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European Journal of Cancer 41 (2005) 555–563

European Journal of Cancer

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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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Received 4 November 2004; accepted 5 November 2004
Available online 22 January 2005

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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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.11.021

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)).