Published in final edited form as:

Invest New Drugs. 2016 April ; 34(2): 176–183. doi:10.1007/s10637-015-0316-5.

Phase I trial of vandetanib in combination with gemcitabine and capecitabine in patients with advanced solid tumors with an expanded cohort in pancreatic and biliary cancers

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Abstract

BACKGROUND—Vandetanib is a multitargeted tyrosine kinase inhibitor that affects vascular endothelial growth factor receptor (VEGF), epidermal growth factor (EGF), and rearranged during transfection (*RET*) mediated receptors which are important for growth and invasion of biliary and pancreatic cancers. This phase I study evaluated the safety profile of vandetanib in combination with standard doses of gemcitabine and capecitabine in order to determine the maximum tolerated dose (MTD).

METHODS—In this single center phase I trial, patients received gemcitabine intravenously (IV) at 1000mg/m² days 1, 8, 15 in a 28 day cycle, capecitabine orally at 850mg/m² twice daily on days 1-21, and escalating doses of vandetanib (200 or 300mg orally daily). Once the MTD was defined, an expansion cohort of patients with advanced biliary cancers and locally advanced or metastatic pancreatic cancer was enrolled. Blood samples were also collected at predetermined time points for biomarker analysis.

RESULTS—Twenty-three patients were enrolled: 9 in the dose escalation and 14 in the dose expansion cohort. One dose limiting toxicity (DLT), of grade 4 neutropenia, occurred in the 200mg vandetanib cohort. The most common adverse effects were diarrhea (39%), nausea and vomiting (34%), and rash (33%). There were 3 partial responses and stable disease of >2 months

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Portions of this data were previously presented at the 2008 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics and the 2010 ASCO General meeting

(range 2-45, median 5) was observed in 15/23 patients. There was no association between changes in biomarker analytes and disease response.

CONCLUSION—The combination of gemcitabine, capecitabine and vandetanib is well tolerated at the recommended phase II dose of gemcitabine 1000mg/m² weekly for three consecutive weeks, capecitabine 850mg/m² BID days 1-21, and vandetanib 300mg daily, every 28 days. This combination demonstrated promising activity in pancreaticobiliary cancers and further evaluation is warranted in these diseases.

Keywords

Phase I; pancreatic cancer; cholangiocarcinoma; VEGF; EGF; RET; vandetanib

INTRODUCTION

Surgery remains the only curative option for pancreatic and biliary cancers. However, the majority of the estimated 45,000 new cases of pancreatic adenocarcinoma and the 7100 biliary cancers diagnosed in the US will be unresectable at the time of diagnosis [1]. Chemotherapy is the main treatment option for these patients. Gemcitabine (Gem) has remained the backbone of systemic therapy [2-5]; however, recent advances have led to new combination regimens such as FOLFIRINOX and Gem/nab-paclitaxel [6,7]. At the time of the development of this trial, the combination of gemcitabine and capecitabine had demonstrated activity in early phase trials, with less promising results in phase III studies [8-11].

Three oncogenic signaling pathways have been implicated in both pancreatic and biliary cancers: the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways, as well as pathways regulated by the rearranged during transfection (*RET*) proto-oncogene. EGFR with its ligand, EGF and transforming growth factor alpha (TGFα) are important in cell growth, proliferation, motility, adhesion, invasion, survival, and angiogenesis [12-14]. EGFR is overexpressed in many pancreatic and biliary tumors and is correlated with poor survival [15-18]. The VEGF pathway is critical in cell survival and induces vascular permeability [14]. Overexpression of the VEGF receptors, or ligands, has been identified in pancreatic and biliary cancers and is associated with poorer outcomes [19-21]. The *RET* protooncogene encodes for tyrosine kinase receptors that activate multiple signaling pathways including RAS/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3/Akt (PI3K/Akt) pathways. Research has suggested that polymorphisms in *RET* may contribute to invasion of pancreatic and biliary cancer cells [22-24].

Vandetanib is an orally available multi-tyrosine kinase inhibitor that inhibits signaling of the EGFR, VEGFR-2, and RET pathways and thus diminishes tumor growth, progression and angiogenesis [25-27]. Vandetanib has been shown to inhibit *in vitro* and *in vivo* tumor growth, prompting evaluation in phase I-III trials [25,27-31]. The agent is well tolerated at a dose of 300mg oral daily, with most common toxicities being hypertension, rash, transaminitis, and diarrhea [28]. Since the initiation of this trial, vandetanib has been approved at 300mg daily for the treatment of unresectable locally advanced or metastatic

medullary thyroid cancer. The early phase activity of gemcitabine and capecitabine made the combination of these cytotoxics and vandetanib a potentially active regimen in the treatment of pancreaticobiliary tumors. The principal objectives of this study were to evaluate the safety profile and to determine the maximum-tolerated dose (MTD) of vandetanib in combination with standard doses of gemcitabine and capecitabine. An expanded cohort of patients with biliary or pancreatic malignancies was enrolled at the MTD to further evaluate the safety of the combination and to assess the antitumor activity in this population.

PATIENTS AND METHODS

PATIENTS

Patients with a histologic or cytopathologic diagnosis of a solid malignancy refractory to standard therapy, or for which no standard therapy existed, were eligible to receive gemcitabine, capecitabine and vandetanib. An expanded cohort of patients with pancreaticobiliary tumors was assessed once the MTD was established. Patients were 18 years old, with an Eastern Cooperative Oncology Group (ECOG) status of 1, and 3 month life expectancy. Patients were required to have adequate hematologic function (ANC $>1500/\text{mm}^3$, platelet $>100,000/\text{mm}^3$, hemoglobin $>9.0\text{ g/dL}$), liver function (transaminases <2.5 times the upper limit of normal [ULN], or <5 times ULN if known liver metastasis; and bilirubin <1.5 times the ULN), and renal function (creatinine <1.5 times the ULN). Eligible patients also had evaluable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.0). Study specific exclusion criteria included therapeutic anticoagulation, uncontrolled hypertension, symptomatic central nervous system involvement, abnormal electrolytes despite therapy, or a significant recent cardiac event. Additionally, patients with refractory or active gastrointestinal symptoms were excluded. Once the MTD was established, the cohort was expanded to include patients with advanced biliary or pancreatic malignancies who had not previously received systemic chemotherapy. The institutional review board approved the protocol and all patients provided written informed consent prior to enrolling.

STUDY DESIGN, DRUG AND TREATMENT

This was a single center phase I trial with dose escalation and expansion cohorts (NCT00551096). The trial incorporated a standard 3+3 design with cohort expansion to 6 patients if a dose limiting toxicity (DLT) was reported. If 2 DLTs were observed at a single dose level, dose escalation was halted. The MTD was defined as the highest dose at which no more than one out of six patients experienced a DLT. Once the MTD dose was defined, an expansion cohort of patients with advanced biliary cancers and locally advanced or metastatic pancreatic cancer was enrolled. All patients received gemcitabine intravenously (IV) at $1000\text{mg}/\text{m}^2$ over 30 minutes on days 1, 8, 15 of each 28 day cycle. Capecitabine dosing was $850\text{mg}/\text{m}^2$ taken orally twice daily on days 1-21. For the dose escalation portion of this combination study dosage Level 1 was 200mg oral daily of vandetanib and Level 2 was 300mg daily.

Patients were monitored for DLTs over the first 28-day cycle. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse

Events (version 3.0). Any of the following adverse events (AE) were considered DLT if they occurred within the first 28 day cycle: grade 4 neutropenia, or febrile neutropenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding requiring transfusion. Any non-hematologic toxicity greater than grade 3 was considered a DLT, as was prolonged QTc, or any treatment delay attributed to study treatment of greater than 2 weeks. Diarrhea, nausea, or vomiting were only considered DLTs if all anti-emetic and anti-diarrheal treatments were maximally utilized and grade 3 symptoms persisted.

DOSE MODIFICATIONS

Generally gemcitabine and capecitabine were held concurrently for hematologic toxicities but dose adjusted separately. At any grade 4 toxicity, discontinuation was recommended but left to the discretion of the treating physician. If patients continued, a 50% reduction of the original dose was recommended; dose reductions of 25% occurred for lesser grade toxicities. The use of colony stimulating factors was not allowed in the management of hematologic toxicities. The protocol designated the following effects as related to vandetanib and requiring dose reduction: grade 3 rash, recurrences of grade 3 diarrhea, or QTc prolongation. Dosing of vandetanib was also altered for any event potentially attributed to study drug with dose reductions allowed to 100 mg daily and no allowance for re-escalation. After two dose reductions, patients could continue for ongoing clinical benefit after discussion with the Principal Investigator. Additional dose reductions occurred at the discretion of the Principal Investigator and treating physician.

PRETREATMENT AND FOLLOW UP STUDIES and SAFETY MONITORING

Once on study, patients were seen weekly for assessment of adverse events, physical exam, vital signs and laboratory analysis until removed from the study. Radiologic disease assessment occurred every 2 cycles [32]. Patients continued on treatment until disease progression, unacceptable toxicities, or withdrawal of consent.

PHARMACODYNAMIC ANALYSIS

Blood samples for plasma soluble VEGFR2 (KDR), VEGFA, FMS-like tyrosine kinase (*FLT1*), basic fibroblast growth factor (bFGF), and placental growth factor (PLGF) were collected immediately prior to dosing on cycle(C) 1, day(D) 1, on C1D8, C1D15, and C2D8. Plasma samples were diluted 1:5 and concentrations determined by enzyme-linked immunosorbent assay (ELISA), per the manufacturer's instructions (R&D Systems). ELISA plates were read at 450 nm on a Synergy 2 plate reader (Biotek).

STATISTICS

All patients who received at least one dose of study medication were included for safety analyses. The DLT-evaluable population included all patients who met DLT assessment criteria as described above. The efficacy-evaluable population included all patients with evaluable disease at baseline. Descriptive statistics were used to summarize patient characteristics, treatment administration/compliance, safety, pharmacodynamics (PD) analysis, and efficacy.

RESULTS

PATIENT CHARACTERISTICS

Twenty-three patients were enrolled into the dose escalation and dose expansion cohorts (Table 1). Patients ranged in age from 35 to 75 years with the most common tumor type being pancreatic at 43% (10/23 median age 55), and biliary tract as the second most common (7/23 patients median age 64). Of the dose escalation cohort, 78% (7/9) had received prior chemotherapy. Twenty-one patients discontinued the study secondary to progressive disease based on RECIST or clinical decline; and 2 withdrew consent for chemoembolization and intolerable side effects, respectively.

DRUG EXPOSURE

Patients in the dose finding cohort received a total of 35 cycles of gemcitabine and capecitabine. Twenty-five cycles of vandetanib at 200mg oral daily and 10 cycles at 300mg daily were given. In the dose expansion cohort, patients received 201 cycles of chemotherapy in combination with study drug (Table 2). Seventeen patients (74%) required dose reduction or schedule adjustment of chemotherapy, and 19/23 (83%) patients required at least one dose delay secondary to AEs. Dose reduction occurred primarily for hematologic toxicities. Only 2 patients required adjustment of the vandetanib but dosing never fell below 200mg daily.

SAFETY AND TOLERABILITY

The adverse events were similar amongst all tumor types. One patient experienced a DLT of grade 4 neutropenia in the 200mg vandetanib cohort. The doses of gemcitabine and capecitabine were then reduced per protocol and the patient continued on study for 6 cycles. The cohort was expanded and escalated to 300mg daily with no further DLTs. A traditional MTD was not reached in this study, as the protocol did not allow for escalation beyond 300mg. As such, this dose is the recommended phase II dose.

Every patient experienced at least one treatment-related AE as described in Table 3. The treatment-related AEs were generally grade 1/2 (94%) with the following as the most common: diarrhea (39%), macular rash (33%), fatigue (34%), and thrombocytopenia (17%). Of the more severe toxicities were palmar plantar erythrodesia (PPE) (15% overall, grade 3/4 in 6/236 cycles), macular rash (grade 3 in 3/236 cycles), and mucositis (grade 3 in 1/236 cycles). However, hematologic toxicities were the most common toxicities grade 3 with neutropenia in 15/236 cycles (6%) and thrombocytopenia in 7/236 cycles (3%). Notably, one patient had vortex keratopathy attributed to study drug causing corneal haze, and one patient suffered a pulmonary embolus. There were reports of low grade QTc prolongation on the study (5 grade 1, 5 grade 2, and 2 grade 3 events). None of these met the criteria of a DLT as defined by the study protocol. There were no deaths while on study.

PHARMACODYNAMICS

The effect of vandetanib on plasma sVEGFR2 (sKDR), VEGFA, FLT1, bFGF, and PLGF was measured prior to dosing on C1D1, C1D8, C1D15, and C2D8. Only 5 patients had samples available for each time point, and the mean plasma concentrations were determined

for each analyte. There was no association between percent increase/decrease in each marker and response of patient tumor in this small subgroup (data not shown).

ANTITUMOR EFFECT

There were no complete responses in the trial, 3 partial responses, and 15 patients with stable disease (Table 4). The partial responses occurred in 2 patients with cholangiocarcinoma and 1 patient with pancreatic cancer. Two of these patients were treated in the dose expansion cohort (300mg) and one in the dose escalation cohort (200mg). Stable disease of greater than 2 months was observed in 11/14 (79%) patients in the expansion cohort. Of those patients with stable disease, 2 continued on trial beyond 3 years of therapy. Response duration was 5-45 cycles (median 9), with one patient withdrawing consent after 5 cycles in order to pursue local interventions; his disease stability on trial and mild tumor shrinkage allowed for chemo-embolization therapy and consideration for liver transplantation.

DISCUSSION

Pancreatic and biliary cancers are notable for having few treatment options. At the time of trial development, the results of gemcitabine in combination with erlotinib and promising phase II results in combination with bevacizumab and capecitabine influenced trial design [33]. The trial follows contemporary design in combining cytotoxic chemotherapy with a targeted agent in order to improve clinical benefit without a marked increase in toxicity.

In the present study, vandetanib was well tolerated in this regimen at the recommended phase II dose of 300mg daily. A classical MTD was not reached due to the planned highest dose levels of 1000 mg/m², 850 mg/m² BID, and 300 mg QD of gemcitabine, capecitabine, and vandetanib, respectively. The only dose limiting toxicity was that of neutropenia at the 200mg vandetanib dose level. Two dose reductions occurred for both vortex keratopathy and rash, each attributed to vandetanib. Each of these toxicities has previously been reported with EGFR inhibitors [34,35]. Only 1 other patient described low grade visual changes. Toxicities of the combination are not markedly different from those observed with capecitabine and gemcitabine in combination, suggesting that vandetanib had minimal contribution to the adverse effects. The AEs in the current trial are consistent with previous reports on the combination of gemcitabine and capecitabine [9]. The percent of hematologic toxicities was similar, or less, in this trial (35% neutropenia previously in comparison to 16% in this trial) and the lack of febrile events was corroborated in the current study[9]. Of those patients that came off study, 2 patients were removed for prolonged drug interruption secondary to hematologic toxicity. In this trial, PPE and diarrhea were increased in comparison to the combination of gemcitabine and capecitabine alone, suggesting a contribution from the vandetanib in keeping with the known side effects of the agent but not increasing to a severity that suggested potentiation by the chemotherapeutic agents. The AEs attributed to vandetanib were similar to previous reports with the exception of less cardiotoxicity and hypertension in the current trial [29,36-38]. Vandetanib has a known incidence of 14% QTc prolongation and 8% grade 3/4 requiring regular monitoring of QTc for patients on continuous drug. The rates of QTc prolongation were lower in this study. In

addition, of the two grade 3 events, one occurred after over one year of therapy. Many patients were on trial for an extended period of time without development of this toxicity. Almost all the patients on study required dose adjustments or alteration in the schedules of the cytotoxic agents however this was mainly due to numerous cycles of treatment received.

The dose of vandetanib in combination with cytotoxic therapy has been explored more broadly in other trials and has ranged from 100-300mg. Interestingly, in the Phase I study of gemcitabine and vandetanib, the MTD was 1000 mg/m² of gemcitabine and 100mg of vandetanib with no objective responses [39]. In another Phase I study the combination of 1000mg/m²/d of capecitabine, 130mg/m² of oxaliplatin and 300mg of vandetanib was well tolerated [40]. Of note, the patients in this study were generally of good performance status and those in the dose expansion cohort had received no previous systemic therapy.

The antitumor activity of this drug combination is interesting in that a majority of patients experienced clinical benefit – mainly in the form of stable disease. Seventy-one percent (10/14) of the dose expansion patients had disease stability for at least five months with over a third of all patients staying on treatment for 10 months or more, some continuing on treatment for a number of years. In addition to RECIST response, tumor markers also supported antitumor activity in that each of the twelve patients with elevated markers experienced a reduction, with a 50% decline in 8/12.

We speculate that the difference in activity may be attributed to the larger dose used in the current trial, which may be necessary to inhibit *RET* [26]. Based on previous pharmacokinetic studies of vandetanib [28,41-43], the steady-state average free plasma concentrations of vandetanib at 100 mg and 300 mg doses is expected to be in the range of 50-100 nM and 140-260 nM respectively (assuming plasma protein binding of 90% [44,45]). This data in conjunction with *in vitro* data suggests that the primary targets of vandetanib, VEGFR-2, EGFR and RET, may not be sufficiently inhibited at the 100 mg dose to produce robust growth inhibitory effects (endothelial cell IC₅₀ = 60-800 nM [44,25]; EGFR expressing tumor cell IC₅₀ = 100 - >2500 nM [25,46]; and RET expressing tumor cell IC₅₀ = 50-260 nM [47,48]). However, at the 300 mg dose plasma concentrations of vandetanib necessary to inhibit RET activity should be adequate enough to produce growth inhibitory effects [47,48].

Since the initiation of this study, there have been two recognized first-line pancreatic chemotherapy regimens, FOLFIRINOX and gemcitabine/nab paclitaxel.[6,7] Although you cannot directly compare the results of this study with these more contemporary phase III studies, the results from this Phase I study appears to have a lower partial response rate (14% v 24% nab paclitaxel and gemcitabine and 32% FOLFIRINOX) but the patients enrolled on this study had longer progression free survival (9 months vs 5 months FOLFIRINOX and nab paclitaxel/gemcitabine) and it was suggestive of better tolerance based on frequency of grade 3 and 4 toxicities.

In addition, while the Phase III trials of gemcitabine and capecitabine for the treatment of advanced pancreatic cancer did not yield statistically significant results, there was a trend towards benefit. The phase III study by Cunningham et al [9] revealed an OS improvement

with a HR of 0.86 but a p-value of 0.08. Further assessment of these data pooled with 2 other large randomized trials [10,49] assessing gemcitabine/capecitabine versus gemcitabine was performed via meta-analysis with an improvement in OS favoring the combination (HR 0.86, p 0.02). Patients with pancreaticobiliary tumors often receive gemcitabine as one of their initial systemic therapies, so the combination of gem-cape is used less frequently but capecitabine is still often used as a subsequent treatment option. This activity of this combination is further supported by the results of this trial and may be bolstered by the addition of vandetanib. The exact contribution of vandetanib to this drug combination is not entirely clear, but the extended duration of treatment for patients with an aggressive subset of cancers makes future study interesting. Vandetanib has shown activity in both thyroid and lung cancers and this trial provides data that the combination of vandetanib with cytotoxic chemotherapy is feasible and may have activity in pancreaticobiliary tumors.

Acknowledgements

Funding provided by: This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca and K12CA086913-10 (SL): K12 Institutional Training Award (Paul Calabresi Award for Clinical Oncology)

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Table 1

Patient baseline characteristics

Characteristic	Escalation Cohort (n=9)	Expansion Cohort (n=14)
Age, years		
Median	55	64
Range	(35-73)	(43-75)
Sex		
Male	4	11
Female	5	3
Tumor primary site		
Endometrial	1	
Ovarian	1	
NSCLC	1	
Thymic	1	
Colon	1	
Cervical	1	
Pancreatic	2	8
Cholangiocarcinoma	1	6
ECOG performance status		
0	2	2
1	7	12
Prior therapy		
Chemotherapy	7	0
Radiotherapy	3	2 alone, 4 with a chemosensitizer
Surgery	5	3
None	2	6

Abbreviations: n, number; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer

Table 2

Cycles of treatment

Drug	# Cycles
Gemcitabine 1000mg/m ²	96
Gemcitabine 25% reduction	36
Gemcitabine 50% reduction	13
Altered Dosing schedule	91
Capecitabine 1660mg/m ² /day	65
Capecitabine 25% reduction	50
Capecitabine 50% reduction	23
Altered Dosing Schedule	98
Vandetanib 300mg/day	211
Vandetanib 200mg/day	25

Table 3

Treatment related adverse events occurring in more than 10% of patients per number of cycle

	G+C+V 200mg Escalation Cycles 25						G+C+V 300mg Escalation Cycles 11						G+C+V 300mg Expansion Cycles 200						All events												
	Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Adverse Event																															
Neutropenia	5	20	7	28	1	4			--			3	27	--				20	10	3	2	1	0.5			25	10	13	5	2	0.8
Mucositis	7	28	--	--	--	--	2	18				--	--	--			9	5	1	0.5					18	7	1	0.4		--	
Maculopathy	10	40	1	4	--	--	4	36				--	--	--			61	31	2	1	--	--			81	33	3	1	--	--	
PP E	7	28	1	4	--	--	1	9				1	9	--			30	15	4	2	--	--			38	15	6	2	--	--	
Thrombocytopenia	3	12	1	4	--	--	3	27				--	--	--			37	19	6	3	1	0.5			43	17	6	2	1	0.4	
Fatigue	11	44	--	--	--	--	8	73				--	--	--			65	33	--	--	--	--			84	34	--	--		--	
Nausea/Vomiting	4	16	--	--	--	--	1	9				--	--	--			30	15	--	--	--	--			35	14	--	--		--	

	G+C+V 200mg Escalation Cycles 25						G+C+V 300mg Escalation Cycles 11						G+C+V 300mg Expansion Cycles 200						All events					
Adverse Event	Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hypertension	1	4	--	--	--	--	3	27	--	--	--	--	23	12	--	--	--	--	27	11	--	--	--	--
Diarrhea	16	64	--	--	--	--	7	64	--	--	--	--	73	37	2	1	--	--	96	39	2	0.8	--	--
DVT/PE	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	0.5	--	--	--	--	1	0.4

Abbreviations: G+C+V, gencitabine, capecitabine, and vandetanib; PPE, palmar plantar erythrodesia; DVT/PE, deep vein thrombosis/pulmonary embolus

Table 4

Summary of best clinical response

			Escalation cohort		Expansion cohort
Response	Patients n=23	%	G+C+V 200mg (n=6)	G+C+V 300mg (n=3)	G+C+V 300mg (n=14)
Partial Response	3	13	1 *		2
Stable disease >2 cycles	15	65	2	3	10
Progressive disease	5	21	3		2

* one PR patient came off study for resection; G+C+V gemcitabine, capecitabine, and vandetanib