A Prospective Observational Study to Examine the Relationship between Quality of Life and Adverse Events of First-line Chemotherapy Plus Cetuximab in Patients with KRAS Wild-type Unresectable Metastatic Colorectal Cancer: QUACK Trial

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We have planned a multicentre prospective study to examine the relative impact of the efficacy and adverse events of cetuximab plus first-line chemotherapy on the quality of life in Japanese patients with KRAS wild-type unresectable colorectal cancer. The Dermatology Life Quality Index and the European Organization for Research Treatment of Cancer Quality of Life Questionnaire Core 30 will be used to assess dermatology-specific and health-related quality of life. The severity of adverse events will be assessed by using the National Cancer Institute Common Terminology Criteria for adverse Events ver. 4.0. The endpoints will be the following associations: adverse events, including skin toxicity and quality of life; efficacy and skin toxicity; efficacy and quality of life; and skin-related quality of life and health-related quality of life. A total of 140 patients are considered to be appropriate for inclusion in this study. The results of this study will provide more information to both patients and physicians regarding the practical use of cetuximab and its impact on quality of life in patients with unresectable colorectal cancer in Japan. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000010985.

Key words: quality of life – colorectal cancer – cetuximab

INTRODUCTION

Colorectal cancer (CRC) remains a major clinical challenge and is the second most common cancer and fourth leading cause of cancer-related death worldwide (1). Although CRC screening programmes including faecal occult blood test and colonoscopy have facilitated mortality reduction by removing precursor lesions and enabling diagnosis at an early stage (2), many patients have locally advanced or metastatic disease at the time of diagnosis.

Cetuximab (Erbitux®, Merck Serono, Darmstadt, Germany and Bristol-Myers Squibb, USA) is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of the epidermal growth factor receptor (EGFR) and induces anti-tumour effects by competitively inhibiting ligand-induced EGFR tyrosine kinase activation (3). Cetuximab initially showed efficacy against irinotecan-refractory and EGFR-positive metastatic CRC (4) and was approved by the US Food and Drug Administration (FDA) in 2004. However, genetic mutations of
KRAS, a downstream component of the EGFR signalling pathway, were found as biomarkers for cetuximab resistance (5), and the indication for cetuximab was amended to include KRAS wild-type metastatic CRC by the FDA in 2009. In the randomized Phase III CRYSTAL study, first-line FOLFIRI plus cetuximab provided a significant survival advantage over FOLFIRI alone for the treatment of KRAS wild-type metastatic CRC (23.5 vs. 20.0 months; hazard ratio 0.796; \( P < 0.0094 \)) (6). Similar results were observed in the randomized Phase II OPUS study (7). Additionally, the pooled analysis of the CRYSTAL and OPUS studies demonstrated that the addition of cetuximab to first-line chemotherapy led to significant improvements in overall survival (OS; hazard ratio 0.81; \( P = 0.0062 \)), progression-free survival (PFS; hazard ratio 0.66; \( P < 0.001 \)) and overall response rate (ORR; odds ratio 2.16; \( P < 0.0001 \)) (6). On the basis of these pivotal findings, the European Society for Medical Oncology guidelines recommended cetuximab plus FOLFIRI or FOLFOX as one of the standard first-line treatment regimens for patients with metastatic CRC (8).

While advances in treatment have been associated with increasing rates of survival, they are also associated with increased rates of long-term adverse events (9). Therefore, for patients with never resectable CRC who are asymptomatic or without imminent symptoms and at limited risk for rapid deterioration, the aim of therapy is to prevent tumour progression and prolong life while maintaining quality of life (QoL) (8). Importantly, incorporating the patient’s perspective, including their values and priorities about treatment can assure personalized and appropriate shared decision making because those patients require information not only related to survival estimated, but also regarding HRQoL in the treatment (10,11). In the CRYSTAL study, the administration of FOLFIRI plus cetuximab was associated with significantly more severe skin toxicity (19.7 vs. 0.2%), including acne-like rash, dry skin, paronychia, infusion-related reactions (2.5 vs. 0%) and diarrhoea (15.7 vs. 10.5%) than administration of FOLFIRI alone (12). Of note, skin toxicity was generally observed during the early treatment phase and developed in >80% of patients receiving cetuximab (4), resulting in a restriction of daily activities, independence, patient satisfaction and compliance (13). Indeed, skin toxicity adversely affected skin-related QoL based on the Dermatology Life Quality Index (DLQI) (14).

On the other hand, the severity of skin toxicity could predict the clinical benefit of cetuximab (15–17), and addition of cetuximab to FOLFIRI enhanced earlier symptom relief for patients symptomatic at baseline (18). Furthermore, the inverse relationships between global health status (GHS)/QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and cetuximab were frequently reported in patients treated as later-lines, who have more symptoms and lower baseline GHS/QoL scores with the further tumour progression than those treated as first-line, and likely to gain improvements in GHS/QoL corresponding to the tumour response (7,19). In contrast to improvements of GHS/QoL in later-lines treatment, adverse events may negate the positive efficacy obtained from cetuximab treatment in patients with relatively higher baseline GHS/QoL scores in first-line treatment (18). Thus, the relative impact between the efficacy and toxicity of cetuximab on health-related QoL (HRQoL) has not been resolved, especially in first-line treatment, and the cetuximab-related adverse event with the greatest negative impact on HRQoL remains unclear. Therefore, further research is needed to clarify these issues.

In Japan, the efficacy and safety of cetuximab plus irinotecan for the treatment of irinotecan-refractory and EGFR-positive metastatic CRC were confirmed in a Phase II study (20), and subsequently, cetuximab received approval in Japan in 2008. In a Japanese post-marketing surveillance analysis of 2006 patients between September 2009 and January 2009, the profiles and incidence of cetuximab-related adverse events were not different from previous reports from other countries (21). However, 99% of these patients received cetuximab as second or further-line treatment, therefore, the clinical efficacy and safety of cetuximab as first-line treatment in Japan remain unclear. Based on this background information, we have planned a prospective observational study to examine the relative impact of the efficacy and adverse events of cetuximab plus first-line chemotherapy on QoL in Japanese patients with KRAS wild-type unresectable CRC. The results of this study will provide more information regarding the practical use of cetuximab and its impact on QoL in patients with KRAS wild-type unresectable CRC. The relevant information for overall burden and efficacy of treatment will facilitate treatment decision making for both patients and physician.

This study has been conducted in accordance with the Declaration of Helsinki and Ethics Guidelines for Clinical Research by the Ministry of Health, Labor, and Welfare Ministry in Japan. Informed consent will be obtained from all patients before registration. The study protocol was approved by the institutional review board or ethics committee of each participating institution and was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000010985 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&reptno=R000012842&language=E) on July 19, 2013.

**STUDY PROTOCOL**

**OBJECTIVES**

The purpose of this study is to examine the relative impact of the efficacy and adverse events of first-line treatment including cetuximab on QoL in Japanese patients with KRAS wild-type unresectable CRC.

**STUDY SETTING**

The study setting is a multi-institutional prospective observational study. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000010985.
ENDPOINTS AND ASSESSMENTS

The endpoints are the following associations: adverse events and QoL; efficacy and skin toxicity; efficacy and QoL; and skin-related QoL using DLQI and HRQoL using EORTC QLQ-C30.

The severity of adverse events will be assessed using the National Cancer Institute Common Terminology Criteria for adverse Events ver. 4.0 (22). The outcomes of treatment efficacy include ORR, time to treatment failure (TTF), PFS and OS. Treatment response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (23). TTF is defined as the time from registration to the time of treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death. PFS is defined as the time from registration to the time of progression after first-line treatment initiation or death from any cause. OS is defined as the time from registration to the time of death or last contact.

The EORTC QLQ-C30, a cancer-specific self-administered core questionnaire, will be used to assess HRQoL because it is valid and reliable in the advanced cancer setting, including CRC (24–26). This 30-item questionnaire contains five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a GHS/QoL and six single scales assessing additional symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact) (25). The response categories will include ‘not at all’, ‘a little bit’, ‘somewhat’, ‘quite a bit’ and ‘very much’, with response scores ranging from 1 to 4. The total scores range from 0 to 100 after linear transformation. Higher scores for the functional and GHS/QoL scales will indicate a higher level of functioning and a better HRQoL, respectively. Higher scores in the symptom scales will represent a higher level of symptoms.

The DLQI, a skin-specific self-administered questionnaire, will be used to assess skin-related QoL and contains 10 questions covering 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment). The total scores range from 0 to 30, with higher scores indicating greater QoL impairment (14,27,28).

ELIGIBILITY CRITERIA

Patients with unresectable CRC who satisfy the inclusion criteria and do not meet the exclusion criteria as described below will be recruited as subjects.

INCLUSION CRITERIA

(1) Patients with unresectable CRC who plan to be treated with cetuximab plus first-line chemotherapy (FOLFIRI or mFOLFOX6)
(2) Not confirmed mutation in KRAS codon 12 or 13
(3) At least one measurable lesion according to the RECIST ver.1.1
(4) No prior chemotherapy (adjuvant chemotherapy more than 6 months prior to enrolment is allowed)
(5) Aged 20 years or older
(6) Eastern Cooperative Oncology Group performance Status 0–2
(7) Adequate organ function
(8) Life expectancy >3 months
(9) Negative hepatitis B surface antigen
(10) Agreement of contraception
(11) Written informed consent
(12) Ability to answer the QoL questionnaires

EXCLUSION CRITERIA

(1) Serious bone marrow suppression
(2) Serious sensory disturbance
(3) A history of mental disturbances or cerebrovascular attack
(4) Previous radiotherapy against evaluable lesions
(5) Severe stenosis of primary site or primary tumour resection within 4 weeks (colostomy within 2 weeks) prior to enrolment
(6) Serious drug hypersensitivity or a history of drug allergy
(7) Uncontrolled hypertension, diabetes or hypercalcemia
(8) Severe liver cirrhosis or hepatic dysfunction
(9) Severe renal dysfunction
(10) Interstitial pneumonia, pulmonary fibrosis or high-grade pulmonary emphysema
(11) Active infection
(12) A history of severe heart disease
(13) Brain metastases
(14) Massive pleural effusion, ascites or pericardial effusion
(15) Uncontrolled diarrhoea
(16) Active concomitant malignancy
(17) Pregnancy, possible pregnancy or nursing
(18) Judged inappropriate for the study by their physicians

REGISTRATION

Any medical institution that would like to participate should contact the Epidemiological and Clinical Research Information Network (ECRIN). Interested institutions will receive registration forms from the ECRIN. Registered patients will be treated with FOLFIRI plus cetuximab or mFOLFOX6 plus cetuximab as determined by a physician in clinical practice.

TREATMENT METHODS

The FOLFIRI plus cetuximab regimen will consist of cetuximab (initial 2 h infusion of 400 mg/m² followed thereafter by a weekly 1 h infusion of 250 mg/m²) with concurrent l-leucovorin (2 h infusion of 200 mg/m²) and irinotecan (90 min infusion of 150 mg/m²), followed by 5-fluorouracil (5-FU; intravenous bolus of 400 mg/m² followed by a 46 h continuous infusion of 2400 mg/m² every 14 days). mFOLFOX6 plus cetuximab will consist of cetuximab (initial 2 h infusion of 400 mg/m² followed thereafter by a weekly 1 h infusion of 250 mg/m²) with concurrent l-leucovorin (2 h infusion of 200 mg/m²) and oxaliplatin (2 h infusion of 85 mg/m²),
followed by 5-FU (intravenous bolus of 400 mg/m² followed by a 46 h continuous infusion of 2400 mg/m² every 14 days). Treatment will be continued until disease progression or occurrence of unacceptable toxicity.

**Follow-up**

Disease progression and occurrence of new diseases will be monitored by abdominal computed tomography (CT), thoracic CT or magnetic resonance imaging at pre-chemotherapy (baseline) and every 8 weeks during the treatment period. Safety will be assessed by monitoring adverse events using physical and laboratory examinations. The survey sheets, including safety, efficacy and compliance with treatment, will be collected at registration and after 4, 8, 16 and 24 weeks. In addition, patient outcome will be investigated 2 years after study initiation and 1 year after accrual of the last patient. The QoL assessments will be performed at baseline and after 2, 4, 8, 16 and 24 weeks using EORTC QLQ-C30 and DLQI. A window of 2 weeks around each follow-up QoL assessment time point will be accepted. If the patient does not complete the study treatment, the last QoL assessment will be performed at the time of judgment of the study termination.

**Statistical Methods**

The association of adverse events with QoL will be analyzed using a linear mixed-effects model, including covariates such as baseline QoL scores, time since the start of chemotherapy, and grade of adverse events at each time point of QoL assessment. The association between efficacy (TTF, PFS and OS) and skin toxicity will be analyzed using the Cox proportional hazard model with skin toxicity as a time-dependent explanatory variable. The association between treatment response and skin toxicity will be analyzed using the Mantel extension test with a contingency table.

The sample size was calculated as 128 patients to assess the association between GHS/QoL in EORTC QLQ-C30 and skin toxicity with a one-sided significance level of 0.025 and a power of 80% based on the hypothesis that the degree of deterioration in GHS/QoL due to Grade 2 or higher skin toxicity, a clinically relevant event, is 50% of the standard deviation because that Grade 2 or higher skin toxicity showed a trend toward a decreased GHS/QoL scores using EORTC QLQ-C30 in first-line treatment (18,29), and that the incidence was ~5% in a Japanese post-marketing surveillance of cetuximab (21). The total sample size to be accrued has been set at 140 to account for potential dropout and ineligible cases.

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**Conflict of interest statement**

Kensei Yamaguchi has received speaker honoraria from Chugai, Bristol-Myers Squibb and Merck Serono. Hirofumi Fujii has received speaker honoraria from Bristol-Myers Squibb and Merck Serono. Atushi Sato received honoraria from Chugai and Yakult. The other authors also declare no conflict of interest.

**References**


