Docetaxel, cisplatin, and capecitabine are three widely used chemotherapeutic agents with different mechanisms of action (1–5). Given these nonoverlapping mechanisms of activity, various doublet combinations have been investigated in a variety of solid tumors. The combination of docetaxel and cisplatin has shown substantial activity in patients with gastric and lung cancers (6–9). The addition of capecitabine to docetaxel has resulted in improved response rates in comparison with historical response rates with either agent alone in gastric and lung cancers (10–12). In a randomized study in anthracycline-resistant metastatic breast cancer, capecitabine plus docetaxel was superior to docetaxel alone (10–12). Cisplatin and capecitabine has not been well studied; however, two phase II studies in gastric and biliary cancers show promising efficacy (13, 14). Based on the encouraging efficacy of various doublets of capecitabine, docetaxel, and cisplatin, we investigated the feasibility of combining these three agents in a phase I trial. To minimize toxicity and maximize dose intensity, we elected to investigate a weekly regimen of cisplatin and docetaxel concurrently with capecitabine orally twice daily for 2 weeks every 3 weeks. This schedule had been previously tested for the combination of docetaxel and capecitabine and was associated with considerable activity, especially in patients with gastric cancer (15).

Materials and Methods

This phase I, open-label, dose escalation study of docetaxel, cisplatin, and capecitabine was conducted at Roswell Park Cancer Institute (Buffalo, NY). The primary objectives of the study were to determine the maximum tolerated dose (MTD) of weekly docetaxel and cisplatin i.v. in combination with daily oral capecitabine and to establish a recommended dose for phase II trials. Secondary objectives included the evaluation of pharmacokinetics of docetaxel and cisplatin when given in the presence or absence of capecitabine, the description of treatment-related toxicities, and the description of any observed clinical responses.

Patient criteria

Patients with a histologically or cytologically confirmed solid tumor that was metastatic or unresectable and for which standard curative or palliative measures did not exist were eligible for the trial. The last
Phase I Study of Docetaxel, Cisplatin, and Capecitabine

Chemotherapeutic or radiation treatment was at least 4 weeks (6 weeks for niosites or mitomycin C) before trial enrollment. Other criteria included age ≥18 years of age, Eastern Cooperative Oncology Group performance status ≤2, estimated life expectancy >12 weeks, no central nervous system involvement, adequate bone marrow function (neutrophils ≥1,500/μL, hemoglobin ≥8.0 g/dL, platelets ≥100,000/μL), hepatic (serum bilirubin ≤ upper limit of normal range (ULN), serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2 × ULN if alkaline phosphatase is ≤ ULN, or alkaline phosphatase ≤ 4 × ULN if AST and ALT are ≤ ULN), and renal function (creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min). The study excluded patients unable to receive oral medications, those with a history of allergic reaction to any of the study agents or peripheral neuropathy or inner ear auditory toxicity grade ≥ 2 or patients receiving other investigational agents. Patients with reproductive potential had to agree to use adequate contraception before study entry and for the duration of study participation. The study and consent form were approved by the Institutional Scientific and Review Committee and the Institutional review board before its activation. All patients provided signed informed consent before study entry. The study was conducted in accordance with the Good Clinical Practice Guidelines as issued by the International Conference on Harmonization and the Declaration of Helsinki.

Study design and treatment plan

Docetaxel and cisplatin were given i.v. on days 1 and 8 of a 21-day cycle. Capecitabine was given orally twice daily on days 1 to 14. Three patients were entered at each dose level. In the absence of dose-limiting toxicity (DLT), the next dose level was explored. If DLT was seen in one patient, three further patients were added at that dose level and, if no additional DLT was seen, escalation to the next dose level occurred. If two patients had DLT at a given dose level, accrual to that dose level was stopped; this was the maximally tolerated dose. Further patients were then added, as required, to the previous dose level (and if necessary to lower dose levels) to establish the highest dose at which less than two of six patients had DLT. This was the MTD. All patients receiving <100% of the intended cisplatin and docetaxel dose or <75% of the intended capecitabine dose in the first cycle were to be replaced, unless a DLT was confirmed in those patients.

Patients received docetaxel in 250 mL of normal saline over 30 minutes followed by a bolus of 250 mL normal saline over 30 minutes and then cisplatin in 250 mL normal saline over 30 minutes. Docetaxel and cisplatin were given on days 1 and 8 of every 21-day cycle on an outpatient basis. Patients were medicated with medetomidine 8 mg oral Q12 hours × 3 doses, starting the night before the scheduled docetaxel dose. All patients were premedicated with granisetron (2 mg oral or 1 mg i.v.) or an equivalent 5-hydroxytryptamine-3 inhibitor. Capecitabine was given orally with water (within 30 minutes followed by a bolus of 250 mL normal saline over 30 minutes) on an outpatient basis. Patients were medicated with dexamethasone 8 mg oral Q12 hours × 3 doses, starting the night before the scheduled cisplatin dose.

Clinical evaluation and follow-up

A complete medical history, physical examination, pregnancy test for women with reproductive potential, complete blood count, and comprehensive chemistry profile (electrolytes, BUN, creatinine, magnesium, lactate dehydrogenase, ALT, AST, and bilirubin) was obtained within a week before treatment initiation and at the start of each cycle. Baseline computerized tomography scans were obtained within 4 weeks before initiation of treatment. Complete blood count and comprehensive chemistry were repeated on a weekly basis while on study. Medical history including toxicity, physical examination, and toxicity assessment as per National Cancer Institute Common Toxicity Criteria version 2.0 were done every 3 weeks (beginning of each cycle) while on study. Computerized tomography scans were repeated every two cycles (6 weeks) to assess response. Responses were categorized according to the Response Evaluation Criteria in Solid Tumors (16).

Pharmacokinetics: sample collection, preparation, and analysis

Sample collection and preparation. Blood samples for docetaxel and cisplatin pharmacokinetic analyses were obtained on the first days of cycles 1 and 2. On cycle 1, docetaxel, cisplatin, and capecitabine were given on day 1. On cycle 2, docetaxel and cisplatin were given alone on day 1, and capecitabine was started on day 2. Docetaxel was given by a 30-minute i.v. infusion and was followed by a 30-minute i.v. infusion of cisplatin. For pharmacokinetic studies of docetaxel, blood samples (6 mL) were obtained before administration and at 15, 30, 45 minutes, 1, 1.5, 3, 5, 5.5, 7.5, and 24 hours after the start of infusion. For pharmacokinetic studies of cisplatin, blood samples (3 mL) were obtained before administration and at 15, 30, 45 minutes, 1, 1.5, 2.5, 4.5, 6.5, and 24.5 hours after the start of infusion. Blood samples were placed in sodium heparinized tubes and centrifuged at 1,200 × g at 4°C for 5 minutes; and resulting plasma was removed, immediately frozen, and stored at −80°C until analyzed. Docetaxel plasma samples were processed via solid phase extraction, and concentrations were quantified by liquid chromatography-mass spectrometry assay developed and validated in our laboratory (17). The lower limit of quantitation for docetaxel was 0.06 ng/mL. Platinum (Pt) concentrations were analyzed using flameless atomic absorption spectroscopy (18, 19). Total Pt (sum of protein bound and unbound Pt) was measured directly from plasma.
Ultrafiltrate Pt in plasma was analyzed by placing 1 mL plasma into an Amicon Centrifree micropartition device (Amicon Division, W.R. Grace, Beverly, MA), then centrifuging at 1,475 × g for 20 minutes at 4°C, before flameless atomic absorption spectroscopy. The lower limit of quantitation for Pt was 0.049 μg/mL.

**Pharmacokinetic analysis.** Pharmacokinetic analysis of docetaxel and cisplatin (as measured by total and ultrafiltrate Pt) was done using the ADAPT II program (20). The estimation procedure and variance models used in the compartmental pharmacokinetic analyses were MAP Bayesian and maximum likelihood estimations for docetaxel and Pt, respectively. The systemic disposition of docetaxel was evaluated using two- and three-compartment models. The systemic disposition of total Pt, after administration of cisplatin, was evaluated using a two-compartment model. The systemic disposition of ultrafiltrate Pt was evaluated using one- and two-compartment models. Akaike’s Information Criteria, Schwartz Criteria, estimated error of the model variables, and residual analysis were used to select the model structures maximizing the fit accuracy while simultaneously minimizing the number of model variables. The final model structures used for the pharmacokinetic analyses produced identifiable variables in all patients.

All docetaxel concentration versus time profiles were fit using a three-compartment linear model. Individual variables estimated by the model were the volume of the central compartment (Vc), elimination rate constant (k01), intercompartmental rate constants (k12, k21, k10, and k20), systemic clearance (CL), and elimination half-life (t1/2). The area under the concentration versus time curves (AUC) from 0 to 24 hours was calculated using the log trapezoidal method by simulating the concentration versus time data from each patient using patient-specific variables (20).

After administration of cisplatin, total Pt concentration versus time profiles were evaluated using a two-compartment linear model. Individual variables estimated by the model were Vc, k10, intercompartmental rate constants k12 and k21, CL, and t1/2. AUCs from 0 to 24 hours were calculated using the log trapezoidal method by simulating the concentration versus time data from each patient using patient-specific variables (20).

After administration of cisplatin, a one-compartment model was fit to ultrafiltrate Pt on cycle 1 in all patients. On cycle 2, a one- and two-compartment model was fit to ultrafiltrate Pt concentration versus time profiles for 19 and three patients, respectively. Individual variables estimated by the model were Vc, k10, intercompartmental rate constants k12, k12, and k21, for two-compartment model only, CL, and t1/2. AUCs from 0 to ∞ were calculated using the log trapezoidal method by simulating the concentration versus time data from each patient using patient-specific variables (20).

The changes in CL, t1/2, and AUC for docetaxel, total platinum, and ultrafiltrate platinum were compared between cycles 1 and 2. Comparisons between cycles 1 and 2 were made using the exact, two-sided, Wilcoxon signed-rank test.

**Results**

**Demographics**

Between February 2003 and July 2004, 25 patients were entered on study. One patient was mistakenly entered on the wrong dose level (received dose level 4 instead of dose level 3) and was taken off study without any DLT. One patient was found ineligible secondary to thrombocytopenia and was removed from study before receiving any treatment. Two patients were taken off study after receiving only one weekly dose of cisplatin and docetaxel (patients withdrew consents because of grade 2 anorexia and fatigue) without any DLT. Twenty-one enrolled patients were eligible and evaluable for toxicity (all received 100% of intended docetaxel and cisplatin and >75% of intended capecitabine in the first cycle). Most patients had received one or more prior chemotherapeutic regimens. Predominant tumor types were lung, pancreatic, and upper gastrointestinal. Detailed characteristics are described in Table 1.

**Treatment administration**

Twenty-four patients received treatment on study. Five dose levels were evaluated. The median number of cycles given was 2 (range, 1-14). Seven patients received six or more cycles.

**Toxicity**

All patients were evaluated for toxicity, including the two patients who were replaced because of early withdrawal from study. Only grade ≥2 toxicity data were collected and reported. Treatment-related grade 3 to 4 toxicities are summarized in Table 2.

**Hematologic toxicity.** Neutropenia was the predominant hematologic toxicity. Grade 3 to 4 neutropenia was noted in three patients at dose levels 4 and 5. Grade 2 neutropenia was more common (five patients), especially with repeated treatment. No grade ≥2 thrombocytopenia was seen.

**Nonhematologic toxicity.** The most common grade ≥2 nonhematologic adverse event was hypomagnesemia (11 patients). Four patients had grade 3 or 4 hypomagnesemia. Hypomagnesemia tended to occur more often in patients receiving multiple cycles of treatment, was asymptomatic, and easily manageable with magnesium supplementation. Only one patient developed grade ≥2 hypomagnesemia during cycle 1 of treatment.

Nine patients developed grade ≥2 diarrhea (five during the first cycle). Only two patients had grade 3 diarrhea and both occurred on dose levels 4 and 5.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Age (median/range), y</td>
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<tr>
<td>ECOG (0/1)</td>
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<tr>
<td>Primary tumor</td>
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<tr>
<td>NSCLC</td>
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<td>Gastric</td>
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<td>Esophageal</td>
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<td>Head and neck</td>
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<tr>
<td>Anal</td>
</tr>
<tr>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Unknown primary</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>SCLC</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
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<td>≥1 line of prior chemotherapy</td>
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<tr>
<td>Prior surgery</td>
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<tr>
<td>Prior radiation therapy</td>
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Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small lung cell cancer.
toxicity or patient withdrawal. An objective response was noted in two previously untreated patients. A previously untreated metastatic gastric cancer patient had a partial response (PR) after four cycles of treatment. She progressed after a total of 14 cycles. A gemcitabine-refractory metastatic pancreatic cancer patient had a PR after two cycles of treatment. He continued to receive the same treatment off study and maintained a PR for a total of 6 months. A previously untreated metastatic squamous cell lung cancer patient had a complete response (CR) after four cycles of treatment that was confirmed after two additional cycles. She was taken off study due to lack of clinically measurable disease. She relapsed 3 months later.

Stable disease was confirmed in nine patients (maintained for five to eight cycles): three patients with non–small cell lung cancer resistant to carboplatin and paclitaxel, two patients with metastatic anal cancer resistant to 5-fluorouracil (5-FU)/cisplatin, one patient with gemcitabine-resistant pancreatic cancer, one patient with metastatic adenocarcinoma of unknown primary, one patient with head and neck cancer resistant to 5-FU/cisplatin, and one patient with esophageal cancer who had progressed on 5-FU/LV/oxaliplatin (FOLFOX).

**Pharmacokinetics**

Representative docetaxel concentration versus time profiles on cycles 1 and 2 for an individual patient are depicted in Fig. 1. A summary of docetaxel pharmacokinetic variables is presented in Table 3. After administration of docetaxel at 20 mg/m², the mean ± SD of docetaxel AUC on cycles 1 and 2 were 508 ± 126 and 528 ± 221 ng·mL⁻¹·h, respectively. After administration of docetaxel at 27 mg/m², the mean ± SD of docetaxel AUC on cycles 1 and 2 were 1,601 ± 460 and 1,159 ± 404 ng·mL⁻¹·h, respectively. After administration of docetaxel at 36 mg/m², the mean ± SD of docetaxel AUC on cycles 1 and 2 were 2,129 ± 406 and 1,875 ± 735 ng·mL⁻¹·h, respectively. The ratio of docetaxel AUC from cycle 1 to cycle 2 after doses of 20, 27, and 36 mg/m² were 1.02 ± 0.36, 0.68 ± 0.16, and

Eight patients developed grade ≥2 nausea or vomiting, three of which occurred during cycle 1 of treatment. Nausea and vomiting were moderate in most instances and resolved with antiemetic therapy. Two patients had grade 3 or 4 vomiting and both were noted on higher dose levels (dose level 4 or 5).

Grade ≥2 stomatitis occurred in two patients (dose levels 2 and 4, cycles 1 and 2, respectively) and grade 3 stomatitis occurred in one (dose level 5, cycle 1).

Fatigue was limited to grade 2 and was more commonly seen with repeated treatment. One patient had pneumonia (grade 3 infection) on the first cycle of treatment (dose level 5).

**Dose-limiting toxicities, maximum tolerated dose, and recommended dose**

No DLTs were noted on the first three dose levels or on the first three patients on dose level 4. Upon escalation to dose level 5, DLTs were noted in two of six patients. The first patient developed pneumonia requiring admission and i.v. antibiotics (grade 3 infection). The second patient developed grade 3 diarrhea and grade 3 vomiting resulting in grade 3 dehydration requiring hospitalization and i.v. hydration. Four more patients were accrued to dose level 4 (one withdrew from study and was replaced), one of whom developed a grade 3 hypomagnesemia that was consistent with the study’s definition of DLT. Dose level 4 was thus considered the MTD and the recommended dose for future clinical studies.

Of six evaluable patients receiving the MTD, four patients had chemotherapy before study entry. All patients at the MTD except the single patient with DLT dose were able to receive the full-intended dose of docetaxel, cisplatin, and capecitabine on cycle 1.

**Antitumor activity**

Sixteen eligible patients were assessable for response. Eight patients were nonevaluable because of early termination due to toxicity or patient withdrawal. An objective response was noted

<table>
<thead>
<tr>
<th>Toxicities in cycle 1 or any cycle</th>
<th>Dose level 2:</th>
<th>Dose level 3:</th>
<th>Dose level 4:</th>
<th>Dose level 5:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Dose level 1:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>20 mg/m² D, 20 mg/m² D, 20 mg/m² P, 600 mg/m² C</td>
<td>27 mg/m² D, 20 mg/m² P, 825 mg/m² C</td>
<td>27 mg/m² D, 20 mg/m² P, 825 mg/m² C</td>
<td>36 mg/m² D, 27 mg/m² P, 825 mg/m² C</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hypomagnesemia</td>
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<tr>
<td>Hyponatremia</td>
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</tbody>
</table>

NOTE: n = number of evaluable patients.
Abreviations: D, docetaxel; P, cisplatin; C, capecitabine.
*DLT.
0.92 ± 0.26, respectively. The change in docetaxel AUC from cycle 1 to 2 of individual patients is presented in Fig. 2.

Representative total and ultrafiltrate Pt concentration versus time profiles on cycles 1 and 2 for an individual patient are depicted in Fig. 3. A summary of total Pt pharmacokinetic variables is presented in Table 4. After administration of cisplatin at 20 mg/m², the mean ± SD of total Pt AUC on cycles 1 and 2 were 13.6 ± 2.8 and 18.7 ± 4.1 µg/mL h, respectively (P = 0.001). After administration of cisplatin at 27 mg/m², the mean ± SD of total Pt AUC on cycles 1 and 2 were 19.5 ± 4.5 and 22.5 ± 5.4 µg/mL h, respectively (P = 0.001). The ratio of total Pt AUC from cycles 1 to 2 after doses of 20 and 27 mg/m² were 1.38 ± 0.17 and 1.21 ± 0.24, respectively. The change in total Pt AUC from cycle 1 to 2 of individual patients is presented in Fig. 4.

A summary of ultrafiltrate Pt pharmacokinetic variables is presented in Table 5. After administration of cisplatin at 20 mg/m², the mean ± SD of ultrafiltrate Pt AUC on cycles 1 and 2 were 0.30 ± 0.06 and 0.41 ± 0.09 µg/mL h, respectively (P = 0.08). After administration of cisplatin at 27 mg/m², the mean ± SD of ultrafiltrate Pt AUC on cycles 1 and 2 were 0.68 ± 0.44 and 0.60 ± 0.41 µg/mL h, respectively (P = 0.08). The ratio of ultrafiltrate Pt AUC from cycle 1 to 2 after doses of 20 and 27 mg/m² were 1.41 ± 0.42 and 1.27 ± 0.51, respectively. The change in ultrafiltrate Pt AUC from cycles 1 and 2 of individual patients is presented in Fig. 5.
The combination of docetaxel, cisplatin, and 5-FU has been recently shown to have significant activity in the treatment of head and neck and gastric cancers. In a phase I-II trial, 43 locally advanced head and neck cancer patients were treated with induction chemotherapy consisting of docetaxel, cisplatin, and fluorouracil (22). Docetaxel was given at 75 mg/m² on day 1, cisplatin at 100 mg/m² on day 1, and 5FU 1,000 mg/m² on days 1 to 4. Mucositis in 48% of cycles, and grade 3 to 4 neutropenia in 19%. Severe stomatitis occurred in 30% of patients. Severe diarrhea occurred in 9%. Major responses were observed in 93% and clinical CRs in 54%. In another phase II trial, 30 treatment-naive patients with locally advanced head and neck cancer were treated with docetaxel, cisplatin, and 5-FU by protracted i.v. infusion on days 1 to 4. Grade 3 to 4 neutropenia was observed in 95% of patients and febrile neutropenia in 19%. Severe stomatitis occurred in 30% of patients. Severe diarrhea occurred in 9%. Major responses were observed in 93% and clinical CRs in 54%. In another phase II trial, 30 treatment-naive patients with locally advanced head and neck cancer were treated with docetaxel, cisplatin, and 5-FU by protracted i.v. infusion infusion, and leucovorin (23). Leucovorin was given as a loading dose at 100 mg orally before docetaxel on day 1. Docetaxel was given at 60 mg/m² over 1 hour on day 1. Cisplatin was given at 31.25 mg/m² over 1 hour on days 1 to 4. 5-FU (700 mg/m²/d) and leucovorin (500 mg/m²/d) were given by continuous infusion days 1 to 4. The response rate was high at 93% (63% CR and 30% PR). Fifteen of 22 after chemotherapy biopsies were negative for malignancy. Toxicity of this regimen included one treatment-related death, grade 3 neuropathy was limited to grade 1 and 2 levels and occurred in 22% of patients. Five percent of patients developed grade 3 to 4 renal toxicity. The combination of docetaxel, 5-FU, and cisplatin has also been evaluated in patients with recurrent head and neck cancer after definitive radiation or chemoradiation therapy (24). Nineteen patients were entered on this phase II trial. Sixteen percent had febrile neutropenia. Thirteen percent had a CR and 31% had PR. This overall response rate compares favorably with the historical 30% response rate seen with 5-FU plus cisplatin in patients with recurrent or metastatic disease. Whether applied as a frontline or as second-line therapy in recurrent disease of head and neck cancer, this triple combination seems to lead to superior results compared with historical controls using cisplatin plus 5-FU (25–27). The combination of docetaxel, cisplatin, and 5-FU has also been investigated against 5-FU and cisplatin in a phase III study in chemotherapy-naive patients with metastatic or locally recurrent, unresectable gastric cancer (28). The triple combination was superior to 5-FU and cisplatin in terms of response rate, time to progression, and overall survival. The addition of docetaxel to cisplatin and 5-FU was associated with an increased rate of grade 3 to 4 neutropenia (84%) and febrile neutropenia (16%; ref. 28).

The high activity of docetaxel, 5-FU, and cisplatin has been counterbalanced by significant toxicities as described in the regimens above. Of particular importance is a high rate febrile neutropenia in the range of 15% to 20% (22, 24, 28). Furthermore, the application of this regimen is hindered by the protracted i.v. infusion of 5-FU, which requires hospitalization or outpatient infusional therapy after central line placement. Substituting 5-FU with capecitabine results in simpler, less invasive schedule of administration, while potentially maintaining a high degree of activity. A phase I/II study in patients with advanced gastric cancer has determined a dose of 60 mg/m² for both cisplatin and docetaxel every 3 weeks in combination with D1-14 capecitabine at 1,875 mg/m²/d as the recommended dose for treatment. This combination was associated with an impressive 67.5% response rate and a time to progression of 7.8 months (29). We have similarly shown the feasibility of this combination in a variant intermittent weekly schedule of docetaxel and cisplatin. The recommended dose in our study consisted of 27 mg/m² docetaxel and 27 mg/m² cisplatin on days 1 and 8 in combination with 825 mg/m² capecitabine orally bid days 1 to 14. This dose intensity is comparable to the dose intensity described with the every-3-week study reported by Kang. In our study, docetaxel, cisplatin, and capecitabine were well tolerated when used at the MTD or lower levels. Hypomagnesemia was common and noted in

### Table 4. Total platinum pharmacokinetic variables

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Cycle 1 (mean ± SD)</th>
<th>Cycle 2 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{10}$ ($h^{-1}$)</td>
<td>0.04 ± 0.03</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>$k_{12}$ ($h^{-1}$)</td>
<td>1.3 ± 0.8</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>$k_{21}$ ($h^{-1}$)</td>
<td>0.9 ± 1.5</td>
<td>0.7 ± 0.3</td>
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<tr>
<td>$V_c$ (L/m²)</td>
<td>8.0 ± 5.0</td>
<td>6.7 ± 2.9</td>
</tr>
<tr>
<td>CL* (L/h/m²)</td>
<td>0.22 ± 0.09</td>
<td>0.13 ± 0.11</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>108.8 ± 169.4</td>
<td>944.4 ± 8216.3</td>
</tr>
</tbody>
</table>

*CL was significantly reduced in cycle 2 compared with cycle 1 ($P = 0.01$).

### Table 5. Ultrafiltrate platinum pharmacokinetic variables

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Cycle 1 (mean ± SD)</th>
<th>Cycle 2 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{10}$ ($h^{-1}$)</td>
<td>2.0 ± 1.0</td>
<td>5.1 ± 9.9</td>
</tr>
<tr>
<td>$V_c$ (L/m²)</td>
<td>21.8 ± 10.2</td>
<td>26.5 ± 27.7</td>
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<td>CL (L/h/m²)</td>
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<tr>
<td>$t_{1/2}$ (h)</td>
<td>0.39 ± 0.12</td>
<td>0.54 ± 0.25</td>
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</table>

*t$_{1/2}$ was significantly reduced in cycle 2 compared with cycle 1 ($P = 0.03$).
almost half the patient population. This toxicity was easily manageable with magnesium supplementation and was asymptomatic in all affected patients. A broad spectrum of activity was noted in a variety of solid tumors among our patient population. Most notable is a PR in a patient with gastric cancer with a time to progression of 10.5 months (received 14 cycles). Significant activity was also noted in patients with non–small-cell lung cancer. Three patients who failed prior carboplatin and paclitaxel had disease stabilization for 4 to 5 months; one untreated patient had a CR that was maintained for 6 months. Prolonged stabilizations were also noted in patients with head and neck cancer, unknown-primary cancer, pancreatic cancer, anal, and esophageal cancer. Pharmacokinetic studies of docetaxel, total platinum, and ultrafiltrate platinum were done on cycle 1 in combination with capecitabine and on cycle 2 without capecitabine. There was no difference in the disposition of docetaxel on cycles 1 and 2. However, there were differences in the disposition of total and ultrafiltrate platinum on cycles 1 and 2. The AUC of total platinum was significantly greater in cycle 2 compared with cycle 1 ($P < 0.05$). In addition, the AUC of ultrafiltrate platinum was significantly greater in cycle 2 compared with cycle 1 ($P < 0.05$).

The mechanism for the increased exposure of platinum on cycle 2 compared with cycle 1 is unclear. Previous studies have shown that docetaxel does not alter the disposition of cisplatin. Bonetti et al. evaluated the pharmacokinetics of total and ultrafiltrate platinum over four cycles after administration of cisplatin daily for 5 days (30). There was an increase in total platinum over the four cycles of treatment. This change was no longer evident when calculations were made taking into account the pretreatment values of total platinum before each cycle. In our study, the concentrations of platinum in plasma before administration of cycle 2 were not detectable in most patients. In patients with detectable platinum concentrations before cycle 2, taking into account these concentrations did not alter the results of our study. Leone et al. also evaluated the kinetics of single-agent cisplatin on cycles 1 and 2. In all patients, there was an increase in the $t_{1/2}$ and AUC and decrease in clearance on cycle 2 compared with cycle 1 (31). As in our study, the renal function was stable in both cycles. A phase I and pharmacokinetic study of the combination of capecitabine and cisplatin was done in patients with head and neck cancer; however, the study did not evaluate the disposition of cisplatin with and without capecitabine (32). In this study, cisplatin was given in combination with capecitabine on day 1 of cycles 1 and 2 and there was a marked and significant ($P = 0.007$) increase in ultrafiltered cisplatin concentrations between cycle 1 $(0.048 \pm 0.012 \mu g/mL)$ and cycle 2 $(0.071 \pm 0.023 \mu g/mL)$. Thus, a reduction in the clearance and increase in exposure of platinum in subsequent cycles may be inherent with prior cisplatin administration. However, prior administration of capecitabine on cycle 1 cannot be ruled out as a factor associated with increased exposure of platinum on cycle 2 compared with cycle 1 in our study or the study by Pivot et al. A more appropriate regimen to evaluate the effect of capecitabine on the pharmacokinetics of cisplatin and docetaxel would have been to administer cisplatin and docetaxel on day 1 of cycle 1 without capecitabine and compare this to the pharmacokinetics of the drugs with capecitabine on day 1 of cycle 2. In our study, cisplatin, docetaxel, and capecitabine were given on day 1 of cycle 1 to evaluate the toxicity associated with the complete regimen.

This study confirms the feasibility of combining docetaxel, cisplatin, and capecitabine in a weekly intermittent schedule. The MTD of docetaxel, cisplatin, and capecitabine consists of docetaxel $(27 \text{mg/m}^2)$ weeks 1 and 2, cisplatin $(27 \text{mg/m}^2)$ weeks 1 and 2, and capecitabine $(825 \text{mg/m}^2)$ orally bid days 1 to 14. This dose level is recommended for future clinical trials that may target gastric, lung, pancreatic, or unknown primary cancers.

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