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ORIGINAL ARTICLE

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Phase I study of weekly (day 1 and 8) docetaxel in combination with capecitabine in patients with advanced solid malignancies

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Abstract *Purpose*: Capecitabine in combination with docetaxel given every 3 weeks has shown a high degree of activity in a number of tumor types, but at the expense of significant toxicity. To improve the therapeutic index, we evaluated a weekly regimen of docetaxel in combination with capecitabine, and determined the maximum tolerated dose, toxicities and pharmacokinetics of this combination. *Patients and methods*: Patients with advanced solid malignancies were treated with docetaxel on days 1 and 8, and capecitabine, twice daily on days 1–14, of an every-21-day cycle. Pharmacokinetics of docetaxel were assessed on days 1 and 8 of the first cycle of chemotherapy. *Results*: Enrolled in the study were 25 patients. The most frequent toxicities were asthenia, hand-foot syndrome and mucositis. Inability to deliver at least 75% of the planned doses of both drugs during the first two cycles of chemotherapy was noted at dose levels 2, 3 and 4. Dose level 1 (docetaxel 30 mg/m^2 and capecitabine 825 mg/m^2 twice daily) is the recommended dose for phase II studies. Five patients experienced a partial response, and eight patients had stabilization of disease. Coadministration of capecitabine did not alter the pharmacokinetics of docetaxel. *Conclusion*: The regimen consisting of docetaxel 30 mg/m^2 (days 1, 8) and capecitabine 825 mg/m^2 twice daily (days 1–14) was well tolerated. Capecitabine did not alter pharmacokinetics of docetaxel. Further testing of this regimen in tumor-specific trials, especially gastric, lung and breast cancer, is warranted.

Keywords Capecitabine · Combination · Docetaxel · Phase I · Pharmacokinetics

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Introduction

Capecitabine, a novel fluoropyrimidine, is a prodrug of 5-fluorouracil (5-FU) and is approved for the treatment of patients with metastatic breast and colorectal cancer. After oral administration, capecitabine is absorbed intact from the gastrointestinal mucosa and is converted to 5-FU through sequential metabolism by carboxylesterase, cytidine deaminase and thymidine phosphorylase (TP) [1]. TP, which is the rate-limiting enzyme, is selectively overexpressed in certain solid tumors [2–5]. Therefore, oral administration of capecitabine can produce higher concentrations of 5-FU in tumor tissue than in normal tissues. This has been documented in clinical

studies, where administration of capecitabine has been shown to result in approximately 2.5 times higher concentrations of 5-FU in the tumor tissue than in normal tissues [6]. Capecitabine also exhibits synergistic interaction with several other anticancer agents [7].

Docetaxel, a tubulin-binding agent, upregulates the activity of TP in mouse mammary tumor cells in vitro and in xenograft models [8–10]. In a pilot study, Kurosumi et al. demonstrated upregulation of TP activity in breast cancer specimens of women treated with docetaxel [11]. Thus, sequential administration of docetaxel followed by capecitabine could result in enhanced efficacy of capecitabine. The non-overlapping toxicities of the two drugs and preclinical synergy provide the rationale for evaluating the combination of capecitabine with docetaxel clinically.

Pronk et al. evaluated the combination of capecitabine given orally on days 1–14, and docetaxel given intravenously every 3 weeks in a phase I trial [12]. The phase II recommended doses were docetaxel (75 mg/m^2) in combination with capecitabine (1250 mg/m^2 twice daily) or docetaxel (100 mg/m^2) with capecitabine (825 mg/m^2 twice daily). Subsequently, a large phase III trial evaluated the efficacy of docetaxel (75 mg/m^2, intravenously every 3 weeks) in combination with capecitabine (1250 mg/m^2 twice daily on days 1–14) in patients with metastatic breast cancer [13]. That study demonstrated a survival advantage for this regimen, which led to its approval by the Food and Drug Administration for the treatment of patients with metastatic breast cancer. However, the regimen was also associated with considerable toxicity. Of the 251 patients treated with the combination, the incidence of grade 4 neutropenia with fever was 13%. Other commonly reported grade 3/4 toxicities included neutropenia (16%), stomatitis (17%), diarrhea (14%) and hand-foot syndrome (HFS) (24%). About two-thirds of the patients treated with the combination regimen required dose reduction of capecitabine alone, docetaxel alone or both drugs for adverse events. The toxicities noted with the combination of capecitabine and docetaxel were more common than in the control arm of therapy with docetaxel alone. Another study evaluated the same regimen, docetaxel (75 mg/m^2) and capecitabine (1250 mg/m^2 twice daily), in patients with advanced gastric cancer. A high degree of activity was seen, but there was significant toxicity, and the authors recommended lower doses of both agents for subsequent trials [14].

In preclinical experiments, upregulation of TP activity was noted within 4 days of docetaxel treatment, and the effect was maximal at about 6–8 days [9]. Hence, we hypothesized that a weekly schedule of docetaxel would provide improved synergy for administration in combination with capecitabine (which is administered for 14 days per cycle). Furthermore, weekly schedules of docetaxel are associated with a lower incidence of myelosuppression than is the every-3-week regimen. Two separate studies in patients with non-small-cell lung cancer demonstrated comparable efficacy between the weekly and the every-3-week schedule of docetaxel, while the incidence of myelosuppression was lower with the weekly schedule [15–17]. Hence we performed a phase I clinical study to evaluate the combination of capecitabine and a weekly schedule of docetaxel for patients with advanced solid tumors.

Patients and methods

Eligibility

Patients with histologically confirmed solid organ tumors refractory to standard therapy or with tumors for which there was no effective therapy were eligible for the study. Other eligibility criteria included: age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; life expectancy >12 weeks; acceptable renal function, defined as serum creatinine not more than the upper limit of normal (ULN) or creatinine clearance >50 ml/min/1.73 m^2 for patients with serum creatinine above the ULN; acceptable hepatic function, defined as serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) not more than 2.5 times the ULN if serum alkaline phosphatase (AP) was less than the ULN, or AP not more than 4 times the ULN if AST and ALT were less than the ULN; serum total bilirubin less than the ULN; peripheral neuropathy not more than grade 1; and the ability to take oral medications. All patients provided written informed consent according to institutional guidelines. Exclusion criteria were: chemotherapy or radiotherapy within 4 weeks prior to enrollment (6 weeks for patients who had received nitrosoureas or mitomycin C); untreated brain metastases; pregnancy; uncontrolled intercurrent illnesses such as symptomatic congestive heart failure, unstable angina, cardiac arrhythmia, etc.; and a history of positive human immunodeficiency virus antibody. Patients of reproductive age were required to use appropriate contraception during participation in the study.

Dosage and dose escalation

Protocol therapy was administered in 3-week cycles. Docetaxel was administered as a 30-min intravenous infusion on days 1 and 8 of each cycle. Capecitabine was administered orally twice a day on days 1–14. Capecitabine therapy was started on day 2 of the first cycle so that samples could be obtained to study the pharmacokinetics of docetaxel in the absence of capecitabine. Dexamethasone (4 mg) premedication was administered orally the night before, and the morning and evening of each dose of docetaxel. During the initial phase of dose escalation, capecitabine was fixed at 825 mg/m^2, and the docetaxel dose started at 30 mg/m^2 and was escalated in 10 mg/m^2 increments in subsequent cohorts of patients. Once the phase II recommended dose of docetaxel was

established, the dose of docetaxel was reduced by one dose level, and capecitabine dose was to be escalated to 1000 mg/m^2 and 1250 mg/m^2 for subsequent cohorts. No intrapatient dose escalation was allowed.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Dose-limiting toxicity (DLT) was defined as the occurrence of one or more of the following events: grade 3 or higher non-hematological toxicity except alopecia or grade 3 nausea, vomiting and diarrhea lasting more than 48 h despite appropriate medical therapy; grade 4 neutropenia lasting more than 1 week; fever accompanied by absolute neutrophil count (ANC) $\leq$1000 μl^{-1}; platelet count $\leq$25,000 μl^{-1}; or delay in treatment lasting longer than 2 weeks due to toxicity from chemotherapy. Between three and six patients were treated at each dose level. If none of the patients in the cohort experienced DLT, patients were accrued to the next higher dose level. The cohort was to be expanded to six patients if DLT was noted in one out of the first three evaluable patients treated in that cohort. The phase II recommended dose was defined as the dose level at which fewer than two of six patients experienced DLT. Once this was defined, ten additional patients were treated at that dose level for more thorough characterization of the safety profile of the regimen in patients with advanced solid malignancies. Tumor responses were evaluated by the RECIST criteria [18].

Dose modifications for toxicity

All patients were required to have laboratory parameters within acceptable limits, as defined in the eligibility criteria, on the first day of each treatment cycle. Dose modifications were based on the most severe toxicity experienced by the patient. HFS, mucositis and diarrhea are common toxicities associated with capecitabine. In the event of grade 2 or 3 HFS, capecitabine was withheld until resolution of toxicity to not more than grade 1. Subsequent doses were administered at 75% of the original dose. For the patients who developed grade 2 or 3 HFS for the second time, treatment was withheld until resolution of toxicity to not more than grade 1 and then restarted at 50% of the original dose. Patients were discontinued from study for subsequent episodes of HFS. Diarrhea was treated with loperamide tablets. Patients were instructed to take one tablet every 2 h until they were free from diarrhea for at least 12 h. For patients with an ANC $\leq$750 μl^{-1} or platelet count $\leq$75,000 μl^{-1} on day 8 of the treatment cycle, capecitabine therapy was withheld for the rest of the cycle.

Reduction in docetaxel dose by 25% was required for patients who developed grade 4 thrombocytopenia, grade 4 neutropenia lasting more than 7 days, or accompanied by fever or elevation in AST and/or ALT from 1.6–5 times the ULN. Docetaxel therapy was withheld for up to 3 weeks for serum bilirubin above the ULN or ALT, AST, or alkaline phosphatase level more than 5 times the ULN, and was reduced by 25% for subsequent doses. Patients were removed from further protocol therapy if serum bilirubin did not normalize, or if ALT, AST and/or alkaline phosphatase did not return to less than 5 times the ULN upon withholding therapy for up to 3 weeks. For patients who developed grade 2 neuropathy, docetaxel was held until neuropathy decreased to not more than grade 1, after which docetaxel was restarted with a 25% dose reduction. Patients who experienced grade 4 anaphylactic reactions were removed from the study.

Pharmacokinetic studies

Blood samples for docetaxel pharmacokinetic analysis were obtained on days 1 and 8 of the first cycle of therapy. Samples were obtained at the following timepoints: 30 min before docetaxel administration, and at 15, 25, 45, 60, 90, 210, 330 and 450 min after the docetaxel infusion was started. Another plasma sample was obtained at 24 h after the end of the infusion. At each sampling time, approximately 6 ml of blood were collected in heparinized tubes and centrifuged at 1200 *g* at 4°C for 5 min. The resulting plasma was removed and immediately frozen and stored at −70°C until analyzed. Docetaxel concentrations were quantified by a high-performance liquid chromatography/mass spectrometric (HPLC/MS) assay developed and validated in our laboratory [19]. Compartmental pharmacokinetic analysis of docetaxel was performed using maximum likelihood estimation in the computer program ADAPT II (Biomedical Simulations Resource, University of Southern California, Los Angeles, Calif.). A three-compartment, open, linear model was fitted to docetaxel concentration versus time profiles. Individual parameters estimated by the model were the volume of the central compartment (V_c), the elimination rate constant (k_{10}) and intercompartmental rate constants (k_{12}, k_{21}, k_{13}, k_{31}). The area under the docetaxel plasma concentration versus time curves (AUC) from zero to infinity were calculated using patient-specific parameters to simulate the concentration versus time data for each patient. Clearance was calculated from the expression: clearance = dose/AUC. The difference in docetaxel clearance on days 1 and 8 was evaluated by calculating the ratio of docetaxel clearance on day 1 and to that on day 8.

Results

Between October 2001 and March 2003, 25 patients were enrolled at the University of Pittsburgh Cancer Institute (Table 1), and of these patients, 23 received at least one cycle of therapy. One patient in dose level 2 developed symptomatic progression of disease and did not complete the first cycle of therapy. He was replaced in order to obtain complete clinical and pharmacokinetic data. Another patient, who was enrolled to dose level 1, had

Table 1 Baseline characteristics

Number of patients	25
Males/females	16/9
Age (years)	
Median	59
Range	51–74
Primary tumor	
Esophagus	3
Gastric	4
Colorectal	4
Lung	3
Pancreatic	2
Bladder	2
Head and neck	2
Other*	5
Performance status (ECOG)	
0	10
1	15
2	0
Number of prior chemotherapy regimens	
0	3
≤2	13
>2	9
Patients with prior radiotherapy	20

*Includes one case each of mesothelioma, carcinoma of unknown primary site, biliary, hepatocellular and ovarian cancer

Table 2 Dose escalation scheme (treatment cycles were repeated every 21 days)

Dose level	Capecitabine (days 1–14)	Docetaxel (day 1, 8)	Number of patients
1	825 mg/m^2 twice daily	30 mg/m^2	13
2	825 mg/m^2 twice daily	40 mg/m^2	7
3	825 mg/m^2 twice daily	50 mg/m^2	3
4	1000 mg/m^2 twice daily	40 mg/m^2	2

acute deterioration in PS and did not receive any protocol therapy. Twenty-two patients had received prior chemotherapy, whereas 20 patients had undergone prior radiation. All of the patients enrolled in the study had an ECOG PS of 0 or 1. Because no DLT was observed at the first three dose levels, dose escalation proceeded with three patients per cohort (Table 2). However, it was noted that due to grade 2 non-hematological toxicities, several patients at dose levels 2, 3 and 4 required frequent dose modifications and dose delays during the first two cycles. Therefore, patient accrual was halted, and an amendment was made to expand the definition of DLT to include the inability to deliver at least 75% of the intended doses of capecitabine and docetaxel during the first two cycles of therapy. Because one out of three patients at dose level 2 experienced DLT by the new criteria, an additional three patients were enrolled to dose level 2. In two out of the three additional patients, it was not possible to deliver at least 75% of the planned doses of chemotherapy during the first two cycles. Hence, we expanded dose level 1 to include a total of six patients. In that no DLT occurred in the expanded cohort, dose level 1 (docetaxel 30 mg/m^2 days 1 and 8, capecitabine 825 mg/m^2 twice daily days 1–14) was deemed the dose recommended for future studies. We enrolled seven more patients to dose level 1 to obtain additional toxicity data and evaluate the tolerability of the regimen. In the 13 patients treated at dose level 1, grade 3 non-hematological toxicity was noted in only one patient. A combined total of 80 cycles of chemotherapy were administered to patients as part of the entire trial. The median number of cycles of chemotherapy was three (range one to six), and 12 patients received four or more cycles of chemotherapy.

Toxicity

Dose reductions for one or both of the study medications were necessary in 12 patients overall. At dose level 1 (phase II recommended dose), doses were modified in 3 out of 13 patients. HFS and mucositis were the most common reasons for reducing the dose of capecitabine. Reduction of the dose of capecitabine was necessary in 13 out of the total of 80 cycles of chemotherapy administered as part of the study. Docetaxel required dose modification in five cycles due to fatigue and neutropenia. Only one patient treated at dose level 1 required dose reduction/modification during the first two cycles of chemotherapy. Another patient, who developed febrile neutropenia during the first cycle, was discontinued from further treatment. The most common reason for discontinuation of protocol therapy was progression of disease. One patient with head and neck cancer developed bleeding from an ulcerated tumor site, requiring external beam radiation. Hence, the patient was removed

Table 3 Grade 3 Hematological toxicity (number of patients)

Toxicity	Dose level 1 (docetaxel 30 mg/m^2, capecitabine 825 mg/m^2)	Dose level 2 (docetaxel 40 mg/m^2, capecitabine 825 mg/m^2)	Dose level 3 (docetaxel: 50 mg/m^2, capecitabine 825 mg/m^2)	Dose level 4 (docetaxel: 40 mg/m^2, capecitabine: 1000 mg/m^2)
Number of patients treated	13	7	3	2
Leukopenia	0	1	2	0
Neutropenia	0	4	2	0
Febrile neutropenia	1	0	0	0
Anemia	1	0	1	0
Thrombocytopenia	0	0	0	0

Table 4 Non-hematological toxicity (the only grade 3 non-hematological toxicities noted were anorexia and vomiting in one patient each at dose level 2)

Toxicity	Dose level 1 (docetaxel 30 mg/m^2, capecitabine 825 mg/m^2)		Dose level 2 (docetaxel 40 mg/m^2, capecitabine 825 mg/m^2)		Dose level 3 (docetaxel 50 mg/m^2, capecitabine 825 mg/m^2)		Dose level 4 (docetaxel 40 mg/m^2, capecitabine 1000 mg/m^2)	
Grade	1	2	1	2	1	2	1	2
Hand-foot syndrome	2	3	0	0	0	2	0	1
Mucositis	3	2	1	2	1	0	0	2
Fatigue	5	1	4	0	0	1	2	0
Neuropathy	1	1	3	0	1	1	0	0
Skin rash	3	0	2	0	1	0	0	0
Anorexia	1	0	3	1	0	0	0	0
Fever	1	1	0	1	1	0	0	0
Nausea	2	0	2	0	2	0	0	1
Vomiting	2	0	1	0	0	0	0	0
Diarrhea	4	1	4	0	1	0	0	1
Edema	2	0	3	0	0	0	1	0
Alopecia	0	0	1	0	0	0	1	1
Arthralgia/myalgia	2	0	1	0	0	0	0	0

from further protocol therapy. The hematological and non-hematological toxicities experienced by patients in the study are summarized in Tables 3 and 4.

Efficacy

Five patients experienced a partial response (three gastric cancer, one colon cancer, one esophageal cancer). Four patients with gastric cancer were accrued among whom there were three partial responses. One partial responder with gastric cancer, who had received three prior chemotherapy regimens, experienced marked reduction in the size of metastatic hepatic lesions. Another patient with gastric cancer experienced marked reduction in size of the primary tumor and several peritoneal implants along with complete resolution of ascites. Stabilization of disease was seen in eight patients after two cycles, and three of these patients remained stable after four cycles of therapy. These three patients had esophageal, colon and bladder carcinoma, respectively. Six of 13 patients treated at dose level 1 (phase 2 recommended dose) received four or more cycles of chemotherapy.

Pharmacokinetics

Pharmacokinetic studies for docetaxel were performed on 14 patients (ten patients at dose level 1). Figure 1 shows representative plasma docetaxel concentration versus time profiles from day 1 (alone) and day 8 (in combination with capecitabine) in a patient treated at the phase II recommended dose. On day 1, the mean ± SD AUCs of docetaxel after administration at doses of 30, 40, and 50 mg/m^2 were 1620 ± 1379, 1847 ± 726 and 3470 ± 504 ng/ml h, respectively. On day 8, the mean ± SD AUCs of docetaxel after administration at doses of 30 and 40 mg/m^2 were 1406 ± 698 and 1768 ± 611 ng/ml h, respectively. The mean ± SD docetaxel clearances on day 1 (alone) and day 8 (in combination with capecitabine) were 23.1 ± 6.5 and 19.7 ± 6.5 l/h/m^2, respectively. The mean ± SD of the ratio of docetaxel clearance on day 1 to that on day 8 for individual patients was 1.0 ± 0.1, indicating that capecitabine did not alter the disposition of docetaxel.

Discussion

The combination of docetaxel and capecitabine is active in the treatment of metastatic breast cancer and other solid tumors [13–15]. However, the excessive toxicity noted with the conventional regimen, which involves administering docetaxel every 3 weeks, necessitates the evaluation of novel schedules of combining the two drugs. Administering docetaxel on a weekly basis not only improves the tolerability of the regimen, but may also improve the anticancer effect of the combination. The results of our phase I trial, illustrate both of these aspects. At the phase II recommended dose, the regimen was well tolerated and was associated with promising anticancer activity.

Our study provides indirect clinical evidence for the observation in preclinical studies that docetaxel upregulates TP activity. For example, the most notable toxicity observed with the combination of docetaxel and capecitabine was HFS, which is exclusively attributable to capecitabine. At the capecitabine doses studied in our trial (825 mg/m^2 twice daily), one would expect a much lower incidence of HFS. The frequent occurrence of early HFS in our study implies upregulated TP activity in normal tissues resulting in higher concentrations of 5-FU, an effect presumably mediated by docetaxel. This observation was also noted in a phase I study in which a slightly different schedule of docetaxel and capecitabine was evaluated [20]. In that study, Nadella et al. admin-

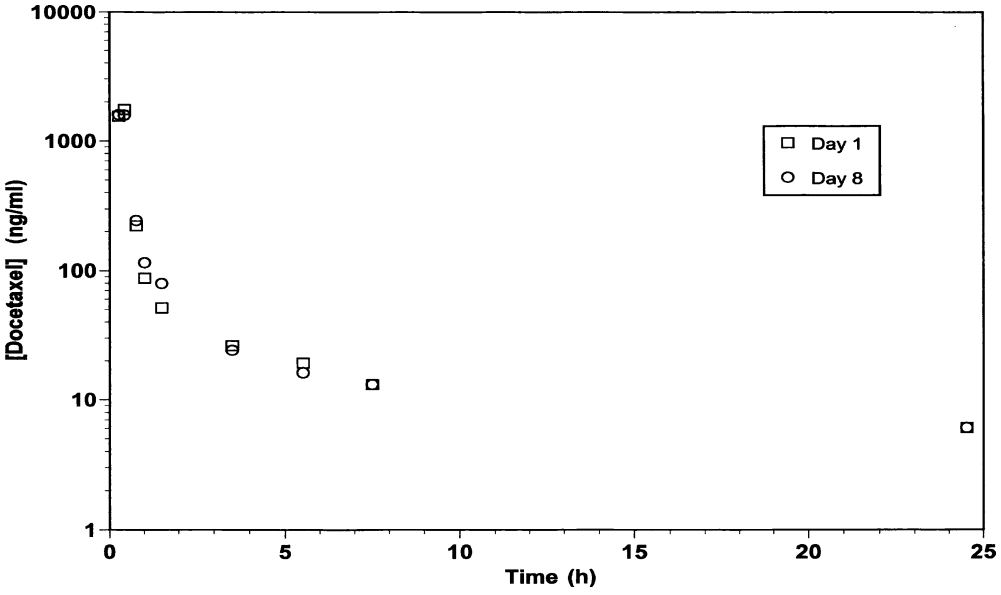

Fig. 1 Representative plasma docetaxel concentration versus time profiles from day 1 (alone) (*squares*) and day 8 (in combination with capecitabine) (*circles*) in a patient treated at the phase II recommended dose

istered docetaxel on days 1, 8 and 15 of an every-28-day cycle, while capecitabine was given twice daily on days 5–18. Of the total 77 courses of chemotherapy, 26 were complicated by the occurrence of HFS, which necessitated frequent dose modifications to reduce the incidence of this toxicity. Encouraging anticancer activity noted in heavily pretreated patients in both of these studies could also be attributed to upregulated TP activity.

The optimum sequence of docetaxel and capecitabine needs to be determined in future studies. In preclinical studies induction of TP by docetaxel occurred within 4–8 days of therapy. In patients with breast cancer receiving preoperative docetaxel-based therapy, TP levels were significantly increased compared to baseline levels in the surgical specimen [21]. The maximum duration of TP induction in response to therapy with docetaxel needs to be determined in future studies, which will allow optimum sequencing of capecitabine.

Our study also highlights the limitations of the "traditional" phase I trial design, where DLT is based upon toxicity observed during the first cycle of chemotherapy, and raises the need for continuing assessment of toxicity data when defining the optimal dose of a regimen. The initial study design defined DLT based on toxicity that occurred during the first cycle of chemotherapy. According to that definition, none of the patients treated at the first four dose levels experienced DLT. Had those initial criteria been used to determine DLT, higher doses of docetaxel and capecitabine compared to dose level 1 would have been recommended for future studies, and would not have been applicable to routine practice due to excessive cumulative toxicity. The observation of increased occurrence of HFS beyond the first cycle of chemotherapy prompted us to expand the definition of DLT to include the inability to deliver at least 75% of the planned dose of the regimen during the first two cycles, an important determinant of the practical applicability of the regimen. When this criterion was applied, dose level 1 was the optimum dose, which was confirmed by accruing a total of 13 patients at that dose level. Our findings are supported by a phase II study conducted by Han et al. in 39 patients with lung cancer. The schedule used in that study was identical to our regimen, but higher doses of docetaxel (36 mg/m^2) and capecitabine (1000 mg/m^2) were used. The regimen appeared to be active, but significant toxicity including two treatment-related deaths in addition to asthenia, stomatitis, HFS and diarrhea were seen. The authors recommended dose adjustments for subsequent studies [22].

The pharmacokinetic results of our study revealed that the calculated docetaxel clearances were comparable to those previously reported in the literature [12, 23]. In addition, there was no evidence that capecitabine altered the pharmacokinetics of docetaxel.

While antitumor activity was noted against a variety of tumor types, partial responses were noted in three out of four patients with gastric cancer treated in our study. Based on this, we have developed a phase II clinical trial evaluating this regimen in patients with advanced gastric cancer.

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