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ORIGINAL ARTICLE

A drug interaction study evaluating the pharmacokinetics and toxicity of sorafenib in combination with capecitabine

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Abstract
Purpose To address tolerability and a possible pharmacologic interaction of capecitabine with sorafenib.
Methods Patients with advanced solid tumors (ECOG PS 0-1) were included. Cohort A received capecitabine 750 mg/m^2 BID and Cohort B received capecitabine 1,000 mg/m^2 BID, both for 14 days of a 21-day cycle. Steady-state PK was obtained for capecitabine alone, sorafenib alone, and in combination. Cohort C explored an alternate schedule of 7-day on/7-day off flat dose capecitabine 1,000 mg BID with continuous dosing of sorafenib 400 mg BID.
Results A total of 32 patients were enrolled between February 08 and April 09. Hand-foot skin reaction (HFSR) was the primary toxicity with 16 (50%) of the 32 patients experiencing grade 3 events (75% occurring during cycles 1–2). Grade 3 HFSR defined the maximum tolerated dose (MTD) of Cohort C at 1,000 mg BID flat dose of capecitabine. Other grade 3/4 toxicities were rare (diarrhea 6%, mucositis 3%, and fatigue 3%). Capecitabine did not change the C_{max} or $AUC_{(0\text{-}12)}$ of sorafenib. Co-administration of sorafenib with capecitabine 750 mg/m^2 ($n = 6$ patients) increased capecitabine $AUC_{(0–12)}$ 15% and produced no change in the 5FU $AUC_{(0–12)}$. At the capecitabine 1,000 mg/m^2 dose level ($n = 12$ pts), there was a 16% increase in capecitabine $AUC_{(0–12)}$ and an 8% increase in 5FU $AUC_{(0–12)}$. However, these trends were not statistically significant.
Conclusions Co-administration of sorafenib resulted in a mild increase in capecitabine AUC, although not statistically significant. Capecitabine did not affect the exposure of sorafenib. The rate of grade 3 HFSR is concerning and limits the feasibility of prolonged dosing of sorafenib with capecitabine 1,000 mg/m^2 on the 21-day schedule.

Keywords Pharmacokinetics · Sorafenib · Capecitabine · Hand-foot skin reaction

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Background

Sorafenib (Nexavar®) is an oral, multi-targeted inhibitor approved by the Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma in December 2005 [1] and hepatocellular cancer in November 2007 [2]. Sorafenib has been shown to affect both tumor proliferation and tumor angiogenesis in a variety of solid tumor types by inhibiting both serine/threonine kinases and

receptor tyrosine kinases [3]. Additionally, sorafenib inhibits B-RAF, vascular endothelial growth factor receptor-2 (VEGFR-2), and platelet-derived growth factor (PDGFR), and impairs pivotal components of the RAS/RAF/MEK/ERK signaling pathway, an important mediator of responses to growth factors [4].

Sorafenib (BAY43-9006) is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70–85% of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma is the pyridine N-oxide (M2, BAY 67-3472). M2 shows in vitro potency similar to that of sorafenib and comprises approximately 9–16% of circulating analytes at steady state. The des-methyl metabolite (M4, BAY 43-9007) and the N-oxide of the des-methyl metabolite (M5, BAY 68-7769) are also present in circulation, to a lesser degree.

Capecitabine (Xeloda®) is an oral fluoropyrimidine with anti-neoplastic activity [5], which provides an oral alternative to long-term 5-fluorouracil (5FU) infusion with demonstrated activity in multiple solid tumor types, including breast and colorectal tumors. The FDA approved dose is 1,250 mg/m^2 twice daily; however, 1,000 mg/m^2 is better tolerated [6], and doses are often rounded with week on/week off schedules commonly used in the community setting [7].

The addition of multi-targeted kinase inhibitors like sorafenib to standard chemotherapy regimens holds promise in several advanced solid tumor types. This paradigm is supported by preliminary reports of improvement in progression-free survival from the SOLTI-0701 trial, a randomized double-blind phase 2b study evaluating the efficacy and safety of sorafenib versus placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer [8]. Though combination therapy holds promise for increased efficacy, it may also result in increased toxicity. Indeed, the initial phase 1 study presented by Awada et al. found the MTD of the combination to be sorafenib 400 mg BID plus capecitabine 1,700 mg/m^2 [9]. Hand-foot skin reaction (HFSR) was very common (89% all grades) and was the primary dose-limiting toxicity (DLT). Pharmacokinetic (PK) assessments from that trial showed that the addition of capecitabine did not alter sorafenib exposure, yet a possible increase in capecitabine exposure in combination with sorafenib was suggested. This study was designed to address a possible PK interaction upon co-administration of sorafenib with capecitabine and to further characterize the overall safety and toxicity of this combination in 21- and 14-day schedules.

Patients and methods

This open-label phase 1 study (ClinicalTrials.gov Identifier NCT00613145) was conducted at the Drug Development Unit (DDU) of the Sarah Cannon Research Institute in Nashville, Tennessee between February 2008 and May 2009. The protocol was approved by the institutional review board, and patients provided written informed consent prior to enrollment.

Eligibility

To be eligible, male and female patients aged ≥18 years had advanced solid tumors. Additional eligibility criteria included: ECOG performance status 0–1; ≤4 prior cytotoxic regimens; ability to swallow and retain oral medications; agreement to use effective contraception in men and women of childbearing potential; no untreated brain metastases, uncontrolled hypertension or recent bleeding events; adequate bone marrow, hepatic, and renal function. Patients previously treated with capecitabine or 5FU were eligible if not part of the immediately prior regimen. Prior bevacizumab was allowed >3 months prior to study treatment; however, other prior anti-angiogenic therapy was excluded. Patients with known thromboembolic disease were eligible if on stable dose anti-coagulation for >3 months.

Study design and treatment

Patients were randomized 1:1 into Cohort A or B (Table 1), with a minimum of 6 patients enrolled. Cohort B then expanded to an additional 6–12 patients in order to provide 12 paired PK profiles, while a third cohort (Cohort C) explored a 14-day treatment schedule. The total sample for the study was planned to be 32 patients, with a maximum of 40 patients allowed after enrolling the additional patients for PK analyses.

Cohorts A and B received sorafenib (400 mg BID daily) and capecitabine (Cohort A 750 mg/m^2 BID days 1–14; Cohort B 1,000 mg/m^2 BID days 1–14). Cycles were repeated every 21 days. During cycle 1 only, capecitabine alone was given on days 1–7, and sorafenib was started on day 8.

Following the enrollment of Cohorts A and B, a third cohort (Cohort C) explored a 7-day on/7-day off schedule of capecitabine BID in combination with continuous BID dosing of sorafenib (Table 1). Capecitabine started at a flat dose of 1,000 mg BID for the first 3–6 patients, with sorafenib 400 mg BID. If 1,000 mg of capecitabine BID was deemed safe and tolerable, a second group of 6 patients were to be accrued to Cohort C at capecitabine 1,250 mg BID. Dosing escalation was to be halted if ≥2 of 6 patients

Table 1 Study design for 21- and 14-day schedules, including designated PK sampling days

Cohort	Cycle length (days)	Capecitabine dose	Sorafenib dose	PK collection
A	21	750 mg/m^2 BID × 14 days	400 mg BID continuous[a]	Day 7, 14, 21
B	21	1,000 mg/m^2 BID × 14 days	400 mg BID continuous[a]	Day 7, 14, 21
C	14	1,000 mg flat BID × 7 days	400 mg BID continuous	N/A

[a] Sorafenib continuous dosing was held cycle 1 days 1–7 to allow for steady-state capecitabine PKs

at a dose level experienced a DLT during the first 4 weeks of treatment. DLTs were any of the following: ANC nadir <500/μl or platelets <50,000/μl for >5 days, febrile neutropenia, grade 4 thrombocytopenia, grade 3 or 4 non-hematologic toxicity due to treatment despite maximal supportive care, the inability to administer full dose during cycle 1 or to begin Cycle 2 or 3 of treatment as scheduled, secondary to toxicity. No pharmacokinetic analyses were planned for Cohort C.

Routine granulocyte colony-stimulating factor prophylaxis was not recommended. Following 6 weeks of treatment, patients in all cohorts were re-staged to determine whether they were achieving a clinical benefit based on RECIST criteria [9]. Patients without evidence of progression continued treatment, with subsequent re-staging every 6 weeks.

Dose modifications

Dose modifications were outlined in the protocol for hematologic and non-hematologic toxicities. If toxicities resulted in a delay of treatment of >3 weeks or >2 dose reductions, the patient's study participation was discontinued. Dose reductions for drug-related toxicities were not re-escalated.

Capecitabine was held for grade ≥2 HFSR until recovery to grade ≤1; for grade 3 or 4 events, the dose was restarted at 75% full dose. If HFSR recurred, the capecitabine dose was reduced a second time (e.g. to 75% full dose for grade 2 recurrences, and 50% full dose for grade 3 or 4 recurrences). If HFSR did not resolve to grade ≤1, sorafenib doses were held or reduced if necessary.

A total of 2 reductions of each drug were permitted.

Plasma pharmacokinetics

PK analysis was performed at Northeast Bioanalytical Laboratories, LLC (Hamden, CT) using non-compartmental methods (WinNonlin version 5.2). In Cohorts A and B, capecitabine and 5FU PK were collected on day 7 (predose, and 30 min, 1, 2, 4, 6, 8, and 12 h post-dose). Sorafenib and its metabolites steady-state PK were collected on day 21 at these same time points; by day 21, 5FU exposure would be negligible since the last dose of capecitabine was on day 14. The PK analysis of the combination was initially collected at these same time points on day 28 (i.e. after 7 days of concurrent dosing during cycle 2). An amendment changed the PK sampling of the combination to day 14, in response to unforeseen early HFSR toxicity (causing dose delays or interruptions prior to day 28 in 5 of the first 6 patients enrolled in Cohort B). The AUC_{0-12}, maximum concentration (C_{max}), trough drug level concentration (C_{trough}), time-to-maximum concentration (t_{max}), half-life ($t_{1/2}$), and plasma clearance (CL/F) were determined. Antacids were not permitted 4 h before or after dosing on PK sampling days. Patients for whom the complete set of assessments was not completed were excluded from the PK analysis.

Plasma concentrations of sorafenib, M2, M4, and M5 were measured for this study. Sorafenib, and metabolites M2, M4, M5, assays in human plasma were performed using a validated LC/MS/MS assay procedure (NEBA method MET0036). The LLOQ was approximately 10 μg/l for all 4 analytes.

Statistical considerations

Data from all patients who received one dose of study drug were included in the safety analysis. Median and range for T_{max}, geometric mean, and geometric percent coefficient of variation for C_{max}, AUC, and $t_{1/2}$ were used for describing the pharmacokinetic parameters (summary statistics computed using Excel 2003 SP3). The 90% confidence interval around the LS geometric means ratio for C_{max} and AUC was calculated using ANOVA.

Results

Patient characteristics

Thirty-two patients were enrolled between February 2008 and April 2009; patient disposition is shown in Table 1 (Cohort A = 9, Cohort B = 12, and Cohort C = 11 patients) with characteristics detailed in Table 2. Fifteen patients (47%) had previous exposure to 5FU or

Table 2 Combined patient characteristics of the 32 patients enrolled in all cohorts

Characteristics	Number of patients (%)
Median age, years (range)	63 (35–87)
Gender: male	18 (56)
ECOG performance status: 0	24 (75)
Number of prior therapies: 0–1	14 (44)
2–3	13 (41)
4	5 (15)
Prior therapy: 5-fluorouracil	13 (41)
Capecitabine	4 (13)
Bevacizumab	6 (19)
Primary tumor type: pancreatic	6 (19)
Colorectal	6 (19)
NSCLC	4 (13)
Head and neck	3 (9)
Hepatocellular	2 (6)
Prostate	2 (6)
Other[a]	9 (28)

[a] One patient each of the following: angiosarcoma, appendicular, bladder, endometrial, neuroendocrine, ovarian, renal cell, thyroid, and unknown primary

capecitabine. Six patients (19%) had previous exposure to bevacizumab (only 1 of which was with the previous regimen).

Safety and tolerability for all cohorts

The median number of cycles received for all 32 patients was 2 (range: 1–13+). Table 3 outlines treatment-emergent adverse events in ≥10% of patients. HFSR was the primary toxicity with 16 (50%) of 32 patients experiencing grade 3 events. Grade 3 HFSR by dose level and schedule is shown in Table 4. On the 21-day schedule, 75% of patients at the 1,000 mg/m^2 capecitabine dose level experienced grade 3 HFSR as compared to 33% at the 750 mg/m^2 dose level; 75% of grade 3 HFSR occurred during cycles 1–2. No patients discontinued treatment early due to HFSR. T-squared tests did not show correlation between the development of HFSR and the following covariates: age ($P = 0.083$), sex ($P = 0.7224$), previous bevacizumab use ($P = 0.772$), and previous 5FU/capecitabine-based regimens ($P = 0.758$).

Other non-hematologic toxicities were usually grade 1 or 2, with the most common being fatigue [17 (53%)], nausea/vomiting [17 (53%)], diarrhea [17 (53%)], and mucositis [13 (41%)]. Serious hematologic toxicities were uncommon (grade 3 neutropenia, 2 patients; grade 3 thrombocytopenia, 1 patient).

Dose delays or modifications were fairly common throughout the course of treatment. Thirteen patients required a dose reduction of sorafenib, capecitabine, or both drugs. Nine of these required dose reductions due to grade 2 or grade 3 HFSR, one required a dose reduction due to grade 3 neutropenia, and three were removed at the treating physician's discretion. Three patients discontinued therapy due to treatment-related toxicity (neutropenia, mucositis, and sepsis—1 patient each); the remainder required dose reductions and then came off-study for disease progression.

Cohort A and B pharmacokinetic analyses

The mean plasma profiles for capecitabine and 5FU, after capecitabine alone and after capecitabine/sorafenib combination treatment, are plotted in Fig. 1 (online only). The PK parameters for capecitabine and its metabolite, 5FU, after single-agent and combination treatments are summarized in Table 5. The summary statistics shown for T_{max} are median and range (in parenthesis) and for C_{max}, AUC,

Table 3 Common hematologic and non-hematologic adverse events in ≥10% of patients

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4[a]	Totals
Hematologic					
Anemia	6 (19%)	3 (9%)	2 (6%)	0	11 (34%)
Thrombocytopenia	5 (16%)	2 (6%)	1 (3%)	0	8 (25%)
Neutropenia	3 (9%)	0	2 (6%)	0	5 (16%)
Non-hematologic					
Hand-foot skin reaction	2 (6%)	5 (16%)	16 (50%)	0	23 (72%)
Fatigue	14 (44%)	2 (6%)	1 (3%)	0	17 (53%)
Nausea/vomiting	15 (47%)	2 (6%)	0	0	17 (53%)
Diarrhea	10 (31%)	5 (16%)	2 (6%)	0	17 (53%)
Mucositis/stomatitis	11 (34%)	1 (3%)	1 (3%)	0	13 (41%)
Anorexia	10 (31%)	2 (6%)	0	0	12 (38%)
Arthralgia	9 (28%)	1 (3%)	0	0	10 (31%)
Constipation	7 (22%)	1 (3%)	0	0	8 (25%)

[a] There were no grade 4 hematologic or non-hematologic toxicities reported

Table 4 Prevalence of HFSR (hand-foot skin reaction) by grade and cohort

Cohort	*N*	Grade 1	Grade 2	Grade 3	Grade 4	Totals
A	9	0	1 (11%)	3 (33%)	0	4 (44%)
B	12	0	2 (17%)	9 (75%)	0	11 (92%)
C	11	2 (18%)	2 (18%)	4 (36%)	0	8 (73%)
Totals	32	2 (6%)	5 (16%)	16 (50%)[a]	0	23 (72%)

[a] 75% of the grade 3 HFSR events occurred within cycle 1 or cycle 2

and terminal half-life are geometric mean and percent CV (in parenthesis). One patient in Cohort A and three in Cohort B had high capecitabine and 5FU drug concentrations at 12 h post-dose. These values were not PK plausible due to previous time points having concentrations below or near the lower limit of quantification. These implausible values were excluded for the PK calculation as these patients had possibly taken their evening dose of capecitabine prior to the 12-h blood draw.

Consistent with previous studies [5], capecitabine alone had a short plasma half-life of approximately 0.5 h. Orally administered capecitabine is absorbed rapidly with a median T_{max} of approximately 1 h. There was a 15% increase in the capecitabine AUC when 750 mg/m^2 BID capecitabine was co-administered with sorafenib 400 mg BID. Similarly, there was a 16% increase in capecitabine AUC when 1,000 mg/m^2 BID capecitabine was co-administered with sorafenib 400 mg BID. The half-life and T_{max} of capecitabine also increased when capecitabine was co-administered with sorafenib. The half-life of capecitabine increased from 0.5 to 1.1 h for Cohort A and 0.6 to 1.2 h in Cohort B.

There was no change in 5FU AUC when capecitabine 750 mg/m^2 BID was co-administered with 400 mg BID sorafenib. When capecitabine 1,000 mg/m^2 was co-administered with sorafenib 400 mg BID, an 8% increase in 5FU AUC was observed. At both the 750 and 1,000 mg/m^2 BID capecitabine doses, the ratio of 5FU to capecitabine (metabolite to parent) AUCs was unchanged after combination treatment. The statistical tests show that the 90% confidence interval in all cases overlaps the ratio of 1.00; therefore, there is no significant difference in these parameters between the drugs alone and drugs in combination (Table 6).

The pharmacokinetic parameters for sorafenib and its metabolites (M2, M4, and M5) after single-agent and combination treatments are summarized in Table 7 (online only). The C_{max} and AUC obtained for sorafenib and its metabolites (M2, M4, and M5) when administered alone are consistent with previously reported findings [1, 2, 10]. There was no apparent change in sorafenib AUC, metabolites AUC, or the metabolite to parent (M/P) AUC ratios following co-administration of sorafenib with capecitabine at 750 mg/m^2 BID or 1,000 mg/m^2 BID, as observed with a −4 to 8% change in sorafenib AUC and an 8–17% change in sorafenib C_{max}.

Cohort C 14-day treatment schedule escalation

Cohort C explored a 14-day treatment schedule of capecitabine 1,000 mg BID days 1–7 with sorafenib 400 mg BID continuously. Though initially planned to explore two dose levels, the escalation was halted at the initial level (1,000 mg flat dosing of capecitabine). Of the 11 patients treated at this dose level, 4 experienced DLTs of HFSR.

Efficacy

Twenty-seven of 32 patients received at least 2 cycles and were evaluated for response. One patient presented with pancreatic cancer previously treated with gemcitabine and a MEK inhibitor had a partial response to treatment, and remained active on study as of November 09 completing 16

Table 5 Pharmacokinetic parameters of capecitabine and 5FU

Parameter	Cohort A		Cohort B	
	C alone	C & S	C alone	C & S
Capecitabine				
T_{max} (h)	0.9 (0.5–2.0)	1.0 (0.5–4.0)	1.0 (0.5–4.0)	1.5 (0.5–4.0)
C_{max} (μg/l)	5,037.2 (61.2)	2,831.4 (97.7)	4,131.9 (143.4)	3,632.3 (84.9)
AUC (μg h/l)	5,284.8 (37.3)	5,536.7 (56.4)	5,581.6 (80.0)	6,503.0 (51.0)
$T_{1/2}$ (h)	0.51 (22.4)	1.05 (44.6)	0.59 (34.3)	1.19 (63.0)
5FU				
T_{max} (h)	1.0 (0.5–2.0)	1.5 (0.5–4.0)	1.0 (0.5–4.0)	2.0 (0.5–4.0)
C_{max} (μg/l)	245.9 (27.8)	178.8 (41.0)	309.7 (63.3)	284.4 (70.9)
AUC (μg h/l)	404.9 (34.3)	413.8 (19.4)	562.1 (40.5)	634.9 (47.5)
M/P AUC ratio(%)	8.2 (39.2)	8.2 (41.6)	11.4 (55.4)	10.3 (33.5)
$T_{1/2}$ (h)	0.79 (17.8)	1.39 (69.9)	0.82 (32.7)	0.95 (40.5)

C alone Capecitabine alone, *C & S* capecitabine + sorafenib

Table 6 Capecitabine and 5FU AUC and C_{max} geometric means (%CV) and the ratio of the geometric means (90% CI) following administration of capecitabine in the absence and presence of sorafenib

	N	C Alone (reference)	C + S (test)	Ratio of test/reference (90% CI)
Capecitabine				
Cohort A				
C_{max} (μg/l)	6	5,038 (61%)	2,831 (98%)	0.56 (0.32, 1.00)
AUC $_{(0–12)}$ (μg h/l)	5	5,499 (40%)	6,317 (49%)	1.15 (0.90, 1.46)
AUC $_{(0–tn)}$ (μg h/l)	6	5,285 (37%)	5,537 (56%)	1.05 (0.80, 1.36)
Cohort B				
C_{max} (μg/l)	12	4,132 (143%)	3,632 (85%)	0.88 (0.58, 1.33)
AUC $_{(0–12)}$ (μg h/l)	9	5,405 (76%)	6,255 (54%)	1.16 (0.94, 1.43)
AUC $_{(0–tn)}$ (μg h/l)	12	5,582 (80%)	6,503 (51%)	1.17 (0.97, 1.40)
5FU				
Cohort A				
C_{max} (μg/l)	6	246 (28%)	179 (41%)	0.73 (0.56, 0.94)
AUC $_{(0–12)}$ (μg h/l)	5	443 (29%)	436 (16%)	0.99 (0.84, 1.15)
AUC $_{(0–tn)}$ (μg h/l)	6	405 (34%)	414 (19%)	1.02 (0.89, 1.18)
Cohort B				
C_{max} (μg/l)	12	310 (63%)	284 (71%)	0.92 (0.68, 1.24)
AUC $_{(0–12)}$ (μg h/l)	9	570 (40%)	614 (49%)	1.08 (0.86, 1.35)
AUC $_{(0–tn)}$ (μg h/l)	12	562 (40%)	635 (48%)	1.13 (0.95, 1.34)

cycles. An additional 6 patients had minor radiographic improvement, and one of these patients also remained on study as of November 09 completing 14 cycles; 11 of 32 (34%) patients had stable disease lasting m ≥4 cycles.

Discussion

Co-administration of sorafenib resulted in a mild increase in capecitabine AUC. At the 750 mg/m^2 and 1,000 mg/m^2 dose levels, there was an ~15% increase in capecitabine steady-state $AUC_{(0–12)}$. Though these findings did not meet statistical significance, it should be noted that this study was not powered to detect a 15% change in these parameters. Interestingly, the changes in capecitabine exposure did not directly translate to changes in 5FU exposure with only an 8% increase in $AUC_{(0–12)}$ at the 1,000 mg/m^2 dose level and no change at the 750 mg/m^2 dose level. Changes in capecitabine and 5FU AUC observed in this study are not as dramatic but trend in the same direction as those observed by Awada et al., where there was a 38% increase in capecitabine AUC and a 12% increase in 5FU AUC upon co-administration with 400 mg BID sorafenib [9]. In addition to the changes in AUC, the half-life of capecitabine nearly doubled in both Cohorts A and B.

Capecitabine and 5FU C_{max} were decreased by 12–44% when dosed in combination with sorafenib. The changes may be due to difficulty in accurately estimating C_{max} of this rapidly absorbed and rapidly eliminated compound. This is supported by the high variability observed in the reported C_{max} values (28–143% CV). The mechanism by which sorafenib may increase capecitabine exposure is not clear. There was no apparent change in sorafenib AUC, metabolites AUC, or the M/P AUC ratios following co-administration of sorafenib with capecitabine.

HFSR was the predominant toxicity observed in all three cohorts tested. The high prevalence and rapid onset of HFSR occurred despite preventative and therapeutic measures of hand moisturizers and aggressive nurse education [11, 12]. The overall grade 3 HFSR rate was 50% for all 32 patients enrolled in the study and 75% for those at the 1,000 mg/m^2 BID dose level of capecitabine on a 21-day schedule. The grade 3 HFSR events occurred early in the treatment course, 75% within the first 2 cycles. HFSR was always reversible, but often required dose interruptions (4 held doses) and subsequent dose modifications (12 reduced doses).

It is unlikely that the high prevalence of HFSR was due solely to the mild increase in capecitabine exposure when co-administered with sorafenib. Neither the mean AUC nor C_{max} of sorafenib or capecitabine correlated with the development of HFSR. As a single institution study in the US, it is possible that the high frequency of grade 3 HFSR was partially due to regional differences in fluoropyrimidine tolerability compared with other countries [13]. However, our results mirror the high prevalence of HFSR noted in the initial phase 1 escalation trial and preliminary results from the SOLTI phase 2 trial in metastatic breast cancer, both conducted outside of North America [8, 9].

Previous exposure to 5FU or capecitabine may have falsely elevated the HFSR rate. Hennig et al. reported a safety risk for patients with colon cancer transitioning from an infusional 5FU-based regimen directly to a capecitabine-based regimen [14]. Though prior treatment with capecitabine and/or 5FU was allowed, patients were not allowed on trial if it was included in the immediate regimen prior to going on study; bevacizumab was the only prior anti-angiogenesis therapy allowed. There was no correlation between HFSR development and previous exposure to capecitabine/5FU or bevacizumab.

The mechanism of the increased HFSR remains elusive. Single-agent sorafenib and capecitabine have reported rates of HFSR 21 and 14%, respectively [5, 15]. It is unknown whether the increased frequency and severity of HFSR in combination with capecitabine are sorafenib specific or a class effect for all oral anti-angiogenesis tyrosine kinase inhibitors (TKIs). Indeed, a phase 1 dose escalation trial of capecitabine in combination with sunitinib reported grade 3 HFSR as a DLT in each of the three different schedules explored [14, 16] Interestingly, the addition of bevacizumab to capecitabine does not seem to markedly increase the rates of HFSR; Miller et al. reported a mildly increased rate grade 3 HFSR of 27.5% with bevacizumab, as compared to 24.2% for capecitabine alone [17]. Similarly, the capecitabine trials in metastatic colon cancer have shown minimal increase in the rates of HFSR with the addition of bevacizumab [13, 18, 19]. It remains possible that oral TKIs with greater selectivity and specificity for the VEGF receptors 1, 2, and 3 will have more favorable toxicity profiles in combination with capecitabine [20, 21].

The study also evaluated a week on/week off schedule (Cohort C) at 1,000 mg BID flat dose capecitabine with continuous 400 mg BID sorafenib. Unfortunately, Grade 3 HFSR halted the escalation of this schedule. We did not explore whether an interrupted schedule of both drugs on a week on/week off schedule would attenuate the rate of HFSR and allow higher doses of capecitabine in combination. It is also possible that by using 400 mg daily of sorafenib, one may be able to give higher doses of capecitabine in combination.

With the exception of HFSR, the combination had minimal other grade 3/4 adverse events. Fatigue, nausea/vomiting, diarrhea, and mucositis were the most common non-hematologic toxicities (primarily grade 1/2). Despite a heterogeneous population, in which many of the patients had $\geq$2 prior treatment regimens, the combination did show antitumor activity with a confirmed partial response and some evidence of prolonged stable disease.

The pharmacokinetic results from this trial suggest there may be a mild interaction between capecitabine and sorafenib when administered in combination. The modest increases in exposure of capecitabine do not solely explain the frequency and severity of the associated HFSR. Unfortunately, the week on/week off schedule of capecitabine had a similar rate of HFSR and did not improve the dose intensity over a 6-week period. The overall rate of grade 3 HFSR with the combination is concerning. Future trials should consider 750 mg/m^2 BID or an intermediate dose of capecitabine on a 21-day schedule, as prolonged dosing at 1,000 mg/m^2 in combination with continuous full-dose sorafenib does not appear feasible. Alternatively, sorafenib doses of less than 400 mg BID may allow higher doses of capecitabine in combination.

Conflict of interest None.

References

1. Escudier B, Eisen T, Stadler WM et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125–134
2. Llovet JM, Ricci S, Mazzaferro V et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390
3. Jemal A, Murray T, Ward E et al (2005) Cancer statistics, 2005. CA Cancer J Clin 55:10–30
4. Wilhelm SM, Carter C, Tang L et al (2004) BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 64:7099–7109
5. Xeloda® Tablets package insert. New Jersey Roche Laboratories, Inc.:April 2006
6. Bajetta E, Procopio G, Celio L et al (2005) Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 23:2155–2161
7. Theodoulou M, Dugan U, Feigin K et al (2008) A novel capecitabine dosing schedule combined with bevacizumab is safe and active in patients with metastatic breast cancer: a phase II study. J Clin Oncol 26:66s Abstract #1101
8. Baselga J, Segalla JGM, Roche H et al (2009) SOLTI-0701: a double-blind, randomized phase 2b study evaluating the efficacy and safety of sorafenib (SOR) compared to placebo (PL) when administered in combination with capecitabine (CAP) in patients with locally advanced breast cancer. Eur J Cancer (ECCO-EMSO) 7:3–4
9. Awada A, Gil T, Whenham N et al (2009) Phase I dose escalation trial evaluating the safety and pharmacokinetics of sorafenib combined with capecitabine in patients with advanced solid tumors. Eur J Cancer (EORTC-NCI-AACR) 4:33 (Abstract #98)
10. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, National cancer institute of the United States, National cancer institute of Canada. J Natl Cancer Inst 92:205–216
11. Lacouture ME, Wu S, Robert C et al (2008) Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. Oncologist 13:1001–1011
12. Gressett SM, Stanford BL, Hardwicke F (2006) Management of hand-foot syndrome induced by capecitabine. J Oncol Pharm Pract 12:131–141

13. Haller DG, Cassidy J, Clarke SJ et al (2008) Potential regional differences for the tolerability profiles of fluoropyrimidines. J Clin Oncol 26:2118–2123
14. Chiorean EG, Sweeney CJ, Verschraegen CF et al (2007) Tolerability/safety of sunitinib (SU) on schedule 2/1 in combination with capecitabine (C) in patients (pts) with advanced solid tumors (STs): a phase I dose-finding study. ASCO Meeting Abstracts 26:3562
15. Nexavar® Tablets Package Insert. New Jersey Bayer HealthCare Pharmaceuticals, Inc.:2009
16. Sweeney C, Verschraegen C, Chiorean G et al (2007) A phase I dose escalation study of sunitinib plus capecitabine in patients with advanced solid tumors. J Clin Oncol 25(18):3592
17. Miller KD, Chap LI, Holmes FA et al (2005) Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 23:792–799
18. Saltz LB, Clarke S, Diaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26:2013–2019
19. Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 26:3523–3529
20. Bhargava P, Esteves B, Nosov DA et al (2009) Updated activity and safety results of a phase II randomized discontinuation trial (RDT) of AV-951, a potent and selective VEGFR1, 2, and 3 kinase inhibitor, in patients with renal cell carcinoma (RCC). J Clin Oncol (ASCO Meeting Abstracts) 27:5032
21. Sharma S, Abhyankar V, Burgess RE et al (2009) A phase I study of axitinib (AG-013736) in combination with bevacizumab plus chemotherapy or chemotherapy alone in patients with metastatic colorectal cancer and other solid tumors. Ann Oncol