Cancer Chemother Pharmacol (2010) 65:597–605
DOI 10.1007/s00280-009-1157-8

CLINICAL TRIAL REPORT

Phase I clinical trial to determine maximum tolerated dose of oral albendazole in patients with advanced cancer

Mohammad H. Pourgholami · Michael Szwajcer · Melvin Chin · Winston Liauw · Jonathan Seef · Peter Galettis · David L. Morris · Matthew Links

Received: 26 May 2009 / Accepted: 27 September 2009 / Published online: 11 November 2009

Abstract
Purpose Albendazole is a potential anticancer agent that is currently under development for the treatment of cancer. We carried out a dose-finding phase I study of oral albendazole in patients with advanced malignancies.
Patients and methods Thirty-six patients with refractory solid tumors were enrolled. Albendazole was given orally on a day 1–14 of a 3 weekly cycle, starting at 400 mg BD with dose escalation until 1,200 mg BD. Serial blood samples were collected up to 96 h and also on day 8 of cycles 1 and 4.
Results The maximum tolerated dose was 2,400 mg per day (1,200 BD). Myelosuppression was the main dose limiting toxicity. Fatigue and mild gastrointestinal upset were the other major adverse effects. 4 out of 24 assessable patients (16%) had a tumor marker response with a fall of at least 50% from baseline values and another patient had a prolonged period of stable marker response. A decline in plasma vascular endothelial growth factor levels was observed.
Conclusions Albendazole was well tolerated on the schedule tested in this trial. The results of this study suggest that the recommended dose for further study is 1,200 mg twice daily for 14 days in a 21-day cycle.

M. Szwajcer · M. Chin · W. Liauw · P. Galettis · M. Links (✉)
Cancer Pharmacology and Therapeutics,
St George Hospital Cancer Care, Sydney, Australia
e-mail: Matthew.Links@sesiahs.health.nsw.gov.au

M. Chin · W. Liauw · P. Galettis · M. Links
St George Clinical School, University of New South Wales,
Kogarah, Sydney, Australia

M. H. Pourgholami · D. L. Morris
Department of Surgery, St George Clinical School,
University of New South Wales, Kogarah, Sydney, Australia

J. Seef
Southern Radiology, Bondi Junction, Kogarah, Sydney, Australia

Keywords Albendazole · Phase I · Ovarian cancer · Vascular endothelial growth factor · CA-125

Introduction

Albendazole, methyl 5-propylthio-1H-benzimidazole-2-yl carbamate, is a benzimidazole carbamate, originally developed as a veterinary product back in 1975, but is now widely used in man and animals as an anthelmintic [1]. It is considered the drug of choice in the chemotherapy of hydatid disease where it is administered at 10 mg/kg per day in two divided doses as oral tablets for a period of 28 days. Cycles of treatment are repeated after a rest period of 2 weeks. After oral administration, albendazole concentrations in the plasma are either not detectable or extremely low [2]. The parent drug is rapidly converted in the liver to the active metabolite albendazole sulfoxide (ABZSO) [3]. Review of literature reveals that, despite its extensive use in man and farm animals, few adverse events have been associated with its use [4]. The accepted mechanism behind the anthelmintic action of benzimidazole carbamates has been attributed to their binding to parasite β-tublin leading to inhibition of polymerization [5]. The microtubule disrupting property of albendazole and other benzimidazole carbamates has led to renewed interest in these drugs, this time as anticancer agents. We have previously shown the antiproliferative activity of albendazole against a range of tumor cell lines. In cell culture, depending on the concentration used, albendazole disrupts the cell cycle resulting in accumulation of cells in the G0–G1 (lower concentrations) or the G2–M (higher concentrations) phases of the cycle [6]. In tumor cells, induction of apoptosis by benzimidazole carbamates, such as albendazole, mebendazole, and carbendazim has been verified by various means [7–10].

Inhibition of tumor growth by these compounds has also been demonstrated in hepatocellular [6], lung [11], colorectal [12], adrenocortical [13], and ovarian cancer nude mice xenografts [14]. More recently, albendazole has been shown to inhibit vascular endothelial growth factor (VEGF) and to suppress malignant ascites formation in mice bearing intraperitoneal tumors [15]. The anti-VEGF property of albendazole and other benzimidazoles is currently under investigation.

Furthermore, results from a pilot study of oral albendazole (10 mg/kg per day given orally in two divided doses for a period of 28 days) in patients with predominantly colorectal cancer with liver metastases or hepatocellular cancer. Some evidence of efficacy was obtained with 2/7 patients showing a fall in tumor markers and three patients showing stable disease [16]. However, toxicity in this group of patients was seen with three patients developing neutropenia. This was severe in one but mild in the other two patients. As albendazole is extensively metabolized in the liver [2], the development of neutropenia was thought to be related to the presence of liver metastases and hence exposure to increased albendazole concentrations after a conventional dose. The presence of myelosuppression suggested exploration of a cyclical intermittent dosing schedule to allow marrow recovery.

Based on these observations, we performed a phase I dose escalation trial in patients with advanced cancer. The primary objective was to determine the safety, tolerability, and the maximal tolerated dose of albendazole when given on a day 1–14 of a 3 weekly cycle. Secondary objectives included characterization of the pharmacokinetics and preliminary evidence of efficacy.

Patients and methods

Patient selection

Patients were recruited at St. George Cancer Centre between September 2001 and July 2006. Patients selected to participate in this study had biopsy proven advanced or metastatic cancer refractory to conventional treatments. They had to be ≥18 years of age, able and willing to give informed consent and have an Eastern Cooperative Group (ECOG) functional status of 0–3. All patients had evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients had to have recovered from reversible side effects of prior therapy with at least 3 weeks from prior chemotherapy (or at least 6 weeks for agents known to be toxic to stem cells such as nitrosoureas, melphalan, or mitomycin). If patients had radiotherapy, at least 2 weeks from any prior radiotherapy was required and not more than 25% of bone marrow was to have been irradiated in total. Patients with previously treated CNS metastases were eligible, provided there was no clinical or radiological evidence of on-going CNS disease progression. Other eligibility criteria included (1) adequate hematological function defined as absolute neutrophil count (ANC) >1,500/mm^3 and platelets >100,000/mm^3; (2) adequate liver function as defined by bilirubin <2 × upper limit normal, AST/ALT <10 × upper limit of normal; (3) adequate renal function defined as a calculated creatinine >60 ml/min. Prior to the start of treatment, a complete medical history and physical examination, measurement of height, weight, vital signs, pain rating, ECOG performance score, urinalysis, pregnancy test (if relevant), chest X-ray, ECG, serum biochemistry including electrolytes, urea, creatinine (EUC), liver function tests (LFT) serum calcium, phosphate and glucose, full blood count (FBC), and measurement of relevant tumor markers were done.

Patients were excluded if they had unresolved ongoing infection requiring treatment; decompensated liver disease with non-malignant ascites, coagulopathy, or encephalopathy; other severe co-morbidity felt unsuitable by the investigators or were pregnant or breast-feeding. Patient pretreatment characteristics are outlined in Table 1. All patients provided written informed consent in accordance with federal and institutional guidelines before study treatment.

Study design

This was an open label, non-controlled, phase I dose escalation study designed to determine the safety and tolerability of albendazole in patients with advanced solid tumors. Albendazole was administered as oral tablets (400 mg tablets; GlaxoSmithKline, Australian Subsidiary). Patients were instructed to take the medication on an empty stomach. To overcome the potential cytotoxic effects of treatment and in particular hematological toxicity, a treatment break was incorporated within each cycle of treatment. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse events (version 2.0). Acute dose limiting toxicity (DLT) was defined as: (a) grade 3 neutropenia for >7 days or associated with fever, (b) grade 4 neutropenia of any duration, or (c) non hematologic toxicity of ≥grade 3.

Maximum tolerated dose (MTD) was defined as that dose level at which 2 out of 6 patients exhibit dose limiting toxicity during the first 8 weeks of treatment.

Drug administration and dose escalation

The starting albendazole dose was chosen based on previous experience with the drug [16]. The initial patient cohort started at level 1 (400 mg BD). A reserve dose level below level 1 was also planned in case of dose limiting toxicity

Table 1 Patient demographics

Characteristic	Number of patients
Total screened	66
Total enrolled	36
Total assessable	33
Age at enrollment (years)	
Median	65
Range	25–81
Gender	
Male	22
Female	14
ECOG at entry to study	
0	6
1	17
2	8
3	5
Tumor type	
Colorectal	12
Gastric	3
Mesothelioma	3
Pancreas	2
Lung (NSCLC)	2
SCC	2
Ovarian	2
Prostate	2
Biliary	2
Head and Neck	1
Uterine	1
Breast	1
Melanoma	1
Renal Cell	1
Unknown primary	1
Previous chemotherapy regimens	
0	2
1	11
2	8
3 or more	15
Previous radiotherapy	
Yes	11
No	25
Baseline weight (kg)	
Mean	69.2
Range	42.5–102.5

being experienced at that level. For dose escalation to occur, three assessable patients had to complete their first cycle without DLT. The last patient on one cohort was observed for a minimum of 3 weeks before dose escalation to the next dose levels was allowed. Dose interruptions and alterations were allowed in response to toxicity (Table 2).

Table 2 Schedule of dose reductions for toxicity

Hematological Toxicity	Dose
ANC $\geq$ 1,500 and Plat > 100,000	100%
ANC $\geq$ 1,000 but <1,500 or Plat $\geq$75,000 <100,000	Decrease one level
ANC < 1,000 or febrile neutropenia or plat >50,000 but <75,000	Decrease two levels
Recurrent or dose reduction < level −1	Off study
Non Hematological Toxicity	**Dose**
Grade $\leq$ II and duration < 7 days	100%
Grade II > 7 days or requiring dose delay	Decrease one level
Grade III or recurrent	Off study

Intra-patient dose escalation was not allowed. Subsequent cycles were withheld if the neutrophil count was $<1.500 \times 10^6$/L, platelet count <100,000 or if there was grade 2 non-hematological toxicity which did not resolved to <grade 1. If treatment was withheld, relevant laboratory measurements were repeated weekly (or more frequently if indicated) until resolution. Following resolution, re-treatment at a reduced dose level was considered at the discretion of the investigators. A patient was taken off the study, if there was progression of disease, if the patient was unable or unwilling to comply with the study, if the patient requested to discontinue, and if severe toxicity occurred as defined by any non-hematological NCI Common Toxicity Criteria grade III or IV toxicity judged to be due to the drugs; grade III or IV hematological toxicity causing treatment delays for more than 2 weeks and recurrent Grade III/IV hematological toxicity after dose modification.

Assessment of treatment

Radiological tumor evaluation and staging as clinically indicated was undertaken within 4 weeks of starting therapy. Laboratory testing was performed using standard techniques by the Southern Eastern Area Laboratory Services (Sydney, Australia). Glomerular filtration rate was calculated using the Cockcroft–Gault method and/or by isotope scanning. The patients were followed up weekly for toxicity and blood tests including FBC, serum biochemistry, and tumor markers. In addition, detailed history and physical examination, vital signs, KPS, and neurological examination were performed every fourth week. A formal assessment of measurable and evaluable disease was undertaken every 8 weeks. Upon removal or completion of study, the patients were followed monthly until disease progression with clinical assessment, tumor markers, FBC, and serum biochemistry. All sites of known disease were to

be reassessed 8 weekly in responding patients until disease progression.

Additionally, looking for an anti-angiogenic biomarker, we considered evaluating circulating VEGF levels, serial FDG-PET scans, Dynamic Contrast Enhanced Perfusion Computerized Tomography (DCEP-CT) of the liver and Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCEP-MRI). Measuring serum VEGF levels and DCEP-CT were logistically feasible.

Circulating VEGF levels were measured in seven subjects in the final dose level cohort. Plasma VEGF levels were measured according to manufacturer's instructions using an ELISA kit that detects soluble VEGF165 (Quantikine, R&D Systems, Minneapolis, MN, USA).

We sought to evaluate the use of DCEP-CT to detect changes in blood flow and volume in liver metastases. The patients in the final cohort were evaluated for liver metastases greater than 2 cm. If this was present, they proceeded to have a DCEP-CT scan at baseline and week 8. Scans were performed using the same Lightspeed Plus 8-slice multidetector CT scanner (GE Medical Systems, Milwaukee, WI, USA). The scans were performed by one designated radiographer following strict procedural guidelines overseen by a radiologist. Scan data after contrast infusion were processed using a liver perfusion software (GE Medical Systems, Milwaukee, WI, USA).

Pharmacokinetics

Blood samples for pharmacokinetic studies were collected prior to treatment and then at 1, 2, 4, 6, 8, 24, 48, 96 h, and day 8 of cycles 1 and 4. Samples were collected in heparinized tubes and centrifuged at 2,400 rpm for 5 min; plasma was aliquoted and stored at −80°C. Albendazole and albendazole sulfoxide in these samples were quantified using a validated HPLC method as previously described [17]. Briefly, plasma samples were extracted by placing 200 µl of the sample in a glass tube. Sodium metabisulphite (100 µl) and 2 ml of ethyl acetate were added. Following extraction, and centrifugation (2,000 rpm for 10 min), the organic layer was removed and evaporated in a Thermo Savant rotary vacuum chamber (Thermo Electron Corporation, Melbourne, Australia). The residue was resuspended in 200 µl of methanol for HPLC analysis. All data were recorded and analyzed on a computer with Class-vp Chromatography Data System Software (Shimadzu, Sydney, Australia). Plasma concentrations of albendazole and albendazole sulfoxide were determined by reference to corresponding standard curves, calculating the mass of samples, multiplying with appropriate dilution and recovery factor. Results are presented as mean ± SD.

Results

Patient characteristics

Thirty-six patients with refractory advanced solid tumors were enrolled onto this study. The dose levels, number of patients treated at each dose level, those completing at least one course of therapy and the number exhibiting DLT at each dose level are presented in Table 3.

Toxicity

The most common adverse events were fatigue, myelosuppression, and minor gastrointestinal side effects. Grade 2 Neuropathy and hyperglycemia were also seen infrequently. Grade 1 or 2 toxicity in more than one patient was seen for cough (8), Neuropathy (10), Alopecia (5), peripheral edema (7), rash (4), mucositis (3), visual disturbance (2), flushing (3), and haemoptyis (2). Drug-related grade 3 and 4 toxicities are outlined in Tables 4 and 5. One patient died from neutropenic sepsis that resulted from being on treatment. This patient was in the final dose cohort and had a history of metastatic colorectal cancer with extensive liver disease.

Table 3 Dose levels, enrollment, and dose limiting toxicities

Dose level	Dose (mg)	Treated (days)	Break (days)	Cycle (days)	Patients enrolled	Completed at least one cycle	Dose Limiting Toxicity
−1	400	7	21	28	0	NA	NA
1	400 BD	7	21	28	6	5	0
2	400 BD	14	14	28	3	3	0
3	400 TD	14	14	28	3	3	0
4	800 BD	14	14	28	3	3	0
5	800 BD	14	7	21	3	3	0
6	1,200 AM + 800 PM	14	7	21	9	9	1
7	1,200 BD	14	7	21	9	7	2

NA not applicable

Table 4 Albendazole-related grade 3 or 4 laboratory toxicity according to dose level

Dose level	Grade 3	Grade 4	Toxicity (Common Toxicity Criteria)
1	2	0	Lymphopaenia (2/6)
2	3	0	Anemia (1/3)
			Hyperglycemia (1/3)
			Elevated GGT (1/3)
3	2	0	Elevated GGT (1/3)
			Lymphopaenia (1/3)
4	2	0	Elevated GGT (1/3)
			Anemia (1/3)
5	4	0	Elevated GGT (1/3)
			Hypokalaemia (1/3)
			Hyponatraemia (1/3)
			Lymphopaenia (1/3)
6	7	1	Anemia (2/9)
			Thrombocytopaenia (1/9)
			Elevated GGT (2/9)
			Leukopaenia (1/9)
			Neutropaenia (1/9)
			Hypoalbuminaemia (1/9)
7	9	5	Elevated GGT (4/9)
			Leukopaenia (2/9)
			Lymphopaenia (2/9)
			Neutropaenia (2/9)
			Thrombocytopaenia (1/9)
			Anemia (1/9)
			Hyperglycemia (1/9)
			Hypoalbuminaemia (1/9)

Therapeutic response

No patients achieved partial or complete response by the RECIST criteria. However, 4 patients out of 24 with assessable tumor marker (16%) demonstrated a decrease of tumor markers of more than 50% and sustained for more than 28 days upon commencement of albendazole at dose levels 6 and 7. Another patient had a significant decrease in tumor markers and a prolonged period of stable disease. Effect of albendazole on tumor marker levels (CA125) of three patients with peritoneal carcinomatosis are presented in Fig. 1.

The starting VEGF levels varied in the range of 36–279 ng/ml (126.0 ± 102.8 ng/ml; mean ± SD). There was a trend to an initial decrease in circulating VEGF levels in the first 8-h post drug administration of serial sampling with the concentrations declining by 80% in the 8-h samples (Fig. 2a). However, VEGF levels in the later taken samples (24–528 h) were extremely variable with huge fluctuations (Fig. 2b).

Table 5 Frequency of clinical adverse effects with severity grade 3 or 4

	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	1	11	5	1
Infection/Fever	3	2	1	1
Confusion	0	1	0	1
Dyspnoea	0	7	3	
Pain	2	6	3	
Diarrhea	6	2	2	
Drowsiness	1	1	2	
Nausea	6	7	1	
Vomiting	3	5	1	
Anorexia	4	4	1	
Constipation	5	1	1	
Weight loss	1	1	1	
Dizziness	1	1	1	
Amennorhoea	0	0	1	
Indigestion	3	0	1	
Foot drop	0	0	1	
Hallucinations	0	0	1	
Dehydration	0	0	1	
Ascites	1	0	1	

Five patients underwent a baseline DCEP-CT. However, only two patients were able to have the second scan at 8 weeks. The values for blood flows and volumes for the two patients on two separate occasions revealed high inter-patient and temporal variability for all these values (data not presented).

Pharmacokinetics

The rapid metabolism of albendazole in both the gut and especially in the liver leads to undetectable concentrations in the systemic circulation and hence, the parent drug is not detected in plasma samples [18, 19] and was not expected to be measured in this study either. It is thus common to measure the sulfoxide metabolite. Samples from the seven patients in the final dose cohort were analyzed for albendazole and its major metabolite albendazole sulfoxide. All patients had samples collected for the first 24 h. Albendazole was not measurable in any technically reliable quantity. This is in line with previous reports on albendazole plasma concentration after oral dosing. However, the major metabolite, albendazole sulfoxide that is also pharmacologically active was detected in high concentrations. In this study, the mean of maximum concentration (C_{max}) for albendazole sulfoxide was 2.7 ± 2.1 (0.80–4.7) μg/ml. Notably, there was an outlier in the C_{max} values with the maximum recorded of 7.2 μg/ml. This value was achieved by the patient who developed neutropenic sepsis and died.

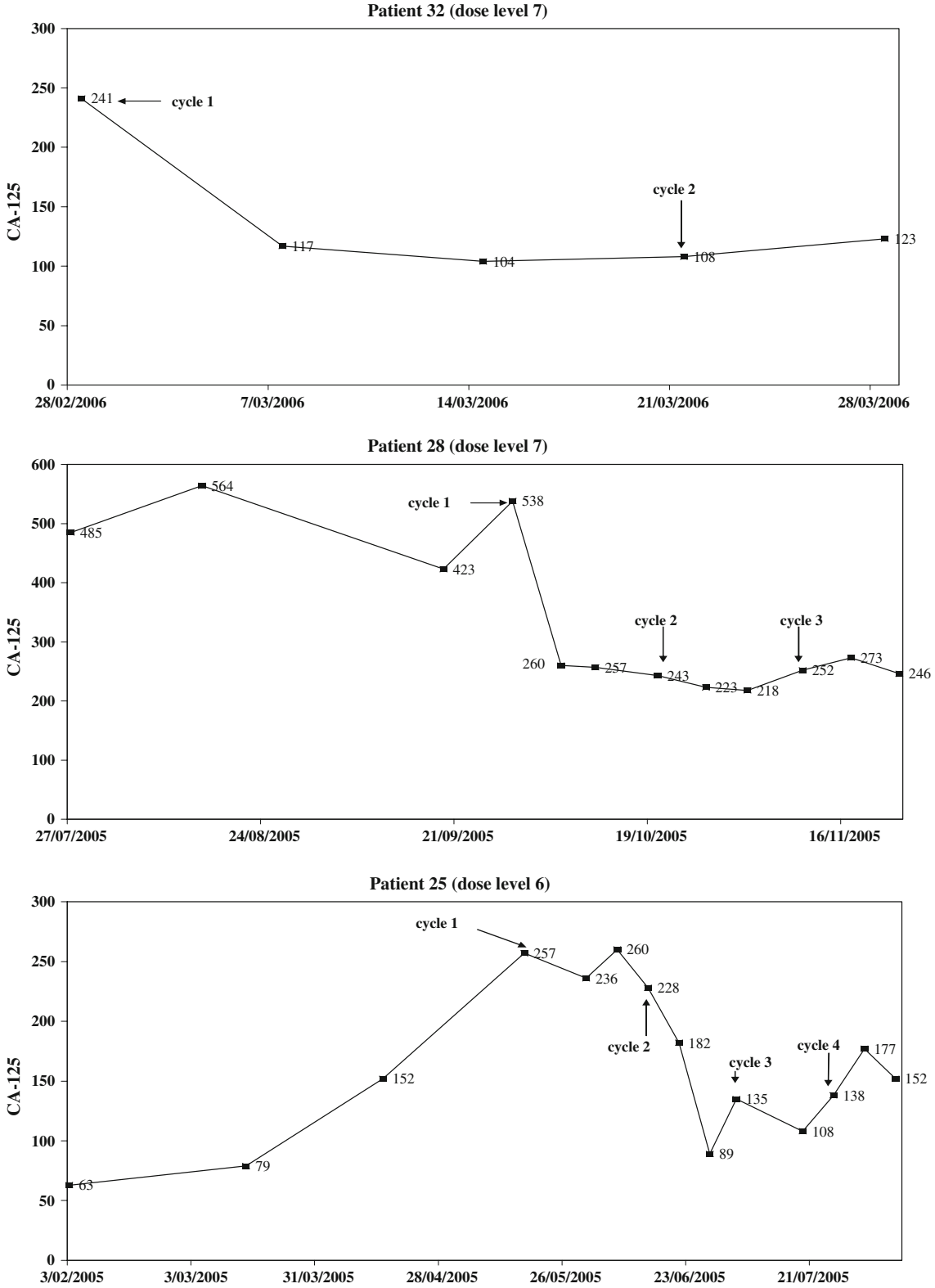

Fig. 1 Change in tumor maker levels (CA-125; U/ml) in patients with advanced cancer receiving oral albendazole. Each *plot* represents plasma CA-125 levels in a single patient

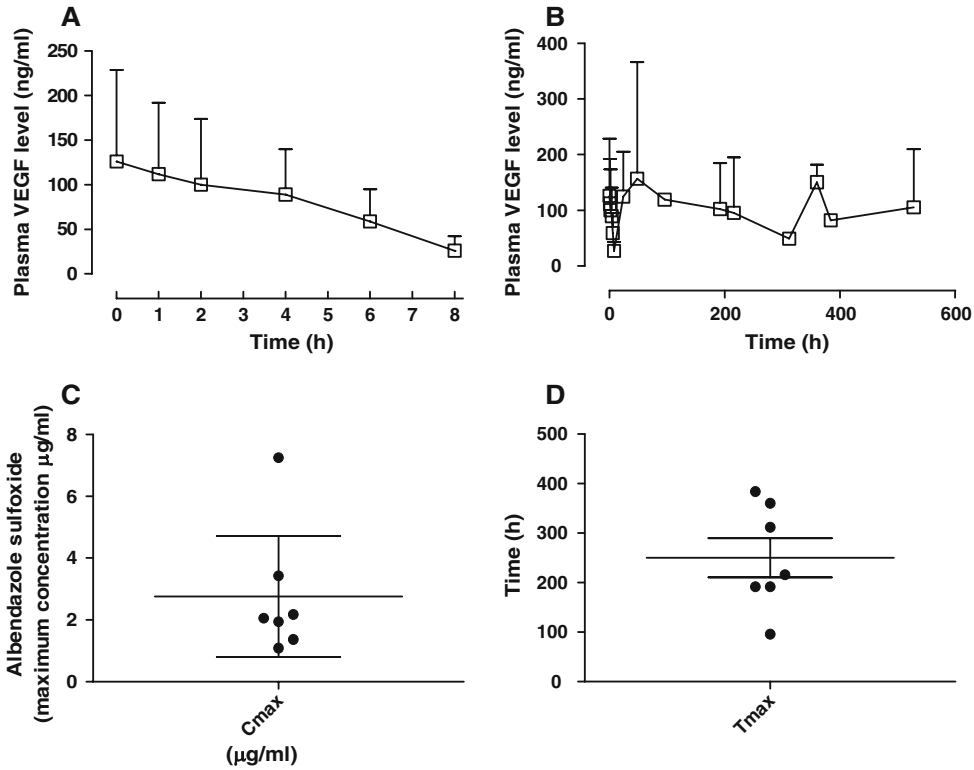

Fig. 2 Change in VEGF concentrations (ng/ml) in patients ($n = 7$) on the final dose level (1,200 mg BD) cohort in the first 8 h (**a**) and over the 528 h of monitoring (**b**). Maximum plasma albendazole sulfoxide concentration (C_{max}) (**c**) and the time to reach C_{max} (T_{max}) (**d**) in these patients

The time to reach C_{max} (T_{max}) was 250.3 ± 104 (153–346) h. Graphs of albendazole sulfoxide C_{max} and T_{max} are presented in Fig. 2c and d, respectively.

Discussion

Based on pre-clinical studies and the pilot study conducted previously, this phase I dose escalation trial examined the safety and determined the maximal tolerated dose of albendazole in patients with advanced malignancy refractory to conventional treatment. The doses used in this study were escalated beyond that used in the pilot study and in usual anthelmintic treatment. Given in an intermittent schedule, on a whole, the treatment was well tolerated symptomatically. The known side effects of marrow suppression and derangement of liver enzymes were encountered. The side effect profile seen here is consistent with a conventional microtubule-disrupting agent. The patient who developed febrile neutropenia and who subsequently died had significant metastatic liver disease and thus an ABZSO C_{max} of 2.6 times the mean. The hepatic metabolism and variability in oral variability raises caution on the use of the full dose of albendazole in subjects who have significant liver disease. Although considered as a relatively safe drug, albendazole as an anthelmintic has been associated with side effects including mild and transient epigastric distress, diarrhea, nausea, dizziness, lassitude, and insomnia in short term treatments and reversible low grade transaminase elevation, jaundice, gastrointestinal symptoms, alopecia, rash or pruritus, and leukopenia have been reported in patients under 3 month treatment courses for hydatid disease [9]. Gastrointestinal disturbances, fatigue, and neuropathy were the most common side effects encountered in the present study. Dose escalation produced albendazole sulfoxide concentrations that are expected to be cytotoxic in their own right (unpublished data), these concentrations also produced conventional cytotoxic toxicities such as alopecia and cytopenia. We are therefore confident that at these doses albendazole is acting at least partly as a conventional cytotoxic.

Although there were no objective responses by RECIST criteria, 4 out of the 33 assessable patients (12%) had a tumor marker response with a fall of at least 50% from baseline values while on treatment. Another patient had a prolonged period of stable marker response. The anti-tumor effect is believed to be through the interaction of the drug with the β-tubulin leading to cell cycle arrest and cytotoxicity. Inhibition of polymerization of tubulin into microtubules by benzimidazole carbamates in both helminthes and human tumor cells is well documented [7, 10, 12, 20, 21]. In terms of tubulin binding, albendazole is more potent than its sulfoxide metabolite, while the sulfone metabolite is an inactive derivative [22]. Evidence suggests that the common mechanism underlying the antitumor activity of microtubule disrupting agents may mainly rely on their

binding to β-tubulin, inhibition of spindle microtubule dynamics, slowing down of the metaphase–anaphase transition, mitotic block, and subsequent induction of apoptosis [23]. Nonetheless, involvement of other mechanisms, which may or may not be a consequence of the microtubule effect, cannot be ruled out. In cell culture and experimental models of cancer, albendazole has been shown to be an inhibitor of VEGF [14]. Reports from other laboratories have also shown suppression of microtubule dynamics, induction of apoptosis and inhibition of tumor growth for other benzimidazole carbamates [7, 9–11].

In this study, circulating VEGF levels fell sharply in the first 8 h in a time-dependent manner. However, in samples collected at 24 h, VEGF levels very variable and had dramatically increased. This may indicate a brief unsustained anti-VEGF effect, however, an artifact as a result of the method of collection should also be considered such as whether the subsequent collection of blood from the same cannula in the first 24 h may affect the platelet release of VEGF, leading to distortions in circulating VEGF levels. In terms of pharmacokinetics, albendazole is poorly soluble in water with a highly variable absorption profile and extensive first pass metabolism [18]. Both animal and human studies have demonstrated rapid conversion of albendazole to albendazole sulfoxide, some of which is then further oxidized to albendazole sulfone. Studies have suggested involvement of two systems in the metabolism of albendazole. The flavin containing monooxygenases (FMO) and cytochrome P450, principally CYP3A4 [12, 24].

Undetectable albendazole levels coupled with large inter-patient variability observed in the albendazole sulfoxide plasma concentrations makes any reliable pharmacokinetic analysis difficult. New formulations of albendazole suitable for intraperitoneal and intravenous routes are thus currently being developed.

Although there is a plethora of other antiangiogenic agents under development, we believe this data justify further development of this drug. The availability of affordable antiangiogenic agents with diverse mechanisms of activity will continue to be relevant.

Given the toxicity seen in the patient with high albendazole sulfoxide levels further studies with this agent should attempt to standardize the conditions of absorption (separating concomitant medications and food) and generate more detailed data on pharmacokinetics and the relationship to toxicity and response. It will be important for such studies to continue to assess the potential antiangiogenic effects of albendazole through in vivo imaging and biomarkers of angiogenesis (such as thrombospondin, ICAM and circulating endothelial cells).

In summary, results from this study have suggested that albendazole is well tolerated, relatively safe and has evidence of anti-tumor effects in patients with advanced cancer refractory to conventional treatments. Myelosuppression seen in two out of six patients on the 2,400 mg/day dose ($\times 3$ the conventional anthelmintic dose), was found to be the main dose limiting toxicity.

References

1. Dayan AD (2003) Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. Acta Trop 86:141–159
2. Marriner SE, Morris DL, Dickson B et al (1986) Pharmacokinetics of albendazole in man. Eur J Clin Pharmacol 30:705–708
3. Sotelo J, Jung H (1998) Pharmacokinetic optimisation of the treatment of neurocysticercosis. Clin Pharmacokinet 34:503–515
4. Horton J (2002) Albendazole: a broad spectrum anthelminthic for treatment of individuals and populations. Curr Opin Infect Dis 15:599–608
5. Lacey E, Brady RL, Prichard RK et al (1987) Comparison of inhibition of polymerisation of mammalian tubulin and helminth ovicidal activity by benzimidazole carbamates. Vet Parasitol 23:105–119
6. Pourgholami MH, Woon L, Almajd R et al (2001) In vitro and in vivo suppression of growth of hepatocellular carcinoma cells by albendazole. Cancer Lett 165:43–49
7. Sasaki J, Ramesh R, Chada S et al (2002) The anthelmintic drug mebendazole induces mitotic arrest and apoptosis by depolymerizing tubulin in non-small cell lung cancer cells. Mol Cancer Ther 1:1201–1209
8. Khalilzadeh A, Wangoo KT, Morris DL et al (2007) Epothilone-paclitaxel resistant leukemic cells CEM/dEpoB300 are sensitive to albendazole: involvement of apoptotic pathways. Biochem Pharmacol 74:407–414
9. Doudican N, Rodriguez A, Osman I et al (2008) Mebendazole induces apoptosis via Bcl-2 inactivation in chemoresistant melanoma cells. Mol Cancer Res 6:1308–1315
10. Yenjerla M, Cox C, Wilson L et al (2009) Carbendazim inhibits cancer cell proliferation by suppressing microtubule dynamics. J Pharmacol Exp Ther 328:390–398
11. Mukhopadhyay T, Sasaki J, Ramesh R et al (2002) Mebendazole elicits a potent antitumor effect on human cancer cell lines both in vitro and in vivo. Clin Cancer Res 8:2963–2969
12. Pourgholami MH, Akhter J, Wang L et al (2005) Antitumor activity of albendazole against the human colorectal cancer cell line HT-29: in vitro and in a xenograft model of peritoneal carcinomatosis. Cancer Chemother Pharmacol 55:425–432
13. Martarelli D, Pompei P, Baldi C et al (2008) Mebendazole inhibits growth of human adrenocortical carcinoma cell lines implanted in nude mice. Cancer Chemother Pharmacol 61:809–817
14. Pourgholami MH, Yan Cai Z, Lu Y et al (2006) Albendazole: a potent inhibitor of vascular endothelial growth factor and malignant ascites formation in OVCAR-3 tumor-bearing nude mice. Clin Cancer Res 12:1928–1935
15. Pourgholami MH, Cai ZY, Wang L et al (2009) Inhibition of cell proliferation, vascular endothelial growth factor and tumor growth by albendazole. Cancer Invest 27:171–177
16. Morris DL, Jourdan JL, Pourgholami MH (2001) Pilot study of albendazole in patients with advanced malignancy. Effect on serum tumor markers/high incidence of neutropenia. Oncology 61:42–46
17. Cai ZY, Galettis P, Lu Y et al (2007) Pharmacokinetics of albendazole in New Zealand white rabbits: oral versus intraperitoneal administration. Anticancer Res 27:417–422
18. Alvarez LI, Sanchez SF, Lanusse CE (1999) In vivo and ex vivo uptake of albendazole and its sulphoxide metabolite by cestode

parasites: relationship with their kinetic behaviour in sheep. J Vet Pharmacol Ther 22:77–86
19. Edwards G, Breckenridge AM (1988) Clinical pharmacokinetics of anthelmintic drugs. Clin Pharmacokinet 15:67–93
20. Lacey E, Watson TR (1985) Structure—activity relationships of benzimidazole carbamates as inhibitors of mammalian tubulin, in vitro. Biochem Pharmacol 34:1073–1077
21. Lacey E, Watson TR (1985) Activity of benzimidazole carbamates against L1210 mouse leukaemia cells: correlation with in vitro tubulin polymerization assay. Biochem Pharmacol 34:3603–3605
22. Lubega GW, Prichard RK (1991) Interaction of benzimidazole anthelmintics with Haemonchus contortus tubulin: binding affinity and anthelmintic efficacy. Exp Parasitol 73:203–213
23. Jordan MA, Kamath K (2007) How do microtubule-targeted drugs work? An overview. Curr Cancer Drug Targets 7:730–742
24. Rawden HC, Kokwaro GO, Ward SA et al (2000) Relative contribution of cytochromes P-450 and flavin-containing monoxygenases to the metabolism of albendazole by human liver microsomes. Br J Clin Pharmacol 49:313–322