Cancer Chemother Pharmacol (2011) 68:1565–1573
DOI 10.1007/s00280-011-1639-3

ORIGINAL ARTICLE

Tesetaxel, a new oral taxane, in combination with capecitabine: a phase I, dose-escalation study in patients with advanced solid tumors

Muhammad Wasif Saif · John Sarantopoulos · Amita Patnaik · Anthony W. Tolcher · Chris Takimoto · Murali Beeram

Received: 8 March 2011 / Accepted: 17 March 2011 / Published online: 6 May 2011

Abstract
Purpose This phase I study was conducted primarily to determine the maximum tolerated dose (MTD) of tesetaxel, a novel, orally active, semisynthetic microtubule inhibitor of the taxane class, administered with oral capecitabine to patients with advanced solid tumors.

Methods During each 21-day cycle, patients were to receive tesetaxel on Day 1 and capecitabine twice daily on Days 1 through 14. The starting dose was tesetaxel 18 mg/m^2 and capecitabine 1,250 mg/m^2/day. These doses were increased based on tolerability during the first cycle according to the protocol-specified dose-escalation scheme. Response was evaluated every other treatment cycle according to RECIST. Serial blood samples were collected during the first and second cycles to explore possible pharmacokinetic drug interactions.
Results Twenty-seven patients were enrolled and treated. The most frequently reported dose-limiting toxicities were neutropenia and febrile neutropenia, with individual patients experiencing dose-limiting stomatitis and diarrhea. The MTD for the treatment regimen was defined as tesetaxel 27 mg/m^2 and capecitabine 2,500 mg/m^2/day. The most common ≥Grade 3 treatment-related adverse events included leukopenia (44% of patients) and neutropenia (41%). Of 22 evaluable patients, the best overall response was stable disease in 82% and progressive disease in 18%. No meaningful pharmacokinetic drug interactions were apparent.
Conclusions The results of this study demonstrate that these two orally active agents can be combined at the individual MTD of each drug with acceptable toxicity. These data further support the continued clinical development of tesetaxel both as a single agent and in combination with other active cancer therapeutics.

Keywords Tesetaxel · Oral taxane · Capecitabine · Oral fluoropyrimidine · Advanced solid tumors

Preliminary data were presented in abstract form at the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO), May 13–17, 2005, Orlando, FL and the 42nd Annual Meeting of ASCO, June 2–6, 2006, Atlanta, GA. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=32680 and http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=40&abstractID=34424.

M. W. Saif
University of Alabama at Birmingham,
Comprehensive Cancer Center, Birmingham, AL, USA

J. Sarantopoulos · A. Patnaik · A. W. Tolcher · C. Takimoto · M. Beeram
Institute for Drug Development, Cancer Therapy & Research Center, San Antonio, TX, USA

Present Address:
M. W. Saif (✉)
Columbia University, College of Physicians and Surgeons and the Herbert Irving Cancer Center, New York, NY 10032, USA
e-mail: mws2138@columbia.edu

Present Address:
J. Sarantopoulos
University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Present Address:
C. Takimoto
Ortho Biotech Oncology R&D/Centocor R&D, Inc., Radnor, PA, USA

Introduction

Tesetaxel is a novel, semisynthetic, orally bioavailable microtubule inhibitor of the taxane class with demonstrated

antitumor activity in multiple cell lines, various animal models, and clinical trials. Its mechanism of action involves the inhibition of tubulin depolymerization and, in turn, the arrest of unscheduled cell division and induction of apoptosis, similar to the taxanes, eribulin, and indibulin.

Preclinical research suggests that tesetaxel may overcome P-glycoprotein-mediated multidrug resistance, thereby facilitating extended intracellular retention and possibly clinical effectiveness [1]. Tesetaxel exhibited potent cytotoxicity against various human and murine cancer cell lines and was particularly potent against cell lines expressing P-glycoprotein [2]. Orally administered tesetaxel showed potent in vivo antitumor activity in murine syngeneic and human xenograft models [2] and was more potent against xenografts overexpressing P-glycoprotein than paclitaxel and docetaxel, probably due to a higher intracellular drug concentration [1]. The cytotoxic effect of tesetaxel, unlike that of other taxanes, was not influenced by the level of P-glycoprotein expression or by the presence of a P-glycoprotein modulator [1].

In early phase 2 clinical trials, tesetaxel was found to be an active single agent in second-line breast and gastric cancer [3, 4]. Limited single-agent activity was also observed in colorectal cancer [5], suggesting a different spectrum of activity than usually is associated with the taxane class and possibly related to its ability to overcome P-glycoprotein resistance.

Capecitabine is an oral fluoropyrimidine prodrug that is converted to its active metabolite 5-fluorouracil (5-FU) via a 3-step, enzymatic cascade. The final step in this process—conversion of the intermediate metabolite 5′-deoxy-5-fluorouridine to the cytotoxic agent 5-FU—is mediated by thymidine phosphorylase, an angiogenic factor preferentially expressed in tumor cells. Capecitabine cytotoxicity correlates with the activity of thymidine phosphorylase and dihydropyrimidine dehydrogenase, an enzyme that initiates 5-FU catabolism. Intracellular concentrations of 5-FU achieved with capecitabine are reported to be >100-fold those achieved with infusional 5-FU [6]. Importantly, the tumor-selective activation of capecitabine may minimize systemic exposure to 5-FU, possibly leading to improved safety and tolerability. Capecitabine is approved for use in colorectal cancer and is a convenient oral alternative to infusional 5-FU in this clinical setting.

The efficacy of capecitabine appears to be enhanced in human cancer xenografts with concurrent administration of taxanes, which upregulate levels of thymidine phosphorylase in tumor tissues [7]. Consistent with this finding, in vivo research showed that tesetaxel in combination with capecitabine was superior to capecitabine alone in targeting human colon cancer xenografts (Data on file, Genta Incorporated. Berkeley Heights, New Jersey, United States).

Given these preclinical observations, combination therapy with tesetaxel and capecitabine warranted investigation in the clinical setting, especially since the combination of these two orally active agents avoids the complications frequently associated with intravenously administered chemotherapy.

The present study was designed to explore the safety, antitumor activity, and possible pharmacokinetic interactions of tesetaxel combined with capecitabine in patients with advanced solid tumors.

Patients and methods

Study design and objectives

This phase 1, open-label, nonrandomized, dose-escalation study was conducted at two centers in the United States. Primary objectives were to determine the maximum tolerated dose (MTD), as well as the dose-limiting toxicities (DLTs) and non-DLTs, of tesetaxel and capecitabine administered in combination in a 21-day cycle to patients with advanced solid tumors. Secondary objectives were to characterize the safety profile and explore the antitumor activity of this combination treatment, as well as to identify any pharmacokinetic interactions between tesetaxel and capecitabine.

The protocol and consent form were approved by the institutional review board at each of the two participating centers before study initiation. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines of the International Conference on Harmonization, and Good Clinical Practice regulations of the U.S. Food and Drug Administration. All patients provided signed informed consent prior to participating in any study-related procedures.

Patient selection

Men or women who were at least 18 years of age and of any racial or ethnic group and had a histologically or cytologically confirmed locally advanced or metastatic solid tumor were eligible for enrollment. Patients were to be minimally pretreated, which was defined as <6 cycles of alkylating agent-containing chemotherapy, ≤6 cycles of carboplatin, <2 cycles of mitomycin C or a nitrosourea as a part of a single regimen, no prior bone marrow transplantation, and radiation therapy to ≤25% of hematopoietic reserves.

Other eligibility criteria included a life expectancy of ≥3 months; full recovery from previous surgery (≥4 weeks since major surgery); recovery from prior chemotherapy or radiation therapy (≥4 weeks since prior myelosuppressive therapy); Eastern Cooperative Oncology Group (ECOG)

performance status of ≤2; adequate bone marrow function (absolute neutrophil count [ANC] ≥1,500/μl and platelet count ≥100,000/μl), adequate kidney function (serum creatinine level ≤1.5 × upper limit of normal [ULN]), and adequate liver function (total bilirubin level ≤1.5 × ULN and serum glutamic oxaloacetic transaminase [SGOT] and serum glutamic pyruvic transaminase [SGPT] levels ≤2.5 × ULN or ≤5 × ULN when liver metastases were present). Before enrollment, patients with reproductive potential were to agree to practice approved methods of birth control, and women of childbearing potential had to have a negative pregnancy test documented during screening.

Patients were disqualified from entering the study if they had a history of other prior malignancy (except nonmelanoma skin cancer or in situ carcinoma of the uterine cervix), unless complete remission had been apparent and therapy discontinued for ≥2 years; major surgery of the stomach or small intestine; chronic diarrhea; severe or life-threatening hypersensitivity reaction to a taxane or capecitabine; or positive serology for human immunodeficiency virus. Pregnant or lactating women and patients who were receiving any cancer chemotherapy or radiotherapy or who had received any investigational drug within 28 days before tesetaxel administration also were excluded from the study.

Additional exclusion criteria included concurrent serious infection; symptomatic brain metastases; neuropathy ≥Grade 2 at baseline; swallowing difficulties or malabsorption disorder; diarrhea (i.e., more than 2–3 stools per day above the normal frequency during the previous month); psychiatric disorder that precluded informed consent or prevented patient compliance; and severe or uncontrolled underlying nononcologic medical condition that could compromise patient safety or affect study outcome.

Treatment schedule

The starting dose was 18 mg/m^2 for tesetaxel, which was administered once every 21 days, and 1,250 mg/m^2/day for capecitabine, which was administered in equally divided oral doses every 12 h for 14 consecutive days followed by 7 days of rest. The tesetaxel starting dose represented about 50% of the MTD for tesetaxel when given as a single agent to patients with advanced solid tumors in a previous phase I trial. The capecitabine starting dose represented 50% of the recommended dose of capecitabine when given as monotherapy or in combination with docetaxel [8–11]. The actual tesetaxel dose was rounded to the nearest 10 mg, and the capecitabine dose was rounded to the nearest dose that could be given with the 150-mg and 500-mg tablets.

On Day 1, patients received tesetaxel (supplied by Daiichi Sankyo Pharma Development, Tokyo, Japan, as 10-mg capsules) with water after an overnight fast and capecitabine (Xeloda™; supplied by Roche Laboratories Inc., Nutley, NJ, as 150-mg or 500-mg tablets) with food 2 h later. Subsequent capecitabine doses were given every 12 h, within 30 min of a meal, on Days 2 through 14. In Cycles 1 and 2 only, the dosing schedule was modified slightly to allow evaluation of possible pharmacokinetic interactions: capecitabine was administered as a single dose on Day −1 and on Day 1 of Cycle 1 and tesetaxel was given alone on Day 1 of Cycle 2.

Treatment cycles were administered every 21 days provided that the following conditions were met: ANC was ≥1,500/μl; platelet count was ≥100,000/μl; all associated nonhematologic toxicities (excluding alopecia) had recovered to Grade 0, Grade 1, or the baseline value; and diarrhea (without anti-diarrheals) had not occurred for ≥24 h before the start of the next cycle. The start of the next cycle was delayed if these criteria were not met. If recovery did not occur after a 2-week delay, treatment was discontinued. Treatment continued unless disease progression or unacceptable toxicity occurred, a concurrent nononcologic medical condition interfered with the study, or the patient withdrew consent or did not comply with study procedures.

Patients received study drugs on an outpatient basis. Tesetaxel was administered at study centers; capecitabine usage was recorded by patients in a diary and verified with tablet counts.

Dose escalation

Doses of tesetaxel and capecitabine were increased in cohorts of evaluable patients according to the protocol-specified dose-escalation scheme (Table 1) until the MTD was determined. The decision to escalate the dose was based on toxicity during Cycle 1. Specifically, a minimum of 3 patients were to be followed for at least one complete treatment cycle (21 days in the absence of a dose delay) at

Table 1 Dose-escalation scheme

Cohort	Tesetaxel dose (mg/m^2)[b]	Capecitabine dose (mg/m^2/day)[b]
1	18	1,250
2	27	1,250
3	27	1,900
4[a]	35	1,900
5	27	2,500
6[a]	35	2,500

[a] These cohorts could be omitted based on the toxicity at prior dose levels

[b] The actual tesetaxel dose was rounded to the nearest 10 mg, and the actual capecitabine dose was rounded to the nearest dose that could be given with the 150-mg and 500-mg tablets

the starting dose level before escalation to the next dose level. The dose level was escalated in successive cohorts of 3 patients each provided that no DLT was observed. If one DLT occurred among the initial 3 patients treated at a given dose level, an additional 3 patients were treated at that dose level without DLT in order for dose escalation to proceed. When ≥2 patients experienced a DLT at a particular dose level, that dose level was considered intolerable. Further patients were then recruited at the previous dose level to ensure that a minimum of 6 evaluable patients were treated at the MTD to confirm tolerability (i.e., ≤1 DLT in 6 patients). Tesetaxel was to be increased to a maximum dose of 35 mg/m^2 and capecitabine to a maximum total daily dose of 2,500 mg/m^2.

Dose-limiting toxicity was defined as the occurrence in Cycle 1 of any one of the following: febrile neutropenia (temperature ≥38.5°C and ANC $<0.5 \times 10^3$/mm^3); Grade 4 neutropenia (ANC $<0.5 \times 10^3$/mm^3) lasting for >5 days; thrombocytopenia (platelet count $<25 \times 10^3$/mm^3); ≥Grade 3 vomiting despite maximum supportive care; ≥Grade 3 neurotoxicity; any other ≥Grade 3 nonhematologic toxicity (excluding nausea, vomiting, and certain transient Grade 3 nonhematologic toxicities); or inability to start a second treatment cycle after a 1-week delay. The MTD was defined as the combination dose of tesetaxel and capecitabine below the dose level at which 2 patients of a cohort of 2–6 patients experienced DLTs during the first treatment cycle.

Concomitant treatment

It was recommended that patients receive full supportive care, including blood transfusions, antibiotics, antiemetics, anti-diarrheals, and analgesics, as clinically appropriate. Prophylactic use of granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor was not allowed in Cycle 1; it could be used after Cycle 1 to prevent recurrence of prolonged Grade 4 neutropenia (>5 days) or neutropenic fever (>38.5°C with ANC <1,000/μl). Continuation of any regular treatment (except antineoplastic therapy) and use of erythropoietin products were permitted. Caution was to be exercised in patients receiving substrates or strong inhibitors or inducers of CYP3A and P-glycoprotein activity due to their possible effect on plasma levels of tesetaxel.

Clinical assessments and follow-up

Safety

Baseline and screening procedures comprised a complete physical examination, including determination of ECOG performance status; medical history; complete blood count (CBC) with differential and platelet count; serum-chemistry profile; urinalysis; pregnancy testing (as applicable); and 12-lead electrocardiography.

During therapy, patients were followed with weekly CBCs. If the ANC fell to <500/μl, the CBC was to be repeated twice weekly until the recovery. CBCs and serum chemistry tests were completed within 72 h before each treatment cycle. A physical examination was performed and adverse events and concomitant medications assessed before each treatment cycle.

At the end of the treatment, a physical examination, CBC, serum chemistry tests, and pregnancy test (if clinically indicated) were performed and concomitant medications documented.

Efficacy

Appropriate radiographic imaging studies were performed at baseline to determine measurable and non-measurable lesions. Assessment of lesions was repeated at the end of Cycle 2 and every other cycle thereafter until patient discontinuation. The best overall response was determined from the start of treatment until disease progression or recurrence using guidelines on Response Evaluation Criteria in Solid Tumors (RECIST) [12]. Partial or complete responses were confirmed by repeat assessment no less than 4 weeks after first documentation.

Pharmacokinetics

Serial blood samples were collected from each patient during Cycles 1 and 2. On Day −1 of Cycle 1 only, blood samples were collected prior to administration of capecitabine and 0.5, 1.0, 2.0, 6.0, and 10.0 h postdose. On Day 1 of Cycle 1 only, 12 blood samples were collected periodically over 24 h after capecitabine administration. On Day 1 of Cycle 2 only, blood samples were collected prior to administration of tesetaxel and 0.25, 0.5, 1.0, 2.0, 6.0, 12.0, and 24.0 h postdose. Additional samples were obtained at 168 h (Day 8) and 504 h (Day 22) after tesetaxel dosing in Cycles 1 and 2.

Separate samples (5.0 ml and 7.0 ml per time point for tesetaxel and capecitabine, respectively) were collected via venipuncture or indwelling intravenous cannula. Heparin-containing vacutainer tubes for tesetaxel sampling and EDTA-containing vacutainer tubes for capecitabine sampling were utilized. Blood samples were centrifuged at 3,000 rpm for 15 min; the resulting plasma was removed, immediately frozen, and stored at −20°C until processing.

Plasma levels of tesetaxel, capecitabine, and relevant metabolites (5-FU, 5′-deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine, and ∞-fluoro-β-alanine) were measured

using previously validated assays. A noncompartmental analysis of pharmacokinetic data was performed.

Statistical methods

A total of 30 to 40 patients were to be enrolled depending upon when the MTD was reached. The intent-to-treat (ITT) population comprised all patients who registered in the study. All patients who received any treatment with tesetaxel and capecitabine were included in the safety population. All patients who completed one entire treatment cycle and had measurable disease were included in the efficacy population.

Descriptive summary statistics were tabulated for all safety variables. Hematologic and nonhematologic adverse events were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0, revised 2003) and coded using the Medical Dictionary for Regulatory Activities Thesaurus, Version 8.0. Clinical laboratory test results were graded according to the NCI-CTCAE (Version 3.0), if applicable. Descriptive statistics for efficacy variables were summarized. Duration of response was defined as the time from first documentation of response to documentation of disease progression. Time to tumor progression was defined as the number of days between the first dose of study drug and the date of progression or death when the cause of death was progression. Survival time was defined as the number of days between the first dose of study medication and the date of death. Patients without an event of progression or death were censored at the time of last contact and known status. Patient survival status was monitored every 3 months from the patient's last dose of study drug. Time to tumor progression and overall survival time were also analyzed using Kaplan–Meier survival plots.

Descriptive statistics for plasma concentrations at each time point and for pharmacokinetic parameters were tabulated by dosing cohort and cycle/day. Geometric means were calculated for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from time zero to the last time point (AUC_{0-t}) and from time zero extrapolated to infinity (AUC_{inf}). Analyses of variance (ANOVA) were performed on log-transformed AUC_{0-t}, AUC_{inf}, and C_{max} to assess any pharmacokinetic interactions between study drugs. Least-squares means (LSM) ratios were calculated using the exponentiation of the LSM from analyses on log-transformed parameters; ratios were expressed as a percentage relative to study drug given alone. Corresponding 90% confidence intervals (CI) for ratios also were calculated. Intrasubject variability after accounting for differences between patients and days was derived from analyses of log-transformed data.

Results

Patient population

A total of 27 patients were enrolled at two centers from Jan 2004 to Mar 2005 and included in ITT and safety populations. Five patients did not complete Cycle 1 (3 patients due to disease progression, 1 patient due to noncompliance/request to withdraw, and 1 patient who was lost to follow-up); thus, the efficacy population included 22 patients.

Relevant patient characteristics at baseline are summarized in Table 2. All patients had measurable disease. The most common primary tumor locations were the pancreas, liver (HCC), and colon (CRC) in 9 (33%), 8 (30%), and 6 (22%) patients, respectively.

All (100%) patients had previously undergone surgery for their cancer, and 5 (19%) patients had received radiation therapy. A total of 21 (78%) patients had been previously treated with systemic therapy; the median number of prior regimens was 2 (range, 1–12; see Table 2). The most common antitumor medications were pyrimidine analogs (i.e., 5-FU, capecitabine, and gemcitabine) in 18 (67%) patients (see Table 2).

All patients received tesetaxel and capecitabine during Cycle 1, with the proportion of patients being treated gradually decreasing over subsequent cycles; few patients received study drugs beyond Cycle 4. The most frequently reported reasons for study discontinuation were disease progression in 15 (56%) patients and adverse events in 7 (26%) patients. Mean duration of exposure was 48.0 days ± 39.7 days (median: 43 days; range: 1–162 days) for tesetaxel and 62.2 days ± 42.4 days (median: 64 days; range: 4–176 days) for capecitabine. Mean number of cycles across all 5 dose levels analyzed was 3.0 ± 1.7 (median: 3; range: 1–8). Tesetaxel was administered at study centers, ensuring compliance. Mean compliance with capecitabine administration across all dose levels combined was ≥92% in all treatment cycles except for Cycle 5.

Safety

Determination of MTD

None of the 3 patients in the T18/C1250 group experienced a DLT (Table 5). The dose was escalated to T27/C1250 and 3 patients were treated; 1 of the 3 patients had DLTs (Grade 4 neutropenia lasting >5 days and Grade 3 stomatitis), and 1 of the 3 did not receive the full dose of study medication in Cycle 1. Thus, 4 additional patients were enrolled in the T27/C1250 group. As no further DLTs occurred at the T27/C1250 dose level, the dose was escalated to T27/C1900 and 6 patients were treated, 1 of whom had DLTs (Grade 4 febrile neutropenia, Grade 4

Table 2 Patient characteristics at baseline

Characteristics	Safety/ITT population ($N = 27$)
Gender, n (%)	
Male	18 (67)
Female	9 (33)
Age, years	
Mean (± SD)	56.7 ± 10.5
Median	58
Range	33–70
Race, n (%)	
White	24 (89)
Black/African American	3 (11)
ECOG performance status[a]*, n(%)*	
0	8 (30)
1	18 (67)
Location of primary tumor, n (%)	
Pancreas	9 (33)
Liver	8 (30)
Colon	6 (22)
Breast	1 (4)
Head and neck	1 (4)
Rectum	1 (4)
Stomach	1 (4)
Location of measurable lesions, n (%)	
Liver	20 (74)
Lymph nodes	10 (37)
Pancreas	8 (30)
Lung	6 (22)
Adrenal gland	3 (11)
Abdomen	2 (7)
Pelvis	2 (7)
Other	3 (11)
Location of nonmeasurable lesions, n (%)	
Lung	7 (26)
Liver	5 (19)
Lymph nodes	1 (4)
Adrenal gland	1 (4)
Pleura	1 (4)
History of prior systemic therapy, n (%)	21 (78)
No. of prior regimens, n (%)	
1	8
2	4
3	6
4	1
6	1
12	1
Mean	2.7 ± 2.50
Median	2
Range	1–12
Prior systemic therapy, n (%)	
Pyrimidine analogs	18 (67)
Platinum compounds	12 (44)
Topoisomerase I inhibitors or tyrosine kinase inhibitors	12 (44)
Monoclonal antibodies or investigational agents	6 (22)

[a] Performance status was not assessed in 1 patient

neutropenia lasting >5 days, and Grade 3 diarrhea). The dose was escalated to T27/C2500 and 3 patients were treated, none of whom had a DLT. The dose was escalated to T35/C1900 and 3 patients were treated, 2 of whom developed a DLT (Grade 4 febrile neutropenia and Grade 4 neutropenia lasting >5 days in 1 patient each). The dose was de-escalated to the T27/C2500 level and 5 additional patients were treated (including 1 who incorrectly received a dose of T27/C1900). None of the 4 additional patients treated at the T27/C2500 dose level had a DLT. Thus, the MTD for the combined treatment regimen was determined to be tesetaxel 27 mg/m^2 given once every 21 days with capecitabine 2,500 mg/m^2/day administered twice daily in equally divided doses for 14 consecutive days during each 21-day treatment cycle.

Hematologic and nonhematologic toxicities

All patients had at least 1 adverse event, and 25 (93%) patients experienced adverse events considered by the investigator to be related to treatment. The most frequently reported treatment-related hematologic adverse events were leukopenia in 12 (44%) patients and neutropenia in 11 (41%) patients; most patients with leukopenia also had neutropenia. Treatment-related nonhematologic events with the highest incidence were nausea and vomiting among 12 (44%) patients each and diarrhea and palmar-plantar erythrodysaesthesia syndrome (HFS) among 11 (41%) patients each. Eighteen (67%) patients experienced at least 1 treatment-related adverse event ≥Grade 3 in severity (Table 3).

The most common treatment-related adverse events leading to dose reduction were HFS and hypokalemia in 4 (15%) patients each. Four (15%) patients had treatment-related adverse events leading to study discontinuation: 2 patients with Grade 1 or 2 thrombocytopenia and 1 patient each with Grade 2 peroneal nerve palsy and Grade 2 HFS. Two (7%) patients died within 30 days of the last dose of

Table 3 ≥Grade 3 treatment-related adverse events occurring in ≥2 patients by dose level (Safety population, $N = 27$)

System organ class/preferred term	*n* (%)[a]					
	T18/C1250 ($n = 3$)	T27/C1250 ($n = 7$)	T27/C1900 ($n = 7$)	T27/C2500 ($n = 7$)	T35/C1900 ($n = 3$)	All doses (n = 27)
At least 1 treatment-related Grade 3 or 4 adverse event	1 (33)	4 (57)	6 (86)	5 (71)	2 (67)	18 (67)
Blood/lymphatic						
Anemia	0	1 (14)	2 (29)	0	1 (33)	4 (15)
Febrile neutropenia	0	0	2 (29)	1 (14)	1 (33)	4 (15)
Leukopenia	0	3 (43)	4 (57)	3 (43)	2 (67)	12 (44)
Neutropenia	0	2 (29)	4 (57)	3 (43)	2 (67)	11 (41)
Thrombocytopenia	0	0	2 (29)	0	0	2 (7)
Gastrointestinal						
Diarrhea	0	0	1 (14)	1 (14)	0	2 (7)
General and administration site						
Fatigue	0	0	1 (14)	1 (14)	0	2 (7)
Metabolic/nutritional						
Hypokalemia	0	1 (14)	2 (29)	1 (14)	0	4 (15)
Skin/subcutaneous						
Palmar-plantar erythrodysaesthesia syndrome	1 (33)	0	1 (14)	2 (29)	0	4 (15)

[a] *T18* tesetaxel 18 mg/m^2, *T27* tesetaxel 27 mg/m^2, *T35* tesetaxel 35 mg/m^2, *C1250* capecitabine 1,250 mg/m^2/day, *C1900* capecitabine 1,900 mg/m^2/day, *C2500* capecitabine 2,500 mg/m^2/day

study drug: 1 patient after disease progression and 1 patient after cardiac arrest, which was considered unrelated to treatment.

Antitumor activity

The best overall tumor response for the efficacy population across all dose levels combined was stable disease in 18 (82%) patients and progressive disease in 4 (18%) patients. The proportions of patients in the efficacy population experiencing stable disease among dosing cohorts were as follows: 3/3 in the T18/C1250 group, 5/7 in the T27/C1250 group, 4/7 in the T27/C1900 group, 5/7 in the T27/C2500 group, and 1/3 in the T35/C1900 group. One patient in the T27/C1900 dosing group, who had locally advanced HCC and no prior systemic or radiation therapy, had an unconfirmed partial response (the patient withdrew from the study due to an adverse event after Cycle 2 and thus response was not confirmed).

Median time to tumor progression in the efficacy population was 3.3 months (95% CI: 2.7–4.8 months). Median overall survival time was estimated to be 13.1 months (lower bound of 95% CI: 5.5 months; upper bound not defined) for the efficacy population and 8.8 months (lower bound of 95% CI: 4.6 months; upper bound not defined) for the ITT population.

Pharmacokinetics

Plasma concentrations of tesetaxel, capecitabine, 5-FU, 5′-deoxy-5-fluorocytidine, and 5′-deoxy-5-fluorouridine were determined in 26 subjects. For the metabolite ∞-fluoro-β-alanine, plasma concentrations were determined in 25 subjects.

LSM ratios for AUC_{0-t} and C_{max} for capecitabine (Table 4) were within the 80 to 125% range deemed acceptable according to the U.S. Food and Drug Administration, with similar findings being observed for capecitabine metabolites. Corresponding 90% CIs included 100%, suggesting no statistical difference between pharmacokinetic parameters when capecitabine was given alone or in combination with tesetaxel. The 90% CIs for ∞-fluoro-β-alanine fell within the acceptance range; other 90% CIs, however, fell outside acceptance criteria, possibly due to a lack of power, as suggested by the high intrasubject variability observed for all analytes except ∞-fluoro-β-alanine. Although the combination of tesetaxel with capecitabine appeared to increase exposure to 5-FU based on AUC_{0-t}, this finding was likely due to high intersubject variability rather than a clinically significant pharmacokinetic interaction between study drugs.

LSM ratios for AUC_{0-t}, AUC_{inf}, and C_{max} for tesetaxel (Table 4) fell within the 80 to 125% acceptance range. Corresponding 90% CIs, however, did not fall within acceptance criteria, possibly due to a lack of power.

Table 4 Summary of pharmacokinetic results for capecitabine, its metabolites, and tesetaxel: ratios of LSM% (90% CIs)

Analyte	AUC^{a}_{0-t}	AUC^{b}_{inf}	C^{c}_{max}
Capecitabine versus capecitabine and tesetaxel			
Capecitabine ($n = 24$)	112.6 (92.2, 137.5)	NC[d]	86.9 (62.3, 121.3)
5′-deoxy-5-fluorocytidine ($n = 17$)	110.0 (96.0, 126.0)	NC[d]	106.5 (85.1, 133.4)
5′-deoxy-5-fluorouridine ($n = 17$)	118.9 (96.3, 146.7)	NC[d]	111.7 (80.8, 154.3)
5-fluorouracil ($n = 24$)	144.0 (115.1, 180.1)	NC[d]	101.3 (78.8, 130.3)
∞-fluoro-β-alanine	102.6 (92.9, 113.4) ($n = 16$)	105.3 (98.3, 112.9) ($n = 8$)	107.6 (96.7, 119.7) ($n = 16$)
Tesetaxel versus tesetaxel and capecitabine			
Tesetaxel	105.1 (84.8, 130.3) ($n = 10$)	89.3 (74.1, 107.7) ($n = 10$)	117.6 (96.3, 143.6) ($n = 14$)

[a] AUC_{0-t} area under the plasma concentration–time curve from time zero to the last time point

[b] AUC_{inf} area under the plasma concentration–time curve from time zero extrapolated to infinity

[c] C_{max} maximum plasma concentration after dosing

[d] *NC* not calculated due to insufficient data for statistical analysis

Table 5 Dose-escalation findings

Dose level	No. of patients treated	No. of patients with DLT	Action taken
T18/C1250	3	0	Dose escalated
T27/C1250	3	1	4 additional patients enrolled[a]
T27/C1250	4	0	Dose escalated
T27/C1900	6	1	Dose escalated
T27/C2500	3	0	Dose escalated
T35/C1900	3	2	Dose reduced
T27/C2500	5[b]	0	Dose of T27/C2500 declared MTD

[a] 4 subjects treated rather than 3, as 1 of the first 3 subjects treated did not complete a full cycle

[b] Includes 1 patient who incorrectly received the dose of T27/C1900

Discussion

An all-oral combination of a fluoropyrimidine and a taxane could offer patients a highly convenient treatment option, as well as reduce the occurrence of DLTs associated with intravenous infusion of some of the most commonly prescribed chemotherapy agents.

In our phase I, dose-escalation study, 27 patients with locally advanced or metastatic solid-tumor malignancies were treated orally with tesetaxel in combination with capecitabine to determine the MTD and to investigate potential antitumor activity and pharmacokinetic drug interactions. Both drugs were able to be administered at full single-agent doses. The MTD for this oral combination therapy was tesetaxel 27 mg/m^2 given once every 21 days and capecitabine 2,500 mg/m^2/day given twice daily in equally divided doses for 14 consecutive days during each 21-day cycle.

The most frequently reported DLTs were neutropenia and febrile neutropenia, with individual patients experiencing dose-limiting stomatitis and diarrhea. The most frequently reported Grade 3 or 4 treatment-related toxicities were leukopenia and neutropenia, with an incidence of 44 and 41%, respectively, as well as anemia, febrile neutropenia, hypokalemia, and HFS, each occurring in 15% of patients. No patient died due to a treatment-related adverse event. The median number of treatment cycles was 3; thus, limited data were available to assess the potential for cumulative toxicity in our patient population.

The best overall tumor response from combination treatment in this heavily pretreated population was stable disease, occurring in 82% of patients, with a median time to tumor progression of 100 days for the efficacy population.

Pharmacokinetic data suggested that tesetaxel in combination with capecitabine increased exposure to 5-FU. Because co-administration of tesetaxel seemed to have no meaningful effect on the pharmacokinetics of 5-FU precursors and its major catabolite (∞-fluoro-β-alanine), it is expected that the pharmacokinetics of 5-FU would be similarly unaffected given the cascade of events in capecitabine metabolism, and this finding was likely due to high inter-patient variability. The pharmacokinetic disposition of tesetaxel did not appear to be significantly altered when tesetaxel was given as a single dose in combination with capecitabine.

Phase II studies are ongoing to evaluate tesetaxel as a single agent in the first-line treatment of patients with advanced or metastatic breast or prostate cancer and in the second-line treatment of patients with gastric, bladder, and prostate cancer and melanoma. A phase I study evaluating a weekly dosing regimen of tesetaxel is also in progress.

The results of our study support the continued clinical development of tesetaxel and further exploration both alone and in combination with other anticancer agents.

Acknowledgment This study was funded by Daiichi Sankyo, G. Schwartz, P. Cheverton, M. Kimura, and M. Danna.

References

1. Shionoya M, Jimbo T, Kitagawa M, Soga T, Tohgo A (2003) DJ-927, a novel oral taxane, overcomes P-glycoprotein-mediated multidrug resistance in vitro and in vivo. Cancer Sci 94:459–466
2. Tohgo A, Shionoya M, Iwahana M, Uesugi Y, Jimbo T, Soga T (2002) DJ-927, a novel orally active taxane: 1. Preclinical anti-tumor activity and toxicity profile. Proceedings of the AACR 43:790 (Abstract 3916)
3. Chan S, Paridaens R, Awada A, Mukherjee A, Lawton P, Dumez H et al (2004) Efficacy and prediction of response to the new oral taxane DJ-927 in anthacycline <sic> pre-treated advanced breast cancer (ABC). Eur J Cancer Suppl 4 (No.12):193 (Abstract 641)
4. Evans T, Dobrila R, Berardi R, Sumpter KA, Wall LR, Oyama R et al (2006) A Phase II study of DJ-927 as second-line therapy in patients (pts) with advanced gastric cancer (GC) who have failed a 5-FU non taxane based regimen. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings Part I. 24 (No. 18S) (Abstract 4081)
5. Moore MR, Jones C, Harker G, Lee F, Ardalan B, Saif MW et al (2006) Phase II trial of DJ-927, an oral tubulin depolymerization inhibitor, in the treatment of metastatic colorectal cancer. J Clin Oncol ASCO Annual Meeting Proceedings Part I. 24 (No. 18S) (Abstract 3591)
6. Ishikawa T, Utoh M, Sawada N, Nishida M, Fukase Y, Sekiguchi F et al (1998) Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. Biochem Pharmacol 55:1091–1097
7. Maher JF, Villalona-Calero MA (2002) Taxanes and capecitabine in combination: rationale and clinical results. Clin Breast Cancer 2:287–293
8. Xeloda™ prescribing information. Genentech USA, Inc
9. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M et al (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized Phase III study. J Clin Oncol 19:2282–2292
10. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M et al (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097–4106
11. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812–2823
12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al (2000) New guidelines to evaluate the response to treatment of solid tumors. J Natl Cancer Inst 92:205–216