Phase II Study of Combination Chemotherapy with Biweekly Cetuximab and Irinotecan for Pre-treated Metastatic Colorectal Cancer Harboring Wild-type KRAS

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Standard weekly cetuximab and irinotecan is an effective regimen in heavily pre-treated patients with metastatic colorectal cancer. The aim of this study is to prospectively evaluate the efficacy of combination chemotherapy with biweekly cetuximab and irinotecan in patients with pre-treated metastatic colorectal cancer harboring wild-type KRAS. A total of 30 patients will be enrolled at four medical institutions. The primary endpoint is response rate. The secondary endpoints include adverse events, progression-free survival and overall survival. The pharmacokinetics of cetuximab will also be evaluated in five patients.

Key words: colorectal cancer – chemotherapy – cetuximab – irinotecan

INTRODUCTION

Cetuximab, a recombinant, human/mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor, has been shown to significantly improve the prognosis of metastatic colorectal cancer (MCRC) compared with best-supportive care alone in the third-line setting (1). Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease (2), suggesting that cetuximab may restore chemosensitivity in these patients. Because of these results, cetuximab plus irinotecan has become the standard chemotherapy in MCRC after failure with 5-fluorouracil, oxaliplatin and irinotecan. Following these two pivotal studies, several retrospective reports suggested that cetuximab is not efficacious in patients with cancers harboring KRAS mutations (3–7). Therefore, the indications for cetuximab are considered to be limited to cancers bearing wild-type KRAS based on these retrospective studies (8). We conducted a Phase II study employing weekly cetuximab plus biweekly irinotecan for wild-type KRAS MCRC (9). An objective response rate of 30.0% and a disease control rate of 80.0% were shown in our previous study (9). Although KRAS testing is not yet approved here in Japan as of November 2009, early approval is expected.

On the basis of past pivotal studies, the standard schedule for cetuximab is weekly administration (1,2). In principal, cetuximab is administered weekly with an initial intravenous infusion of 400 mg/m² on day 1 infused over 120 min, with subsequent weekly doses of 250 mg/m² infused over 60 min. This regimen was used in a Japanese Phase II study (10) and in our prior study (9) with acceptable toxicity. However, in Japan, irinotecan has been commonly administered biweekly. Therefore, if we could achieve similar efficacy and safety with biweekly administration of cetuximab, it would be more convenient both for the patient and for the treating...
Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan

Purpose
The aim of this study is to evaluate the efficacy and safety of combination chemotherapy with biweekly cetuximab plus irinotecan for the treatment of patients with MCRC that has progressed after irinotecan-, oxaliplatin- and fluoropyrimidine-based chemotherapy.

Study Setting
The study was a multi-institutional prospective Phase II trial, where participating institutions include four specialized centers, as of November 2009.

Endpoints
The primary endpoint is response rate. The tumor response will be assessed objectively after each course according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the maximum response rate will be taken as the antitumor effect for that patient. The secondary endpoints include adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, progression-free survival and overall survival. A pharmacokinetic (PK) study of cetuximab is also planned to be evaluated in five patients.

Eligibility Criteria

Inclusion Criteria
Prior to enrollment in the study, patients must fulfill all of the following criteria: (i) patients with histopathologically proven metastatic colorectal adenocarcinoma with wild-type KRAS are eligible for this study. KRAS status is evaluated in each institution using one of the following methods; cycleave PCR (Aichi Cancer Center Hospital) (14,15) or direct sequence methods (BML, Tokyo, Japan). Wild-type KRAS means patients without KRAS mutations in codons 12 and 13, regardless of the KRAS testing method. (ii) Patients have Eastern Cooperative Oncology Group performance status 0–2. (iii) The presence of measurable metastatic disease, as defined by the RECIST criteria. (iv) The presence of radiographically confirmed disease progression during previous chemotherapy using irinotecan, or within 3 months after the last chemotherapy dose. (v) Treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy. (vi) Adequate hepatic function [aspartate aminotransferase and alanine aminotransferase <2.5 times the institutional upper normal limit (<5 times in patients with liver metastases) and total bilirubin <1.5 times the upper normal limit]. (vii) Adequate renal function (serum creatinine <2.0 times the upper normal limit).

Exclusion Criteria
Patients are excluded if they meet any of the following criteria: (i) having uncontrollable ascites or pleural effusion; and (ii) having serious co-morbidities such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation or other serious medical conditions.

Treatment Methods
The treatment schedule is based on the results of prior studies (10–12). Cetuximab is administered initially at a dose of 500 mg/m² as a 2 h infusion followed by biweekly administration of 500 mg/m² as a 1 h infusion. Irinotecan is administered biweekly. The dose of irinotecan (100–150 mg/m²) is selected by each physician according to each individual patient, based on prior toxicities experienced with irinotecan. Patients receive premedication with antihistamine [e.g. 50 mg diphenhydramine hydrochloride intravenously (i.v.)] to minimize the risk of infusion-related reactions associated with cetuximab. The following anti-emetic treatments are administered on demand: dexamethasone 4 mg prior to cetuximab, and dexamethasone 8–16 mg plus granisetron 1 mg i.v. prior to irinotecan. Grade 3–4 hypersensitivity necessitates cetuximab discontinuation; infusion is slowed to 50% of the prior infusion rate for Grade 1–2 allergic/hypersensitivity reactions. Cetuximab is withheld for Grade 3 skin toxicity until resolution to ≤Grade 2. Dose modification and treatment alterations are also performed for irinotecan-associated toxicities. For Grade 4 thrombocytopenia or Grade 3–4 neuropathy, irinotecan is discontinued. The irinotecan dose is reduced by 20 mg/m² in the case of Grade 4 neutropenia, Grade 2–3 thrombocytopenia or Grade
3–4 non-hematological toxicity. Other dose adjustments are made on an individual patient basis. Treatment is discontinued if the tumor progresses, severe toxicity occurs or at the patient’s request. There is no set maximum number of courses.

**Cetuximab PK Analysis**

Blood samples for PK analysis are taken in five patients at day 1 (end of infusion), day 15 (pre-dose and end of infusion) and day 29 (pre-dose). PK parameters are calculated according to standard non-compartmental methods.

**Follow-up**

Physical examination, safety evaluation and laboratory tests are performed prior to starting treatment and biweekly thereafter. Responses are evaluated every 8 weeks or earlier if there are indications of treatment failure due to toxicity. All eligible subjects are included in the assessment of efficacy and safety. Non-evaluable subjects are only added into the efficacy assessment data set as ‘not evaluable’. The following dates are recorded: (i) date of starting treatment, (ii) date achieving best tumor response, (iii) date of disease progression, (iv) final date assessing survival and (v) date of death.

**Study Design and Statistical Methods**

A one-stage design employing binomial probability is used to determine the sample size. A patient receiving at least one chemotherapy study dose is considered evaluable for response. The response rate threshold is defined as 5%, and the expected response rate is set at 25%, since the response rate in the BOND-1 study was 22.9% (2). The sample size of this trial is 25 patients (α- and β-error probabilities, 0.05 and 0.2, respectively). Considering an ~10% drop-out rate, 30 patients are required for this study. Progression-free survival is measured from the date of entry into the trial to the time when progression or death without evidence of progression occurs. The median survival time is estimated from the date of study entry to the date of death or last follow-up visit using Kaplan–Meier methodology.

**Participating Institutions (from North to South)**

Hokkaido University Hospital, Aichi Cancer Center Hospital, Nagoya Kyoritsu Hospital and Osaka Medical College.

**Conflict of interest statement**

None declared.

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