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Intravenous aflibercept administered in combination with irinotecan, 5-fluorouracil and leucovorin in patients with advanced solid tumours: Results from the expansion cohort of a phase I study

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Abstract ***Background:*** Following the dose-escalation stage, this double-blind expansion stage of the phase I study evaluated the safety, pharmacodynamics, pharmacokinetics, anti-vascular effects and antitumour activity of aflibercept 4 mg/kg with irinotecan, 5-fluorouracil and leucovorin (LV5FU2).

Patients and methods: Patients with advanced solid tumours were randomised at cycle-1 to placebo or aflibercept (4 mg/kg) on day 1 then irinotecan–LV5FU2 on days 1 and 2. Subsequently, all patients received aflibercept with irinotecan–LV5FU2 every 2 weeks. Anti-vascular effects were assessed using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Results: Twenty-seven patients were treated; 14 received placebo in cycle-1 followed by aflibercept in later cycles and 13 received aflibercept 4 mg/kg upfront. The median number of aflibercept cycles was 16 (range 1–44), 12 patients received $\geqslant$20 cycles. Most frequent grade 3/4 adverse events were neutropenia (37%), fatigue (33%) and hypertension (30%). No

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anti-aflibercept antibodies were detected. Four patients achieved partial responses and 17 had stable disease, lasting >3 months in 14 patients. Plasma levels of free over vascular endothelial growth factor-bound aflibercept were adequate, with steady-state achieved from cycle-3. Exploratory DCE-MRI showed no significant perfusion changes with aflibercept.
Conclusion: Aflibercept 4 mg/kg plus irinotecan–LV5FU2 every 2 weeks had acceptable toxicity and pharmacokinetics, and showed promising antitumour activity.

1. Introduction

Vascular endothelial growth factor (VEGF) mediates angiogenesis through binding to the tyrosine kinase receptors, FLT1 (fms-related tyrosine kinase 1, also known as vascular endothelial growth factor receptor-1 [VEGFR-1]) and KDR (kinase domain-containing receptor: VEGFR-2).[1,2] Angiogenesis is critical to tumour progression,[1,3] where the expression of VEGF and VEGFR in solid tumours has been associated with patient prognosis.[4–6] A number of agents have been investigated in preclinical studies that target VEGF, VEGFR-1 and VEGFR-2 and components of VEGF-mediated downstream signalling, with a view to providing novel and effective anticancer approaches that might complement standard chemotherapy regimens.[7–10] One such agent is the anti-VEGF monoclonal antibody, bevacizumab, which has been approved for the treatment of advanced metastatic colorectal cancer (CRC) based on clinical data demonstrating a significant prolongation of progression-free survival (PFS) when administered with standard chemotherapy regimens.[11]

Aflibercept (VEGF Trap) is a recombinant fusion protein comprising domain 2 of VEGFR-1 and domain 3 of VEGFR-2 attached to the hinge region of the Fc domain of human IgG1.[12] Aflibercept is a decoy receptor, with the ability to bind all VEGF-A isoforms at high affinity and placental growth factor, and inhibits tumour angiogenesis and growth in preclinical models.[12–15] A recent phase I dose-escalation study by Lockhart et al. investigated aflibercept administered intravenously (IV) as monotherapy every 2 weeks to 47 patients with advanced solid tumours.[16] Three RECIST (Response Evaluation Criteria in Solid Tumour)-defined partial responses were observed and aflibercept was well tolerated. In addition, changes in pharmacokinetic parameters and pharmacodynamic markers were indicative of VEGF blockade at aflibercept doses >2 mg/kg.

The clinical utility of aflibercept in combination with irinotecan and LV5FU2 (5-fluorouracil and leucovorin) has recently been evaluated in a phase I study of 38 patients with advanced solid tumours. The initial dose-escalation part of this study established aflibercept 4.0 mg/kg every 2 weeks as the recommended dose for further evaluation (recommended phase II trial dose, RPTD).[17] We now report the findings of the expansion part of this study. New patients were randomised to receive irinotecan and LV5FU2 with aflibercept 4 mg/kg every 2 weeks or to receive placebo at cycle-1, all patients received irinotecan and LV5FU2 plus aflibercept at the RPTD in subsequent cycles. The objectives of this part of the study were to investigate further the safety and pharmacokinetics of the aflibercept RPTD as combination therapy in an additional cohort of patients. The potential additive anti-vascular effects of aflibercept at the RPTD were measured using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), at cycles-1 and -2. Finally a preliminary assessment of the antitumour effects of aflibercept at the RPTD in combination with standard therapy was performed.

2. Patients and methods

2.1. Eligibility

Key eligibility criteria included patients aged ⩾18 years with histologically or cytologically confirmed solid malignancy that was metastatic or unresectable or for which no standard conventional therapy existed, but for which treatment with irinotecan–LV5FU2 was considered appropriate; Eastern Cooperative Oncology Group (ECOG) performance status ⩽2; adequate organ function; and resolution (grade ⩽1) of any toxic manifestations (except for alopecia) from other anticancer treatments. Patients also had to have at least one measurable lesion amenable to DCE-MRI. Exclusion criteria included primary central nervous system tumour or metastases; squamous cell lung carcinoma and uncontrolled hypertension. All patients provided informed consent. The study was approved by the local ethics committees and was conducted according to the Declaration of Helsinki.

2.2. Study design and objectives

This was a double-blind, multicentre, randomised, parallel-group, placebo-controlled study conducted in Belgium and France. Patients received an IV infusion of irinotecan 180 mg/m^2 over 1 h on day 1 of each cycle and received an IV infusion of leucovorin 200 mg/m^2 (or L-leucovorin 100 mg/m^2) over 2 h, and 5-FU 400 mg/m^2 IV bolus then 5-FU 600 mg/m^2 IV infusion over 22 hours on days 1 and 2. Prior to cycle-1, patients were