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ORIGINAL RESEARCH

# Phase I and pharmacokinetic study of vatalanib plus capecitabine in patients with advanced cancer

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**Abstract** Angiogenesis inhibition is now a proven therapeutic strategy in treatment of several solid tumors. Vatalanib is a potent inhibitor of all known vascular endothelial growth factor receptor (VEGFR) tyrosine kinases. In view of the effectiveness of angiogenesis inhibitor therapy when combined with chemotherapy and the established role of capecitabine in treatment of colorectal and breast cancer, we undertook a phase I clinical trial of the combination of capecitabine and vatalanib with the goal of developing a combination oral regimen. The study objectives were to determine the maximally tolerated dose of vatalanib that could be safely administered daily with capecitabine given orally for 14 out of 21 days to patients with advanced cancer; to characterize the safety, tolerability, and pharmacokinetic profile of vatalanib given in combination with capecitabine; and to describe any pharmacokinetic interactions between the drugs. The study had an initial dose escalation phase followed by a dose expansion phase. During the dose escalation phase, cohorts of at least three patients each were treated with capecitabine and escalating doses of vatalanib until the maximally tolerated dose of vatalanib was determined. Vatalanib given continuously at a dose of 1,250 mg/day could be safely combined with capecitabine at a dose of 2,000 mg/m$^2$/day given for 14 of 21 days. Dose-limiting toxicities of the combination included fatigue, hypertension, dizziness, and proteinuria. Vatalanib did not alter the pharmacokinetics of 5-FU, the active metabolite of capecitabine. Vatalanib and capecitabine can be safely combined without unexpected toxicities or significant pharmacokinetic interactions.

**Keywords** Vatalanib · Capecitabine · Angiogenesis · Phase I · Vascular endothelial growth factor receptor

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## Introduction

Angiogenesis inhibition is now a proven therapeutic strategy with established clinical benefit in treatment of colorectal cancer [1], non-small cell lung cancer [2], breast cancer [3], and renal cell cancer [4, 5]. Vascular endothelial growth factor (VEGF), secreted by tumor cells and macrophages, is a multifunctional cytokine that increases microvascular permeability and directly stimulates endothelial cell growth and angiogenesis [6]. The angiogenic signal is transmitted via cell surface receptors (VEGFR1 and 2) located on the tumor vascular endothelium. Commercially available anti-angiogenic agents interact with either the VEGF ligand (bevacizumab) or one or more VEGF receptors (sorafenib, sunitinib) to inhibit tumor angiogenesis.

Vatalanib (PTK787/ZK222584), an oral agent belonging to the chemical class of aminophthalazines, is a potent inhibitor of all known vascular endothelial growth factor

receptor (VEGFR) tyrosine kinases (VEGFR1, 2 and 3) [7]. Vatalanib inhibits both VEGFR1 ($IC_{50}$=0.077 μM) and VEGFR2 ($IC_{50}$=0.037 μM) kinases with slightly greater potency against VEGFR2. Vatalanib also inhibits other kinases belonging to the same family of protein tyrosine kinases such as the platelet-derived growth factor (PDGF) receptor β tyrosine kinase ($IC_{50}$=0.58 μM), c-kit protein tyrosine kinase ($IC_{50}$=0.73 μM), and c-Fms ($IC_{50}$=1.4 μM) [7]. The antitumor and anti-metastatic effects of vatalanib were assessed in various rodent tumor models, using either human tumors in immunodeficient mice or rodent syngeneic tumors. Results show that vatalanib inhibits growth of subcutaneously implanted human tumor xenografts in immunodeficient nude mice, associated with a reduced number of microvessels in the interior of the tumors. Vatalanib has demonstrated inhibition of growth of primary tumors and metastases in several animal models and has additive or synergistic cytotoxicity with irinotecan and gemcitabine [7–10].

In phase I monotherapy studies, a group of central nervous system (CNS) symptoms (euphoria, imbalance, unsteady gait, lightheadedness, vertigo, dizziness, disorientation, and ataxia) appeared to be the primary dose-related toxicity of vatalanib [11, 12]. These symptoms usually occurred during the first week of treatment and were self-limited. Other toxicities were nausea, vomiting, hypertension, proteinuria, and elevation of liver function tests [13]. No hematologic toxicity was observed. During chronic dosing studies in rats, effects on the duodenum ranging from diffuse hyperplasia of the mucosa to infiltrative growth with invasion of the intestinal wall were demonstrated on histopathological examination [14]. No such changes were observed in mice or dogs. Because of these findings, clinical trials of vatalanib have incorporated pre-treatment and post-treatment upper gastrointestinal (GI) x-rays and endoscopy. No drug-related duodenal abnormalities have been observed in human studies thus far.

In vitro studies using human and animal liver microsomes have shown that vatalanib is metabolized by a number of liver P450 isoenzymes (CYP 1A2, CYP 2A6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 and CYP 3A4), but predominantly by CYP 3A4 [15]. While in vitro results do not always reliably translate into human studies, they suggest that vatalanib could decrease the clearance of any co-administered drug metabolized by one or more of these P450 enzymes.

Capecitabine, an oral fluoropyrimidine, is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred, as adjuvant treatment for early stage colon cancer and for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen [16–18]. In view of the effectiveness of angiogenesis inhibitor therapy when combined with chemotherapy and the established role of capecitabine in treatment of colorectal and breast cancer, we undertook a phase I clinical trial of the combination of capecitabine and vatalanib. The study objectives were to determine the maximally tolerated dose (MTD) of vatalanib that could be safely administered daily with capecitabine administered orally for 14 out of 21 days to patients with advanced cancer; to characterize the safety, tolerability, biologic activity, and pharmacokinetic profile of vatalanib given in combination with capecitabine; and to describe any pharmacokinetic interactions between these drugs. Since capecitabine is not metabolized by the cytochrome P450 system, we did not expect to observe a significant drug interaction with vatalanib. However, preliminary pharmacokinetic data from this study revealed that exposure to capecitabine and its metabolites, 5′-FUDR, and particularly 5-fluorouracil (5-FU), was higher following co-administration with vatalanib, raising the possibility that vatalanib could increase exposure to 5-FU. However, since capecitabine has non-linear pharmacokinetics and its exposure is known to increase [19] with repeated dosing, we decided to undertake a more extensive pharmacokinetic evaluation during the dose-expansion phase of this study to determine whether or not a drug interaction with vatalanib occurs.

## Patients and methods

Adult patients (>18 years) with histologically confirmed advanced cancer that was refractory to standard therapy or for which there was no standard therapy were eligible to be enrolled in the study. Patients were not permitted to have received more than four prior chemotherapy regimens for metastatic disease and at least 4 weeks must have elapsed (6 weeks for nitrosoureas or mitomycin-C) since the last dose of chemotherapy. Patients could not have received immunotherapy, radiation therapy or surgery within 2 weeks of entry on study and must have recovered from the side effects of any prior treatment. Patients were required to have measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [20], a Karnofsky performance status of at least 70%, and a life expectancy of at least 3 months. Organ function was required to meet the following parameters: absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L; hemoglobin (Hgb) ≥9 g/dL; platelets $\geq 100\times10^9$/L; aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤3.0×upper limit of normal (ULN); serum bilirubin ≤1.5×ULN; serum creatinine ≤1.5×ULN; 24-hour creatinine clearance ≥50 mL/min; and total urinary protein in a 24-hour urine collection ≤500 mg.

Patients were excluded from participation if they had a hematologic malignancy, known bone marrow involvement by tumor, a history of a primary central nervous system (CNS) malignancy or CNS metastases, or if they had previously received a bone marrow or stem cell transplant. Pregnant and lactating women were excluded from participation because of concerns about administering cytotoxic and antiangiogenic therapy to a developing fetus or nursing infant. Patients were also excluded if they had concurrent severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, congestive cardiac failure, myocardial infarction within 6 months, poorly controlled hypertension, history of labile hypertension, history of poor compliance with antihypertensive treatment, chronic renal disease, or active uncontrolled infection); acute or chronic liver disease (e.g., hepatitis, cirrhosis); a confirmed diagnosis of HIV infection; gastrointestinal (GI) dysfunction or GI disease that could significantly alter the absorption of vatalanib; or were taking warfarin. The protocol was approved by the University of Chicago Institutional Review Board, and all patients provided written informed consent for their participation.

## Study design and treatment administration

The study included a dose-escalation phase followed by a dose-expansion phase. During the dose-escalation phase, cohorts of at least three patients were treated with capecitabine and escalating doses of vatalanib until the MTD was determined. The capecitabine starting dose was 2,500 mg/$m^2$/day given in divided dose, however this was subsequently reduced to 2,000 mg/$m^2$/day due to significant toxicity in the initial patient cohorts. Vatalanib was provided by Bayer Schering Pharma as 250 mg tablets. It was administered once daily, within 30 min of completing a meal, at doses ranging from 750 mg/day, the lowest dose shown to have biological effects in monotherapy studies, to 1,250 mg/day, the highest dose planned. Vatalanib dosing was begun on day 2 of cycle 1 and was then continued without interruption. Patients were instructed to take vatalanib immediately prior to taking capecitabine. Escalation of the vatalanib dose was to continue until the MTD was determined based on observed toxicities in cycle 1 of treatment.

The first three patients at each dose level were observed for at least 21 days before the next cohort of new patients was treated at the next higher dose level. Patients who did not receive all doses of study drug for reasons other than drug toxicity were considered non-evaluable for the MTD determination and were replaced.

If no dose-limiting toxicity (DLT) was seen in a cohort of three patients at a given dose level, the next cohort of three new patients was treated at the next higher dose level. If treatment-related DLT was encountered in one patient, then at least three additional patients were enrolled at the same dose level. If DLT was not observed in the additional patients, new patients were treated at the next higher dose level. Similarly, if the incidence of DLT among six patients was one in six, then the next cohort was treated at the next higher dose level. When a minimum of two patients experienced DLT at a given dose level, that dose level was defined as the DLT dose level and dose escalation was stopped. A maximum of six patients could be treated at the DLT dose level. Once the DLT dose level was established, up to three more patients were enrolled at the previous lower dose level up to a maximum of six patients. The recommended dose for further study (MTD dose level) was defined as the vatalanib dose at which no more than one of six patients experienced DLT with at least two patients experiencing DLT at the next higher dose level.

DLT was defined as National Cancer Institute Common Toxicity Criteria (CTC) grade 4 neutropenia lasting 5 or more days; grade 4 thrombocytopenia of any duration; any grade 3–4 drug-related adverse event except alkaline phosphatase elevation, nausea/vomiting or grade 3 hypertension (following protocol amendment); CTC grade 2 or higher proteinuria or hematuria; CTC grade 3 ataxia/dizziness lasting more than 10 days or CTC grade 4 dizziness/ataxia of any duration. Known toxicities of capecitabine were not considered DLTs unless they were thought to be exacerbated by vatalanib.

During the dose-expansion phase, the plan was to enroll 22 evaluable patients at the recommended doses determined in the dose escalation phase to evaluate potential PK interactions. This number of patients was considered sufficient to have 80% power to detect a 20% change in 5-FU AUC when capecitabine was administered with vatalanib. During this phase of the study, capecitabine was given alone during cycle 1 and capecitabine plus vatalanib were given in cycle 2 and continued in subsequent cycles.

## Patient assessment

Patients were evaluated by a physician on day 1 of each 21-day cycle. A complete blood count, differential count, platelets, and serum chemistries were obtained on days 1 and 8 of cycle 1, then on day 1 of each subsequent cycle. Coagulation parameters and urine protein were assessed on day 1 of each cycle. Patients underwent upper GI examination by double contrast barium meal prior to beginning treatment and again after 12 weeks of treatment. Tumor measurements were obtained at baseline and every 2 cycles.

## Pharmacokinetic sampling and analysis

During the dose-escalation phase of the study blood samples were obtained according to the following schedule:

**Table 1** Patient characteristics: dose-escalation phase

| Patient characteristics | |
|---|---|
| Number of patients | 41 |
| Male | 29 |
| Female | 12 |
| White | 30 |
| Black | 5 |
| Other | 6 |
| Median age, year | 61 (34–78) |
| Median KPS | 100 (70–100) |
| Prior treatment | |
| Chemotherapy alone | 17 |
| Chemotherapy + RT | 24 |
| Diagnosis | |
| Colorectal | 10 |
| Head and neck | 7 |
| Sarcoma | 5 |
| Renal | 4 |
| Pancreas | 3 |
| Unknown | 3 |
| Esophagus | 2 |
| Gastric | 2 |
| GIST | 2 |
| Mesothelioma | 1 |
| Neuroendocrine | 1 |
| Ovary | 1 |

*GIST* gastrointestinal stromal tumor, *KPS* Karnofsky performance status, *RT* radiation therapy

1. Day 1, cycle 1: Blood samples for measurement of capecitabine and its metabolites (5 mL, EDTA tube) were obtained pre-treatment then at 30 min, 1, 2, 3, 4, 6, and 8 h after the capecitabine dose.
2. Day 14, cycle 1: Blood samples (5 mL, EDTA tube for capecitabine and 3 mL, heparinized tube for vatalanib) were obtained pre-treatment then at 30 min, 1, 2, 3, 4, 6, 8 and 24 h after dosing.
3. Day 21, cycle 1: Blood samples for vatalanib were obtained as on day 14.

### Dose-expansion phase

Blood sampling for capecitabine and its metabolites was performed as described above on days 1 and 14 of cycle 1, and on days 1 and 14 of cycle 2.

Blood samples were collected into pre-cooled vacutainer tubes and immediately centrifuged at 4°C (ca. 2,000×g, 10 min). Following centrifugation, plasma was transferred by pipette to a polypropylene, cryogenic, freezing vial and stored frozen at −80°C until shipment and analysis.

### Analytical methods

Capecitabine, 5′-DFUR, and 5-FU were measured in plasma by Xendo Laboratories, Groningen, The Netherlands, using a validated liquid-chromatography mass spectroscopy assay with a lower limit of quantitation of 25 ng/mL for capecitabine and 5′-DFUR, and 5 ng/mL for 5-FU (16). Pharmacokinetic (PK) parameters of capecitabine, 5′-DFUR and 5FU were estimated by non-compartmental PK analysis using WinNonlin® (Pharsight, Carry, NC). Dose administration records for all patients during cycles 1 and 2 were reviewed, and profiles were excluded from the PK analysis if there were dose reductions of either capecitabine or vatalanib.

Descriptive statistics were provided for all PK parameters by analyte and study day. For $T_{max}$, median, minimum and maximum were determined. For all other PK parameters, geometric means and coefficient of variation (CV%) were calculated. Analyses were conducted separately for the three analytes. Following log-transformation, PK parameters ($AUC_{0-last}$ and $C_{max}$) were analyzed using a linear mixed effects model, including terms for study day as a fixed factor and subject as a random factor. Three comparisons were performed:

1. Cycle 1, day 14 versus cycle 1, day 1: the accumulation of capecitabine with multiple dosing
2. Cycle 2, day 1 versus cycle 1, day 1: the interaction of vatalanib with capecitabine at a single dose for both drugs

**Table 2** Dose-escalation phase: dose-limiting toxicity cycle 1

| PTK dose (mg) | Cape dose ($mg/m^2$) | Number of patients | Number of patients evaluable for DLT[a] | Number of cycles for evaluable patients | Number of patients with DLT |
|---|---|---|---|---|---|
| 750 | 2,500 | 11 | 6 | 23 | 1 (f) |
| 1,000 | 2,500 | 4 | 2 | 8 | 2 (f, h) |
| 750 | 2,000 | 7 | 3 | 19 | 0 |
| 1,000 | 2,000 | 15 | 12 | 54 | 2 (d; h, s, c) |
| 1,250 | 2,000 | 6 | 6 | 41 | 1 (p) |

[a] Some patients not evaluable for DLT due either to rapid disease progression and failure to complete cycle 1 or to interruption of study drug during cycle 1

*c* cerabrovascular accident secondary to hypertension, *d* dizziness, *f* fatigue, *h* hypertension, *s* seizure, *p* proteinuria, *PTK* vatalanib, *Cape* capecitabine, *DLT* dose-limiting toxicity

**Table 3** Patients with hand-foot syndrome during dose-escalation phase

| Vatalanib/capecitabine dose level | Number of patients | Grade 1[a] | Grade 2 | Grade 3 |
|---|---|---|---|---|
| 750/2,500 | 11 | 2 | 0 | 2 |
| 1,000/2,500 | 4 | 1 | 0 | 3 |
| 750/2,000 | 7 | 0 | 3 | 2 |
| 1,000/2,000 | 15 | 1 | 1 | 8 |
| 1,250/2,000 | 6 | 2 | 1 | 1 |

[a] Worst grade per patient

3. Cycle 2, day 14 versus cycle 1, day 14: the interaction of vatalanib with capecitabine at steady state for both drugs.

## Results

Of the 74 patients enrolled in the study, nine patients never received vatalanib due to rapid disease progression. Thus we report results of the 65 patients who received the combination of capecitabine and vatalanib, 41 in the dose-escalation phase and 24 in the dose-expansion phase.

### Dose-escalation phase

The characteristics of the 41 patients enrolled in the dose-escalation phase of the study are summarized in Table 1. Their median age was 61 years (range, 34–78 years), median Karnofsky performance status 100 (range, 70–100) and all had previously been treated with either chemotherapy or chemotherapy and radiation therapy. The dose levels tested and dose-limiting toxicities are summarized in Table 2. Patients enrolled in the first two dose levels received capecitabine at the standard dose of 2,500 mg/m$^2$/day. However, three of eight evaluable patients in the first two dose levels experienced dose-limiting hypertension and fatigue, and five patients experienced grade 3 hand-foot syndrome (Table 3). As it was not possible to determine whether these toxicities were related primarily to capecitabine, vatalanib or the combination, the protocol was amended to reduce the dose of capecitabine to 2,000 mg/m$^2$/day for all new patients and to re-start the vatalanib dose escalation. An additional 28 patients were enrolled of whom 21 were fully evaluable for DLT determination. The non-evaluable patients had either rapid disease progression resulting in removal from therapy or failure to receive all doses of study drug during cycle 1. No DLTs were observed at the 750 mg (vatalanib)/2,000 mg/m$^2$ (capecitabine) dose level so additional patients were enrolled at the next dose level of 1,000 mg/2,000 mg/m$^2$. At this dose level, one patient experienced grade 3 hypertension, one patient experienced grade 3 dizziness that lasted longer than 10 days, and a third patient had a seizure and cerebrovascular accident in the setting of uncontrolled grade 4 hypertension. This patient was a 44 year old woman with metastatic colorectal cancer and no previous history of hypertension. Two seizures occurred on day 12 of cycle 1 of therapy following several days of headache and complaints of blurred vision. On admission to the hospital, the patient was awake and oriented with a normal neurological examination. A CT scan of the brain was normal however a magnetic resonance imaging scan of the brain revealed a patchy increase in T2 signal in the right parietal and both occipital lobes that was interpreted as a possible ischemic infarct. The patient was removed from protocol therapy, treated successfully with anti-seizure and anti-hypertensive medications and discharged after three days with normalization of her blood pressure and without neurological sequelae.

In view of these toxicities and with permission of the study sponsor and the IRB, a total of 12 evaluable patients were enrolled at this dose level. The protocol was also amended to remove grade 3 hypertension, i.e., hypertension requiring therapy or more intensive therapy than previously, as a dose-limiting toxicity. No changes were made to the protocol specifications for patient monitoring. When no additional DLTs were observed, enrollment was begun in the final planned dose level of 1,250 mg/2,000 mg/m$^2$. As

**Table 4** Number of patients with grade 2 events related to vatalanib (any cycle)

| Vatalanib/capecitabine dose level | Number patients/cycles | Fatigue | Anorexia | HBP* | Proteinuria | Liver function tests elevation | Hives | Pain |
|---|---|---|---|---|---|---|---|---|
| 750/2,500 | 11/36 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1,000/2,500 | 4/20 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| 750/2,000 | 7/24 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 1,000/2,000 | 15/62 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| 1,250/2,000 | 6/41 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |

*HBP* high blood pressure

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