

Phase I trial of axitinib combined with platinum doublets in patients with advanced non-small cell lung cancer and other solid tumours

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BACKGROUND: This phase I dose-finding trial evaluated safety, efficacy and pharmacokinetics of axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors, combined with platinum doublets in patients with advanced non-small cell lung cancer (NSCLC) and other solid tumours.

METHODS: In all, 49 patients received axitinib 5 mg twice daily (b.i.d.) with paclitaxel/carboplatin or gemcitabine/cisplatin in 3-week cycles. Following determination of the maximum tolerated dose, a squamous cell NSCLC expansion cohort was enrolled and received axitinib 5 mg b.i.d. with paclitaxel/carboplatin.

RESULTS: Two patients experienced dose-limiting toxicities: febrile neutropenia ($n = 1$) in the paclitaxel/carboplatin cohort and fatigue ($n = 1$) in the gemcitabine/cisplatin cohort. Common nonhaematologic treatment-related adverse events were hypertension (36.7%), diarrhoea (34.7%) and fatigue (28.6%). No grade ≥ 3 haemoptysis occurred among 12 patients with squamous cell NSCLC. The objective response rate was 37.0% for patients receiving axitinib/paclitaxel/carboplatin ($n = 27$) and 23.8% for patients receiving axitinib/gemcitabine/cisplatin ($n = 21$). Pharmacokinetics of axitinib and chemotherapeutic agents were similar when administered alone or in combination.

CONCLUSION: Axitinib 5 mg b.i.d. may be combined with standard paclitaxel/carboplatin or gemcitabine/cisplatin regimens without evidence of overt drug–drug interactions. Both combinations demonstrated clinical efficacy and were well tolerated.

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New therapeutic strategies are needed to improve the efficacy of chemotherapy regimens for advanced solid tumours. For patients with advanced non-small cell lung cancer (NSCLC), platinum-based doublets remain a standard of care (Stinchcombe and Socinski, 2009). However, these treatments result in only modest improvements in survival (Burris, 2009). Addition of targeted agents, which act on specific signalling pathways involved in tumour progression, to chemotherapy regimens may improve clinical outcomes.

The vascular endothelial growth factor (VEGF) pathway has a key role in tumour-related angiogenesis, and its deregulation is characteristic of many solid tumours (Brown *et al*, 1993; Ikeda *et al*, 1999; Berns *et al*, 2003; Saad *et al*, 2004; Keedy and Sandler, 2007). Novel agents have been developed to target the VEGF ligand

or its receptor. In several phase III studies, inhibition of VEGF signalling by the anti-VEGF antibody bevacizumab in combination with chemotherapy improved patient outcomes compared with chemotherapy alone (Hurwitz *et al*, 2004; Sandler *et al*, 2006; Miller *et al*, 2007; Reck *et al*, 2010). In patients with advanced non-squamous NSCLC, bevacizumab prolonged overall survival (OS) when combined with paclitaxel and carboplatin compared with chemotherapy alone (median OS, 12.3 vs 10.3 months) (Sandler *et al*, 2006), and prolonged progression-free survival, but not OS, when combined with gemcitabine and cisplatin (Reck *et al*, 2010). Investigation of antiangiogenic agents with different mechanisms of action, such as tyrosine kinase inhibition, in combination with chemotherapy is warranted. Results from a phase III study showed that adding sorafenib, an inhibitor of multiple tyrosine kinases, to carboplatin/paclitaxel did not prolong OS compared with chemotherapy alone in patients with NSCLC (Scagliotti *et al*, 2010). Nevertheless, other tyrosine kinase inhibitors that selectively inhibit VEGF receptors may still offer clinical benefit when added to chemotherapy.

Axitinib is an oral, potent and selective second-generation tyrosine kinase inhibitor of VEGF receptors 1, 2 and 3 (Hu-Lowe

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et al, 2008). When combined with docetaxel, carboplatin or gemcitabine in human tumour models, axitinib enhanced the antitumour efficacy of these agents (Hu-Lowe *et al*, 2008). In phase II studies of several tumour types, axitinib showed single-agent activity and was well tolerated (Rixe *et al*, 2007; Cohen *et al*, 2008; Rini *et al*, 2009; Schiller *et al*, 2009). In a phase II study of patients with advanced NSCLC receiving single-agent axitinib, median OS was 14.8 months (Schiller *et al*, 2009), which compares favourably with chemotherapy (Burris, 2009). These data suggest axitinib may enhance the efficacy of standard chemotherapy regimens for the treatment of selected solid tumours, including NSCLC.

Here, we report safety, efficacy and pharmacokinetic findings from a phase I study of combination treatment with axitinib plus paclitaxel/carboplatin or gemcitabine/cisplatin in patients with advanced solid tumours, including squamous cell NSCLC.

PATIENTS AND METHODS

Study design and end points

This was a phase I, open-label, multicentre, dose-finding study consisting of nine treatment cohorts, plus an expansion cohort of patients with squamous cell NSCLC who were enrolled after determination of the maximum tolerated dose (MTD) of axitinib plus paclitaxel/carboplatin. Here, we report findings from cohorts that received axitinib in combination with either paclitaxel/carboplatin (cohorts 1, 2 and 3 plus expansion) or gemcitabine/cisplatin. Findings from other treatment cohorts are presented in an accompanying article (Martin *et al*, 2012). Primary end point was MTD of axitinib combined with either paclitaxel/carboplatin or gemcitabine/cisplatin. Secondary end points included safety, tumour response rates and plasma pharmacokinetic profiles.

This study was performed in accordance with the study protocol approved at each participating centre, International Conference on Harmonisation Guidelines on Good Clinical Practice and applicable local regulatory requirements and laws. All patients provided written informed consent. This trial is registered on ClinicalTrials.gov (NCT00454649).

Patients

Patients aged ≥ 18 years with any histologically or cytologically proven advanced solid malignancy suitable for treatment with paclitaxel/carboplatin or gemcitabine/cisplatin were eligible. Inclusion criteria for all cohorts included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; no pre-existing uncontrolled hypertension (antihypertensive medications were permitted); adequate organ function; and no prior chemotherapy with platinum salts or taxanes for metastatic disease except as noted below; adjuvant treatment with platinum salts or taxanes must have been completed ≥ 12 months before enrolment. For patients receiving gemcitabine/cisplatin, any type of previous chemotherapy was allowed and, for patients in the expansion cohort, any type of previous treatment was allowed. Patients with NSCLC with squamous cell histology, or mixed histology that was predominantly squamous, were eligible for the expansion cohort, which received axitinib plus paclitaxel/carboplatin.

Exclusion criteria included myocardial infarction, congestive heart failure, cerebrovascular accident (including transient ischaemic attack) or pulmonary embolus < 12 months before enrolment; haemoptysis (> 0.5 teaspoon blood per day) within 1 week of enrolment; and at least one lung lesion with cavitation or any lesion invading and/or supporting large blood vessels.

Study treatments

Treatment schedules are shown in Figure 1. All patients received axitinib twice daily (b.i.d.) with food. *In vitro* studies indicate

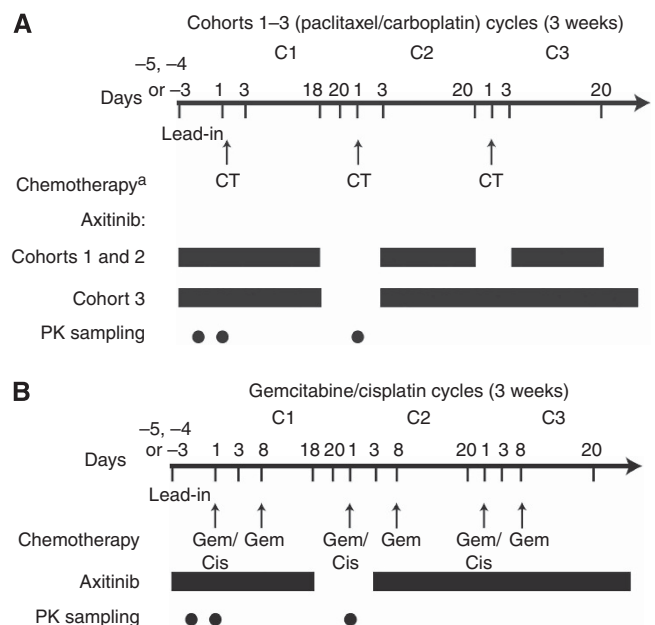


Figure 1 Treatment schedule for (A) paclitaxel/carboplatin cohorts and (B) gemcitabine/cisplatin cohort. ^aChemotherapy (CT) = paclitaxel/carboplatin for cohort 1, 2 and 3. C = cycle; Cis = cisplatin; Gem = gemcitabine; PK = pharmacokinetic.

Table 1 Axitinib dose escalation in patients receiving paclitaxel/carboplatin

Cohort	Lead-in dose of axitinib (b.i.d.)	Patients enrolled (n)	Dose-limiting toxicities
1	1 mg ^a	3	None
2	3 mg ^a	5	None
3	5 mg	20 ^b	Febrile neutropenia (n = 1)

Abbreviation: b.i.d. = twice daily. ^aLead-in dose of axitinib was started 3–5 days before the first dose of chemotherapy and continued for 2 days after the first chemotherapy dose (from day -5, -4 or -3 through cycle 1 day 2). ^bIncludes patients enrolled in the expansion cohort.

axitinib noncompetitively inhibits the cytochrome P450 (CYP) 2C8 enzyme (unpublished data) involved in paclitaxel metabolism (Monsarrat *et al*, 1993; Steed and Sawyer, 2007). Owing to potential for drug–drug interactions between axitinib and paclitaxel, the axitinib lead-in dose was administered at 1, 3 and 5 mg b.i.d. for sequential cohorts 1, 2 and 3, respectively, started 3–5 days before the first dose of chemotherapy and continued for 2 days after the first chemotherapy dose. Cohorts 1, 2 and 3 were to enrol three to six patients, depending on the number of patients that experienced a dose-limiting toxicity (DLT) during the first cycle (Table 1). If none of the first three patients experienced a DLT during the first cycle, the lead-in dose of axitinib was escalated in the subsequent cohort. If one of the three patients experienced a DLT during the first cycle, the cohort was expanded to include a total of six patients, and if one of six patients experienced a DLT during the first cycle, the lead-in dose of axitinib was escalated in the next cohort. The lead-in dose of axitinib for the gemcitabine/cisplatin cohort was 5 mg b.i.d. After the lead-in period, axitinib 5 mg b.i.d. was administered continuously in all cohorts. Axitinib was interrupted 3 days before cycle 2 day 1 of chemotherapy administration and dosing was resumed on cycle 2 day 3; for cohorts 1 and 2, starting with cycle 2, axitinib was interrupted 1 day before chemotherapy infusion (day 21) and resumed on day 3 of each subsequent cycle. For the expansion cohort, axitinib was

administered at the MTD defined in cohorts 1–3, beginning cycle 1 day 1. All patients continued treatment with axitinib until disease progression or unacceptable toxicity. After cycle 1, patients with no grade >2 adverse events (AEs) related to axitinib for consecutive 2-week periods could have their axitinib dose titrated to 7 mg b.i.d. and then to a maximum of 10 mg b.i.d., unless BP measured $>150/100$ mmHg or the patient was receiving anti-hypertensive medication. The axitinib dose was reduced to 3 mg b.i.d., and then to 2 mg b.i.d. in patients with grade ≥ 3 nonhaematologic treatment-related AEs. For patients who developed systolic BP >150 mmHg or diastolic BP >100 mmHg, new or additional antihypertensive therapy was started or the dose of existing medication increased. If patients developed haemoptysis (>0.5 teaspoon of bright red blood per day), axitinib was discontinued and a radiologic assessment was to be considered. For patients in the squamous cell NSCLC expansion cohort who developed cavitation after enrolment, axitinib was withheld and patients were assessed on a case-by-case basis. Patients who permanently discontinued axitinib because of toxicity could continue to receive chemotherapy as long as treatment was considered clinically beneficial.

Patients in cohorts 1–3 and the expansion cohort received paclitaxel (200 mg m^{-2} ; 3-h infusion) followed by carboplatin (area under the plasma concentration–time curve (AUC) target of 6 mg min ml^{-1} ; 30-min infusion) every 3 weeks. Patients in the gemcitabine/cisplatin cohort received cisplatin (80 mg m^{-2} on day 1) and gemcitabine (1250 mg m^{-2} on days 1 and 8; 30-min infusion), followed by a 1-week rest period, in 3-week cycles. Chemotherapy regimens were modified on an individual basis according to patient tolerability at the discretion of the investigator. Paclitaxel/carboplatin was delayed in patients with absolute granulocyte counts <1500 cells mm^{-3} or platelet counts $<100\,000$ cells mm^{-3} and discontinued if recovery did not occur after 4 weeks. Paclitaxel/carboplatin was withheld in patients with grade ≥ 3 haematologic or nonhaematologic toxicities and resumed at one lower dose level when the toxicity was grade ≤ 1 . Paclitaxel was reduced in patients with grade 2 neurotoxicity or withheld until neurotoxicity was grade ≤ 1 . The gemcitabine/cisplatin dose was reduced to 75% in patients with febrile neutropenia, grade 4 neutropenia for ≥ 7 days, grade 4 thrombocytopenia, bleeding grade >2 with grade 3 thrombocytopenia or grade 3 nonhaematologic toxicities during the prior cycle. The gemcitabine/cisplatin dose was reduced to 50% or delayed in patients with grade 4 nonhaematologic toxicities during the prior cycle. Gemcitabine/cisplatin was delayed by 1 week if the absolute neutrophil count was $<1.0 \times 10^9 \text{ l}^{-1}$ and/or the platelet count was $<100 \times 10^9 \text{ l}^{-1}$. If on day 8, the absolute neutrophil count was $<1.0 \times 10^9 \text{ l}^{-1}$ and/or the platelet count was $<100 \times 10^9 \text{ l}^{-1}$, gemcitabine was not administered. Cisplatin was discontinued in patients with grade ≥ 2 peripheral neurotoxicity, tinnitus or hearing loss during the prior cycle. Prophylactic use of colony-stimulating factors was permitted in patients who experienced infection or grade 4 neutropenia during the previous cycle. Patients who discontinued chemotherapy because of toxicity or because they completed the maximum number of cycles according to institutional practice could continue to receive axitinib as a single agent.

Assessments

The MTD for axitinib plus paclitaxel/carboplatin or gemcitabine/cisplatin was defined as the dose level at which no more than one of the first six patients enrolled in each cohort experienced a DLT during the first cycle of therapy, with two or more of the six patients experiencing a DLT at the next highest dose level. If the MTD was not exceeded within the planned dose levels, MTD was defined as the maximum dose tested. Dose-limiting toxicities were defined as grade 4 neutropenia or thrombocytopenia for ≥ 14 days, or grade 4 febrile neutropenia; proteinuria $\geq 2 \text{ g}/24 \text{ h}$;

haemoptysis (≥ 0.5 teaspoon per day) for ≥ 7 days; uncontrolled grade ≥ 3 nonhaematologic toxicity for ≥ 7 days; or inability to resume study treatment within 14 days after stopping because of axitinib-related toxicity.

Safety was monitored throughout the study, and AE severity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (Trotti *et al*, 2003). Physical examinations, assessment of ECOG PS, chest X-rays and laboratory tests were conducted at baseline, day 1 of each cycle and at follow-up (28 days after the last dose). Additional physical examinations and haematology tests were performed at days 8 and 15 of each cycle. For the squamous cell NSCLC expansion cohort, chest X-rays were performed to assess tumour cavitation on even-numbered cycles when other tumour assessments were not performed. BP was monitored at each clinic visit, and patients were issued a home BP monitoring device and diary and asked to record their BP at least twice daily before each axitinib dose. Patients were instructed to contact their physicians for systolic BP >150 mmHg or diastolic BP >100 mmHg. Home BP measurements were not used for DLT assessments. Tumours were radiologically assessed every two cycles, according to Response Evaluation Criteria in Solid Tumours (RECIST version 1.0) (Therasse *et al*, 2000).

Pharmacokinetic analysis

The pharmacokinetics of steady-state axitinib alone and chemotherapy alone, as well as the combination of steady-state axitinib plus chemotherapy, were evaluated in each patient in all cohorts except the expansion cohort. Pharmacokinetics of steady-state axitinib when administered alone were determined using blood samples collected pre-dose and 1, 2, 3, 4, 6 and 8 h after dosing on cycle 1 day –1. Pharmacokinetics of chemotherapy when administered alone were determined using blood samples collected on cycle 2 day 1. Pharmacokinetics of the combination of steady-state axitinib and chemotherapy were determined using blood samples collected on cycle 1 day 1. Samples for paclitaxel/carboplatin analysis were collected pre-dose and 1, 2, 3, 3.25, 3.5, 4, 5, 6, 8, 24 and 30 h after the start of paclitaxel infusion. Samples for gemcitabine analysis were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3 and 4 h after the start of infusion in tubes containing tetrahydrouridine, which prevented continued metabolism of gemcitabine during the processing of samples. Samples for cisplatin analysis were collected pre-dose and 0.5, 1, 1.5, 2.5, 3.5, 5.5 and 7.5 h after the start of infusion.

Plasma concentrations of axitinib were measured using a validated high-performance liquid chromatography with tandem mass spectrometric detection method (LC/MS/MS) (Charles River Discovery and Development Services; Shrewsbury, MA, USA) (Rugo *et al*, 2005). Concentrations of paclitaxel, gemcitabine and the gemcitabine metabolite 2',2'-difluorodeoxyuridine (dFdU) in sodium heparin plasma were measured using a validated LC/MS/MS assay (Covance Bioanalytical Services; Indianapolis, IN, USA) with ranges of $10\text{--}2000 \text{ ng ml}^{-1}$, $50\text{--}50\,000 \text{ ng ml}^{-1}$ and $500\text{--}50\,000 \text{ ng ml}^{-1}$ for paclitaxel, gemcitabine and dFdU, respectively. Concentrations of platinum from carboplatin and cisplatin in sodium heparin plasma and plasma ultrafiltrate (PUF) were measured using a validated inductively coupled plasma-MS assay (Covance Laboratories; Madison, WI, USA) with ranges of $2.0\text{--}1000 \text{ ng ml}^{-1}$ and $1.0\text{--}500 \text{ ng ml}^{-1}$ in plasma and PUF, respectively. All pharmacokinetic analyses were conducted using WinNonlin Professional (version 4.01, Pharsight Corp.; Mountain View, CA, USA).

Statistical analysis

All patients receiving at least one dose of study medication were included in the safety analysis. Patients having one or more target

lesion according to RECIST and a baseline assessment of disease and who received at least one dose of study medication were included in the analysis of best objective response. Data were summarised using means, medians, s.d. and ranges for continuous data and frequencies and percentages for categorical data.

RESULTS

Patient demographics and disposition

In all, 49 patients were enrolled, including 28 patients in the paclitaxel/carboplatin cohorts and 21 patients in the gemcitabine/cisplatin cohort (Table 2). The most common tumour type was NSCLC in 17 patients (34.7%), all of whom were in the paclitaxel/carboplatin cohorts.

Study treatment duration for individual patients is shown in Figure 2. Patients received axitinib for a median of 174 days (range 10–656) and 89 days (range 5–992) in the paclitaxel/carboplatin and gemcitabine/cisplatin cohorts, respectively. The median daily axitinib dose was 9.8 mg (range 4.7–15.1) in patients receiving paclitaxel/carboplatin and 9.0 mg (range 6.0–10.0) in patients receiving gemcitabine/cisplatin. Dosing of axitinib was reduced in 16 patients (35.7% and 28.6% of patients in the paclitaxel/carboplatin and gemcitabine/cisplatin cohorts, respectively) and was interrupted in 24 patients (35.7% and 66.7% of patients in the paclitaxel/carboplatin and gemcitabine/cisplatin cohorts, respectively). Median number of paclitaxel/carboplatin cycles was 6, 5 and 4 (range 1–6) for cohorts 1, 2 and 3, respectively; median number of chemotherapy cycles was 4 (range 1–29) and 3 (range 1–9) for gemcitabine and cisplatin, respectively. A total of 26 patients receiving axitinib plus paclitaxel/carboplatin discontinued the study, including 14 patients because of insufficient clinical response, 4 patients because of AEs and 8 patients for other reasons. In the gemcitabine/cisplatin cohort, 20 patients discontinued, including 10 because of insufficient clinical response, 6 because of AEs and 4 for other reasons.

DLTs and MTD

One of the first six patients in cohort 3 receiving axitinib/paclitaxel/carboplatin experienced a DLT of febrile neutropenia during the first cycle (Table 1), and the MTD was determined to be axitinib 5 mg b.i.d. continuously in combination with paclitaxel 200 mg m⁻² and carboplatin (AUC 6 mg min ml⁻¹). One of the first six patients receiving axitinib/gemcitabine/cisplatin experienced a DLT of fatigue during the first cycle; the MTD was determined to be axitinib 5 mg b.i.d. continuously in combination with cisplatin 80 mg m⁻² (day 1) and gemcitabine 1250 mg m⁻² (days 1 and 8). Dose titration to 10 mg b.i.d. was achieved in three patients receiving paclitaxel/carboplatin.

Safety and tolerability

Six patients discontinued the study because of treatment-related AEs, which were fatigue, cerebrovascular accident and haemoptysis ($n=1$ each) in the paclitaxel/carboplatin cohorts and hypertension ($n=2$) and cerebrovascular accident ($n=1$) in the gemcitabine/cisplatin cohort. Common treatment-related nonhaematologic AEs were hypertension ($n=18$; 36.7%), diarrhoea ($n=17$; 34.7%) and fatigue ($n=14$; 28.6%) (Table 3). Common grade ≥ 3 treatment-related nonhaematologic AEs across both treatment arms were fatigue ($n=5$; 10.2%) and hypertension ($n=5$; 10.2%). In addition to the patient in cohort 3 receiving axitinib/paclitaxel/carboplatin who had a DLT of febrile neutropenia during the first cycle, one patient in cohort 2 experienced grade 4 febrile neutropenia; chemotherapy was reduced in this patient. In the paclitaxel/carboplatin cohorts, two patients (7.1%) developed treatment-related stomatitis; both cases were classified

Table 2 Patient baseline characteristics

	Axitinib +	
	Paclitaxel/ carboplatin, <i>n</i> = 28	Gemcitabine/ cisplatin, <i>n</i> = 21
Male/female, <i>n</i>	21/7	9/12
Age, median (range), years	60 (37–75)	52 (40–79)
ECOG PS 0/1, <i>n</i>	16/12	9/12
Primary tumour type, <i>n</i> (%)		
NSCLC	17 (60.7)	0
Melanoma	4 (14.3)	0
Ovarian	3 (10.7)	1 (4.8)
Pancreatic	0	4 (19.0)
Breast	0	3 (14.3)
Head and neck	1 (3.6)	1 (4.8)
Cholangiocarcinoma	0	2 (9.5)
CRC	0	2 (9.5)
Other	3 (10.7) ^a	8 (38.1) ^b
Prior therapy, <i>n</i> (%)		
Surgery	14 (50.0)	20 (95.2)
Radiotherapy	5 (17.9)	9 (42.9)
Drug therapy ^c	8 (28.6)	15 (71.4)

Abbreviations: CRC = colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer. ^aRenal cell carcinoma, unknown primary tumour ($n=2$). ^bBladder, cervical, ectopic hormone secretion syndrome associated with neoplasia, gastrointestinal, prostate, sarcoma, small intestine, unknown primary tumour. ^cIncludes cytotoxic chemotherapy and targeted agents.

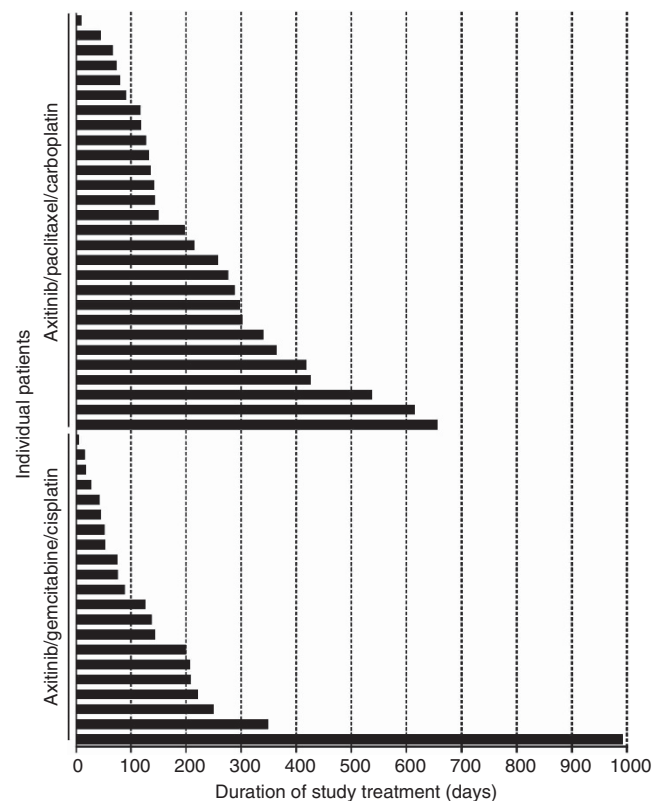


Figure 2 Duration of study treatment.

Table 3 Safety and tolerability findings

(A) Treatment-related nonhaematologic AEs,^a n (%)

	Total, N = 49 All grades	Axitinib +			
		Paclitaxel/carboplatin, n = 28		Gemcitabine/cisplatin, n = 21	
		All grades	Grade 3/4 ^b	All grades	Grade 3/4 ^b
Hypertension	18 (36.7)	10 (35.7)	1 (3.6)	8 (38.1)	4 (19.1)
Diarhoea	17 (34.7)	11 (39.3)	1 (3.6)	6 (28.6)	1 (4.8)
Fatigue	14 (28.6)	9 (32.1)	4 (14.3)	5 (23.8)	1 (4.8)
Proteinuria	10 (20.4)	7 (25.0)	1 (3.6)	3 (14.3)	0
Hand-foot syndrome	9 (18.4)	8 (28.6)	1 (3.6)	1 (4.8)	1 (4.8)
Epistaxis	8 (16.3)	5 (17.9)	0	3 (14.3)	0
Nausea	8 (16.3)	0	0	8 (38.1)	0
Decreased appetite	7 (14.3)	3 (10.7)	0	4 (19.1)	0
Headache	7 (14.3)	1 (3.6)	0	6 (28.6)	1 (4.8)
Rash	7 (14.3)	5 (17.9)	1 (3.6)	2 (9.5)	1 (4.8)
Dysphonia	7 (14.3)	4 (14.3)	0	3 (14.3)	0
Dysgeusia	6 (12.2)	4 (14.3)	0	2 (9.5)	0
Dizziness	5 (10.2)	4 (14.3)	0	1 (4.8)	0

(B) Haematologic laboratory abnormalities, n (%)

	Total, N = 48 All grades	Axitinib +			
		Paclitaxel/carboplatin, n = 27		Gemcitabine/cisplatin, n = 21	
		All grades	Grade 3/4 ^b	All grades	Grade 3/4 ^b
Anaemia	48 (100)	27 (100)	0 (0)	21 (100)	2 (9.5)
Neutropenia	46 (95.8)	26 (96.3)	25 (92.6)	20 (95.2)	13 (61.9)
Leukopenia	46 (95.8)	26 (96.3)	10 (37.0)	20 (95.2)	10 (47.6)
Thrombocytopenia	43 (89.6)	25 (92.6)	7 (25.9)	18 (85.7)	10 (47.6)
Lymphopenia	40 (83.3)	19 (70.4)	5 (18.5)	21 (100)	14 (66.7)

Abbreviation: AE = adverse event. ^aReported in ≥10% of patients. ^bNo grade 5 AEs were reported.

as grade 2. No cases of grade ≥3 haemoptysis or grade 5 treatment-related AEs were reported.

Haematologic laboratory abnormalities occurred in most patients (Table 3). With the exceptions of lymphopenia in the gemcitabine/cisplatin cohort and neutropenia in both cohorts, the majority of abnormalities were grade ≤2. Grade 3/4 treatment-related abnormalities reported as AEs were thrombocytopenia (n=4; 8.2%), neutropenia (n=2; 4.1%) and anaemia and leukopenia (n=1 each; 2.0%).

Clinical activity

Of the evaluable patients, 15 (31.3%) achieved an objective response (Table 4), including 3 complete responses (6.3%). An additional 16 patients (33.3%) had stable disease for >8 weeks. Objective responses were observed in patients with NSCLC (n=5), ovarian cancer (n=3), melanoma (n=2) and other tumour types (n=5).

Pharmacokinetic results

Plasma pharmacokinetic parameters (maximum plasma concentration, AUC, clearance and volume of distribution) for paclitaxel, carboplatin, gemcitabine and its metabolite dFdU and cisplatin were similar in the absence or presence of axitinib (Table 5; Figure 3). Axitinib pharmacokinetic parameters were similar in the absence or presence of co-administered paclitaxel/carboplatin or gemcitabine/cisplatin (Table 5; Figure 3).

Table 4 Best response to therapy, by RECIST^a

	n (%)	
	Axitinib +	
	Paclitaxel/carboplatin, n = 27	Gemcitabine/cisplatin, n = 21
Objective response rate ^b	10 (37.0)	5 (23.8)
Complete response	2 (7.4)	1 (4.8)
Partial response	8 (29.6)	4 (19.0)
Stable disease	11 (40.7)	5 (23.8)
Disease progression	3 (11.1)	3 (14.3)
Indeterminate/missing	3 (11.1)	8 (38.1)

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumours. ^aIncludes treated patients with at least one target lesion according to RECIST and a baseline assessment of disease. ^bComplete responses + partial responses.

DISCUSSION

Combination treatment with chemotherapy and an agent targeting the VEGF pathway has been shown to improve clinical outcome for several tumour types compared with chemotherapy alone (Hurwitz *et al*, 2004; Sandler *et al*, 2006; Miller *et al*, 2007; Reck *et al*, 2010). In this study, axitinib combined with paclitaxel/carboplatin or gemcitabine/cisplatin was well tolerated and demonstrated clinical

Table 5 Plasma pharmacokinetic parameters of (A) paclitaxel, carboplatin, gemcitabine and cisplatin in the absence or presence of axitinib and (B) axitinib in the absence or presence of paclitaxel, carboplatin, gemcitabine and cisplatin

Treatment arm	Mean (%CV)				
	C_{max} (ng ml ⁻¹)	AUC _{0-∞} ^a (ng · h ml ⁻¹)	CL (lh ⁻¹)	V _z (l)	t _{1/2} (h)
(A) CT treatment with/without axitinib					
Paclitaxel ^{b,c} (n = 12)					
(+ Carboplatin)	6182 (34)	20266 (28)	21.6 (43)	285 (82)	8.36 (26)
(+ Carboplatin) + axitinib	7182 (24)	23320 (34)	18.2 (24)	229 (31)	8.64 (12)
Carboplatin ^{b,c} (n = 12)					
(+ Paclitaxel)	24101 (29)	57519 (17)	12.6 (32)	45.2 (18)	2.62 (21)
(+ Paclitaxel) + axitinib	24250 (32)	52768 (15)	13.7 (31)	44.8 (15)	2.44 (29)
Gemcitabine ^d (n = 17)					
(+ Cisplatin)	22445 ^e (66)	11680 ^e (31)	224 (33)	91.5 (35)	0.29 (24)
(+ Cisplatin) + axitinib	22182 (34)	12270 (33)	217 (36)	95.5 (63)	0.30 (33)
dFdU (+ cisplatin)	48981 (39)	212828 (39)	–	–	3.32 (44)
dFdU (+ cisplatin) + axitinib	47024 (17)	184794 (20)	–	–	3.12 (16)
Cisplatin ^f (n = 13)					
(+ Gemcitabine)	1899 ^g (30)	3366 ^g (25)	46.3 (32)	173 (53)	2.61 (49)
(+ Gemcitabine) + axitinib	1757 (33)	3057 (30)	52.8 (44)	184 (96)	2.27 (77)
(B) Axitinib treatment with/without CT					
Axitinib ^{h,i} (n = 12)					
Alone	39 (40)	404 (68)	39 (87)	108 (42)	2.8 (53)
+ Paclitaxel/carboplatin	46 (71)	535 (76)	37 (114)	133 (126)	2.7 (36)
Axitinib ^j (n = 20)					
Alone	41 (81)	416 (108)	50.1 (113)	157 (102)	2.68 (41)
+ Gemcitabine/cisplatin	41.7 (94)	444 (84)	46.7 (104)	168 (116)	2.66 (51)

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration–time curve (AUC) from time 0 to 24 h; AUC_{0-∞} = AUC from time zero to infinity; b.i.d. = twice daily; CL = plasma clearance; CL/F = apparent oral plasma clearance; C_{max} = maximum plasma concentration; CT = chemotherapy; CV = coefficient of variation; dFdU = 2',2'-difluorodeoxyuridine; PK = pharmacokinetic; PUF = plasma ultrafiltrate; t_{1/2} = plasma terminal elimination half-life; V_z = volume of distribution of the drug during the elimination phase; V_z/F = apparent oral volume of distribution during the elimination phase. ^aAUC reported for cisplatin is from time 0 to 8 h. ^bPooled data from cohorts 1–3. PK parameters for carboplatin are in PUF. ^cTwo patients excluded because PK samples were not collected on cycle 1 day 1. ^dFour patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed. ^eC_{max} and AUC_{0-∞} on cycle 2 dose-normalised for patients who underwent gemcitabine dose reduction on cycle 2 compared with cycle 1. ^fSeven patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed; one patient excluded because of non-estimable half-life; one patient excluded because of dose infusion interruption. PK parameters for cisplatin are in PUF. ^gC_{max} and AUC₀₋₈ on cycle 2 dose-normalised for patients who underwent cisplatin dose reduction on cycle 2 compared with cycle 1. ^hData were pooled from patients in cohorts 1, 2 and 3 who received 1, 3 and 5 mg b.i.d. doses of axitinib, respectively. Data were dose-normalised to 5 mg b.i.d. ⁱFor three patients, AUC₀₋₂₄, CL/F, V_z/F and t_{1/2} were not reported because of non-estimable half-life. ^jOne patient excluded because matching cycle 1 and cycle 2 PK evaluations were not completed; for five patients AUC₀₋₂₄, CL/F, V_z/F, and t_{1/2} were not reported because of non-estimable half-life.

efficacy without any overt pharmacokinetic interactions for various advanced solid tumours. The MTD for axitinib in combination with paclitaxel/carboplatin or gemcitabine/cisplatin was 5 mg b.i.d.; however, further dose escalation of axitinib was achieved in some patients tolerating 5 mg b.i.d.

Most AEs reported in this study were of mild-to-moderate grade, and the most common treatment-related nonhaematologic, grade ≥3 AEs (hypertension, diarrhoea and fatigue) were anticipated, based on results from prior phase II studies of axitinib (Rixe *et al*, 2007; Cohen *et al*, 2008; Spano *et al*, 2008; Rini *et al*, 2009; Schiller *et al*, 2009). Unlike DLTs observed with other VEGF receptor tyrosine kinase inhibitors, for example, sorafenib, where skin toxicities such as rash and hand–foot syndrome were predominant (Moore *et al*, 2005; Strumberg *et al*, 2005), DLTs associated with axitinib in combination with paclitaxel/carboplatin or gemcitabine/cisplatin were febrile neutropenia and fatigue. Potential overlapping toxicities between axitinib and the chemotherapeutic agents, such as fatigue, nausea, diarrhoea and stomatitis, did not appear to be appreciably exacerbated.

Patients receiving anti-VEGF therapies have an increased risk of developing hypertension (Jain and Townsend, 2007; Zhu *et al*, 2007; Wu *et al*, 2008), and the incidence of hypertension in this study was consistent with previous axitinib trials (Rixe *et al*, 2007; Cohen *et al*, 2008; Rini *et al*, 2009; Schiller *et al*, 2009). Moreover,

grade ≥3 hypertension reported here was comparable to that reported in phase III studies in various advanced solid tumours treated with the VEGF inhibitor bevacizumab plus chemotherapy (4–14.8%) (Sandler *et al*, 2006; Miller *et al*, 2007; Saltz *et al*, 2008). These data favour the use of antihypertensive medication and suggest the possible need for axitinib dose adjustments in patients who develop hypertension while receiving axitinib plus chemotherapy.

Of note, no cases of grade ≥3 haemoptysis were reported in this study, although mild haemoptysis was reported in one patient who received axitinib plus paclitaxel/carboplatin. Bevacizumab is contraindicated in patients with squamous cell NSCLC because of the incidence of severe or fatal pulmonary haemorrhage (2004); thus, patients with squamous cell NSCLC were excluded from the phase III study evaluating bevacizumab combined with paclitaxel and carboplatin for NSCLC (Sandler *et al*, 2006). In this study, additional eligibility requirements, for example, exclusion of patients who had blood vessels with possible tumour involvement, may have mitigated, in part, the potential risk of haemoptysis. It will require further investigation in a larger study to confirm whether axitinib plus chemotherapy may be safely administered to patients with squamous cell NSCLC. A phase II trial (NCT00735904) evaluating axitinib combined with gemcitabine/cisplatin for squamous cell NSCLC was recently completed.

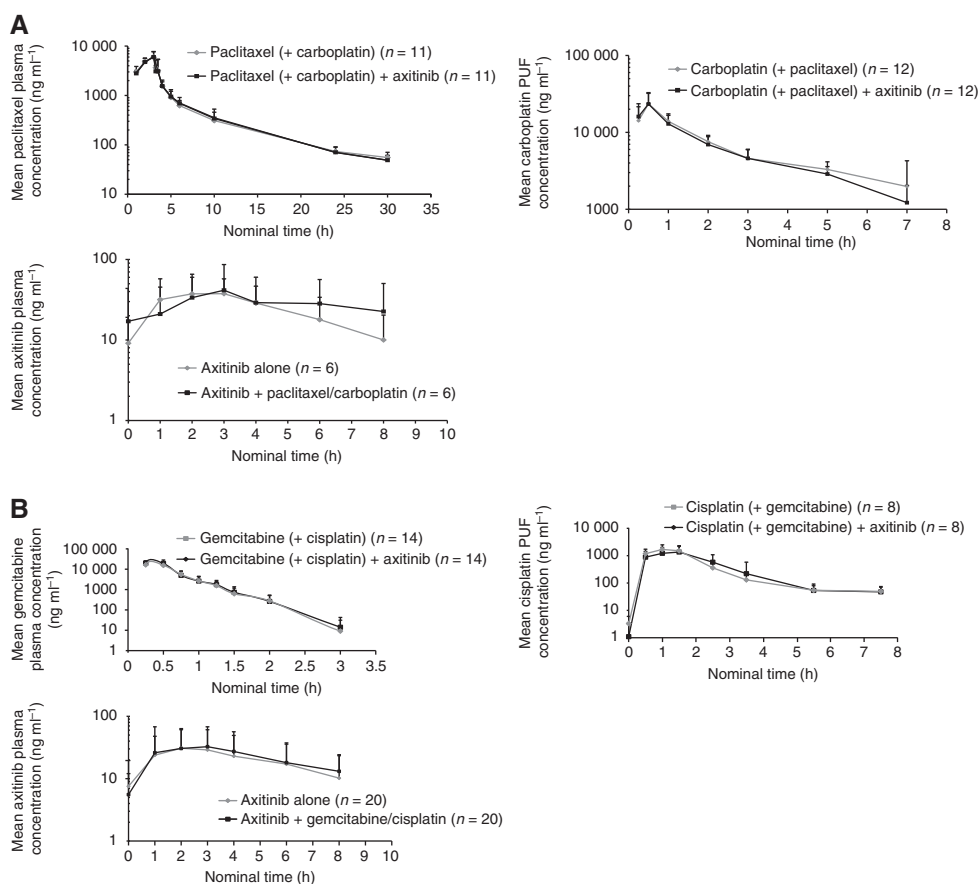


Figure 3 Plasma concentration–time curves for (A) axitinib, paclitaxel and carboplatin and (B) axitinib, gemcitabine and cisplatin. Abbreviation: PUF = plasma ultrafiltrate.

Data reported here suggest the ability to administer paclitaxel/carboplatin or gemcitabine/cisplatin with axitinib without altering pharmacokinetics of these agents. Axitinib metabolism is primarily mediated by CYP3A4 and to a lesser extent by CYP1A2, CYP2C19 and UDP-glucuronosyltransferase 1A1 as determined from *in vitro* studies with human liver microsomes (unpublished data). *In vitro* studies indicate that axitinib competitively inhibits CYP1A2 and non-competitively inhibits CYP2C8 with inhibitor constants of 0.7 μM (0.27 $\mu\text{g ml}^{-1}$) and 0.5 μM (0.19 $\mu\text{g ml}^{-1}$), respectively (unpublished data). Since paclitaxel is an established CYP2C8 substrate (Monsarrat *et al*, 1993; Steed and Sawyer, 2007) and axitinib inhibits CYP2C8 *in vitro*, increases in plasma concentrations of paclitaxel when administered in combination with axitinib were possible. Thus, patients were administered escalating lead-in doses of axitinib (starting at 1 mg b.i.d.) in sequential cohorts in combination with paclitaxel/carboplatin. Similar paclitaxel pharmacokinetics in the absence and presence of axitinib indicate that at clinically relevant plasma concentrations of axitinib, significant clinical CYP2C8 inhibition does not occur. In addition, there were no clinically apparent exacerbations of known paclitaxel toxicities.

Similarly, no overt changes in pharmacokinetics were observed between axitinib and cisplatin, carboplatin or gemcitabine and its metabolite dFdU, although interactions were not anticipated since axitinib is metabolised via pathways that are distinct from these agents. Both carboplatin and cisplatin are eliminated by glomerular filtration (Duffull and Robinson, 1997; Yao *et al*, 2007). Gemcitabine (2',2'-difluorodeoxycytidine) is sequentially phosphorylated intracellularly by deoxycytidine kinase and converted to di- and triphosphate products. Observed plasma concentrations of axitinib in combination with either paclitaxel/carboplatin or gemcitabine/cisplatin were consistent with those reported in other

phase I studies of axitinib as monotherapy or in combination with chemotherapy (Rugo *et al*, 2005; Sharma *et al*, 2010). Plasma exposures observed in this study of paclitaxel, carboplatin (PUF), cisplatin (PUF) and gemcitabine when administered alone were similar to those previously reported in the literature (Villalona-Calero *et al*, 2004; Kobayashi *et al*, 2007; Ricart *et al*, 2008; Okamoto *et al*, 2010).

Combinations of bevacizumab with chemotherapy have shown promising results in phase III studies of different tumour types; however, randomised trials of tyrosine kinase inhibitors targeting VEGF receptors in combination with chemotherapy have not shown a benefit for these combinations. Although the efficacy data for axitinib in combination with chemotherapy reported here are encouraging, they are exploratory, as would be expected from any phase I trial. The number of patients in each cohort was small, making it difficult to draw any definitive conclusions about the utility of axitinib combined with paclitaxel/carboplatin or gemcitabine/cisplatin in these patient populations. Nevertheless, they offer direction for ongoing and future clinical studies with sufficient statistical power for comprehensive analysis of the safety and efficacy of these combinations for the treatment of various cancers.

In conclusion, axitinib at a starting dose of 5 mg b.i.d. may be combined with paclitaxel/carboplatin or gemcitabine/cisplatin at standard doses, with no apparent overlapping toxicities and no overt changes in plasma pharmacokinetic parameters. Both combinations showed antitumour activity in patients with advanced solid tumours, including squamous cell NSCLC. Phase II studies of axitinib in combination with paclitaxel/carboplatin, gemcitabine/cisplatin and pemetrexed/cisplatin for NSCLC were recently completed.

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