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Phase Ib study of dovitinib in combination with gemcitabine plus cisplatin or gemcitabine plus carboplatin in patients with advanced solid tumors

Matthew D. Galsky, M.D.¹, Marshall Posner, M.D.¹, Randall F Holcombe, M.D.¹, Karen M. Lee, M.D.², Krzysztof Misiukiewicz, M.D.¹, Che-Kai Tsao, M.D.¹, James Godbold, Ph.D.³, Rothschild Soto¹, Kiev Gimpel-Tetra¹, Nancy Lowe¹, and William K. Oh, M.D.¹

¹Department of Medicine, Division of Hematology/Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai

²Department of Radiology, Icahn School of Medicine at Mount Sinai

³Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai; New York, NY

Abstract

Purpose—Dovitinib is a small molecule kinase inhibitor with activity against the fibroblast growth factor and vascular endothelial growth factor receptor families. The purpose of this phase Ib study was to define the recommended phase 2 dose of the combinations of gemcitabine and cisplatin or gemcitabine and carboplatin plus dovitinib.

Methods—Patients with advanced solid tumors were enrolled in two parallel dose escalation arms (cisplatin- or carboplatin-based regimens). Treatment was administered with gemcitabine (1000 mg/m² on days 1 and 8), cisplatin (70 mg/m²) or carboplatin (AUC 5) on day 1, and dovitinib (orally on days 1-5, 8-12 and 15-19), every 21 days. The starting dose of dovitinib was 300 mg and was dose escalated in successive cohorts using 3+3 dose escalation rules.

Results—Fourteen patients with advanced solid tumors were enrolled, 5 to the cisplatin arm and 9 to the carboplatin arm. Patients enrolled in the cisplatin arm received a median of 2 cycles of treatment (range, 1-5) and patients enrolled in the carboplatin arm received a median of 1 cycle of treatment (range, 1-4). There were no protocol-defined dose-limiting toxicities in the cisplatin arm. However, the cohort was closed due to the need for frequent dose delays and/or reductions and two patients experiencing severe thromboembolic events. There were two dose-limiting toxicities in the carboplatin arm at the starting dose level of dovitinib (both prolonged neutropenia) and the dose of dovitinib was de-escalated to 200 mg. Two additional dose-limiting toxicities (prolonged neutropenia and febrile neutropenia) occurred in the lower dose cohort and the study was closed. No patients achieved an objective response to treatment.

Conclusions—Dovitinib in combination with gemcitabine plus cisplatin or gemcitabine plus carboplatin was poorly tolerated due to myelosuppression.

Keywords

Dovitinib; TKI-258; gemcitabine; cisplatin; carboplatin; solid tumors; urothelial cancer; bladder cancer; fibroblast growth factor receptor

Background

Several processes central to tumor progression, including growth, invasion, and metastasis, depend on an adequate blood supply. Angiogenesis, the process by which the neovasculature is recruited, is orchestrated by a host of stimulatory and inhibitory factors released by both tumor and stromal cells.¹ Among these stimulatory factors, vascular endothelial growth factor (VEGF) is among the most well characterized. Targeting the VEGF/vascular endothelial growth factor receptor (VEGFR) signaling axis has proven effective in the treatment of multiple solid tumors, particularly when administered in combination with chemotherapy.²⁻⁴

The fibroblast growth factors (FGFs), and their receptors (FGFRs), also control a number of critical cellular functions including migration, proliferation, and survival.⁵ There is substantial cross-talk between the VEGF and FGF signaling pathways, and FGF signaling has emerged as an important mediator of resistance to VEGFR inhibition.⁶ FGF/FGFR signaling has also been shown to have an oncogenic role in multiple cancers via a variety of mechanisms including receptor and ligand gene amplification as well as through activating mutations and gene fusions.^{5,7,8} Importantly, activating mutations in FGFR3 are among the most common recurrent oncogenic alterations in bladder cancer.⁹⁻¹²

Dovitinib is a potent small molecule tyrosine kinase inhibitor with activity against FGFR1-3, VEGFR1-3, as well as PDGFR, RET, Flt3, and c-kit.¹³ Dovitinib has demonstrated anticancer effects as a single agent, and in combination with cytotoxic chemotherapy, in a range of preclinical models both in cell culture and *in vivo*.¹⁴⁻¹⁹ In single-agent phase I studies in patients with advanced solid tumors, dovitinib demonstrated safety, linear pharmacokinetics, and modulation of downstream signaling (e.g., decrease in phosphorylated ERK in peripheral blood mononuclear cells post-treatment).^{14,20,21} Based on the established role of combining antiangiogenic and cytotoxic agents, the role of FGF/FGFR signaling in mediating resistance to VEGF/VEGFR signaling, and the oncogenic role of FGF/FGFR signaling in multiple solid tumors, we initiated a phase Ib study of dovitinib given in combination with gemcitabine plus cisplatin or gemcitabine plus carboplatin. Our ultimate goal was to define the recommended phase 2 dose (RP2D) of these combinations for further study in cisplatin-eligible and cisplatin-ineligible patients with advanced bladder cancer, respectively.

Patients and Methods

Patients

Eligible patients were age ≥ 18 years with metastatic solid tumors refractory to standard therapy or for whom gemcitabine plus cisplatin/carboplatin would constitute appropriate therapy. Patients had discontinued all prior chemotherapy and immunotherapy at least 4

weeks prior to enrollment and had a Karnofsky performance status of $\geq 70\%$. Required baseline laboratory values included: absolute neutrophil count $\geq 1.5 \times 10^9/L$; platelets $\geq 125 \times 10^9/L$; hemoglobin ≥ 9 g/dL; serum creatinine clearance ≥ 60 mL/min or creatinine ≤ 1.5 for the cisplatin arm or a serum creatinine clearance ≥ 30 mL/min for the carboplatin arm; bilirubin $\leq 1.5 \times$ upper limit of normal (ULN); alanine transaminase and aspartate transaminase $\leq 1.5 \times$ ULN; and a normal cardiac ejection fraction. Patients were excluded from participation for any of the following reasons: treatment with more than three prior chemotherapy regimens; impairments interfering with the ability to swallow or absorb pills; clinically significant infections; or impaired cardiac function.

The study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board and each patient provided written informed consent prior to enrollment.

Study Design

This study was a single center, nonrandomized, open-label phase Ib trial of dovitinib given in combination with chemotherapy. The study included two arms, one exploring the combination of gemcitabine, cisplatin, plus dovitinib and the other exploring the combination of gemcitabine, carboplatin, plus dovitinib. Enrollment to the cisplatin- versus carboplatin-arm was based on patient suitability (e.g., creatinine clearance) and investigator discretion. Enrollment and dose escalation of both arms proceeded in parallel. Treatment was administered in 21-day cycles, with cisplatin (70 mg/m^2 intravenously) or carboplatin (area under the curve of 5 using the Calvert formula) administered on day 1 and gemcitabine (1000 mg/m^2 intravenously) administered on day 1 and 8; the starting doses of gemcitabine and cisplatin/carboplatin remained fixed in successive cohorts (Fig 1). A 3+3 design was employed for dose escalation of dovitinib, and dosing began at 300 mg orally once daily on days 1-5, 8-12 and 15-19, every 21 days (with plans to dose escalate to 400 mg and 500 mg administered via the same schedule in successive cohorts). Decisions regarding dose escalation/de-escalation were based on safety assessments during the first cycle of treatment using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Dose limiting toxicities (DLTs) were defined as: Grade 4 neutropenia lasting > 7 days; Grade 4 neutropenia with fever, regardless of duration; Grade 4 thrombocytopenia lasting > 7 days; Grade ≥ 3 thrombocytopenia with bleeding, regardless of duration; any Grade 3 or 4 non-hematological toxicity optimally treated with supportive care (excluding alopecia) lasting ≥ 7 days; Liver function test abnormalities (ALT $> 3 \times$ ULN and bilirubin of $> 2 \times$ ULN or bilirubin $> 3 \times$ ULN); any toxicity considered to be attributable to dovitinib preventing delivery of the first cycle of combination therapy. If 1 of 3 patients enrolled in a cohort experienced a DLT within the first cycle of treatment, 3 additional patients were enrolled at that dose level. If a DLT was observed in 2 or more patients at any dose level, escalation ceased and the dose of dovitinib was de-escalated or the previous dose level was declared the RP2D.

Dose delays and modifications were based on algorithms for specific hematologic and non-hematologic toxicities. In the event that an adverse event could be attributable to a specific agent (e.g., hypertension related to dovitinib), only that particular agent was dose-adjusted. Two permanent dose reductions of gemcitabine and cisplatin/carboplatin and one permanent

dose reduction of dovitinib were permitted. Patients were allowed to continue on treatment, in the absence of prohibitive toxicities, until the time of disease progression.

Pharmacokinetic Assessments

Whole blood samples were collected on the following days of cycle 1: day 19 pre-dose, 3, 6, 9 hours; day 20 post-dose (~2 hours); day 21 post-dose (~2 hours); cycle 2 day 1 pre-dose; cycle 2 day 19 pre-dose; for the determination of plasma dovitinib concentration using a validated assay as previously described.²¹

Antitumor Activity

Restaging computed tomography scans of the chest, abdomen, and pelvis were performed after every 2 cycles of treatment. Response assessments were based on RECIST v1.1.

Results

Patient Characteristics

Between 3/2012-6/2013, 14 patients with various tumor types were enrolled, 9 to the carboplatin arm and 5 to the cisplatin arm. The baseline patient characteristics are outlined in Table 1. Patients enrolled in the cisplatin arm received a median of 2 cycles of treatment (range, 1-5) and patients enrolled in the carboplatin arm received a median of 1 cycle of treatment (range, 1-4). The reasons for treatment discontinuation included adverse events (43%), disease progression (29%), and withdrawal of consent (20%).

Safety and Tolerability

Three patients were initially enrolled in the cisplatin arm with dovitinib administered at the 300 mg dose level (Table 2). Though none of these patients experienced protocol-defined DLTs, due to the need for frequent dose delays and reductions after cycle 1 predominantly due to neutropenia and/or thrombocytopenia (Tables 3 + 4), a decision was made to expand the cohort to better define the tolerability of the regimen. An additional two patients were enrolled and neither patient experienced a DLT. However, both patients developed thromboembolic events requiring hospitalization during cycle 2. One patient with a uterine leiomyosarcoma was hospitalized with an iliac artery occlusion requiring surgical intervention while the other patient, with renal medullary carcinoma, was admitted with an upper extremity deep venous thrombosis requiring catheter-directed thrombolysis and stenting. Though the attribution of these events to the study drug was not clear, given the severity of the events and the multiple dose delays and reductions required by the other patients enrolled, a decision was made to close the cisplatin cohort for poor tolerability.

Among the 3 patients enrolled in the carboplatin arm with dovitinib administered at the 300 mg dose level (Table 2), 1 patient experienced prolonged grade 4 neutropenia consistent with a DLT. The cohort was expanded but another patient experienced prolonged grade 4 neutropenia, and the cohort was closed. The dose of dovitinib was de-escalated to 200 mg (orally once daily on days 1-5, 8-12 and 15-19); however, 2 of the 4 patients enrolled at the lower dose level experienced DLTs (prolonged grade 4 neutropenia and febrile neutropenia)

and the cohort was closed and a decision was made to close the study due to poor tolerability of both regimens.

The most prominent adverse events in both the cisplatin- and carboplatin-arms were cytopenias (Table 3): 64% of patients experienced grade 3-4 neutropenia, and 36% of patients experienced grade 3-4 thrombocytopenia. The remainder of the adverse events were consistent with the known side effect profiles of gemcitabine, cisplatin/carboplatin, and dovitinib.

Recurrent thrombocytopenia and neutropenia prohibited maintaining the planned dose density and intensity of the combination regimens (Tables 2 and 4). The majority of patients could not receive dovitinib dosing on days 15-19 (of any cycle) due to neutropenia and/or thrombocytopenia (Table 2). Most patients required at least 1 dose delay and/or reduction of each drug with many patients requiring multiple dose delays and reductions, particularly patients receiving treatment beyond cycle 1.

Pharmacokinetics

Because the majority of patients could not receive day 15-19 dovitinib dosing during cycle 1 due to neutropenia and/or thrombocytopenia, there were insufficient pharmacokinetic samples drawn to proceed with the planned analysis.

Antitumor activity

No patients achieved a partial or complete response to treatment. Four patients achieved a minor regression/stable disease for 6+ months, 3+ months, 3+ months, and 4+ months with cholangiocarcinoma, laryngeal carcinoma, colon carcinoma, and non-small cell lung carcinoma, respectively. Notably, the patient with cholangiocarcinoma had previously been treated with gemcitabine plus cisplatin and subsequently with gemcitabine as a single agent before progressing and enrolling in the gemcitabine, cisplatin, plus dovitinib cohort.

Discussion

In this phase Ib trial of gemcitabine, cisplatin/carboplatin, plus dovitinib, treatment was poorly tolerated due to cytopenias preventing maintenance of the planned dose density and dose intensity of the regimens. Though most patients had received prior lines of chemotherapy, the eligibility precluding more than three prior chemotherapy regimens resulted in a somewhat less heavily pre-treated cohort compared with many phase I clinical trials. Still, treatment was only delivered for a median of 1 and 2 cycles in the carboplatin and cisplatin cohorts, respectively, and the majority of patients discontinued study treatment due to adverse events or withdrawal of consent. The high proportion (20%) of patients withdrawing consent was largely a result of extended dose delays due to cytopenias.

Regimens combining gemcitabine and a platinum agent (particularly carboplatin) are associated with frequent thrombocytopenia and neutropenia and the contribution of dovitinib to the observed toxicities is difficult to ascertain in this uncontrolled phase Ib study. As a single agent, dovitinib has generally been administered at a dose of 500 mg orally on a 5-days-on/2-days-off schedule in phase II and III studies. In a recently reported large phase III

study in patients with metastatic renal carcinoma, single-agent dovitinib was associated with any grade thrombocytopenia in 17% of patients and any grade neutropenia in 16% of patients; however, grade 3-4 thrombocytopenia and neutropenia were rare events (both <3%).²² In enzymatic kinase assays, dovitinib inhibits both FLT3 and c-kit likely contributing to the observed myelosuppression. While pharmacokinetic analyses could not be completed due to the majority of patients requiring holding of dovitinib on days 15-19 of cycle 1 due to cytopenias, no drug-drug interactions were expected between dovitinib and gemcitabine plus carboplatin. Dovitinib binds to plasma proteins such as albumin up to 96% in humans while gemcitabine and carboplatin do not bind to plasma proteins. Therefore, the free concentration of dovitinib in plasma, the driving force of dovitinib distribution to the tissue, was not expected to have been altered by coadministration of gemcitabine plus carboplatin. Alternatively, the possibility that cisplatin could have affected dovitinib exposure cannot be excluded. The platinum from cisplatin binds to several plasma proteins, including albumin. Whether this binding could compete with the binding of dovitinib to albumin, increasing the free concentration of dovitinib and resulting in increased tissue levels, is unclear. Despite these considerations, the cytopenias observed in the cisplatin and carboplatin arms were overall similar (though perhaps slightly worse in the carboplatin arm) and the toxicity of the combination regimens is likely due to overlapping adverse event profiles rather than drug-drug interactions. Aside from the protein binding considerations, neither dovitinib nor the cytotoxic agents was anticipated to impact the metabolism of the other drug(s) based on their known pharmacology.

An alternative dosing schedule may have resulted in a more tolerable regimen. However, given that the majority of patients were unable to receive week 3 dovitinib dosing, the current study essentially tested a “2 week on, 1 week off” dovitinib regimen. Despite dose reductions of the cytotoxic agents as per protocol guidelines, this regimen still proved difficult to administer. While even less frequent (e.g., pulsatile dosing around each cytotoxic treatment), or lower dose, dovitinib could be considered, whether intermittent engagement of FGFR and VEGFR is sufficient to achieve the desired anticancer effects is not known.

Combining cytotoxic chemotherapy with multi-targeted kinase inhibitors has been problematic in several studies. We previously demonstrated that the combination of gemcitabine, cisplatin, plus sunitinib, in patients with metastatic urothelial cancer, was also poorly tolerated due to the need for frequent dose delays and reductions related to cytopenias.²³ Furthermore, in a systematic review and meta-analysis of clinical trials combining VEGFR or epidermal growth factor receptor (EGFR)-family kinase inhibitors with cytotoxic chemotherapy in solid tumors, we have shown that compared with chemotherapy alone, the addition of a kinase inhibitor significantly increased the risk of treatment discontinuation and adverse events including neutropenia and thrombocytopenia.²⁴

The cisplatin cohort of our study was closed due to both poor tolerability and the development of severe thromboembolic events in two patients. Whether VEGFR kinase inhibitors increase the risk of thromboembolic events has been controversial and prior meta-analyses have suggested an increase in arterial, but not venous, events.^{25,26} Alternatively we have demonstrated an increase in the risk of venous thromboembolic events with the use of

cisplatin, compared with other cytotoxic agents, but not an increase in arterial thromboembolic events.^{27,28} Patients with advanced malignancies are at high risk for thromboembolic disease and the relative contribution of the platinum-agents, and dovitinib, to the two events observed in our study cannot be delineated.

A goal of our study was to define a RP2D of the combination regimens for further study in advanced urothelial cancer, a disease characterized by a high frequency of activating mutations in FGFR3.²⁹ Since the initiation of our study, dovitinib has been explored as a single agent in a phase II clinical trial enrolling patients with FGFR3 mutated urothelial cancers and demonstrated negligible anticancer activity.³⁰ Whether the lack of activity reflects the importance of FGFR3 as a therapeutic target in urothelial cancer, possible feedback with EGFR signaling³¹, or the pharmacology of this particular agent, is unclear, though recent clinical proof-of-concept established with novel selective pan-FGFR inhibitors suggests the former is unlikely.³²

Despite being generally associated with unique non-hematologic side effects, small molecule multi-targeted kinase inhibitors have generally been difficult to combine with cytotoxic chemotherapy regimens, particularly due to myelosuppression. Given the importance of FGFR signaling in a range of solid tumors, and preclinical data supporting targeting this pathway concurrently with cytotoxic chemotherapy, efforts to combine cytotoxic agents with more selective FGFR small molecule inhibitors or blocking monoclonal antibodies, are worthy of further investigation.

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Figure 1. Treatment schema

Two study arms were enrolled, and dose-escalated, simultaneously, gemcitabine plus cisplatin plus dovitinib and gemcitabine plus carboplatin, plus dovitinib. Gemcitabine plus cisplatin or gemcitabine plus carboplatin were administered at standard doses. The dose of dovitinib was to be escalated in successive cohorts. Treatment in both arms was administered in 21-day cycles and treatment was continued until the time of prohibitive toxicities or disease progression.

Table 1**Baseline Characteristics**

Characteristic	N = 14
Age, years [median (range)]	68 (24-81)
Gender	
Male	10 (71%)
Karnofsky performance status [median(range)]	90% (80-100)
Tumor type	
Colon cancer	3
Bladder cancer	2
Adenoid cystic carcinoma	1
Cervix cancer	1
Cholangiocarcinoma	1
Esthesioneuroblastoma	1
Kidney (renal medullary) carcinoma	1
Larynx carcinoma	1
Lung (non-small cell) cancer	1
Oral cavity cancer	1
Prostate cancer	1
Number of prior chemotherapeutic regimens	
0	2
1	8
2	4

Table 2

Dose levels and dose limiting toxicities

Patient	Cohort	Dovitinib Dose	Notable Adverse Event	DLT	# cycles received	# days dovitinib administered cycle 1/reason held	# days dovitinib administered cycle 2/reason held	# days dovitinib administered cycle 3/reason held
1	carboplatin	300			2	10 days/Held days 15-19 for grade 3 neutropenia and grade 3 thrombocytopenia	10 days/Held days 15-19 for grade 3 neutropenia and grade 3 thrombocytopenia	Off study
2	carboplatin	300	Grade 4 neutropenia and thrombocytopenia	Yes	1	5 days/Held days 8-12 and 15-19 for grade 4 neutropenia and grade 4 thrombocytopenia	Off study	Off study
3	carboplatin	300			1	3 days/Patient declined further treatment	Off study	Off study
4	carboplatin	300			2	15 days	0 days/Held for prolonged grade 3 neutropenia and patient came off study	Off study
5	carboplatin	300	Grade 4 neutropenia	Yes	1	10 days/Held days 15-19 for grade 4 neutropenia	Off study	Off study
6	carboplatin	200			3	5 days/Held days 8-12 and 15-19 for fatigue and hypertension	15 days	5 days/Held for fatigue and anemia and patient came off study
7	carboplatin	200	Febrile neutropenia	Yes	1	10 days/Held days 15-19 for febrile neutropenia	Off study	Off study
8	carboplatin	200	Grade 4 neutropenia	Yes	1	10 days/Held days 15-19 for grade 4 neutropenia and grade 3 thrombocytopenia	Off study	Off study
9	carboplatin	200			4	10 days/Held days 15-19 for grade 3 neutropenia	10 days/Held days 15-19 for grade 4 thrombocytopenia	10 days/Held days 8-12 for fatigue and dyspnea
10	cisplatin	300			2	10 days/Held days 15-19 for grade 3 neutropenia and grade 2 thrombocytopenia	10 days/Off study due to disease progression	Off study
11	cisplatin	300			5	10 days (days 8-12 and 15-19)/Grade 3 neutropenia and Grade 2 thrombocytopenia	10 days (days 8-12 and 15-19)/Grade 2 thrombocytopenia	5 days/Held days 8-12 and 15-19 for Grade 2 thrombocytopenia
12	cisplatin	300			4	10 days/Held days 15-19 for grade 4 neutropenia and grade 4 thrombocytopenia	10 days/Held days 15-19 for grade 3 thrombocytopenia	5 days/Held days 8-12 and 15-19 due to grade 3 neutropenia
13	cisplatin	300	Upper extremity deep venous thrombosis		2	5 days/Held 8-12 and 15-19 for anorexia and fatigue	5 days/Hospitalized for thrombosis	Off study

Patient	Cohort	Dovitinib Dose	Notable Adverse Event	DLT	# cycles received	# days dovitinib administered cycle 1/reason held	# days dovitinib administered cycle 2/reason held	# days dovitinib administered cycle 3/reason held
14	cisplatin	300	Iliac artery thrombosis		2	15 days	5 days/Held days 8-12 and 15-19 for grade 4 neutropenia	Off study

DLT, dose limiting toxicity

Table 3
Treatment emergent grade 3-4 adverse events (n=14 patients)*

Adverse Event	Grade	
	3	4
Anemia	2	
Diarrhea	1	
Fatigue	1	
Febrile neutropenia		1
Fever	1	
Nausea	1	
Neutropenia	4	5
Thrombocytopenia	2	3
Thromboembolism	2	

* Highest grade adverse event per patient

Table 4
Dose delays and reductions (n=14 patients)

Drug	Median dose reductions per patient (range)	Median dose delays per patient (range)
Carboplatin *	0 (0-1)	1 (0-3)
Cisplatin **	1 (0-2)	2 (0-14)
Gemcitabine	1 (0-2)	1 (0-14)
Dovitinib	0 (0-1)	2 (0-14)

* median number of cycles administered = 1 (range, 1-4)

** median number of cycles administered = 2 (range 1-5)