Int J Clin Oncol (2011) 16:766–769
DOI 10.1007/s10147-011-0242-2

CASE REPORT

A case of heavily pretreated rectal cancer with disseminated intravascular coagulation that improved following reintroduction of FOLFOX plus bevacizumab

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Received: 1 March 2011 / Accepted: 13 April 2011 / Published online: 12 May 2011

Abstract Disseminated intravascular coagulation (DIC) is a complication that may be experienced by patients with solid tumors. The prognosis of solid tumors with DIC is much poorer than those without DIC. Although treatment of the underlying disease is critical for improvement of DIC, the efficacy and safety of chemotherapy in patients with DIC associated with colorectal cancer are not clear. A 50-year-old man with advanced rectal cancer and multiple liver metastases experienced DIC during third-line treatment with cetuximab plus irinotecan, following 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) plus bevacizumab and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab. Combination chemotherapy consisting of FOLFOX plus bevacizumab was reintroduced. Although platelet and fresh-frozen plasma transfusions were required daily before chemotherapy, the patient's laboratory values improved after two cycles of chemotherapy, without severe toxicity. The patient was discharged, and FOLFOX plus bevacizumab has been continued on an outpatient basis without sign of recurrence of DIC as of December 2010 (4 months after initiation of chemotherapy). This case suggests that reintroduction of combination chemotherapy with FOLFOX plus bevacizumab is effective and feasible in patients with colorectal cancer with DIC and that chemotherapy may be a treatment option for such patients.

Keywords Colorectal cancer · Disseminated intravascular coagulation · FOLFOX · Reintroduction · Bevacizumab

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Introduction

Disseminated intravascular coagulation (DIC) is a fatal thrombohemorrhagic disorder involving the generation of intravascular fibrin and the consumption of coagulation factors and platelets. The resultant clinical condition is characterized by intravascular coagulation and hemorrhage. Underlying diseases causing DIC primarily include hematological malignancies, infection, sepsis, and trauma. Patients with solid tumors may also experience DIC during their clinical course; a frequency of 6.8% has been reported among 1,117 patients with various solid tumors [1]. The prognosis of patients with solid tumors complicated by DIC is much poorer than those without DIC. The frequency and prognosis of DIC in colorectal cancer is unknown, with only a few cases reported in the literature [2]. Although treatment for the underlying disease is critical for improvement of DIC, the efficacy and safety of chemotherapy in patients with DIC associated with colorectal cancer are not clear, because these patients are ineligible for clinical trials. Herein we report a case of heavily treated metastatic rectal cancer with DIC that responded to reintroduction of combination chemotherapy with modified FOLFOX6 (mFOLFOX6; 5-fluorouracil, leucovorin, oxaliplatin) plus bevacizumab.

Case presentation

A 50-year-old man with advanced rectal cancer and multiple liver metastases was referred to our institution in February 2009. He noticed hematochezia for 1 month, and colonoscopy showed a rectal tumor that encircled half the bowel circumference and bled easily. A biopsy specimen of the rectal tumor showed poorly differentiated

adenocarcinoma without *KRAS* mutation, as evaluated by the Cycleave PCR method. Computed tomography (CT) revealed multiple metastases in the bilateral lobes of the liver and a thickness in the rectal wall that reflected the primary tumor (Fig. 1a). Because the multiple liver metastases were apparently unresectable, first-line chemotherapy with FOLFOX plus bevacizumab was initiated (bevacizumab 5 mg/kg, oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, infusional 5-FU 2,400 mg/m^2, bolus 5-FU 400 mg/m^2; biweekly). Although stable disease was initially maintained, tumor progression was observed after 6 months of chemotherapy (Fig. 1b). Second-line chemotherapy with FOLFIRI (5-fluorouracil, leucovorin, irinotecan) plus bevacizumab also resulted in stable disease for approximately 11 months, but the tumor eventually progressed. Therefore, combination chemotherapy with irinotecan and cetuximab was started in July 2010. However, the patient complained of worsened fatigue and yellow-colored urine after two cycles of irinotecan plus cetuximab. He also experienced a small degree of hematochezia similar to that present at initial diagnosis. Physical examination showed icteric conjunctiva, although purpura was not apparent in his skin. Laboratory data included markedly reduced platelet counts (1.8×10^4/μl) and increased total bilirubin (4.5 mg/dl), aspartate transaminase (AST, 91 IU/l), alanine transaminase (ALT, 50 IU/l), and alkaline phosphatase (ALP, 1,427 IU/l). Coagulation tests also showed abnormal values as follows: prothrombin time/international normalized ratio (PT-INR), 2.09, fibrin degradation products (FDP), >80 μg/ml, D-dimer, 135.2 μg/ml, and fibrinogen (FIB), 31.4 mg/dl. A diagnosis of DIC was made according to the diagnostic criteria of the International Society of Thrombosis and Hemostasis [3]. CT on admission showed enlarged multiple liver metastases (Fig. 1c). These clinical features suggested DIC caused by progressed metastatic rectal cancer. Continuous intravenous nafamostat mesilate (0.5 mg/kg/h) and transfusion of platelets and fresh-frozen plasma were initiated. Dexamethasone (6.6 mg/day) was also started for fatigue. Although all effective agents for colorectal cancer had been already used for his cancer, the patient strongly desired to receive further chemotherapy. After written informed consent was obtained from the patient and his family, combination chemotherapy consisting of FOLFOX plus bevacizumab was reintroduced. Bevacizumab 5 mg/kg infused over 30 min was administered biweekly. FOLFOX with a reduced dose of oxaliplatin (50 mg/m^2) and infusional 5-FU (2,000 mg/m^2) was administered biweekly; bolus 5-FU was excluded because of liver dysfunction and icterus. Although platelet and fresh-frozen plasma transfusions were required daily during the first two cycles of chemotherapy, platelet counts, PT-INR, FIB, and D-dimer values improved to 6.1×10^4/μl, 1.06, 297 mg/dl, and 35.6 mg/l, respectively, thereafter (Fig. 2). No significant toxicities other than grade 1 anorexia and diarrhea were observed. CT after six cycles of chemotherapy showed that multiple liver metastases were slightly reduced in size (Fig. 1d). After four cycles of chemotherapy, the patient

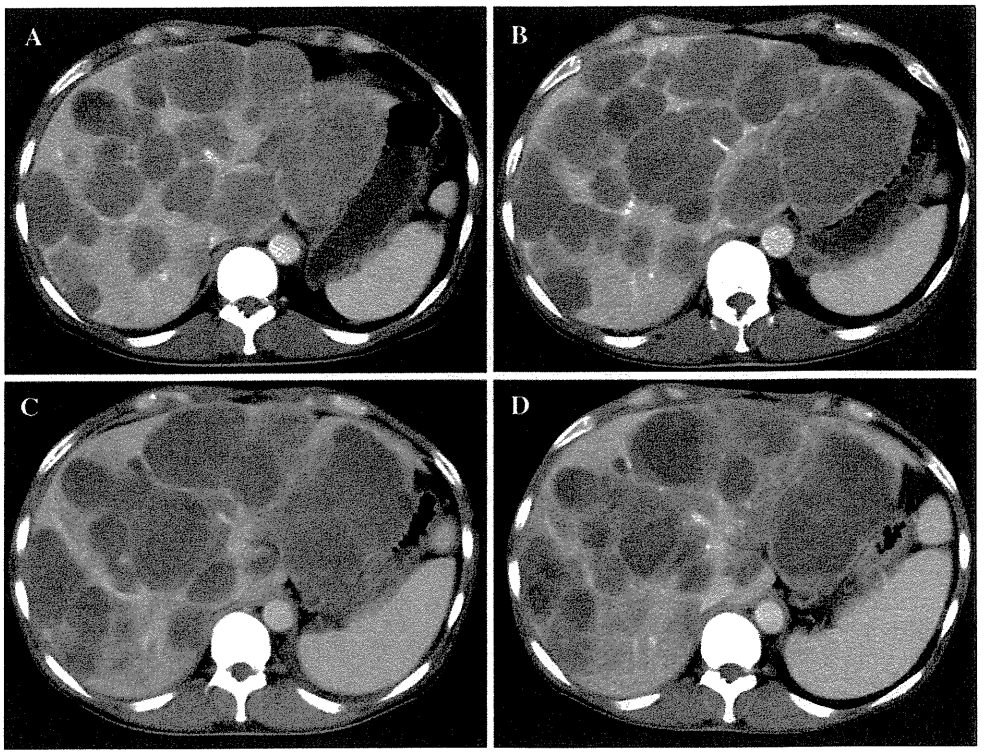

Fig. 1 **a** Computed tomography (CT) scan before introduction of 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) plus bevacizumab shows multiple metastases in the bilateral lobes of the liver. **b** CT scan after 11 cycles of FOLFOX plus bevacizumab shows the multiple liver metastases were slightly enlarged. **c** CT scan before reintroduction of FOLFOX plus bevacizumab shows the multiple metastases in the bilateral lobes of the liver. **d** CT scan after 6 cycles of treatment shows the multiple liver metastases were slightly reduced in size

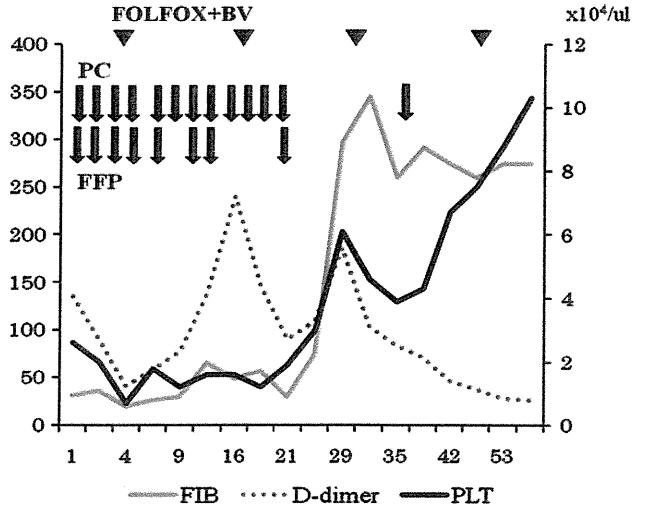

Fig. 2 Clinical course after chemotherapy. After two cycles of chemotherapy, coagulation test results improved; after four cycles of chemotherapy, the patient was discharged. *FIB*, fibrin degradation products; *PLT*, platelet counts; *PC*, platelet transfusion; *FFP*, fresh-frozen plasma transfusion; *FOLFOX*, 5-fluorouracil, leucovorin, oxaliplatin; *BV*, bevacizumab

was discharged, and the same treatment has been continued on an outpatient basis without sign of recurrence of DIC as of December 2010, which was 4 months after initiation of chemotherapy.

Discussion

To the best of our knowledge, this is the first case report of heavily pretreated rectal cancer with DIC that improved following reintroduction of chemotherapy with FOLFOX plus bevacizumab. Although anti-DIC therapy such as nafamostat mesilate may be another reason for improvement of DIC in this patient, the reduction of size of multiple liver metastases by reintroduction of FOLFOX plus bevacizumab suggested that chemotherapy mainly contributed to the improvement of DIC.

In general, the prognosis of solid tumors complicated by DIC is dismally poor. A literature search of the Medline database (January 1966 to November 2010) using the keywords "DIC" and "colorectal cancer" revealed that only one previous report of patients with DIC associated with colorectal cancer who underwent chemotherapy has been published [2]. Nonaka et al. reported a case of rectal cancer with DIC that responded to combination chemotherapy with FOLFOX and summarized 21 cases of colorectal cancer with DIC in Japan, which were indexed in Japana Centra Revuo Medicina (http://search.jamas.or.jp/). These cases were commonly associated with a pathological diagnosis of poorly differentiated or signet ring-like cell adenocarcinoma, as well as bone marrow involvement. The present patient also had poorly differentiated adenocarcinoma, although no bone marrow involvement was detected. Among these 21 cases, 10 patients received chemotherapy but the other 11 patients did not. The median survival was 90 days (range, 68–210 days) in patients who received chemotherapy and 30 days (range, 13–51 days) in patients who did not [2]. However, all cases were chemonaïve at diagnosis of DIC, and no report evaluated the efficacy of chemotherapy for pretreated colorectal cancer with DIC, as in the present case. FOLFOX reintroduction is reported to be effective and associated with better survival in metastatic colorectal cancer [4, 5]. Reintroduction of oxaliplatin was feasible and resulted in a response or disease stabilization in 73% of patients who were previously treated with oxaliplatin for metastatic colorectal cancer [4]. Notably, one response occurred in a patient who had experienced progression during the first course of FOLFOX, similar to that which occurred in the present case. In addition, similar objective response rates to reintroduction of platinum-based chemotherapy have been reported in patients with platinum-resistant ovarian cancer [6]. Although further investigation is required to explain this curious response to reintroduction of FOLFOX plus bevacizumab even after disease progression during FOLFOX plus bevacizumab, we speculate that a relatively longer FOLFOX-free interval in the present patient may have contributed to this phenomenon. Additionally, there could be other reason for this response; existence of distinct clones of cells that respond differentially. Naing et al. [8] reported 4 cases in which patients' cancers responded when they were rechallenged with chemotherapies, despite the fact that their tumors had previously become refractory to those agents (after initial response). They suggested if a tumor responds but then becomes resistant to one or more treatments, it is conceivable that retreatment will be successful if changing therapies allows a clone of cells to re-emerge.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is reported to be associated with thromboembolism and bleeding [7]. However, we elected to use bevacizumab in this patient with life-threatening disease because of the anticipated synergistic antitumor effect with FOLFOX. No bevacizumab-related toxicities were observed in this patient; however, caution must be exercised when administering this agent.

In conclusion, the present case suggests that reintroduction of combination chemotherapy with FOLFOX plus bevacizumab is effective and feasible in patients with colorectal cancer with DIC, and that chemotherapy may be a treatment option for such patients.

Conflict of interest No author has any conflict of interest.

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Int J Clin Oncol (2011) 16:416–420
DOI 10.1007/s10147-011-0216-4

ORIGINAL ARTICLE

Retrospective analysis of cetuximab monotherapy for patients with irinotecan-intolerant metastatic colorectal cancer

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Received: 6 October 2010 / Accepted: 3 February 2011 / Published online: 26 March 2011

Abstract
Background The efficacy and safety of cetuximab for irinotecan-intolerant patients has not yet been evaluated in detail.
Methods We retrospectively analyzed the efficacy and safety of cetuximab monotherapy for patients with metastatic colorectal cancer (MCRC) that was intolerant to irinotecan.
Results Among 105 patients who received cetuximab-containing chemotherapy until March 2010, 22 patients were treated with cetuximab monotherapy due to irinotecan intolerance. Cetuximab was given at the approved dosage to all patients. The performance status was 2 or 3 in 17 patients (77%). All but 1 patient had wild-type *KRAS* tumors. The causes of irinotecan intolerance were icterus ($n = 9$; 41%; median serum total bilirubin, 6.3 mg/dl), symptomatic peritoneal metastasis or obstruction ($n = 8$; 36%), and thrombocytopenia ($n = 1$; 5%). Four patients (18%) refused irinotecan due to previous irinotecan-associated toxicity. Two patients achieved a partial response with an apparent drop of serum bilirubin, for a response rate of 9.1%. The median progression-free survival and overall survival were 1.6 and 3.5 months, respectively. No grade 3 or 4 adverse events or treatment-related deaths were experienced.
Conclusion Cetuximab monotherapy for irinotecan-intolerant MCRC is feasible. However, the overall efficacy was modest in the present cohort, despite the fact that most of the patients had wild-type *KRAS* tumors; further effective therapies should be evaluated to improve the prognosis of this patient population.

Keywords Colorectal cancer · Cetuximab · Irinotecan intolerance

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Introduction

Cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR), has been shown to significantly improve the prognosis of patients with metastatic colorectal cancer (MCRC) compared to best supportive care alone in the third-line setting (CO-17 study) [1]. Additionally, cetuximab plus irinotecan resulted in a higher response rate and longer progression-free survival (PFS) compared to cetuximab monotherapy, even in patients with irinotecan-refractory MCRC (BOND-1 study) [2]. Based on the results of these two trials, cetuximab plus irinotecan is considered to be a standard regimen for patients with irinotecan-refractory MCRC if tolerable, and cetuximab monotherapy is recommended for patients with irinotecan intolerance [3]. However, these two studies excluded patients with organ dysfunction, such as icterus, as well as those with a poor performance status (PS). Therefore, the true efficacy and safety of cetuximab monotherapy for patients with irinotecan-intolerant MCRC remains unclear. The prognosis of patients with MCRC with organ dysfunction and/or poor PS is extremely poor [4, 5]. For example, the median survival of patients with MCRC with icterus has been reported to be <1 month

when treated with either cytotoxic chemotherapy or supportive care alone [4]. In addition, cytotoxic chemotherapy is generally not indicated for patients with a poor PS; these patients tend to have a poor prognosis despite treatment [5].

Since monoclonal antibodies are considered to be metabolized by the reticuloendothelial system without undergoing hepatic or renal metabolism [6–8] and to be associated with low toxicity even in patients with a poor PS [9], we hypothesized that cetuximab would provide a treatment benefit even in patients with irinotecan intolerance due to organ dysfunction or poor PS. To address this issue, we conducted a retrospective analysis to evaluate the efficacy and safety of cetuximab monotherapy for patients with irinotecan-intolerant MCRC.

Patients and methods

Patients

Patients with histopathologically proven metastatic colorectal adenocarcinoma who received cetuximab monotherapy due to irinotecan intolerance were included. Irinotecan intolerance was determined by each physician and confirmed by medical records. No additional eligibility criteria, such as Eastern Cooperative Oncology Group PS or organ function, were used. The *KRAS* status (codon 12 and 13) of primary or metastatic tumors using surgical or biopsied specimens was evaluated using the Cycleave PCR method [10]. Although patients with *KRAS* mutations were generally excluded from receiving cetuximab, a few patients received cetuximab before the implications of *KRAS* mutation status on cetuximab efficacy were known. We treated 105 patients with cetuximab-containing chemotherapy between August 2008 and March 2010. Among them, 22 patients were treated with cetuximab monotherapy due to irinotecan intolerance, and were analyzed in this study. Written informed consent was obtained from each patient prior to chemotherapy.

Treatment plan

Cetuximab was given intravenously at an initial dose of 400 mg/m^2, followed by a weekly maintenance infusion of 250 mg/m^2 (the approved dosage). Patients received premedication with an antihistamine (e.g., diphenhydramine hydrochloride 50 mg IV) and dexamethasone 4 mg to minimize the risk of infusion-related reactions associated with cetuximab. Infusion-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). In general, grade 3–4 hypersensitivity necessitated cetuximab discontinuation; infusion was slowed to 50% of the prior infusion rate for grade 1–2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 skin toxicity until resolution to ≤grade 2. Other dose adjustments were made on an individual patient basis. Treatment was discontinued upon tumor progression, severe toxicity, or at the patient's request.

Evaluation of treatment

Medical history, physical examination, safety evaluation, and laboratory tests were performed prior to starting treatment and weekly thereafter. Toxicity was evaluated by CTCAE ver. 3.0. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) every 6–8 weeks or earlier if there were indications of treatment failure due to toxicity. PFS was measured from the initial date of cetuximab administration to the time when progression or death without evidence of progression occurred. Median survival time was estimated from the initial date of cetuximab administration to the date of death or last follow-up using Kaplan–Meier methodology.

Results

Patient characteristics

The characteristics of patients in this study are shown in Table 1. Their PS was generally poor, with 17 patients (77.3%) having a PS of 2 or 3. Twenty patients (90.9%) had previously received oxaliplatin-containing chemotherapy, 17 patients (77.3%) received irinotecan, and 15 patients (68.2%) received bevacizumab. Sixteen patients (72.7%) had peritoneal metastasis. All patients except for one had wild-type *KRAS* tumors. The causes of irinotecan intolerance were as follows: icterus in 9 patients (40.9%), with a median serum total bilirubin level of 6.3 mg/dl (range 2.3–13 mg/dl); symptomatic peritoneal metastasis or obstruction in 8 patients (36.4%); and thrombocytopenia in 1 patient (4.5%); in addition, 4 patients (18.2%) refused to receive irinotecan due to previous gastrointestinal toxicity associated with irinotecan treatment.

Treatment results

Median administration of cetuximab was 8 cycles (range 1–24). Among the 22 patients, there were 0 complete responses; 2 partial responses, with apparent drops in serum total bilirubin [from 8.9 to 1.1 mg/dl (Fig. 1) and from 2.4 to 0.8 mg/dl]; and 4 patients experienced stable

disease. Four patients had progressive disease, and 14 patients were not evaluable for radiological response due to symptomatic deterioration prior to radiological response evaluation ($n = 12$) and treatment withdrawal due to toxicity prior to response evaluation ($n = 2$). The overall response rate was 9.1% and the disease control rate was 27.3%. The median PFS was 1.6 months (Fig. 2). After a median follow-up of 4.7 months, 16 patients died of tumor progression while the other 6 patients remain alive. The median overall survival was 3.5 months (Fig. 2).

Table 1 Baseline characteristics of the patients

Gender	
Male/female	10/12
Age	
Median (range)	65 (41–83)
ECOG performance status	
0–1/2/3	5/10/7
Prior CTx for advance	
Oxaliplatin base	20
Irinotecan base	17
Bevacizumab	15
Prior CTx line	
1/more	4/18
Disease sites	
Liver	19
Peritoneum	16
Lung	10
Lymph node	12
Number of disease sites	
1–2/more	7/15
KRAS status	
Wild/mutant	21/1

ECOG Eastern Cooperative Oncology Group, *CTx* chemotherapy

Adverse events

Adverse event data related to cetuximab treatment are summarized in Table 2. Skin toxicity was the most common adverse event, with an incidence of 86.4%. Fever was observed in 7 patients (31.8%), and an infusion reaction occurred in 1 patient (4.5%). Fatigue and anorexia were observed at a high frequency, but these events may possibly have occurred due to disease progression. Chemotherapy was discontinued in 2 patients (9.1%) due to toxicity: grade 2 infusion reaction in 1 patient and patient refusal due to skin toxicity in 1 patient. There were no treatment-related deaths, and no patient experienced grade 3 or 4 adverse events during treatment.

Discussion

In this report, we retrospectively evaluated the efficacy and safety of cetuximab monotherapy in irinotecan-intolerant MCRC due to severe complications, such as icterus and gastrointestinal obstruction. The present results suggest

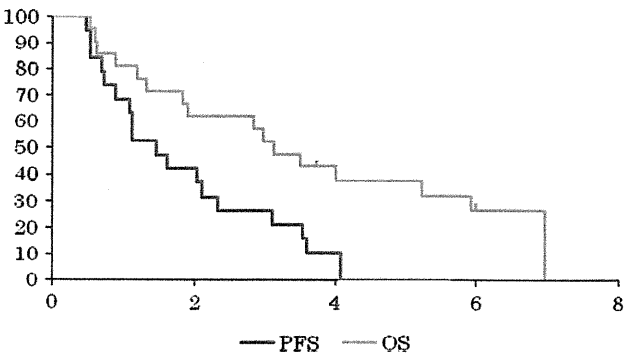

Fig. 2 Kaplan–Meier curves for progression-free survival (PFS) and overall survival. Median PFS was 1.6 months, and median overall survival was 3.5 months

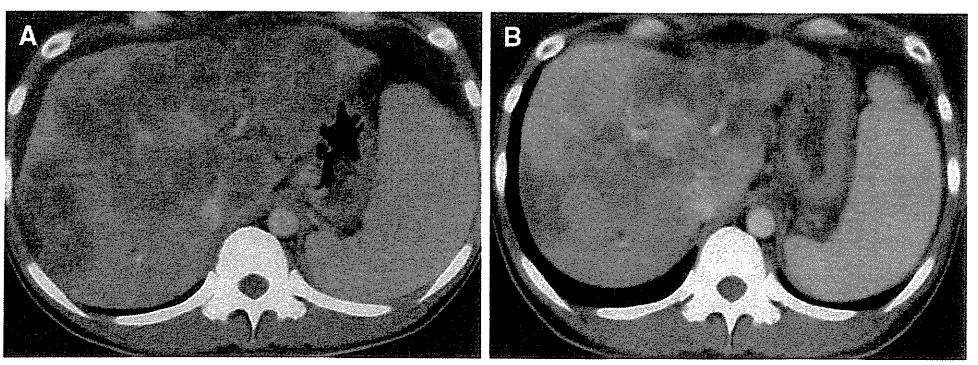

Fig. 1 A 40-year-old female with multiple liver metastases refractory to FOLFOX plus bevacizumab and irinotecan. **a** CT scan acquired prior to cetuximab monotherapy. She had icterus accompanied by serum total bilirubin of 8.9 mg/ml. **b** CT scan acquired after 2 months of chemotherapy. Apparent reductions in the size of multiple liver metastases were observed, and her total bilirubin decreased to 1.1 mg/dl

Table 2 Adverse events

Adverse events	G1–2 (%)	G3–4 (%)
Any	21 (95.5)	0 (0)
Leucopenia	1 (4.5)	0 (0)
Neutropenia	0 (0)	0 (0)
Febrile neutropenia	0 (0)	0 (0)
Anemia	2 (9.1)	0 (0)
Thrombocytopenia	1 (4.5)	0 (0)
Acneform rash	19 (86.4)	0 (0)
Fatigue	19 (86.4)	0 (0)
Anorexia	11 (50)	0 (0)
Fever	7 (31.8)	0 (0)
Nausea	5 (22.7)	0 (0)
Diarrhea	2 (9.1)	0 (0)
Infusion reaction	1 (4.5)	0 (0)

Grades were determined according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0

that cetuximab monotherapy is safe even in this patient population, and 2 patients achieved apparent tumor shrinkage with improvement of icterus.

In the BOND-1 study [2], cetuximab plus irinotecan showed a superior response rate and PFS compared to cetuximab monotherapy, even in patients with irinotecan-refractory MCRC. However, irinotecan is not suitable for many patients, including those with poor PS, liver dysfunction, and/or gastrointestinal obstruction. Irinotecan is primarily metabolized to 7-ethyl-10-hydroxy camptothecin (SN-38) in the liver [11]. SN-38 is primarily eliminated via conjugation by hepatic uridine-diphosphoglucuronosyl transferase, and is then excreted into the bile and stool. Therefore, irinotecan is toxic to patients with icterus or gastrointestinal obstruction, due to delayed excretion of SN-38. In the CO-17 study, cetuximab monotherapy was shown to significantly improve the prognosis of MCRC compared to supportive care alone [1]. However, both the CO-17 and BOND-1 studies excluded patients with organ dysfunction or PS3, and the proportion of patients with PS2 was low (23.4%); thus the true efficacy and feasibility of cetuximab monotherapy for patients with irinotecan-intolerant MCRC was previously unclear.

In the present study, there were no treatment-related deaths, and no patients experienced grade 3 or 4 adverse events during treatment, although grade 2 skin toxicity was observed in most patients and grade 2 infusion reaction occurred in 1 patient. The frequency and severity of toxicities did not differ from those of past pivotal studies [1, 2]. Since cetuximab is metabolized by the reticuloendothelial system without undergoing hepatic or renal metabolism, we planned to use cetuximab without dose reduction, even in patients with icterus or gastrointestinal obstruction.

Although 2 patients achieved an apparent response in this study, the overall response rate of 9.1% with median survival of 3.5 months was considered as modest and far from satisfactory despite the fact that most patients had wild-type *KRAS* tumors. In contrast, gefitinib showed impressive results for EGFR-positive non-small cell lung cancer patients with a poor PS, with an objective response rate of 66% and median survival of 17.8 months [12]. Recently, several biomarkers and clinical factors other than *KRAS* have been reported as predictive markers of the efficacy of anti-EGFR antibodies such as cetuximab or panitumumab [13]. However, further investigation to identify MCRC patients most likely to benefit from anti-EGFR antibody treatment appears to be necessary.

In conclusion, although the small sample size and retrospective design were major limitations of this study, the present results suggest that cetuximab monotherapy is feasible for irinotecan-intolerant MCRC with modest efficacy. Additional effective therapies should be evaluated to improve the prognosis of this patient population.

Conflict of interest No author has any conflict of interest.

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Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. 684–690, 2011

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doi:10.1016/j.ijrobp.2010.06.033

CLINICAL INVESTIGATION **Esophagus**

PHASE II STUDY OF CHEMORADIOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN FOR STAGE II–III ESOPHAGEAL SQUAMOUS CELL CARCINOMA: JCOG TRIAL (JCOG 9906)

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Purpose: In this Phase II study, we evaluated the efficacy and toxicity of chemoradiotherapy (CRT) with cisplatin (CDDP) and 5-fluorouracil (5-FU) for Stage II–III esophageal squamous cell carcinoma (ESCC).
Patients and Methods: Patients with clinical Stage II–III (T1N1M0 or T2–3N0–1M0) thoracic ESCC were enrolled between April 2000 and March 2002. Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) on Days 1 and 8; this regimen was repeated every 5 weeks. Concurrent radiotherapy involved 60-Gy irradiation (30 fractions) for 8 weeks with a 2-week break. Responders received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1. Final analysis was conducted in March 2007. Survival and late toxicities were monitored for 5 years.
Results: The characteristics of the 76 patients enrolled were as follows: median age, 61 years; male/female, 68/8; performance status 0/1, 59/17 patients; Stage IIA/IIB/III, 26/12/38 patients. Of the 74 eligible patients, 46 (62.2%) achieved complete response. Median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Acute toxicities included Grade 3/4 esophagitis (17%), nausea (17%), hyponatremia (16%), and infection without neutropenia (12%). Late toxicities comprised Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusion, and radiation pneumonitis (4%), causing 4 deaths.
Conclusions: CRT is effective for Stage II–III ESCC with manageable acute toxicities and can provide a nonsurgical treatment option. However, further improvement is required for reduction in late toxicity. © **2011 Elsevier Inc.**

Esophageal squamous cell carcinoma, Chemoradiotherapy, Long-term toxicity, Salvage surgery.

INTRODUCTION

Esophageal cancer, a highly virulent malignancy, was responsible for 11,182 deaths in Japan in 2005, accounting for 3.4% of the country's total cancer deaths (1), with 35–40% of the patients diagnosed with Stage II–III disease. When this study was planned, the standard treatment for Stage II–III esophageal squamous cell carcinoma (ESCC) in Japan was esophagectomy with three-field lymph node dissection, followed by postoperative chemotherapy; the 5-year survival rate is reported to be 36.8–61% (2–4), with a high morbidity rate.

Chemoradiotherapy (CRT) has proved effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with cisplatin (CDDP), 5-fluorouracil (5-FU), and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T1–3N0–1M0 esophageal cancer (5), in which the final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the

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Supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest: none.

Acknowledgment—The authors thank Ms. Aya Kimura, Ms. Naoko Murata, Mr. Taro Shibata, Dr. Kenichi Nakamura, Dr. Naoki Ishizuka, and Dr. Seiichiro Yamamoto for statistics and writing advice for this study.

Received April 12, 2010, and in revised form June 4, 2010. Accepted for publication June 9, 2010.

radiation-alone arm (6). Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment.

CRT was introduced in Japan in the early 1990s as a treatment for potentially unresectable locally advanced ESCC. In a Phase II trial, 18 of 54 (33%) patients with clinical T4 and/or M1 lymph node ESCC, who received CDDP/5-FU with concurrent 60-Gy irradiation, achieved complete response (CR) with a 3-year survival rate of 23% (7). Since then, CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T1–3NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a CR of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery (8). However, the results were retrospective. Thus, we conducted a Phase II study to evaluate the efficacy and toxicity, particularly the long-term outcome, of CRT for Stage II–III ESCC.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: pathologically confirmed thoracic ESCC; clinical Stage II–III excluding T4 (T1N1M0 or T2–3N1–0M0: International Union Against Cancer [UICC] 1997); Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had previously undergone therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had had other active malignancies were excluded. All the patients had to meet the following laboratory criteria within 14 days before registration: leukocytes $\geq$3,000/mm^3; platelet count $\geq$100,000/mm^3; hemoglobin level $\geq$10 g/dL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$2 $\times$ the upper normal limit at the institution; total bilirubin $\leq$1.5 mg/dL; serum creatinine $\leq$1.2 mg/dL; creatinine clearance $\geq$50 mL/min; PaO_2 $\geq$70 mm Hg; and no major electrocardiogram abnormalities. Written informed consent was obtained from all the patients. The study protocol was approved by the JCOG Clinical Trial Review Committee and institutional review boards of the participating institutions.

Chemotherapy

Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) with adequate hydration and antiemetic coverage on Days 1 and 8; this regimen was repeated every 5 weeks. Responders additionally received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1 (Fig. 1), repeated every 4 weeks. No further treatment was administered to patients with CR until disease progression. Additional chemotherapy courses were optional for patients with visible disease.

Administration of both chemotherapy agents was discontinued until toxicity improved to $\leq$Grade 2. The doses were reduced by 25% in the subsequent course after at least

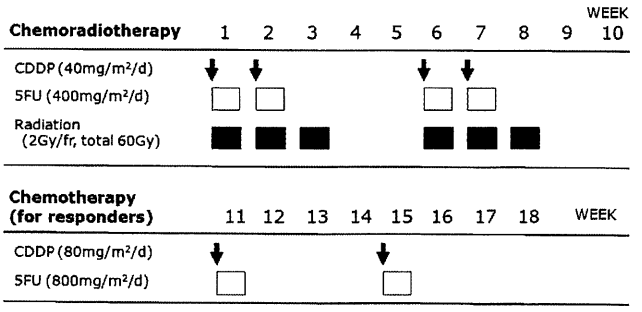

Fig. 1. Protocol scheme.

one of the following toxicities was observed: leukocytes <1,000/mm^3; platelet count <30,000/mm^3; total bilirubin >2.0 mg/dL; serum creatinine $\geq$2.0 mg/dL; Grade 3/4 stomatitis; or Grade 3/4 esophagitis. Total parenteral nutrition was provided as necessary. Treatment was terminated when disease progression was observed, patients refused to continue, or recovery from toxicity delayed the initiation of the second course by >3 weeks from the planned schedule.

Radiotherapy

Radiotherapy was delivered using megavoltage ($\geq$6 MV) x-rays; a total dose of 60 Gy was administered in 30 fractions. A 2-week break was provided after 30-Gy irradiation, and radiotherapy was resumed on Day 36 with the second chemotherapy course. The clinical target volume (CTV) for 60-Gy irradiation included the primary tumor plus a 5-cm craniocaudal margin, and the metastatic lymph nodes plus a 1-cm margin. Planning target volume was defined as CTV plus 5- to 20-mm margins for uncertainty. Elective nodal irradiation (40 Gy) of mediastinal and perigastric lymph nodes for all cases, cervical lymph nodes for an upper thoracic primary tumor, and celiac lymph nodes for a lower thoracic primary tumor was also performed. Three-dimensional computed tomography (CT) or X-ray simulation was performed, allowing two-dimensional anterior–posterior opposed fields and bilateral oblique boost. Heterogeneity-uncorrected doses were used.

Assessments

Esophagoscopy and CT were carried out after each course to assess the response. Primary tumor response was evaluated by endoscopy using the modified criteria of the Japanese Society for Esophageal Diseases (9). Complete response of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on the CT or size reduction to $\leq$1 cm for $\geq$3 months after the completion of treatment. Overall CR was declared by an attending physician when CR at both a primary tumor and a lymph node was obtained without the appearance of a new lesion. Complete response was confirmed by reassessment at $\geq$4 weeks after the first assessment. Complete response cases were centrally reviewed, and CR was confirmed by extramural review of the CT scan and images of endoscopy.

Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after the completion of CRT. Toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity, which first occurred 90 days after CRT initiation, was assessed using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Statistical methods

The primary endpoint was overall survival (OS), which was defined as the time from the date of registration to that of death resulting from any cause, and it was censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression or death resulting from any cause, and it was censored at the date of the last visit for patients without progression. Based on the JCOG 9204 trial results (2), in which the 3-year survival rate was 61% for esophagectomy with adjuvant chemotherapy, we initially calculated the sample size expecting a 3-year survival rate of 60%, with a threshold of 45%. With the alpha and beta error levels set at 0.05 and 0.2, respectively, the required number of eligible patients was 68. We finally decided on a sample size of 76, including ineligible patients. The planned accrual and follow-up periods after registration was closed were 1 and 2 years, respectively. For early termination of this study, an interim analysis was planned once 50% of the patients were accrued. A CR point estimate of <60% at the interim analysis would result in early termination of the study.

The JCOG 9204 had enrolled patients based on the pathologic stage after surgery, whereas we enrolled patients based on the clinical stage diagnosed from CT scans. Therefore, this study might include patients with more advanced stages than those in the JCOG 9204. Thus, the protocol was amended to recalculate the sample size from the expected 50% 3-year survival rate and a threshold of 35% in December 2000. The required sample size was 67. The target sample size remained unchanged. The second amendment in February 2007 prolonged the follow-up period to 5 years after the last enrollment to evaluate late toxicity. These amendments were approved by the Data and Safety Monitoring Committee of JCOG.

Secondary endpoints included CR rate, PFS, and acute and late adverse events. Time-to-event distribution was estimated using the Kaplan-Meier method, and confidence intervals (CIs) were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 software (SAS Institute, Cary, NC, USA) at the JCOG Data Center, with the final analysis conducted in March 2007.

RESULTS

Patient characteristics

Seventy-six patients, whose characteristics are summarized in Table 1, were accrued between April 2000 and March 2002. The median age was 61 years (range, 39–70). Fifty-nine (78%) and 17 (22%) patients showed ECOG PS of 0 and 1, respectively. Fifty-two patients had T3 disease, and 50 had N1 disease. The clinical stages (UICC-TNM) were IIA for 26 patients, IIB for 12 patients, and III for 38.

Table 1. Patient characteristics

Characteristic	Patients (n = 76)	(%)
Male	68	89.4
Female	8	10.6
Age (y)		
Range	39–70	
Median	61	
Performance status		
0	59	77.6
1	17	22.4
Tumor location		
Upper	3	3.9
Middle	44	57.9
Lower	29	38.2
T factor		
T1	8	10.5
T2	16	21.1
T3	52	68.4
N factor		
N0	26	34.2
N1	50	65.8
Stage		
IIA	26	34.2
IIB	12	15.8
III	38	50.0

Response

Two patients were excluded from the efficacy analysis because of inadequate liver function and T4 disease diagnosed after registration (Fig. 2). Of the 74 eligible patients, 46 achieved CR, resulting in a CR rate of 62.2% (95% CI, 50.1–73.2). The confirmed CR rate in 23 patients with T1–2 disease was 78.3% (95% CI, 56.3–92.5), and that in 51 patients with T3 disease was 54.9% (95% CI, 40.3–68.9).

Survival

There were 49 deaths in the final analysis, and all except 5 patients were followed up for >5 years. The median survival time was 2.4 years (Fig. 3); the 3- and 5-year survival rates were 44.7% (90% CI, 35.2–53.8) and 36.8% (95% CI, 26.1-47.5), respectively. The lower limit of 90% CI for the 3-year survival rate exceeded the threshold of 35%, and the

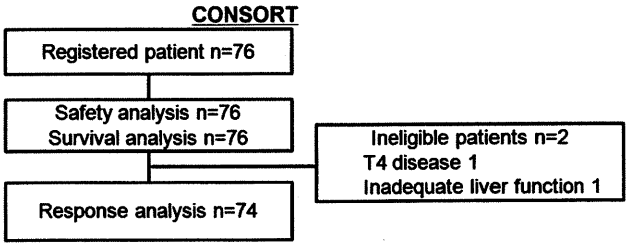

Fig. 2. Consolidated Standards of Reporting Trials diagram.

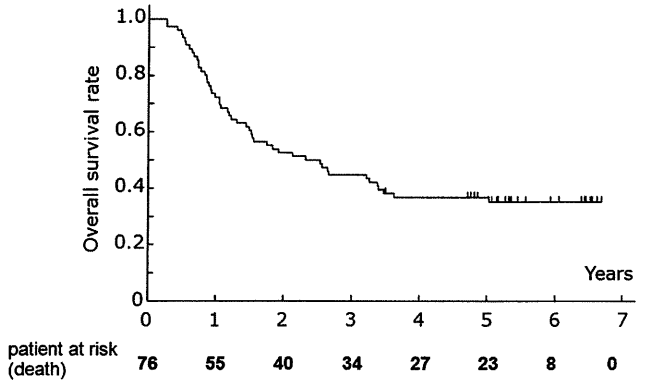

Fig. 3. Overall survival of the 76 patients enrolled in the study.

null hypothesis was rejected ($p = 0.019$). The median PFS was 1 year; the 3- and 5-year PFS rates were 32.9% and 25.6%, respectively (Fig. 4).

Acute toxicity

Data of adverse events for all 76 patients occurring within 90 days after CRT completion are shown in Table 2. Grade 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 1.3%, 1.3%, 2.6%, and 0% of the patients, respectively, whereas Grade 3/4 esophagitis, nausea, infection without neutropenia, and hyponatremia were observed in 17%, 17%, 12%, and 16% of the patients, respectively.

Fifty-three (69.7%) patients completed the 2-course CRT and 2-course additional chemotherapy. Seventy-two (95%) patients received the full dose (60 Gy) of radiation. The treatment protocol was terminated in 23 patients because of disease progression ($n = 10$), toxicity ($n = 11$), patient refusal ($n = 1$), and other reasons ($n = 1$). One early death occurred from esophageal perforation caused by disease progression 21 days after CRT completion. A relationship between early death and the treatment protocol was considered unlikely by the Data and Safety Monitoring Committee.

Late toxicity

Late toxicity data are shown in Table 3. Grade 3–4 late toxicities included pleural (9%) and pericardial (16%) effusion, stenosis, or esophageal fistula (13%), and radiation pneumonitis (4%). Four (5.3%) patients possibly died of treatment-related late toxicity at 3.1, 8.5, 21.3, and 27.8 months after registration. The cause of death were pneumonitis ($n = 2$), pericarditis ($n = 1$), and pleural effusion ($n = 1$). There was no evidence of residual or recurrent disease in these patients. The proportion of any Grade 3/4 late toxicity was 30.1% after 5 years from the initiation of chemoradiation.

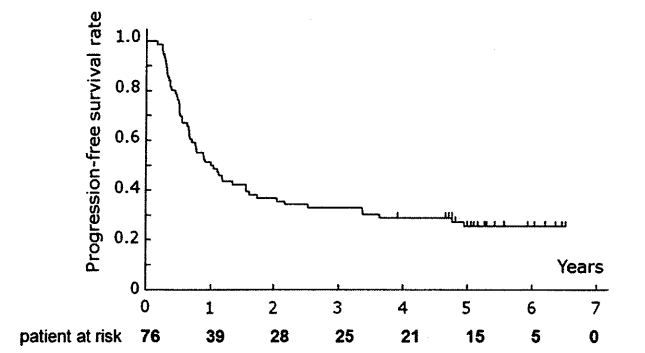

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

Salvage treatment

Twenty-six (34.2%) patients had residual disease or locoregional recurrence without distant metastasis after CRT. Because of inadequate conditions or patient refusal, 7 and 5 patients received chemotherapy and the best supportive care, respectively; the remaining 14 patients received unplanned curative-intent salvage therapy. Eleven patients underwent salvage esophagectomy for residual ($n = 4$) and recurrent ($n = 7$) disease, and the remaining 3 patients underwent endoscopic treatment such as endoscopic mucosal resection (EMR) or argon plasma coagulation. The characteristics of the patients who underwent salvage surgery are described in Table 4.

The median time to salvage surgery after CRT initiation was 13.9 months (range, 4.0–22.7). Six patients underwent esophagectomy with two- or three-field lymph node dissection, 3 patients underwent simple esophagectomy, and 1 underwent only lymphadenectomy; 1 patient could not undergo any resection because of extensive lymph nodes metastasis detected at thoracotomy. Reconstruction was performed using a gastric tube in 7 patients who had R0 resection. There was no operative mortality or hospital death. The median survival time and 3-year survival rate for these 10 patients who received salvage esophagectomy was 16.7 months and 40% (95%C.I: 12.3%–67.0%), respectively.

Of the 3 patients who underwent endoscopic treatment, 1 had mediastinal lymph node metastasis 3 months after argon plasma coagulation, 1 died of surgery-related complication of the pharynx detected 1 year after EMR, and 1 survived for >5 years with no evidence of disease.

DISCUSSION

From the results, CRT for Stage II–III ESCC showed a CR rate of 62.2% (95% CI, 50.1–73.2), a 3-year survival rate of 44.7% (90% CI, 35.2–53.8), and a 5-year survival rate of 36.8% (95% CI, 26.1–47.5). The 3-year survival rate, which is the primary endpoint of this study, met the decision criteria.

Clinically, it is very important to know whether definitive CRT can achieve survival comparable with surgery plus postoperative adjuvant chemotherapy. In this regard, there were several differences in the background between the present study and JCOG 9204 (2) described in Statistical Methods. The study conducted after JCOG 9204, which compared preoperative and postoperative adjuvant chemotherapy comprising the administration of 5-FU and CDDP to Stage II–III esophageal cancer patients (JCOG 9907) (10), could be a reference for this study, because the patients were registered before surgery based on the clinical stage. In the recently

Table 2. Toxicity (n = 76)

Toxicity	NCI-CTC Version 2.0				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	5	34	32	1	43
Neutrophils	17	31	19	1	26
Hemoglobin	13	35	15	2	22
Platelets	15	13	4	0	5
Dysphagia, esophagitis	29	14	13	0	17
Nausea	25	20	13	–	17
Vomiting	16	6	0	0	0
Diarrhea	10	5	1	0	1.3
Stomatitis/pharyngitis	15	9	6	0	8
Radiation dermatitis	18	4	0	0	0
Febrile neutropenia	–	–	1	0	1.3
Infection without neutropenia	7	8	8	1	12
Hyponatremia	40	–	11	1	16
AST	35	4	3	0	3.9
ALT	43	7	2	1	3.9
Creatinine	15	13	1	0	1.3

Abbreviations: NCI-CTC Version 2.0 = National Cancer Institute Common Toxicity Criteria Version 2.0; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

published results of JCOG 9907, the preoperative chemotherapy arm was highly superior to the postoperative chemotherapy arm in terms of OS. The 5-year survival rate of the postoperative chemotherapy arm in JCOG 9907 did not differ significantly from that in the present study, that is, 38.4% and 36.8%, respectively (10). By contrast, the 5-year survival rate of the preoperative chemotherapy arm in JCOG 9907 was 60.1%, although further follow-up is needed to verify the data. CRT may produce comparable outcomes with surgery plus postoperative adjuvant chemotherapy; however, surgery after preoperative chemotherapy is considered to be superior to CRT. Nevertheless, CRT is one of the treatment options for patients with Stage II and III ESCC because of its apparent advantage of preserving the esophagus, which may provide better quality of life.

Chemoradiotherapy achieves prolonged survival with possibly more late toxicity. Late toxicity after thoracic radiotherapy has been reported in patients with esophageal cancer, lung cancer, and Hodgkin's lymphoma (11–13). Some reports have described that long-term toxicity after CRT results in serious, life-threatening complications. In a previous study, 2 of 78 patients with CR after CRT died of myocardial infarction, and 8 (10.2%) died of pericardial or pleural effusion (14) Late toxicity after CRT against ESCC has not yet been investigated in detail, and early reports of trial outcomes generally seem to underestimate the risk of late toxicity in long-term survivors (15). In the present study, the incidence of ≥Grade 3 late toxicity was similar to that reported in a previous study (14). Most of these events occurred several years after CRT. It is considered that reduction in radiation dose, careful observation, and control of late toxicity may improve post-CRT survival. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT was not advantageous with regard to survival and local control, compared with the standard dose (50.4 Gy) (16). One of the reasons was the low tolerability of the high-dose arm because of toxicity. Whereas decreasing the irradiation dose in radiotherapy is essential for reducing late toxicity, the radiation volume is also

Table 3. Late toxicity (n = 76)

Late toxicity	RTOG/EORTC late radiation morbidity scoring scheme					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (nonmalignant)	24	5	7	0	9	0
Esophagus-related (dysphagia, stenosis, fistula)	11	4	4	6	13	8
Pericardial effusion	6	5	9	3	16	4
Radiation pneumonitis	33	6	2	1	4	1.3
Skin-related	3	0	0	0	0	0
Spinal cord—related	3	0	0	0	0	0

Abbreviation: RTOG/EORTC: radiation therapy oncology group/european organization for research and treatment of cancer.
Four (5.3%) patients possibly died of treatment-related late toxicity: pericarditis (n = 1), pleural effusion (n = 1), and pneumonitis (n = 2).

Table 4. Characteristics and outcomes in patients who underwent salvage surgery

Characteristic	Patients (n = 11)	Characteristic	Patients (n = 11)
Male	11	Residual/Recurrent	4 /7
Female	0		
Age (y)		Surgical curability	
Range	46–70	R0	7
Median	59	R1 + R2	4
Tumor location			
Upper	0	Operative mortality or hospital death	0
Middle	6		
Lower	5	Relapse after surgery	8
Clinical stage*		No relapse	3
IIA	5		
IIB	0		
III	6		

* Clinical stage at the time of registration.

important. In this study, late toxicity might have been caused by the extended volume of irradiation, which corresponds to the dissected area in extended surgery. In the near future, three-dimensional conformal radiotherapy, which was not mandatory in this study, or other methods based on advanced technology such as intensity-modulated radiotherapy and proton therapy, may have potential advantages over conventional two-dimensional radiotherapy in terms of reduced doses for the heart. A clinical trial with these latest radiotherapy techniques is required (17).

Salvage treatment—*e.g.*, salvage surgery (18–20) or salvage EMR (21)—has recently been reported to have therapeutic potential for patients with local failure of CRT. In our study, one-third of the patients did not achieve CR, and 50% of the remaining patients had recurrence after achieving CR. For the latter, salvage treatment should be indicated, if applicable. Mucosal disease can be removed by EMR, and locoregional residual or recurrent disease can be curatively resected by surgery. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (22, 23). Although a high rate of hospital deaths (6–33%) is observed compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 5-year survival rate of 25–35% (24–26). In the present study, 11 (14.5%) patients underwent salvage esophagectomy and 7 had R0 resection. There was no operative mortality or hospital death. The limitations of salvage surgery include patient tolerance, capability of medical staff, and early detection of residual or recurrent disease; however, salvage esophagectomy can achieve long-term survival. Some patients benefit from salvage surgery after definitive CRT; therefore, this procedure is worth further investigation.

Neoadjuvant CRT has recently been recognized as a standard therapy for resectable esophageal cancer in Western countries. According to CALGB 9781, CRT followed by surgery prolonged survival (median survival time, 4.48 vs. 1.79 years) compared with surgery alone in the treatment of esophageal cancer (27). However, most participants in CALGB 9781 had esophageal adenocarcinoma. Meta-analysis has revealed the survival benefit of neoadjuvant CRT in patients with esophageal adenocarcinoma (28). According to FFCD 9102, which included 90% patients with squamous cell carcinoma, surgery after neoadjuvant CRT (40 Gy) and continuation of CRT to 60 Gy without surgery had the same impact on survival and quality of life for responders as induction CRT (29). The results of a randomized trial from Germany, in which 172 ESCC patients randomly received CRT with or without additional surgery, indicated equal efficacy of surgery and CRT. The median survival times were 16.4 months and 14.9 months, respectively, and the 2-year survival rates were 39.9% and 35.4% with and without surgery, respectively (30). This suggests that CRT, which can preserve organ function, is equally effective as surgery for responders. For nonresponders, salvage surgery can be a therapeutic option. Importantly, which types of patients are benefited by salvage surgery or how the surgical procedure is performed after CRT should be prospectively evaluated. We are planning a Phase II trial of CRT for resectable ESCC, followed by salvage surgery for residual or recurrent disease.

CONCLUSION

Chemoradiotherapy is effective for Stage II–III ESCC with manageable acute toxicities and can provide a noninvasive treatment option. However, further improvement is required for reduction in late toxicity.

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Invest New Drugs (2012) 30:787–793
DOI 10.1007/s10637-010-9615-z

PHASE II STUDIES

Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type *KRAS* metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines

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Received: 5 November 2010 / Accepted: 30 November 2010 / Published online: 22 December 2010

Summary The aim of this study is to prospectively evaluate the efficacy of combination chemotherapy with every second week cetuximab and irinotecan in patients with pretreated metastatic colorectal cancer harboring wild-type *KRAS*. Patients with wild-type *KRAS* metastatic colorectal cancer that had progressed after chemotherapy with irinotecan, oxaliplatin, and fluoropyrimidine were included. Cetuximab was administered at 500 mg/m^2 biweekly with irinotecan. The primary endpoint was response rate. The pharmacokinetics of cetuximab was also evaluated in 5 patients. From May 2009 to February 2010, a total of 31 patients were enrolled from five institutions. One patient was not eligible. Among the 30 patients who were treated with biweekly cetuximab plus irinotecan, partial response was observed in 9 patients. The objective response rate was 30.0% (95% confidence interval [CI], 14.7%–49.4%) and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95% CI, 57.7%–90.0%). The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Grade 3 skin toxicity was observed in 3 patients (10.0%) and one treatment related death due to pneumonia was observed. Combination chemotherapy with biweekly cetuximab and irinotecan was effective for

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pretreated metastatic colorectal cancer with wild-type *KRAS*.

Keywords Colorectal cancer · Chemotherapy · Cetuximab · Biweekly · Irinotecan

Introduction

Cetuximab, a recombinant, human/mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor (EGFR), has been shown to significantly improve the prognosis for metastatic colorectal cancer (MCRC) compared to 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 (5-FU), 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]. Objective response rate of 30.0% and disease control rate of 80.0% was shown in our previous study [10].

Based on 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/m^2 on day 1 infused over 120 min, with subsequent weekly doses of 250 mg/m^2 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 to patients with metastatic colorectal cancer. 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 institution. There are a few reports that evaluated efficacy and feasibility of biweekly administration of cetuximab [11–13]. Tabernero et al. conducted a phase I study of biweekly cetuximab. In their study, cetuximab could be safely administered biweekly at doses between 400 and 700 mg/m^2 [11]. They concluded that 500 mg/m^2 was the most convenient and feasible dose. Other two studies using biweekly cetuximab 500 mg/m^2 plus irinotecan showed a response rate of 22.5%–25% in pretreated MCRC with a similar toxicity compared with weekly cetuximab [12, 13]. However, to the best of our knowledge, no study using biweekly cetuximab evaluated *KRAS* status prospectively [11–13]. Therefore, we have planned a phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pretreated MCRC harboring wild-type *KRAS*.

Patients and methods

Purpose

The aim of this study was to explore the effectiveness and safety of combination chemotherapy with biweekly cetuximab plus irinotecan for the treatment of patients with MCRC that had progressed after irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapy.

Study setting

A multi-institutional prospective phase II trial, where participating institutions included 5 specialized centers.

Endpoints

The primary endpoint was response rate. The tumor response was assessed objectively once every two weeks after each course according to the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.0), and the best overall response rate was taken as the antitumor effect for that patient. The secondary endpoints included adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, progression-free survival time, and overall survival time. A pharmacokinetic (PK) study of cetuximab was evaluated in 5 patients.

Patients

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* were eligible for this study. EGFR positive staining was not required. *KRAS* status was 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* meant patients without *KRAS* mutations in codons 12 and 13 regardless of the *KRAS* testing method. The remaining criteria were as follows: (ii) Eastern Cooperative Oncology Group performance status (PS) 0–2; (iii) presence of measurable metastatic disease as defined by the

RECIST criteria; (iii) presence of radiographically confirmed disease progression during previous chemotherapy using irinotecan or within 3 months after the last chemotherapy dose; (iv) treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy; (v) adequate bone marrow reserve (neutrophil count >1,000/mm^3, platelet count >100,000/mm^3); (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); and (vii) adequate renal function (serum creatinine <2.0 times the upper normal limit).

Patients were excluded if they met any of the following criteria: (i) uncontrollable ascites or pleural effusion and (ii) serious comorbidities, such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation, or other serious medical conditions.

The institutional review board of each participating center approved the study. This study was registered in the UMIN clinical trial registry (UMIN000001951). Written informed consent was obtained from each patient prior to treatment administration.

Treatment methods

The treatment schedule was based on the results of prior studies [10–12]. Cetuximab was administered initially at a dose of 500 mg/m^2 as a 2-hour infusion followed by biweekly administration of 500 mg/m^2 as a 1-hour infusion. Irinotecan was administered biweekly. The dose of irinotecan (100–150 mg/m^2) was selected by each physician according to each individual patient, based on prior toxicities experienced with irinotecan. Patients received premedication with antihistamine (e.g., 50 mg diphenhydramine hydrochloride intravenously [IV]) to minimize the risk of infusion-related reactions associated with cetuximab. The following anti-emetic treatments were administered on demand: dexamethasone 4 mg prior to cetuximab, and dexamethasone 8–16 mg plus granisetron 1 mg IV prior to irinotecan. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Grade 3–4 hypersensitivity necessitated cetuximab discontinuation; infusion was slowed to 50% of the prior infusion rate for grade 1–2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 skin toxicity until resolution to ≤grade 2. Dose modification and treatment alterations were also performed for irinotecan-associated toxicities. For grade 4 thrombocytopenia or grade 3–4 neuropathy, irinotecan was discontinued. The irinotecan dose was reduced by 20 mg/m^2 in the case of grade 4 neutropenia, grade 2–3 thrombocytopenia, or grade 3–4 non-hematological toxicity. Other dose adjustments were made on an individual patient basis. Treatment was discontinued if the tumor progressed, severe toxicity occurred, or at the patient's request. There was no set maximum number of courses.

Evaluation of treatment and follow-up

Medical history, physical examination, and safety evaluation were performed prior to starting treatment and biweekly thereafter. Laboratory tests were also obtained biweekly or more frequent in the case of severe toxicities, and always prior to each irinotecan infusion. Toxicity was evaluated by CTCAE ver. 3.0. Tumor marker analysis (carcinoembryonic antigen [CEA]) was also performed every 4 weeks. Responses were evaluated using RECIST criteria every 8 weeks, or earlier if there were indications of treatment failure due to toxicity. All eligible subjects were included in the assessment of efficacy and safety. Non-evaluable subjects were only added into the efficacy assessment data set as "not evaluable." The following dates were 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.

Statistical analysis

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

Cetuximab pharmacokinetics (PK) analysis

Blood samples for PK analysis were taken in 5 patients at day 1 (end of infusion), day 15 (predose and end of infusion), and day 29 (predose). PK parameters were

calculated according to standard non-compartmental methods.

Results

Patient characteristics

A total of 31 patients were registered between May 2009 and February 2010. One patient was not eligible due to PS 3, and thirty eligible patients received more than one planned treatment with irinotecan and cetuximab and analyzed for efficacy and safety (Table 1). Most patients had a PS 0–1; 2 patients were PS 2. All patients had wild-type *KRAS* MCRC. All patients had received two or more prior chemotherapy regimens with a median interval from initiation of first-line chemotherapy to study entry of 17.7 months (range, 6.4–46.9 months). Prior oxaliplatin-containing regimens included FOLFOX (infusional and bolus 5-fluorouracil with oxaliplatin) in 29 patients and S-1 plus oxaliplatin in 1 patient. Prior irinotecan-containing regimens included FOLFIRI (infusional and bolus 5-fluorouracil with irinotecan) in 24 patients, irinotecan monotherapy in 2 patients, irinotecan plus hepatic arterial infusion chemotherapy of 5-FU in 3 patients, and S-1 plus irinotecan in 1 patient. Twenty-one patients received oxaliplatin-based therapy prior to irinotecan-based therapy, while the nine patients received these therapies in reverse sequence. Bevacizumab had been previously used in 19 patients prior to study entry. All patients discontinued prior irinotecan based chemotherapy due to disease progression. Prior oxaliplatin-based regimen was discontinued due to disease progression in 24 patients and toxicity in 6 patients (neuropathy in 5 patients and allergy in 1 patient). The median PFS of oxaliplatin-based therapy and irinotecan-based therapy was 6.3 months and 6.7 months, respectively. The most common site of metastasis was the lungs in 24 patients, followed by the liver in 23 patients. Increased CEA was observed in 26 patients (>2 times the upper normal range), with a median value of 194 U/mL (range, 11.6 to 6,050 U/mL).

Table 1 Patient characteristics

Characteristics		No.
Median age, years		61 (29–77)
Gender	Male/female	19/11
ECOG PS	0/1/2	12/16/2
Origin	Colon/rectum	15/15
Prior colorectomy	Yes	26
Prior Radiation	Yes	3
Prior Adjuvant CTx	Yes	5
Prior CTx for advance	FOLFOX/SOX	29/1
	FOLFIRI/irinotecan/IRIS	24/5/1
	Bevacizumab	21
Number of prior CTx	2/3 or more	21/9
Disease sites[a]	Liver	23
	Lung	24
	Lymph node	16
	Peritoneum	7
No. of disease sites	1 or 2/ 3 or more	10/20

[a] Some were overlapping

PS performance status; *ECOG* Eastern Cooperative Oncology Group; *CTx* chemotherapy, *FOLFOX* infusional and bolus 5-fluorouracil with oxaliplatin; *SOX* S-1 plus oxaliplatin; *FOLFIRI* infusional and bolus 5-fluorouracil with irinotecan; *IRIS* S-1 plus irinotecan

Treatment results

The median number of cetuximab and irinotecan administrations was 8 (range, 1 to 24) and 8 (range, 2 to 24), respectively. Irinotecan was administered at a dose of 100 mg/m^2, 120 mg/m^2, and 150 mg/m^2 in 7, 7, and 16 patients, respectively. Four patients continued protocol treatment as of the time of analysis, with a median follow-up of 12.0 months (range, 8.3–19.1 months). Two patients experienced cetuximab dose reductions due to skin toxicities, and 1 patient underwent a 50% infusion rate due to grade 2 infusion reaction. Seven patients required irinotecan dose reductions, primarily due to neutropenia and gastrointestinal toxicity. Protocol treatment was discontinued in 26 patients due to disease progression (n=24), dead by pneumonia (n=1), and lost follow up (n=1).

Efficacy

Among the 30 patients, no patient achieved a complete response, 9 patients experienced a confirmed partial response, and 14 had stable disease using RECIST criteria. Four patients had progressive disease, and three patients were not evaluable for treatment response due to symptomatic deterioration prior to radiological response evaluation in two patients and treatment withdrawal due to toxicity prior to response evaluation in one patient. The overall response rate was 30.0% (95% confidence interval [CI], 14.7%–49.4%) and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95% CI, 57.7%–90.0%). Among the 14 patients with stable disease, 8 patients experienced tumor shrinkage of >10%; therefore a total of 17 of 30 patients (56.7%) achieved >10% tumor shrinkage (Fig. 1). A >50% decline in CEA was observed in 16 of 26 patients (61.6%) with abnormal values. The median progression-free survival was 5.3 months (95% CI; 3.6–7.1) and median overall