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Phase I investigation of recombinant anti-human vascular endothelial growth factor antibody in patients with advanced cancer

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Abstract

We assessed the tolerability, safety, pharmacokinetics and dose-limiting toxicity (DLT) of the recombinant humanized IgG4 anti-vascular endothelial growth factor (VEGF) monoclonal antibody, HuMV833, in patients with advanced cancer. Cohorts of patients with progressive solid tumours received escalating doses of HuMV833 as a 1-h intravenous (I.V.) infusion on days 1, 15, 22, and 29. Twenty patients (median Eastern Cooperative Oncology Group (ECOG) score 1) were accrued. HuMV833 infusions were well tolerated and there were no grade III or IV toxicities definitely related to the antibody. Grade I or II toxicities probably related to the antibody included fatigue, dyspnoea and rash. There were two episodes of asymptomatic hypocalcaemia, one at grade III and one grade IV, which were recorded in early follow-up. There were eight grade I episodes of asymptomatic elevation of activated partial thromboplastin time (APTT) and two grade III events; one in a patient receiving 1 mg/kg and the other receiving extended doses of 10 mg/kg. Pharmacokinetic analysis revealed a non-linear kinetic and an elimination half-life of between 8.2 (0.3 mg/kg) and 18.7 (10 mg/kg) days. One patient with ovarian cancer experienced a partial response (PR) of 9 months duration and eight had disease stabilisation (SD) including one patient with colorectal carcinoma whose disease was stable for 14 months. In 13 of the 14 samples

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taken from 12 patients, the plasma concentration of hepatocyte growth factor (HGF) was reduced 24 h after drug administration. HuMV833 is safe and lacked DLT at doses up to 10 mg/kg on this schedule. Multiple doses were well tolerated, despite occasional asymptomatic elevations in APTT. By combining pharmacokinetic, pharmacodynamic and toxicity data, we can identify doses of 1 and 3 mg/kg for further investigation. HuMV833 appears to possess some clinical activity.

Keywords: Angiogenesis; VEGF; Antibody; Phase I clinical trial

1. Introduction

Angiogenesis is a complex process that involves the release of pro- and anti-angiogenic factors in a series of interrelated steps [1,2]. It is implicated in tumour survival, growth, invasion and metastasis and so represents a promising target for cancer treatment.

Vascular endothelial growth factor (VEGF) is one of the principal cytokines involved in the regulation of angiogenesis. It regulates blood vessel proliferation and permeability, acts as an anti-apoptotic factor for new blood vessels and is frequently expressed in tumours at high levels. VEGF is expressed as a number of isoforms including $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{165b}$, $VEGF_{189}$ and $VEGF_{202}$ [3,4]. Its biological effects are mediated via two signal-transducing tyrosine kinase receptors, VEGFR-1 and VEGFR-2, by the lymphangiogenesis-related receptor, VEGFR-3 [5] and through the accessory molecules that include neuropilins, heparan sulphate proteoglycans [4] and $\alpha_v\beta_5$ integrins [6].

Several approaches have been employed to inhibit VEGF signalling [7]. They include prevention of binding of VEGF to its normal receptors through administration of dominant-negative soluble VEGF receptors[8], disruption of downstream signalling through inhibition of VEGFR-associated tyrosine kinase activity [9–13] or the use of monoclonal antibodies directed against VEGF [14,15].

A recent randomised phase III clinical trial in humans showed that a combination of the anti-VEGF $IgG1_\kappa$ monoclonal antibody, bevacizumab, at 5 mg/kg with irinotecan, fluorouracil and leucovorin (IFL) in 403 patients with advanced colorectal cancer was associated with an improved median overall survival (20.3 months *versus* 15.6 months) and prolonged median progression-free survival (10.6 months *versus* 6.2 months) when compared with the control arm in which 412 patients were treated with IFL and placebo [16]. Further studies showed that bevacizumab increased the progression-free interval in patients with renal cancer [17] and that the antibody had a direct anti-angiogenic effect in rectal cancer [18]. These data support the validity of VEGF as a target and therefore the concept of inhibiting angiogenesis as an anti-cancer strategy.

Toxicities attributable to VEGF inhibitors have included headache, proteinuria, hypertension and, most importantly, haemorrhage and thrombo-embolism [19,20]. It would be highly desirable to improve or maintain the efficacy of these agents whilst reducing the toxicity. This might be achievable with antibody therapy through a switch in the immunoglobulin Fc domain, which controls complement fixation and antibody-dependent cell-mediated cytotoxicity (ADCC). In view of this, we investigated a humanised monoclonal $IgG4_\kappa$ anti-VEGF antibody, HuMV833, that does not fix complement and which therefore might have an improved activity and toxicity profile. HuMV833 antibody has a high affinity for $VEGF_{121}$ and $VEGF_{165}$ isoforms and an equilibrium rate constant of 0.1 nM. Preclinical *in vitro* and *in vivo* investigations indicated that it inhibits the growth of a wide variety of human malignancies *in vivo* [21]. Here, we report the clinical findings that complement the *in situ* imaging-based phase I investigation of HuMV833 [22] that was conducted on behalf of the Eastern Organisation for Research and Treatment of Cancer (EORTC).

2. Patients and methods

2.1. Inclusion criteria

Between January 2000 and March 2001, 20 patients with progressive, measurable, solid tumours were enrolled onto this phase I trial. All patients were aged at least 18 years and had a histologically confirmed diagnosis of advanced solid tumour, refractory to treatment with standard therapies, but with a predicted life-expectancy of 3 months or more. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$, normal haematological function (absolute neutrophil count of $\geqslant 1.5 \times 10^9$/l, haemoglobin $\geqslant 100$ g/l and platelet count $\geqslant 100 \times 10^9$/l), normal renal function (serum creatinine $\leqslant 120$ μmol/l), normal hepatic function (bilirubin $\leqslant 1.5$ times, and aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) = 2.5 times the upper limit of normal regardless of the presence of liver metastases) and normal cardiac function (assessed by 12-lead electrocardiogram (ECG)).

Study exclusion criteria included the presence of clinical signs of brain involvement or leptomeningeal disease, pre-existing serological evidence of infection with human immunodeficiency virus (HIV) or human T-cell leukaemia virus (HTLV-1), the presence of Hepatitis B surface antigen (HbsAg) or the presence of intercurrent infection. Those receiving any steroid or hormone therapies, known allergies to protein therapeutics or those with bleeding or clotting abnormalities, as well as pregnant, lactating or menstruating women, were also excluded. Patients were also excluded if they had received chemo-, immuno-, radio-, or hormonal anti-tumour therapy within four weeks of first drug administration. Voluntary written informed consent was obtained from all patients.

The study was conducted in four International Cancer Centres and in all cases a licence to conduct the trial was obtained from the relevant National Medicines Control Agency. The study protocol was approved by the EORTC Protocol Review Committee and the relevant Local Research Ethics Committee and the trial was conducted and monitored according to International Conference on Good Clinical Practice Harmonization (ICH-GCP) guidelines.

2.2. Study drug formulation and administration

HuMV833 was supplied at a concentration of 10 mg/ml in a sterile solution containing sodium citrate, sodium chloride and 0.01% polysorbate 80. Appropriate quantities of HuMV833 were diluted in a final volume of 250 ml in 0.9% sodium chloride. Patients received HuMV833 as a 60 min infusion without premedication and underwent evaluation of vital signs including blood pressure, pulse, respiratory rate and temperature before treatment and at 15, 30, 60, and 120 min, then at 3 and 6 h after initiation of infusion. Patients were hospitalised for 24 h after their first infusion and during this time underwent serial pharmacokinetic (PK) sampling. PK samples were collected 15 min prior to infusion, at 5 min, 1, 3, 6, 24 and 72 h and at 7 ± 2 and 10 ± 2 days after termination of infusion. Plasma total VEGF levels were monitored at 15 min prior to infusion and 24 h after the termination of the infusion. Further HuMV833 treatments were administered on days 15, 22, and 29. On these occasions, following drug infusion patients were observed for 6 h prior to discharge. All patients were seen weekly whilst on the study and underwent evaluation with physical examination, assessment of ECOG performance status, vital signs, together with laboratory investigations that included full blood count, chemistry evaluation, prothrombin time/partial thromboplastin time and urinalysis. Toxicities associated with the first four doses were graded using the National Cancer Institute Common Toxicity Criteria (version 2).

2.3. Cohorts and treatment doses

Eligible patients were assigned to receive HuMV833 on day 1, 15, 22 and 29 at one of four specified dose levels (0.3, 1, 3 and 10 mg/kg). Each patient at a given dose level was observed for toxicity for at least 4 weeks before additional patients could be entered into the study.

A minimum of three patients were included at each dose level. Dose-limiting toxicity (DLT) was defined as grade III or IV toxicity (except nausea, vomiting or fever). When DLT was observed in one of three patients, a further three patients were recruited at that dose level. If two or more patients experienced DLT at a single dose level, it was considered that the maximum tolerated dose (MTD) was exceeded.

Patients whose disease remained stable or had improved by the end of treatment were eligible to continue further weekly treatment with the same dose of HuMV833 for up to 6 months. No patients were rechallenged with HuMV833 following disease progression. Patients whose disease progressed within 2 weeks of first drug administration were deemed to have developed early progression and were replaced.

2.4. HuMV833, Pharmacokinetics, anti-HuMV833 antibodies and cytokine concentrations

Serum HuMV833 concentrations were determined using an enzyme-linked immunosorbent assay (ELISA), which used truncated recombinant human VEGF for capture and a sheep anti-human IgG4 conjugated to horseradish peroxidase (HRP) as the second step reagent.

Anti-HuMV833 antibodies were determined with a specific ELISA. Unlabelled HuMV833 and HRP-conjugated HuMV833 were used as the capture and detecting reagents. An anti-idiotypic antibody developed specifically against the HuMV833 epitope was used to calibrate the standard curve and to allow the quantitation of the anti-HuMV833 antibody to be expressed as the anti-id equivalence.

At least two patients underwent analysis of angiogenesis-related proteins in each dose level. Measurement of serum levels of VEGF, interleukin-8 (IL-8), soluble vascular cell adhesion molecule-1 (sVCAM-1), human fibroblast growth factor-2 (hFGF-2), sE-selectin, human hepatocyte growth factor (hHGF), sVEGF-receptor 1 were performed using the ELISA technique (R&D,Minneapolis, Minnesota, USA; Biosource International, Camarillo, CA, USA; RELIA Tech, Braunschweig, Germany). The VEGF ELISA does not distinguish free plasma VEGF from that already bound to HuMV833, hence the results of plasma VEGF reflect the total plasma VEGF concentrations (free and bound). Plasma samples for these cytokines were taken before treatment and 1, 3, 6 and 24 h after

the first and fourth treatments, 7 days after the first infusion and otherwise before and 6 h after infusions 2 and 3.

2.5. Response criteria

Response was assessed according to Response Evaluation Criteria in solid tumors (RECIST) criteria [23]. Initial assessment took place within the two weeks prior to administration of the first treatment. Clinical, biochemical and radiological follow-up assessments were performed after the first four doses of treatment and then every 2 months until disease progression. If a complete (CR) or partial response (PR) was detected, confirmatory radiological assessment was performed at least 4 weeks after the initial documentation of response. Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) and Positron Emission Tomography (PET) pharmacokinetic analysis were performed and have been reported [22].

3. Results

3.1. Patient characteristics

Twenty patients (9 male, 11 female) were recruited to the study. All were eligible and assessable for safety and response. The diagnoses and demographic data are presented in Table 1. The median ECOG performance status was 1 (range 0–2). The number of doses given to each patient is shown in Table 2.

Table 1
Patients' characteristics

Characteristics		Number of patients
Total patients		20
Men/women		9/11
Age, years		
Median (Range)	51.5(32–71)	
ECOG performance score		
0		9
1		10
2		1
Cancer type		
Colorectal		7
Ovary		5
Breast		2
Angiosarcoma		1
Larynx		1
Melanoma		1
Neuroblastoma		1
Osteosarcoma		1
Unknown primary		1
Prior therapy		
Surgery		16
Chemotherapy		19
Radiation therapy		7
Hormonal therapy		3
Immunotherapy		3

ECOG, Eastern Cooperative Oncology Group.

Table 2
Numbers of cycles of HuMV833 administered

Dose level	Patient No.	No. of injections	Reason for discontinuation
1	1	4	PD
1	2	4	PD
1	3	1	Early progression*
1	4	4	PD
2	5	4	PD
2	6	59	Trial completed
2	7	3	PD
2	8	4	PD
2	9	28	Symptomatic PD
2	10	9	PD
3	11	4	PD
3	12	8	PD
3	13	12	PD
3	14	31	Trial completed
3	15	4	PD
3	16	24	PD
4	17	4	PD
4	18	9	PD
4	19	4	PD
4	20	7	Patient decision

PD, progressive disease.
* defined as progression within 2 weeks.

3.2. Toxicity

HuMV833 was generally well tolerated at the doses studied and there were no grade III/IV toxicities that were definitely attributed to the drug. Table 3 shows the haematological and biochemical toxicities recorded for the patients in the trial. Largely these were grade I/II toxicities that were present before treatment.

One episode of asymptomatic grade IV hypocalcaemia occurred in a patient with primary breast carcinoma, who received HuMV833 at 3 mg/kg. Of note, this patient had grade I hypocalcaemia at presentation that had not worsened during the first 43 days of drug administration. The hypocalcaemia developed during the follow on phase of her treatment and was associated with grade I hypoalbuminaemia. A second patient with ovarian carcinoma also developed grade III hypocalcaemia by day 43 of treatment. The grade II/III changes in liver function tests (Grade III Alkaline phosphatase, ALAT and GGT; grade II hyperbilirubinaemia) occurred in the patient whose colorectal cancer liver metastases progressed early and who received treatment at the lowest dose level, 0.3 mg/kg.

No grade III or IV haematological toxicities were observed. However, eight patients developed grade I prolongation of activated partial thromboplastin time

Table 3
Haematological and biochemical toxicity

Adverse event	No. of subjects			
	Grade I	Grade II	Grade III	Grade IV
Leucocyte	2	1		
Neutrophils	2			
Platelets	1			
Haemoglobin	7	3		
⩾1 Haematological toxicity	7	4		
APTT	8		(1) 1	
Hypernatraemia	2			
Hypokalaemia	2			
Hypocalcaemia	3		(1)	(1)
Creatinine	1			
Bilirubin		1		
Alkaline phosphatase	5	1	1	
ASAT	2	1		
ALAT	2	2	(1)	
Hypoalbuminaemia	3			
Hyperglycaemia	4	3		
GGT	3	1	1	

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; APTT, activated partial thromboplastic time; GGT, gamma glutamyl transferase.
Figures in parentheses represent toxicities that occurred during follow-up or prolonged treatment after the initial four doses.

Table 4
Symptomatic toxicity

Adverse event	No. of subjects			
	Grade I	Grade II	Grade III	Grade IV
Fatigue/asthenia	7	4	1	
Fever	8	1		
Weight loss	1	2		
Flushing	3			
Rash	4			
Diarrhoea	4	1		
Nausea	6	1		
Vomiting	4	2		
Stomatitis	5	1		
G.I. symptoms	9	2		
Rectal bleeding	(1) 1			
Infection	2	2		
Neurotoxicity	8			
Cough	8			
Myalgia	1			
Cancer pain	2	1	2	

G.I., gastro-intestinal.
Figures in parentheses represent toxicities that occurred during follow-up or prolonged treatment after the initial four doses.

(APTT) and two developed asymptomatic grade III prolongation; one with melanoma treated at 1 mg/kg and one with ovarian cancer who was treated at 10 mg/kg. The patient treated with 10 mg/kg had grade I prolongation of APTT on the day of first treatment and in all cases the APTT returned to baseline on discontinuation of HuMV833.

Fatigue and asthenia were common, as documented in Table 4, but these were most likely to be due to the presence of advanced cancer in the patients. In contrast to other inhibitors of VEGF, HuMV833 was not associated with thrombosis, hypertension or proteinuria. However, two cases of grade I rectal bleeding were recorded. One occurred during the follow-up period of treatment for patient 4 and the other was experienced by patient 7 whose disease progressed at the end of the trial. Both patients had colorectal cancer and the symptom was attributed to the disease.

3.3. Pharmacokinetic studies of HuMV833

Following administration of HuMV833, plasma concentrations declined with an average elimination half-life of between 196 and 448 h (Table 5 and Fig. 1(a)). This was notably longer at the highest dose level suggesting that saturation of clearance may occur at 10 mg/kg. The data for the area under the concentration–time curve (AUC) were in keeping with this observation in that the AUC increased by an order of magnitude between patients treated at 3 and 10 mg/kg [22].

3.4. Antibodies to HuMV833

No patient on this trial developed antibodies to HuMV833 during the initial 35 day observation period or during subsequent treatment.

Table 5
Pharmacokinetic analysis of HuMV833[a]

Dose group (mg/kg)	N	C_{max} (μg/l)	AUC (μg h/l)	V_c (l/kg)	V_{ss} (l/kg)	CL (l/h/kg)	$t_{1/2}$ (h)
0.3	4	3748.4 ± 1987	187664.6 ± 49259	0.0680 ± 0.0706	0.3046 ± 0.141	0.00162 ± 0.0004	196 ± 141
1.0	6	6432.7 ± 3716	438903.5 ± 267731	0.1584 ± 0.0696	0.7009 ± 0.388	0.00239 ± 0.0012	326 ± 237
3.0	6	46510.0 ± 37788	1949261.8 ± 1461648	0.0690 ± 0.0544	0.3688 ± 0.245	0.00171 ± 0.0017	333 ± 384
10.0	4	401101 ± 250875	32597417.9 ± 31359377	0.0268 ± 0.017	0.1681 ± 0.37	0.00045 ± 0.0006	448 ± 1009

AUC, area under concentration *versus* time curve; C_{max}, maximum observed concentration; CL, clearance; $t_{1/2}$, elimination half-life of HuMV833; V_c, volume of distribution in central compartment; V_{ss}, steady-state volume of distribution.
[a] Mean plasma pharmacokinetic (±standard deviations) values for all patients entered at each dose level.

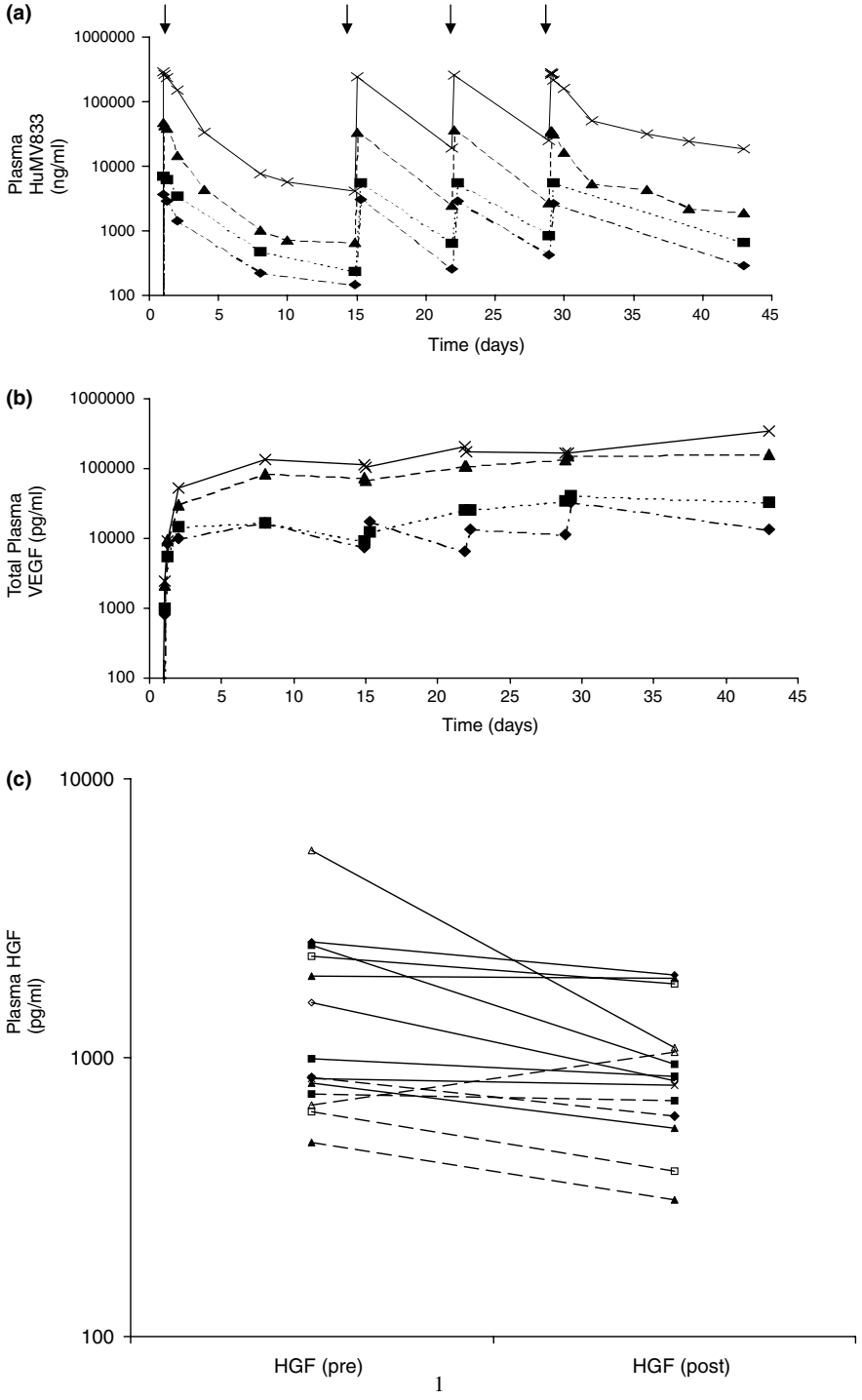

Fig. 1. Changes in circulating HuMV833 and cytokines (a) shows the plasma pharmacokinetics during the trial at each of the four dose levels. The arrows indicate the days of drug administration, (b) shows the plasma total vascular endothelial growth factor (VEGF) concentration during the trial at each of the four dose levels, (c) shows the concentration of hepatocute growth factor (HGF) (pg/ml) before (pre) and 24 h after (post) drug administration. For (a) and (b) solid diamonds; 0.3 mg/kg; solid squares: 1 mg/kg; solid triangles: 3 mg/kg; crosses: 10 mg/kg; arrows represent the days of drug administration. For (c) the data-points represent: patient 1 first cycle solid line solid squares, patient 2 first cycle solid line solid diamonds, patient 2 fourth cycle solid line solid triangles, patient 4 first cycle solid line crosses, patient 5 first cycle solid line open squares, patient 8 first cycle solid line open diamonds, patient 9 first cycle solid line open triangles, patient 10 first cycle coarse broken line closed diamonds, patient 10 fourth cycle coarse broken line closed triangles, patient 12 fine broken line open squares, patient 14 first cycle coarse broken line closed triangles, patient 15 first cycle coarse broken line open squares, patient 18 first cycle coarse broken line open triangles, patient 18 fourth cycle fine broken line closed squares, patient 20 first cycle fine broken line closed triangles.

3.5. Cytokine concentrations

A broad range of cytokines implicated in the angiogenic process were assayed in plasma including IL-8, soluble V-CAM, soluble E-Selectin, HGF, FGF-2,VEGF and soluble flt-1 (VEGF receptors) (sflt-1). The plasma concentrations of IL-8, V-CAM and soluble E-Selectin were remarkably stable throughout the trial in all patients. The concentration of total plasma VEGF, on the other hand, increased by several orders of magnitude and this correlated directly with the amount of antibody present in the blood as the majority of detected VEGF was bound to HuMV833 (Fig. 1(b)). The molar concentration ratio of antibody to VEGF implied that all VEGF was chelated by antibody such that there was no free soluble VEGF in the circulation [22].

We examined the changes in FGF-2 and HGF in a number of patients at each dose level, revealing some consistent changes. Thirteen of 14 samples taken from 12 patients showed a median reduction of 25% in plasma HGF within 24 h of drug administration (Fig. 1(c)). Furthermore, 10 of 14 samples taken from 12 patients assessed for FGF-2 showed a reduction within 24 h after drug administration (data not shown). The median reduction in concentration was 20%. There was no evidence of a dose–response relationship.

3.6. Efficacy

Whilst response was not a primary endpoint of this study, clinically important anti-tumour activity was observed. One PR was observed, in a patient with ovarian cancer treated at 3.0 mg/kg in the cohort of the 20 patients treated with HuMV833. In this patient, there was complete resolution of a 42 mm pelvic tumour (Fig. 2) and normalisation of CA125. Whilst this disease site represented most of the patient's disease load, a CR was not achieved as pelvic stranding and ascites persisted. Therapy was discontinued after 6 months in this patient and the overall response duration was 9 months. Stable disease (SD) was recorded in eight patients with durations of between 7 and 59 weeks. These included

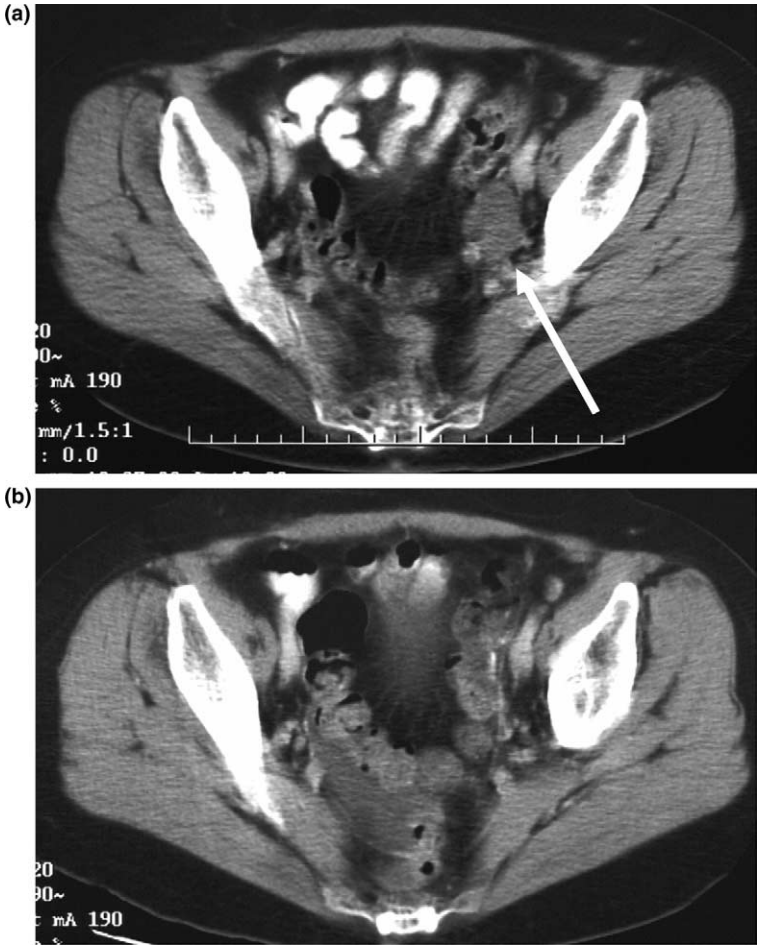

Fig. 2. Partial response in patient with ovarian cancer (a) (arrow) shows a 42 mm lesion in the left side of the pelvis of a patient with ovarian cancer. After 9 weeks of treatment (3 mg/kg), the post-treatment scan (b) shows the mass had resolved completely. The scans were externally reviewed and a partial response (PR) was confirmed on the basis of persistent mesenteric stranding.

four patients with ovarian carcinoma, two with colonic, one with breast and one with laryngeal carcinoma. The longest duration of disease stabilisation occurred in a 71 year old male with liver and intra-abdominal metastases from colon carcinoma. His disease had recurred following previous adjuvant fluorouracil chemotherapy and progressed through therapy for metastatic disease with fluorouracil and irinotecan. His quality of life was excellent during treatment with HuMV833 and his condition remained clinically and radiologically stable for the 59 weeks during which he received therapy. These observations are consistent with the reports of anti-cancer activity in the randomised study of bevacizumab therapy in patients with colon cancer [16], but for the first time highlight the possibility that VEGF inhibition may be a desirable strategy in ovarian cancer. The remaining 11 patients demonstrated progressive disease (PD).

4. Discussion

This study is the first evaluation of an $IgG4_{\kappa}$ humanised monoclonal anti-VEGF antibody. The antibody was well tolerated, such that a DLT and MTD were not defined. In particular, we did not observe any episodes of thrombo-embolic events, although two episodes of grade III prolongation of APTT were recorded. Both cases were asymptomatic and one occurred during the continued treatment phase. They both improved upon cessation of the antibody suggesting a causal association, although the number of episodes was low. Although there have not been other reports of VEGF inhibitors being associated with distortions of the coagulation cascade, this parameter should be monitored in further evaluation of this class of molecule.

Nine patients continued therapy beyond the planned four treatments and this was well tolerated. Long-term administration of anti-VEGF antibodies is likely to be safe, as patients received up to 59 cycles of treatment with an excellent quality of life. In an analogous series of 28 patients with advanced solid tumours, treated with bevacizumab therapy for a median of 14 months, the antibody was also largely well tolerated [24], although there were two episodes of gastrointestinal bleeding (grades II and IV) in patients with colorectal carcinoma and five instances of deep venous thromboses. In addition, hypertension of grade II or III developed in three patients. Although we did not observe thrombo-embolic events during this trial, larger numbers of patients would be needed to substantiate any differences between IgG1 and IgG4 monoclonal anti-VEGF antibodies that might be mediated through differential complement fixation.

The aim of a phase I trial is to identify a dose or doses that could be explored further in the phase II setting. The DCE-MRI data [22] suggested that the 0.3 mg/kg dose level was associated with only minor and non-sustained changes in vascular permeability. When this is analysed in conjunction with the pharmacokinetic data, which showed evidence of saturation of clearance at the 10 mg/kg dose, the implication was that further studies could focus on doses between 1 and 3 mg/kg. Thus, despite the lack of a DLT and MTD, we have been able to combine novel biological data with traditional phase I endpoints to identify doses for further exploration.

One PR and eight cases of SD were observed in this study. However, the inclusion of only 20 patients precludes definitive conclusions being drawn concerning the efficacy of HuMV833 from this trial alone. Complementary data are available for the use in humans of the $IgG1_{\kappa}$ monoclonal anti-VEGF antibody, bevacizumab, which has been administered safely to humans in larger series, both as a single agent and in combination with cytotoxic chemotherapy [14,15]. The efficacy of HuMV833 appears in line with the data reported in the initial monotherapy phase I study of bevacizumab [14], where no objective responses and 12 (48%) instances of SD were observed in a total of 25 patients, while our data suggest that nine (45%) had stable or improved disease.

Around the world there has been a large amount of work devoted to identifying and validating surrogate pharmacodynamic endpoints that could be used to optimise the development of VEGF inhibitors. The most thoroughly investigated of these is the use of DCE-MRI [10,22,25,26]. This technique appears to hold clinical validity and has been incorporated successfully into phase I methodology. However, it is difficult to apply the algorithms across multiple centres. Here a consistent decrease in soluble HGF concentrations 24 h after administration of a monoclonal anti-VEGF antibody to humans is reported for the first time. HGF is a potent angiogenic cytokine and previous associations between HGF, VEGF and disease extent have been reported in cancer patients [27]. As we have shown that there is a common change in plasma HGF concentrations in patients treated with HuMV833 it would be appropriate to investigate this finding in larger studies, particularly as this measure could easily be used in large phase III clinical trials.

In conclusion, we have completed the phase I evaluation of the monoclonal anti-VEGF antibody, HuMV833. The antibody was well tolerated and a MTD was not defined. We saw significant anti-tumour activity identifying ovarian cancer as a disease where single agent VEGF inhibition might be investigated, perhaps as a maintenance therapy. Finally, the data concerning plasma HGF changes are interesting and suggest that further studies are required to investigate HGF as a potential biomarker in anti-angiogenic therapy.

Conflict of interest statement

None declared.

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