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Pharmacokinetic profile of cetuximab (Erbitux™) alone and in combination with irinotecan in patients with advanced EGFR-positive adenocarcinoma

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Abstract

This trial assessed pharmacokinetic interactions between cetuximab and irinotecan.

Patients were placed in either in group A (irinotecan 350 mg/m^2/3 weeks and 400 mg/m^2 cetuximab at week 2 then 250 mg/m^2/week) or group B (cetuximab weekly starting week 1 then irinotecan starting week 4). Patient plasma or serum samples from each treatment arm were analysed using HPLC and ELISA. Among 14 patients, compartmental model showed no significant differences in mean plasma AUC at week 1 *versus* week 4 for irinotecan (44,388 *versus* 39,800 μg/ml/h) and cetuximab (20,441 *versus* 23,363 μg/ml/h), respectively. Half-lifes (standard deviations) for irinotecan were 16.02 (±8.41) h at week 1 and 13.99 (±2.14) h at week 4, and for cetuximab 106 (±32) at week 3 and 111 (±30) h at week 4. Mean concentration-*versus*-time profiles either alone or in combination were superimposable for cetuximab and irinotecan. From this study, we conclude that there is no evidence of pharmacokinetic interaction between irinotecan and cetuximab.

Keywords: EGFR inhibitor; C225; Colon cancer; Phase I

1. Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein [1–4] that is frequently expressed or mutated in a broad range of malignancies and has been proposed as a therapeutic target for cancer treatment [5–8]. Cetuximab (Erbitux™) is a novel IgG1 monoclonal antibody that binds EGFR with high specificity and affinity [9]. Binding of cetuximab to EGFR prevents ligand-induced EGFR phosphorylation and activation of the kinase domain and inhibits the growth of EGFR-driven human cancer cells [10,11]. In preclinical studies, concentrations of $\geqslant$2 nM cetuximab induced a significant reduction of tumoural volume in a variety of human cancer models [12,13]. Phase I studies with cetuximab alone showed moderate skin toxicity and hypersensitivity reactions [14,15]. At doses ranging 200–400 mg/m^2, cetuximab displayed linear predictable pharmacokinetics and a clearance value of approximately 0.02 L/h/m^2. Phase III study confirmed

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acceptable tolerance and showed a high level of disease control [16].

Irinotecan demonstrated significant survival benefits in patients with colorectal cancer [17,18]. Irinotecan has a complex metabolism requiring activation into SN-38 by carboxylesterase [19] and glucuroconjugation for catabolism [20]. Preclinical studies demonstrated additive and synergistic activity between topisomerase I inhibitors and cetuximab [21,22]. Clinical trials combining irinotecan with cetuximab were conduced in patients with colorectal cancer who failed a first line treatment with single agent irinotecan, yielding 20–25% objective responses and strongly suggested that the addition of cetuximab might overcome the resistance to irinotecan [23,16]. Based on these results, the combination of cetuximab with irinotecan was approved for the treatment of patients with advanced EGFR-positive colon carcinoma and has prompted us to investigate the potential pharmacokinetic interactions between the two drugs.

2. Patients and methods

2.1. Inclusion criteria

Patients with EGFR expression in tumours (DAKO Cytomation, Glostrup, Denmark) meeting the following inclusion criteria were eligible: adenocarcinoma; age $\geqslant$18 years; Karnofsky performance status $\geqslant$60%; body mass index (BMI) between 18 and 30 kg/m^2; adequate bone marrow function (leukocyte count $\geqslant 3.0 \times 10^9$/L, absolute neutrophil count $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L and hemoglobin $\geqslant$8 g/dL); serum creatinine value $1.5 \times \leqslant$the upper limit of normal (ULN); total bilirubin level $\leqslant 1.5 \times$ ULN that had no increased by >25% over the preceding 4 weeks; ASAT and ALAT $\leqslant 5 \times$ ULN; no chemotherapy, radiotherapy or surgery (excluding biopsy) within 4 weeks before study entry; no intercurrent history of uncontrolled severe diseases; no concomitant experimental new drug; no previous exposure to monoclonal antibody therapy and signed informed consent.

2.2. Study design

The first six patients were assigned to group A until the primary endpoint was reached, and subsequent patients were assigned to group B.

In group A, the schedule was designed to investigate the effects of cetuximab on pharmacokinetic parameters of irinotecan and its metabolites. Patients received irinotecan at week 1 followed by cetuximab at week 2.

In group B the treatment was scheduled to detect the effect of irinotecan on pharmacokinetic parameters of cetuximab. Patients received cetuximab at week 1 followed by irinotecan at week 4. For both groups, the pharmacokinetic interaction was studied during the first 4 weeks and the combination was monitored until disease progression or unacceptable toxicity.

2.3. Pretreatment and follow-up examinations

Complete medical history, physical examination, laboratory tests (complete blood count, creatinine, serum electrolytes, calcium, uric acid, total protein, albumin level, hepatic and coagulation tests, and LDH) and urinalysis were performed at baseline and repeated weekly.

Toxicity was evaluated weekly and graded using the National Cancer Institute's Common Toxicity Criteria (NCI-CTC), version 2.0. Tumours were evaluated and/or measured at baseline and reassessed every two months, using the World Health Organization standard criteria.

2.4. Drug administration

Cetuximab (prepared by Imclone Systems Inc. as 50 ml ready-to-use vials containing 100 mg of cetuximab, 2 mg/ml) was administrated as a 120-min intravenous infusion at an initial dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2, given as a 1-h infusion with prophylactic intravenous dexchlorpheniramine maleate.

Irinotecan was given at a dose of 350 mg/m^2 as a 60-min intravenous infusion every 21 days with adequate standard antiemetic regimens. Delayed diarrhea was treated with loperamide and antibiotics when associated with grades 3 and 4 leucopenia and/or fever. When combined, cetuximab was given prior to irinotecan with at least 1 h wash out period.

The schedule of treatment, dose and infusion time was not supposed to be modified during the 4-weeks pharmacokinetic phase. If adjustments were made for safety reasons, the patient was considered not evaluable for pharmacokinetic analysis.

2.5. Pharmacokinetic analysis

2.5.1. Pharmacokinetics of irinotecan (group A)

Plasma samples were collected at weeks 1 and 4; before the start of irinotecan infusion, at 1, 2, 3, 6, 10, 24, and 48 h after. Whole blood (2.5 ml) samples were collected in heparinised tubes and centrifuged within 30 min at 2500*g* for 45 min at 4 °C, 250 µl of plasma was transferred into ice-cold tubes and stored at −80 °C, before analysis.

Quantitative analysis of irinotecan and its metabolites was performed using a reverse-phase high-performance liquid chromatography with fluorescence detection (HPLC) as described elsewhere [24,25]. The lower limit