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Phase I Clinical and Pharmacokinetic Evaluation of the Vascular-Disrupting Agent OXi4503 in Patients with Advanced Solid Tumors

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Abstract

Purpose: Preclinical studies show that OXi4503 (combretastatin A1 diphosphate, CA1P) is more potent than other clinically evaluated vascular-disrupting agents.

Experimental Design: Escalating doses of OXi4503 were given intravenously over 10 minutes on days 1, 8, and 15 every 28 days to patients with advanced solid tumors.

Results: Doses were escalated in single-patient cohorts from 0.06 to 1.92 mg/m^2, then expanded cohorts to 15.4 mg/m^2 in 43 patients. Common adverse drug reactions were hypertension, tumor pain, anemia, lymphopenia, and easily controllable nausea/vomiting and fatigue. Five patients experienced different drug-related dose-limiting toxicities, atrial fibrillation, increased troponin, blurred vision, diplopia, and tumor lysis. Prophylactic amlodipine failed to prevent adverse events. Pharmacokinetics showed dose-dependent linear increases in peak plasma concentrations and area under the curve value of OXi4503. One partial response was seen in a heavily pretreated patient with ovarian cancer. Dynamic contrast-enhanced MRI confirmed a dose effect and showed significant antivascular effects in 10 of 13 patients treated at doses of 11 mg/m^2 or higher.

Conclusions: The maximum tolerated dose was 8.5 mg/m^2 but escalation to 14 mg/m^2 was possible with only temporary reversible cerebrovascular toxicity by excluding hypertensive patients. As a tumor response was seen at 14 mg/m^2 and maximum tumor perfusion reductions were seen at doses of 11 mg/m^2 or higher, the recommended phase II dose is from 11 to 14 mg/m^2. *Clin Cancer Res; 18(5); 1415–25. ©2012 AACR.*

Introduction

Tumor angiogenesis is essential for tumor growth and metastatic spread (1). Tubulin-binding vascular-disrupting agents (VDA) such as OXi4503, the investigational product of this study, are a new class of drugs, selectively blocking or destroying preexisting blood vessels of tumors. This leads to the killing of tumor cells through withdrawal of oxygen and nutrients. VDAs exploit the known differences between the immature vascular endothelium and basement membranes of tumors and normal tissues (2). VDAs are distinguished from antiangiogenic agents, which block the formation of new vessels, but do not destroy already existing tumor blood vessels (3).

OXi4503 (combretastatin A1 phosphate) is a novel anticancer agent that has shown vascular disruption and cytotoxic activities in nonclinical models. It is a synthetic, phosphorylated prodrug of combretastatin A1 (OXi4500), a naturally occurring derivative from the bark of the South African bush willow tree, *Combretum caffrum*, that reversibly binds to the β-subunit at the colchicine-binding site of tubulin to inhibit microtubule assembly (3, 4). It is metabolized to a reactive orthoquinone species that is also assumed to be directly cytotoxic in tumor cells (5, 6) because of the production of a quinone metabolite that could bind to nucleic acids and also produces free radicals leading to the enhancement of oxidative stress (7).

Tumor regressions and complete responses were seen in animal studies with single-agent OXi4503. Vascular-disrupting activity already occurs at concentrations 10-fold

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Translational Relevance

This article reports the results of the first clinical evaluation of OXi4503, a novel vascular-disrupting agent (VDA) that targets tumor blood vessels. Preclinical studies showed it to be the most potent agent for reducing tumor perfusion leading to necrosis and, unlike other VDAs, tumor shrinkage. OXi4503 is a synthetic prodrug of combretastatin A1, a naturally occurring derivative from the bark of the South African bush willow tree, which reversibly binds to tubulin. This trial determined the maximum tolerated dose, safety, and pharmacokinetic profile. OXi4503 was shown to produce the toxicity expected from a VDA and showed clinical efficacy, with one patient showing an objective response. Dynamic contrast-enhanced MRI confirmed a dose–response relationship and significant antivascular effects in patients treated at higher doses. This trial confirms preclinical evidence that targeting preexisting tumor vessels with a VDA can lead to tumor shrinkage.

below the cytotoxic threshold. Therefore, it is suggested that OXi4503 might exert its activity below the concentrations where the classic side effects of cytotoxic drugs would appear (5, 8).

This phase I trial was designed to investigate the toxicity, pharmacokinetics, and pharmacodynamics of OXi4503 in a clinical setting.

Patients and Methods

OXi4503

OXi4503 [3-methoxy-6-[(1*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl]benzene-1,2-diol bis(dihydrogen phosphate monopotassium salt] is a water-soluble prodrug of *cis*-combretastatin A1 (OXi4500) and was supplied as a lyophilized powder containing 20 mg of OXi4503 per vial (as the free acid) and then diluted in up to 150 mL 0.9% NaCl. The intravenous infusion set (i.e., infusion bag, intravenous tubing) had to be protected from light. OXi4503 was supplied to Cancer Research UK (CRUK) by OXiGENE and distributed by the CRUK Formulation Unit, University of Strathclyde, Glasgow, UK.

Patients

Eligible patients had histologically proven advanced solid tumors and had declined or were refractory to standard therapy. Patients were excluded if they had prior radical radiotherapy or if they had any ischemic or vascular damage from previous radiotherapy. An amendment after the maximum tolerated dose (MTD) was reached, excluded patients who had blood pressure higher than 140 mm Hg systolic and/or 90 mm Hg diastolic or previous medical history of hypertension. All patients gave written informed consent.

Study design and procedures

This three-center (Mount Vernon Hospital, Middlesex, UK; Christie Hospital, Manchester, UK; and the Radcliffe Hospitals, Oxford, UK), first in-human, open-label, phase I, dose-escalation clinical trial (trial registration ID: NCT00977210) was reviewed by the CRUK external review process and approved by the Central Institutional Review Board (CIRB) and the Main Ethics Committee.

The primary objectives were to determine the MTD, the toxicity profile, and the dose-limiting toxicity (DLT) to propose a safe dose of OXi4503 for phase II evaluation. Secondary objectives included investigating the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of OXi4503 to document possible antitumor activity in patients and to determine the minimum dose of OXi4503 required to achieve significant reductions in tumor blood flow parameters using the imaging methods of dynamic contrast-enhanced MRI (DCE-MRI) and positron emission tomography (PET).

Sequential cohorts of patients received OXi4503 weekly for 3 weeks followed by a week with no treatment. This cycle of treatment could then be repeated up to 6 times. The starting dose was 0.06 mg/m^2 given as an intravenous infusion into a peripheral vein over 10 minutes using a volumetric pump. An accelerated dose-escalation scheme was used to minimize the number of patients treated at ineffective doses of OXi4503 with initial single-patient cohorts and double-dose steps (9). If any patient in the single-patient cohorts experienced drug-related toxicity of grade II or greater, the cohort was to be expanded to 3 patients. Once a dose level had been expanded, subsequent dose-escalation would be at 30% increments with 3 patients per dose level until DLT was observed in any cycle of treatment. A protocol amendment added that a 40% escalation in dose could be implemented following review of available toxicity data. Intrapatient dose-escalation was not permitted. A patient who had been treated previously on the trial at a lower dose level was allowed to be retreated on the trial at a higher dose, provided there had been an interval of 3 months from the last infusion and the first infusion of the retreatment program.

The protocol was amended to include instructions for the management of acute hypertension; if systolic blood pressure increased above 180 mm Hg, glycerol trinitrate (GTN) should be administered orally. This was changed to transdermal GTN patch after 31 patients. A further amendment was added for the use of amlodipine 10 mg as premedication for the prevention of hypertension after 31 patients.

Blood pressure and heart rate were monitored every hour for the first 6 hours. Twelve lead electrocardiographies (ECG) were conducted before treatment and 2 hourly for the first 6 hours. Toxicities were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

DLT was defined as treatment-related grade $\geq$III nonhematologic toxicity (excluding grade III nausea and grade III or IV vomiting or diarrhea in patients who have not received optimal treatment with anti-emetics or anti-diarrheals and

grade III tumor pain) or grade >III hematologic toxicity. MTD was defined as the dose below the dose at which more than 30% (2 of up to 6 patients) of the patient population suffered DLTs.

Pharmacokinetics

Plasma samples were collected serially before and up to 24 hours after, and urine samples were collected for 24 hours after the first treatment with OXi4503. Plasma and urine levels of OXi4503, OXi4500, and metabolites were measured using validated methods by liquid chromatography with fluorescence (10) or mass spectrometric detection. The plasma concentration–time data were analyzed using noncompartmental methods.

Assessment of response

Best response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST; ref. 11). A baseline computed tomographic scan was conducted within 2 weeks before starting treatment and after every 2 cycles of treatment. A minimum of 2 cycles was required for a patient to be considered evaluable for response. An independent review of all the investigators' assessed objective responses was undertaken by an independent oncologist and radiologist.

DCE-MRI

Only patients recruited at Mount Vernon and Radcliffe Hospitals underwent MRI scanning, depending on the evaluability of individual tumor lesions. MRI scans were conducted using a 1.5T Siemens Symphony scanner for patients 1 to 41 and a 1.5T Siemens Avanto scanner for patients 42 to 45 (Siemens Medical Systems) using surface coils appropriate for body part. A tumor marker lesion $\geq$2 cm in diameter was required, in a region not prone to motion artifact.

Two baseline scans were conducted within 1 week before the first dose of OXi4503 and at 4 and 24 hours and 8 weeks after the first dose of OXi4503, using the intravenously injected contrast agent gadopentate dimeglumine (Gd-DTPA, Magnevist, Bayer-Schering Pharma). More detailed analysis of the 4-hour scan plus methodology and analysis of the 24-hour and 8-week scan data, diffusion weighted, R_2^*, and cardiac output are in a separate manuscript (Zweifel and colleagues, personal communication).

DCE-MRI images were analyzed using the Magnetic Resonance Imaging Workbench Software (MRIW, Institute of Cancer Research, London, UK; ref. 12). Mean values of forward transfer constant (K^{trans}, units: min^{-1}) from the vascular to the extravascular space were calculated for each lesion.

Statistics

Nonparametric tests were used to calculate the statistical significance of differences between several groups (Kruskal–Wallis) and between 2 groups for paired (Wilcoxon signed rank) and unpaired (Mann–Whitney U) data and of correlations (Spearman). Fisher's r to Z test was conducted to calculate statistical significance of the correlation between vascular response and pain and Fisher's exact test for the correlations between the different sorts of pain (13). $P < 0.05$ (two-sided) was considered significant.

Results

Between July 2005 and January 2010, 45 patients were recruited onto the trial. Two patients were withdrawn from the study before receiving any OXi4503 treatment (due to rapid deterioration and the study put on hold for an amendment, respectively, after inclusion of the patients) and were excluded from further analysis. Two patients reentered the study at higher dose levels after previous participation: patient 3 was taken off-study due to progressive disease shown on a computed tomographic scan postcycle 2. However, this patient was reconsented and reentered at a later date as patient 13, receiving a higher dose; he then had prolonged stable disease. Patient 10 was taken off-study for surgery to the lesion in his axilla whereas his tumor was showing stable disease, but later recovered and was reentered as patient 15, his tumor showing early progression. Both the toxicity and efficacy data of the 2 reentered patients were analyzed as if they were separate individual patients. Patient characteristics are listed in Table 1. Two

Table 1. Patient characteristics ($n = 43$)

Characteristics	No. of Patients
Gender	
Male	20
Female	23
Age, y	
Median	53
Range	22–74
WHO performance status	
0	20
1	23
Prior therapy	
Chemotherapy	41
Radiotherapy	13
Hormonal or biologic therapy	16
Tumor type	
Colorectal adenocarcinoma	12
Melanoma (skin or uvea)	11[a]
Epithelial ovarian cancer	8
Malignant testicular teratoma	2
Renal cell carcinoma	2
Pancreatic adenocarcinoma	2
Squamous cell carcinoma, lips, and oral cavity	2
Uterine leiomyosarcoma	2[a]
Adenocarcinoma of unknown primary	1
Endometrial adenocarcinoma	1

[a]One patient entered study twice (see Patients and Methods).

patients, one with malignant melanoma and one with renal cell cancer, had not received chemotherapy prior to study entry.

For the first 6 dose-escalations, the trial had been carried out in single-patient cohorts (Table 2). Grade II anemia, considered probably related to OXi4503, was noted in one patient and the 3.84 mg/m^2 dose level expanded to 3 patients. Subsequent dose-escalations were at 30% until after the first 3 patients received 11 mg/m^2. As none of the patients in this cohort experienced a DLT, the decision was taken to escalate the dose by 40% to 15.4 mg/m^2 in the next cohort. DLTs are summarized in Table 3. The first 2 patients in the 15.4 mg/m^2 dose level experienced a DLT (atrial fibrillation and bowel perforation due to tumor lysis) and so it was decided to expand the 11.0 mg/m^2 dose level to 6 patients to define the MTD. However, DLTs were experienced by 2 patients (blurred vision and diplopia) in this expansion of the 11.0 mg/m^2 dose level and so the next lowest dose level of 8.5 mg/m^2 was expanded to determine the MTD. Because hypertension following OXi4503 treatment was suspected to have been a major factor in the underlying mechanism of 3 of the 4 DLTs observed, a protocol amendment excluded patients with prior hypertension and those receiving antihypertensive therapy. The same amendment also introduced intermediate dose levels of 12.5 and 14 mg/m^2 to allow exploration of the therapeutic window anticipated to lie above 8.5 mg/m^2 based on the observed changes in blood flow parameters shown by DCE-MRI and [^{15}O]H_2O-PET and tumor lysis syndrome in patients treated at 11 and 15.4 mg/m^2. Dose-escalation was restarted at 11 mg/m^2. One patient in this cohort experienced DLT of grade III increased troponin levels. This patient was subsequently reported to have had a history of antihypertensive treatment and was therefore not eligible for the study as per protocol amendment and was replaced in the cohort but included in the study population for analysis. Another patient in this cohort was taken off-trial after the first OXi4503 infusion when it was found that she had brain metastases and was replaced. No DLTs were observed in the 12.5 mg/m^2 cohort and the study concluded after 6 patients were treated at 14 mg/m^2. Two patients completed all 6 cycles, one treated at 11 mg/m^2 and one at 14 mg/m^2.

Toxicity

Table 4 lists the toxicities that were possibly, probably, or almost certainly drug related and only these are discussed below.

Hematologic toxicity was mild and there was only one drug-related grade III neutropenia. Anemia was the most common hematologic toxicity in 44% of patients, of which one was grade IV. Thrombocytopenia occurred in 19% of patients, of which one was grade IV. Both anemia and thrombocytopenia were found mostly at higher doses and

Table 2. Dose-escalation

Dose level, mg/m^2	No. of patients	Patient number (number of completed infusions)	No. of patients with DLTs
0.06	1	1 (3)	
0.12	1	3 (6)[a]	
0.24	1	4 (6)	
0.48	1	5 (4)	
0.96	1	7 (12)	
1.92	1	8 (6)	
3.84	3	9 (5), 10 (6)[b], 11 (2)	
5.00	3	12 (4), 13 (12)[a], 14 (15)	
6.50	3	15 (3)[b], 16 (5), 17 (3)	
8.50	3	18 (6), 19 (3), 20 (12)	
11.00	3	21 (6), 22 (12), 23 (18)	
15.40	2	24 (1), 25 (2)	2
11.00	3	26 (1), 27 (3)[c], 28 (2)	2
8.50	3	27 (3)[c], 29 (6), 30 (5), 31 (6)	
11.00	5	32 (6), 33 (2)[d], 34 (1)[e], 35 (6), 36 (13)	1[d]
12.50	3	37 (3), 38 (13), 39 (3)	
14.00	6	40 (1), 41 (18), 42 (6), 43 (6), 44 (4), 45 (12)	
Total	43	Total number of infusions: 272	5[d]

[a,b]Patient reentered the study.

[c]Patient treated one dose level lower after experiencing a DLT.

[d]Patient was later found to be on antihypertensive drugs and therefore ineligible and replaced. The associated DLT was reported but not considered for the decision on dose-escalation.

[e]Patient taken off-trial after one infusion due to detection of brain metastasis and therefore had to be replaced to complete the cohort.

Table 3. Dose-limiting toxicities[a]

Patient 24	15.4 mg/m^2	Grade III fast atrial fibrillation 5 days after first dose
Patient 25	15.4 mg/m^2	Grade III tumor lysis and GI fistula formation[b]
Patient 27	11 mg/m^2	Grade III blurred vision
Patient 28	11 mg/m^2	Grade III hypertension and diplopia
Patient 33[c]	11 mg/m^2	Grade III increased troponin level

Abbreviation: GI, gastrointestinal.

[a]Where multiple DLTs occurred in a patient, the most clinically relevant has been quoted.

[b]Resulting in grade IV peritonitis, contributing to tachycardia, thrombocytopenia, and hypotension.

[c]Patient was later found to be on antihypertensive drugs and therefore ineligible and replaced.

after repeated infusions. Lymphopenia was found in 26% of patients, of which one was grade III.

Tumor pain, nausea and/or vomiting, cardiac (hypertension, tachycardia, and QTc prolongation), and neurologic symptoms were the most common nonhematologic toxicities.

Blood pressure peaked on average at 3 hours and returned to baseline at 6 hours post-OXi4503 infusion. Mean maximum change in systolic blood pressure was +22% (−6% to +75%) and in diastolic blood pressure was +21% (−7% to +104%). The normalization of blood pressure was associated with a significant rebound increase in heart rate at 6 hours. Mean maximum changes in heart rate ranged from −10% to +22%, with maximum individual changes from −32% to +60%. There was a statistically significant relationship between OXi4503 dose and the percentage of maximal increase in systolic blood pressure during cycle one compared with baseline blood pressure measurement ($P = 0.032$). Prophylactic amlodipine was given in 15 patients from the dose of 8.5 mg/m^2 onward. Two of these patients developed symptomatic hypertension possibly related to the study drug, compared with 3 of 13 patients not receiving amlodipine at these doses. Six patients with hypertension after OXi4503 infusion were treated with a GTN patch. Of these, 2 patients developed symptoms possibly related to hypertension, which were considered DLTs.

One 50-year-old female patient with lymph node metastasis of ovarian cancer developed asymptomatic ECG changes with ST depression, negative T wave, and increased troponin T levels, consistent with asymptomatic cardiac ischemia (grade II) after her 13th infusion of OXi4503 while not having an elevated blood pressure. The event resolved within 24 hours, and all cardiac investigations (echocardiography, coronary angiography) were normal, but the patient was withdrawn from the study.

QTc interval prolongations were observed in 13 of 43 (30%) patients. Most were grade I (8 patients) and grade II was seen in 5 patients. There were no grade III or IV QTc interval prolongations.

Pain could be separated into tumor, musculoskeletal, or headache. Tumor pain had a median time to onset of 2 hours and 27 minutes after OXi4503 infusion and was significantly more often seen in patients with ovarian cancer (7 of 8 patients, 88%) than in patients suffering from other tumors. Morphine was used in 25 (58%) patients. Twenty-two of 43 (51%) patients experienced grade I, II, or III tumor pain. Although patients whose tumor showed vascular response (as assessed by DCE-MRI) seemed to be more likely to suffer from tumor pain, this relationship was not statistically significant. Musculoskeletal pain was seen in 17 of 43 (40%) patients and consisted of periodontal, muscle, joint, flank, and back pain. Median time to onset was 4 hours and 15 minutes and was almost exclusively grade I. Headache was seen in 15 of 43 (35%) patients. There was no significant correlation between the patients experiencing tumor pain, musculoskeletal pain, or headache.

Neurotoxicity consisted mainly of a muzzy head, dizziness, or confusion, which was reported by 12 (28%) patients and was almost exclusively grade I. Blurred vision and diplopia, experienced by a total of 4 patients, were initially thought to be related to changes in blood pressure (i.e., hypertension due to OXi4503 or hypotension due to prolonged effect of antihypertensive treatment). However, at least in one patient, a 55-year-old woman with lymph node metastasis of recurrent ovarian cancer, horizontal diplopia occurred regularly without concomitant arterial hypertension after the fifth to eighteenth administration of OXi4503. Mean time to onset was 2 hours and 22 minutes. An MRI of the brain conducted 2 hours after the onset of diplopia showed less distension particularly of the anterior and middle cerebral arteries and of the basilar and vertebral vessels while symptomatic, but there were no signs of cerebral edema (Fig. 1). Diplopia resolved completely within a couple of hours, and there was no cumulative increase in duration or severity over the cycles.

A 64-year-old female patient with lung, lymph node, muscular, and abdominal wall metastasis from malignant melanoma experienced grade I ataxia a couple of days after her first treatment with OXi4503, which resolved completely after the completion of cycle 1.

Sensory and motor neuropathy occurred in 5 (12%) and 1 (2%) patients, respectively, and occurred within 2 to 3 hours after OXi4503 infusion, resolving completely by the next morning. No cumulative effect of neurotoxicity was observed. Neurotoxicity was grade I except in one patient who experienced both grade II sensory and motor neuropathy. This 50-year-old patient with relapsed ovarian cancer started developing decreased sensation of her legs and unsteadiness while standing, 3 hours after her ninth infusion of OXi4503 at 11 mg/m^2, lasting for 2 hours. Computed tomographic scans did not show any spinal compression. The patient, who had stable disease, came off-trial after her 13th infusion of OXi4503 due to

Table 4. Worst drug-related toxicity per patient (all cycles)

Adverse event	Grade I	Grade II	Grade III	Grade IV
Hematologic toxicity				
Anemia	12% (5)	26% (11)	5% (2)	2% (1)
Lymphopenia	16% (7)	7% (3)	2% (1)	0
Neutropenia	7% (3)	12% (5)	2% (1)	0
Thrombocytopenia	9% (4)	2% (1)	4% (2)	2% (1)
Nausea	35% (15)	12% (5)	—	—
Vomiting	28% (12)	16% (7)	2% (1)	—
Fatigue	12% (5)	30% (13)	5% (2)	—
Fever, rigor, chills, pruritus, flu-like symptoms	37% (16)	9% (4)	—	—
Diarrhea	16% (7)	7% (3)	—	—
Anorexia	7% (3)	16% (7)	—	—
Flushing	16% (7)	5% (2)	—	—
Mucositis	12% (5)	2% (1)	—	—
Constipation	7% (3)	5% (2)	—	—
Dyspnea	5% (2)	2% (1)	—	—
Alopecia	7% (3)	—	—	—
Peritonitis (GI fistula/tumor lysis)	—	—	—	2% (1)
Pain				
Tumor pain	19% (8)	19% (8)	14% (6)	—
Other pain[a]	37% (16)	2% (1)	—	—
Headache	19% (8)	16% (7)		
Neurologic				
Muzzy head, dizziness, confusion	26% (11)	2% (1)	—	—
Sensory neuropathy	9% (4)	5% (2)	—	—
Ataxia	2% (1)	2% (1)	—	—
Motor neuropathy	5% (2)	—	—	—
Tinnitus	—	5% (2)	—	—
Blurred vision	2% (1)	—	2% (1)	—
Diplopia	2% (1)	—	2% (1)	—
Cardiac				
Hypertension	40% (17)	14% (6)	5% (2)	—
Sinus tachycardia	40% (17)	—	—	2% (1)[b]
QTc prolongation	19% (8)	12% (5)	—	—
Hypotension	12% (5)	—	2% (1)	2% (1)[b]
Sinus bradycardia	14% (6)	—	—	—
Atrial fibrillation	—	—	2% (1)	—
Ischemia	—	2% (1)	—	—

Abbreviation: GI, gastrointestinal.

[a]Musculoskeletal pain in most patients.

[b]In relation to peritonitis.

asymptomatic ECG changes, but a couple of months later developed similar signs of spinal compression. An MRI scan showed a spinal metastasis, which was probably present when the patient had neurologic symptoms on trial.

Nausea and vomiting were mostly grade I and from the 8.5 mg/m^2 dose level were treated prophylactically in almost all patients with dexamethasone, metoclopramide, and/or ondansetron.

Mild and transient fever, rigors, chills, or flu-like symptoms were also reported in 47% of patients. When dexamethasone (4 mg *per os*) and paracetamol (1 g *per os*) were given prophylactically at higher dose levels, these symptoms were no longer observed. Fatigue was seen in 19 patients (44%), mostly at higher doses and after repeated infusions.

Five DLTs were seen in this study, one in a noneligible patient (Table 3). One 73-year-old male patient with liver metastasis from rectal carcinoma treated at 15.4 mg/m^2 was readmitted 5 days after the first dose of OXi4503 with DLTs of grade III atrial fibrillation, hypotension and acute renal failure, and associated liver failure with thrombocytopenia

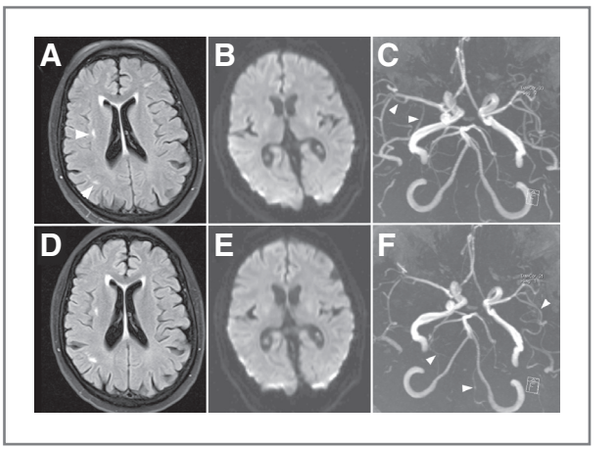

Figure 1. MRI of the brain of a 55-year-old woman with lymph node metastasis of recurrent ovarian cancer and horizontal diplopia before (A–C) and 3 hours after (D–F) the administration of OXi4503. Axial T2 FLAIR (A and D), diffusion weight scans (B and E), and time-of-flight MRI angiograms (C and F) are shown. Less distension particularly of branches of the anterior and middle cerebral arteries and of the cerebellar and vertebral vessels is seen. Arrowheads in A indicate old, small, probably ischemic lesions in the middle and posterior cerebral artery territories that remain unchanged. Arrowheads in C are branches of the right middle cerebral and in F of the left middle cerebral and cerebellar arteries.

and bladder obstruction/spasms. All events resolved completely with the exception of the bladder obstruction/spasms. The patient was withdrawn from the study. A 45-year-old male patient with liver and abdominal metastasis from malignant teratoma treated at 15.4 mg/m^2 developed tumor lysis following the second infusion with OXi4503. Computed tomographic scanning confirmed a dramatic reduction in size of his abdominal tumor masses but showed gastrointestinal fistula formation at the site where the tumor appeared to have infiltrated into small intestine. The patient died 1 month later from tumor progression. The tumor lysis with gastrointestinal fistula formation was a DLT that contributed to DLTs of supraventricular arrhythmia, hypotension, and associated thrombocytopenia. One 64-year-old female patient with lung, lymph node, muscular, and abdominal wall metastasis from melanoma treated at 11 mg/m^2 did not have a history of hypertension prestudy but was pretreated with amlodipine 10 mg because of asymptomatic hypertension after the first and second doses. She experienced nausea and headache followed by sudden blurring of vision in both eyes (grade III) 7 hours after the third dose of OXi4503. The event resolved by the following morning and an MRI scan of the brain was normal. Blurred vision was considered a DLT. The patient continued treatment at a reduced dose of 8.5 mg/m^2. One 74-year-old male patient with lung, bone, skin, peritoneal, and lymph node metastasis of melanoma had a prestudy history of hypertension, which was controlled by propranolol. Two hours after his second administration of 11 mg/m^2 of OXi4503, the patient developed grade III hypertension (maximum 187 mm Hg systolic and 103 mm Hg diastolic, respectively) which was treated with 0.5 mg GTN orally. Forty-five minutes later, the patient became dizzy and developed diplopia, which resolved after 6 hours and incoordination of the right hand. A computed tomographic scan showed a cavernoma, a coincidental finding unrelated to the clinical signs. The hypertension and diplopia were considered DLTs. A 59-year-old female patient with melanoma, who should have been excluded as she was on treatment with ramipril, doxazosin, and bendroflumethiazide, developed hypertension up to 210 mm Hg systolic, left arm ache, and grade III increased troponin levels after the second infusion with 11 mg/m^2 OXi4503, despite prophylaxis with amlodipine. A GTN patch was not given as hypertension spontaneously resolved. A cardiac angiogram was normal and the patient recovered fully. The patient decided to withdraw from the study prior to the scheduled third dose. Increased troponin was considered a DLT.

Response

Of the 23 (53%) patients evaluable for assessment of objective response (by having completed the first 2 cycles of OXi4503 treatment), one patient showed a confirmed partial response. The 55-year-old patient with lymph node metastasis from relapsed papillary serous ovarian carcinoma had a 66% reduction of the size of her target lymph node lesions and a 90% decrease in CA125 levels after 12 weeks of treatment at 14 mg/m^2. She experienced grade III tumor pain upon her second OXi4503 infusion, and after initial hardening of the mass, shrinking was observed clinically until the mass was no longer palpable after 4 cycles of treatment. The patient completed all 6 cycles. Eleven (26%) patients showed stable disease, of which 5 (12%) lasted at least until cycle 4 and 11 (26%) patients showed progressive disease. The remaining 20 (47%) patients treated with OXi4503 were withdrawn prior to the first assessment of disease. Nine (20%) patients experienced "early progression" defined as progressive disease during their first cycle of treatment.

Five patients did not show an objective response but had some clinical benefit of OXi4503 treatment. One 62-year-old patient suffering from ovarian cancer and recurrent ascites pretreated with 6 different lines of chemotherapy was treated at 8.5 mg/m^2. Her tumor showed an initial clinical response with decreasing CA125 levels over 3 months and no recurrence of ascites for 6 months. The CA125 response was not sustained and the tumor relapsed clinically during cycle 4 although computed tomography was showing stable disease according to RECIST.

Pharmacokinetics

OXi4503 was relatively slowly (terminal half-life, 1.7 $\pm$ 0.6 hours, mean $\pm$ SD) dephosphorylated to OXi4500 (CA1; terminal half-life, 5.3 $\pm$ 1.8 hours). Clearance (4.0 $\pm$ 1.7 L/h) was independent of dose but volume of distribution at steady state (V_{ss}; 5.0 $\pm$ 1.1 l) showed a small increase over the dose range studied. CA1 was further metabolized to 2 glucuronides CA1G1 and CA1G2. CA1G2 was cleared with a half-life of 5.0 $\pm$ 2.6 hours, but CA1G1 elimination was very slow and concentrations in general did

not reach a maximum until 8 hours after administration. The half-life was estimated to be approximately 20 hours. In the urine, no parent CA1P was detected and only a small amount of the CA1 (~2.5% of the administered dose) was detected. Approximately, equal amounts of the 2 monoglucuronides CA1G1 and CA1G2, each 26% to 27% of the administered dose, were found, along with 3.1% of the diglucuronide CA1DG. The mean ± SD for total recovery was 58% ± 18%. Dose and area under the curve in plasma showed a linear relationship for both the prodrug OXi4503 (Fig. 2A) and the active molecule OXi4500 (Fig. 2B).

DCE-MRI

DCE-MRI data from 22 of 29 patients were available at baseline and at 4 hours for analysis. Three patients had data from more than one evaluable lesion and these were concatenated and analyzed as a single lesion per patient.

The mean initial tumor K^{trans} value was 0.56 min^{-1} (SD, 0.7). This value is comparable with those in the literature for human tumors (14–16). There was a significant dose effect ($P = 0.0015$) at 4 hours after the first infusion of OXi4503. Ten of 13 patients treated at 11 mg/m^2 or higher dose had significant relative reductions in K^{trans} at 4 hours ranging from −41% to −100% (95% confidence interval, −27.8% and +38.4%, respectively; Fig. 3). One of the 2 patients with the greatest K^{trans} decreases (patient 41; K^{trans} decrease, −79%) had a confirmed partial response with a 68% tumor size reduction by RECIST after 6 cycles.

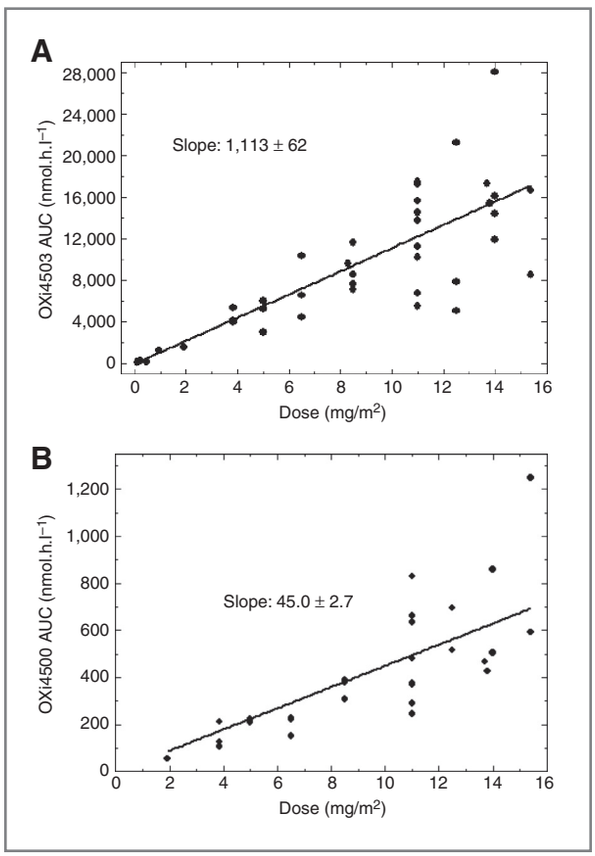

Figure 2. OXi4503 pharmacokinetics. Relationships between dose (in mg/m^2) and area under the curve (AUC; in nmol h/L) were linear for both the prodrug OXi4503 (A) and the active molecule OXi4500 (B).

Discussion

In preclinical studies, OXi4503 has been shown to be at least 10 times more potent than combretastatin A4 phosphate (CA4P) in terms of vascular shutdown (17). In this first in-human phase I trial, we investigated the toxicity, pharmacokinetics, and pharmacodynamics of OXi4503. Hematologic toxicity, apart from anemia was minimal, with only 8 episodes of grade III or IV toxicity seen after 272 cycles. Nausea was seen in 47% of patients with vomiting in 46%. Once prophylactic anti-emetics were given, usually antidopaminergics and/or serotonin antagonists plus dexamethasone, this became easily controlled. Fatigue, fever, or flu-like symptoms were seen in 47% of patients and again were controlled once prophylaxis with dexamethasone and paracetamol was introduced.

Pain was the most common drug-related toxicity. Pain considered to arise from the tumor was recorded in 51% of patients whereas 40% had musculoskeletal pain and 35% had headaches. There was no significant correlation between the 3 different types of pain. Tumor pain was in most cases an exacerbation of preexisting tumor pain, suggesting an effect of OXi4503 on the tumor or its immediate environment. In view of the mechanism of action of the drug, pain may most likely be explained by tumor ischemia. Interestingly, the patient whose tumor showed a partial response and the patient with tumor lysis were among the ones who experienced the most severe tumor pain. Pain is an expected toxicity from VDA therapy and could be controlled, in several cases requiring morphine, with no patient withdrawing because of pain.

Arterial hypertension was expected from preclinical studies of OXi4503 and its close relative, CA4P (18, 19). Hypertension was recorded in 59% of patients and peaked on average at 3 hours and returned to baseline at 6 hours following OXi4503 infusion. This hypertension was dose-related and was frequently followed by an increase in heart rate. QTc prolongation was seen in 30% of patients and 2 patients had troponin levels increased, with minor ECG changes, which resolved. Although the pathophysiology of hypertension in relation to VDAs is debated, this could be a result of highly perfused tumor masses having their circulation shut off by the VDA, thus increasing circulating blood volume, or as a consequence of direct vasoconstriction. Vessels of patients on fully expanded antihypertensive treatment may be less responsive to further antihypertensive medication.

Prophylactic use of amlodipine did not generally prevent hypertension or possibly associated troponin increase. However, no more symptomatic hypertensive-related events were observed in the last 12 patients during the final dose-escalations, when patients with preexisting hypertension were excluded, except in the ineligible patient included

in the study, despite being on antihypertensive medication. Both the patient with asymptomatic ECG changes and troponin release suggestive of cardiac ischemia and the patient with repeated diplopia after every infusion had not been hypertensive while symptomatic. It remains unclear whether hypertension or even the use of GTN to control it was the cause of the cerebral toxicity.

Cardiovascular and neurologic adverse events were reviewed by independent specialists (cardiologist, neurologist, and neuroradiologist). Apart from hypertension, cerebral toxicity might also have been caused by focal cerebral ischemia, although the full recovery in all the patients suggests this is a less likely explanation. Horizontal diplopia and incoordination are common symptoms of increased intracranial pressure. Headache and blurred vision could be compatible with posterior reversible encephalopathy, which is associated with cerebral edema secondary to acute increases in blood pressure, or with a related disorder, known as the reversible cerebral vasoconstriction syndrome. This seems to be supported by the findings in the MRI of the brain of one patient with signs of reduced distension of some arteries. However, the differences between the scans before and after OXi4503 infusion might also be attributable to technical factors because such changes would be expected to cause major neurologic symptoms, not just isolated symptoms such as diplopia. Arteriolar vasoconstriction has been reported to be the mechanism of action of the combretastatin analogue AVE8062 and could explain some of the side effects of OXi4503 such as pain, hypertension, and neurotoxicity (20).

Five cases of DLTs were reported. The two at the highest dose of 15.4 mg/m^2 consisting of atrial fibrillation in one patient and tumor lysis in another were not seen in any other patients treated at lower doses. While it is unclear if the atrial fibrillation, which occurred 5 days after OXi4503 infusion can be attributed to the study drug, tumor lysis might only have led to a DLT because the mass was infiltrating small bowel; a similar response is commonly seen in lymphoma patients. The other DLTs all at 11 mg/m^2 were blurred vision in one patient, hypertension and diplopia in another, and increased troponin level in a third who should have been excluded from the study because of severe preexisting hypertension. All DLTs at 11 mg/m^2 recovered within a few hours.

The observation of a RECIST confirmed partial response in a patient receiving 14 mg/m^2 with platinum-resistant ovarian carcinoma who also had the largest decrease in tumor perfusion on DCE-MRI scan, tumor lysis syndrome, and benefit in another patient with ovarian carcinoma treated at 8.5 mg/m^2, and minor benefit in 3 other patients suggest some single-agent activity. This appears more than in phase I trials with other VDAs such as DMXAA (ASA404, a VDA with a different mechanism of action), ZD6126 (ANG 453), CA4P, a closely related drug to OXi4503, plinabulin (NPI-2358), and BNC105P (21–23).

Evidence of antivascular effects was shown in this trial by DCE-MRI, with significant decreases in K^{trans} 4 hours after the first infusion of OXi4503. A significant dose–response relationship was seen in 10 of 13 evaluable patients having significant decreases in K^{trans} at doses of 11 mg/m^2 or higher compared with only 1 of 9 evaluable patients at lower doses.

Most previous studies with tubulin-binding VDAs have not shown evidence of a dose effect (22–24), with the exception of a limited phase I trial of the tubulin-binding colchicine analogue VDA ZD6126, where significant antivascular effects with increasing drug exposure were seen (25, 26).

This study was the first to show a significant linear dose–vascular response relationship over the entire dose range. Recently, Mita and colleagues used DCE-MRI for the evaluation of the novel VDA plinabulin (NPI-2358), showing a trend in dose relationship with decreasing K^{trans} and a statistically significant K^{trans} reduction at the highest dose level (22). For the clinical evaluation of the novel VDA BNC105P, Rischin and colleagues showed statistically significant declines in whole tumor K^{trans} values in some patients, largely at the 24-hour posttreatment DCE-MRI time point and at the higher dose levels (23).

The dose recommended for phase II trials must take account of the functional imaging, RECIST, and toxicity data. The DCE-MRI and PET data (27) clearly show that OXi4503 is a potent VDA with 12 of 15 evaluable patients receiving 11 mg/m^2 or higher dose having a significant reduction in tumor perfusion based on DCE-MRI (13 patients) or PET (2 patients; ref. 27). As both patients who received 15.4 mg/m^2 had DLTs, this dose appears too high. A case could be made for selecting 14 mg/m^2 as the recommended phase II dose as the only RECIST partial response was seen at this dose. Twenty patients received 11, 12.5, or 14 mg/m^2 with 11 receiving 6 or more infusions, suggesting it was reasonably tolerated in these patients. Although 3

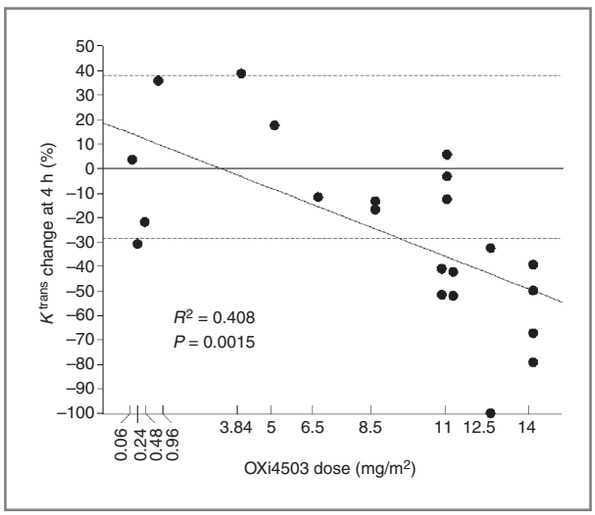

Figure 3. DCE-MRI: K^{trans} changes at 4 hours after OXi4503 infusion according to dose. Individual patient data ($n = 22$), sorted according to dose levels. The dotted lines mark 95% CIs (−27.8% and +38.4%) for change calculated from the 2 baseline measurements for all patients; the solid line is the regression curve.

DLTs were seen at 11 mg/m^2, they were all rapidly reversible and with prior warning patients might well be able to cope with temporary blurred vision as the responding patient did on 14 occasions. Routine prophylaxis with dexamethasone, an anti-emetic, and paracetamol appears to enable most patients to tolerate OXi4503 well. Only 1 of 9 evaluable patients receiving doses below 11 mg/m^2 had a significant reduction in DCE-MRI parameters, suggesting that such doses are too low to be recommended for phase II trials.

In summary, appropriate pain management and guidelines for prophylaxis and treatment of hypertension allow the safe handling of OXi4503 despite these 2 treatable side effects. Neurotoxicity is a common but short-lived and completely reversible side effect. Preclinical data suggest that VDAs are best given in combination as the spared peripheral rim of the tumor can regrow, possibly under the influence of endothelial precursor cells (28). The preferred agents to prevent this are antiangiogenic agents (29–31) but the overlapping toxicities will be important to consider in future combination trials. Because we saw a partial response in a patient with ovarian cancer and this cancer also responds to the antiangiogenic agent pazopanib (32), a phase Ib/II trial is planned combining OXi4503 with pazopanib.

Disclosure of Potential Conflicts of Interest

J. Balkissoon and D.J. Chaplin are employed by OXiGENE Inc. G.J.S. Rustin has an advisory role with OXiGENE Inc., Roche, and AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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