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Clinical Trial Note

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/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. 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 which 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 response rate of 22.5–25% in pre-treated MCRC with the similar toxicity compared with weekly cetuximab (12,13). However, to our best knowledge, no data have been obtained in Japan. Therefore, we have planned a Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pre-treated MCRC harboring wild-type *KRAS*. The institutional review board of each participating center approved the study protocol. This study was registered at the UMIN Clinical Trials Registry as UMIN000001951 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE STUDY

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) Eastern Cooperative Oncology Group performance status 0–2. (iii) The presence of measurable metastatic disease, as defined by the RECIST criteria. (iii) The 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 $>1000/mm^3$ and 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). (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/m^2 as a 2 h infusion followed by biweekly administration of 500 mg/m^2 as a 1 h infusion. Irinotecan is administered biweekly. The dose of irinotecan (100–150 mg/m^2) 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 $\leq$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/m^2 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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Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study)

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Summary

Background Fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are widely used as first-line or second-line chemotherapy for metastatic colorectal cancer. However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient. We therefore planned an open-label randomised controlled trial to verify the non-inferiority of irinotecan plus oral S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate; IRIS) to FOLFIRI as second-line chemotherapy for metastatic colorectal cancer.

Methods Between Jan 30, 2006, and Jan 29, 2008, 426 patients with metastatic colorectal cancer needing second-line chemotherapy from 40 institutions in Japan were randomly assigned by a computer-based minimisation method to receive either FOLFIRI (n=213) or IRIS (n=213). In the FOLFIRI group, patients received folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and a continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks. In the IRIS group, patients received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40–60 mg according to body surface area) twice daily for 2 weeks, repeated every 4 weeks. The primary endpoint was progression-free survival, with a non-inferiority margin of 1·333. Statistical analysis was on the basis of initially randomised participants. This study is registered with ClinicalTrials.gov, number NCT00284258.

Findings All randomised patients were included in the primary analysis. After a median follow-up of 12·9 months (IQR 11·5–18·2), median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group (hazard ratio 1·077, 95% CI 0·879–1·319, non-inferiority test p=0·039). The most common grade three or four adverse drug reactions were neutropenia (110 [52·1%] of 211 patients in the FOLFIRI group and 76 [36·2%] of 210 patients in the IRIS group; p=0·0012), leucopenia (33 [15·6%] in the FOLFIRI group and 38 [18·1%] in the IRIS group; p=0·5178), and diarrhoea (ten [4·7%] in the FOLFIRI group and 43 [20·5%] in the IRIS group; p<0·0001). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.

Interpretation Progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. Treatment with IRIS could be an additional therapeutic option for second-line chemotherapy in metastatic colorectal cancer.

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Introduction

The combination of fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) has been established as the standard first-line chemotherapy for metastatic colorectal cancer.[1] For second-line chemotherapy for patients resistant to fluorouracil, randomised comparative studies have shown that irinotecan monotherapy was effective.[2,3] Rougier and colleagues[4] showed comparable efficacy of FOLFIRI, FOLFOX, and irinotecan and oxaliplatin (IROX) in patients unresponsive to fluorouracil in a randomised phase 2 study.

Tournigand and colleagues[5] showed that, in patients with metastatic colorectal cancer who were randomly assigned to receive FOLFIRI or FOLFOX as first-line chemotherapy and then crossed over to receive the other as second-line chemotherapy, overall survival was similar in both groups. Consequently, initial treatment with FOLFOX and then second-line treatment with FOLFIRI or vice versa is recommended as standard therapy.[6] However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient and sometimes associated with catheter-related problems such as infection and thrombosis.

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See Reflection and Reaction page 808

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S-1 is an oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil, CDHP is a dihydropyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyl transferase, reducing gastrointestinal toxicities. Response rates for monotherapy with S-1 are around 35% for colorectal cancer, and it is suggested that DPD inhibition in tumour cells might contribute to antitumour effects because S-1 has been effective against many solid tumours with high DPD expression.[7] Clinically, responses rates of 52·5–62·5% have been reported in phase 2 studies of irinotecan plus S-1 combination therapy, with median progression-free survival of 7·8–8·6 months for first-line treatment for metastatic colorectal cancer.[8–10] These results suggest that the efficacy of IRIS might be comparable to that of FOLFIRI and that IRIS might also be more convenient for both patients and medical facilities.

We did a phase 2/3 randomised study (FIRIS study) to verify the non-inferiority of IRIS to FOLFIRI in patients with metastatic colorectal cancer in whom first-line chemotherapy failed.

Methods

Patients

Inclusion criteria were histologically confirmed colorectal adenocarcinoma; unresectable metastatic disease; age 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; withdrawal from first-line chemotherapy due to toxicity or progressive disease, or relapse within 24 weeks after the final dose of preoperative or postoperative chemotherapy; no previous treatment with irinotecan; sufficient oral intake; adequate organ function (white blood cell count 3000–12 000 cells per μL, platelet ≥100 000 per μL, aspartate aminotransferase [AST] ≤100 IU/L, alanine aminotransferase [ALT] ≤100 IU/L, total bilirubin ≤25·7 μmol/L [≤15 mg/L], and creatinine ≤106·1 μmol/L [≤12 mg/L]); and no abnormal electrocardiographic findings within 28 days before enrolment. Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhoea; clinically evident gastrointestinal haemorrhage; and ascites or pleural effusion needing treatment.

The protocol of this study was approved by the institutional review board or ethics committee of each institution. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

Randomisation and masking

Investigators provided the patient's details to the central registration centre through a web-based registration system. After an eligibility check, patients were randomly assigned to receive FOLFIRI or IRIS at the central registration centre by a computer program, by use of a minimisation method with stratification by institution, prior therapy (with or without oxaliplatin), and performance status (0 or 1). Assignment of patients was concealed from the investigator. Treatment assignment was not masked from the investigators or patients.

Procedures

Our randomised, open-label, phase 2/3 study in patients with the second-line metastatic colorectal cancer was done in 40 institutions in Japan (mainly hospitals and medical centres). In the phase 2 portion, safety was assessed in patients treated with either FOLFIRI (30 patients) or IRIS (30). Additionally, the response rate in the first 50 patients in the IRIS group was assessed because IRIS is an unfamiliar regimen in Japan. An independent data and safety monitoring board reviewed our results (safety and efficacy in the phase 2 portion; safety in the phase 3 portion), and approved proceeding to the phase 3 portion. The final analysis was done by use of the combined data from phase 2 and 3 portions.

Patients in the FOLFIRI group received concurrent folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and subsequent continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks (4 weeks counted as one cycle). In the FOLFIRI group, the dose of irinotecan was 150 mg/m², the approved dose in Japan.[11] The IRIS group received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40 mg for patients with body surface area [BSA] <1·25 m²; 50 mg for patients with BSA 1·25<1·5 m²; 60 mg for patients with BSA ≥1·5 m²) twice daily for 2 weeks from days 1–14 and then a 2-week pause, on the basis of results of phase 2 studies.[12,13] We selected this regimen from several documented regimens of irinotecan and S-1 to match the regimen of FOLFIRI in the control arm. Regimens in which irinotecan is given every 2 weeks[12,13] and every 3 weeks are in clinical use in Japan.[8]

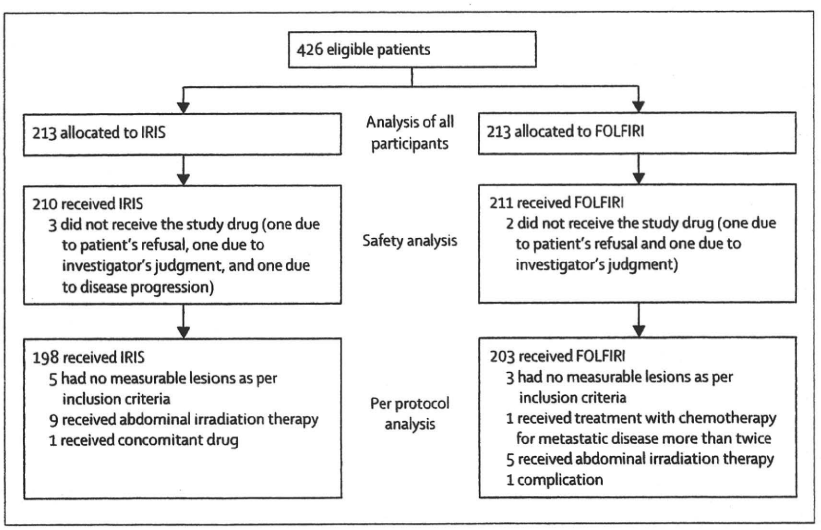

Figure 1: **Trial profile**

In both FOLFIRI and IRIS groups, treatment was delayed until recovery if white blood cell count fell below than 3000 cells per μL, platelets fell below 100 000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25·7 μmol/L, creatinine was higher than 106·1 μmol/L, the patient experienced diarrhoea of grade one or greater, or other non-haematological toxicities greater than grade two. If a patient experienced a grade four haematological or grade three or higher non-haematological toxicity, the dose was decreased by one level for the next course of treatment, and therapy was resumed.

Treatment was continued until progressive disease, unacceptable toxicity, or patient's refusal to continue treatment. Because molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab were not approved in Japan at the start of our study, no restriction for such agents was specifically placed on treatment before or after the study.

Physical examination, electrocardiography, performance status, and laboratory tests were done at baseline and repeated at least every 2 weeks during treatment. Tumours were assessed at baseline (within 1 month before enrolment), and at 2, 3, and 4 months after enrolment, and thereafter every 2 months until progression. Progression was defined as progressive disease on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, clinical progression judged by the investigator, or death from any cause without progression.

Progression-free survival was counted from the date of randomisation to the date when the progressive disease was first confirmed by the investigator's assessment. For patients without documented progressive disease, data was censored on the date of the last tumour assessment with non-progression status. Overall survival was calculated from the date of randomisation to the date of death or confirmation of survival.

Toxicity was evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical analysis

The primary efficacy analysis was done with all randomised patients; we also did a per-protocol analysis in which patients in whom there was a major violation such as inclusion or exclusion criteria or protocol treatments were excluded. Safety was assessed in all patients who received at least one dose of the study drug.

The primary objective of our study was to show non-inferiority of IRIS to FOLFIRI for progression-free survival in the whole randomised population. On the basis of data from previous reports in patients with metastatic colorectal cancer who received second-line chemotherapy, median progression-free survival with both FOLFIRI and IRIS was assumed to be 4 months. The steering committee deemed that response assessment could not be repeated more frequently than once a month, so a difference in progression-free survival shorter than 1 month could not be detected precisely. Thus, progression-free survival with IRIS that was 1 month shorter than with FOLFIRI would be acceptable as a lower margin for inferiority, given the expected hazard ratio [HR] of 1·0. The 95% CI upper limit of the HR, calculated using Cox regression analysis with stratification factors other than institution, was prespecified as less than 1·333, meaning the null hypothesis was that median progression-free survival with IRIS would be 1 month shorter than with FOLFIRI. Because 379 events were needed to show non-inferiority with a two-sided α of 0·05 and a power of 80%, a target sample size of 400 patients was required.

Secondary endpoints were overall survival, response rate, and toxicity. Subgroup analyses were done to establish whether therapeutic efficacy was affected by sex, age, histological type, performance status, and prior chemotherapy with or without oxaliplatin. Progression-free and overall survival were estimated using the Kaplan-Meier method. The 95% CI for median progression-free and overall survival was calculated using the method of Brookmeyer and Crowley.[14] All p values were two-sided. All statistical analyses were done with SAS version 8.2. This study is registered with ClinicalTrials.gov, number NCT00284258.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, or interpretation. All authors had access to all of the data. The corresponding author had final responsibility for decision to submit for publication.

	FOLFIRI (n=213)	IRIS (n=213)
Sex		
Male	123 (57·7%)	120 (56·3%)
Female	90 (42·3%)	93 (43·7%)
Age (years)	63·0 (32–75)	61·0 (29–75)
ECOG performance status		
0	160 (75·1%)	158 (74·2%)
1	53 (24·9%)	55 (25·8%)
Histological type		
Well differentiated	62 (29·1%)	60 (28·2%)
Moderately differentiated	124 (58·2%)	133 (62·4%)
Poorly differentiated	13 (6·1%)	8 (3·8%)
Other	13 (6·1%)	11 (5·2%)
Undetermined	1 (0·5%)	1 (0·5%)
Previous chemotherapy with oxaliplatin		
Yes	128 (60·1%)	129 (60·6%)
No	85 (39·9%)	84 (39·4%)
Number of metastatic sites		
One	92 (43·2%)	88 (41·3%)
Two or more	120 (56·3%)	124 (58·2%)

Data are number (%) or median (range). FOLFIRI=folinic acid, fluorouracil, and irinotecan. IRIS=irinotecan and S-1. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline patient characteristics**

Results

426 patients from 40 institutions in Japan were enrolled in the study from Jan 30, 2006, to Jan 29, 2008, and randomised either to the FOLFIRI or IRIS group (213 patients in each; figure 1). Of the per-protocol population, 203 patients were in the FOLFIRI group and 198 were in the IRIS group; reasons for exclusion are shown in figure 1. All patients who received study treatment (211 patients in the FOLFIRI group and 210 patients in the IRIS group) were included in the safety evaluation. Baseline characteristics were well balanced between the two groups (table 1).

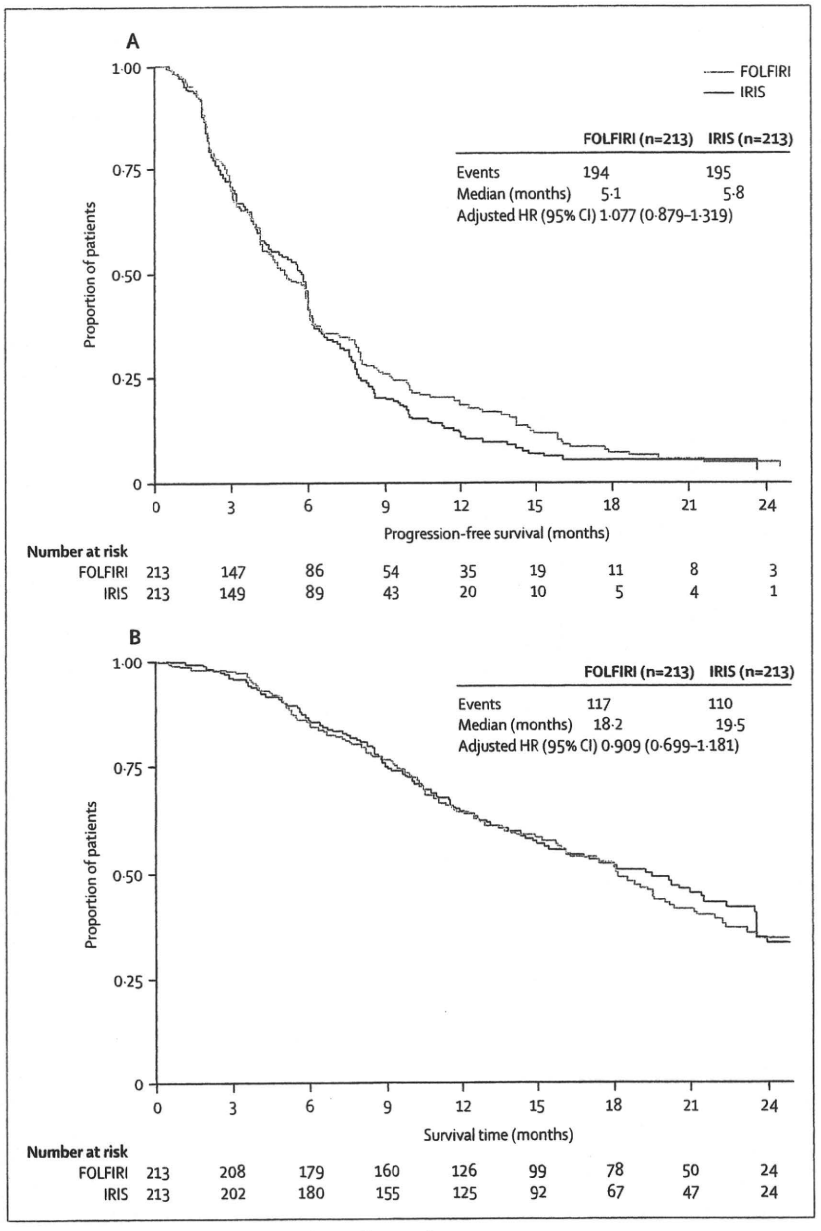

Figure 2: **Progression-free survival (A) and overall survival (B)**
FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

The mean number of cycles of protocol treatment was 4·7 (range 1–20) for FOLFIRI and 4·9 (1–23) for IRIS. Median relative dose intensities to the planned dose were almost identical: irinotecan 78·3%, bolus fluorouracil 76·9%, and infusional fluorouracil 81·5% in the FOLFIRI group, and irinotecan 78·3% and S-1 88·9% in the IRIS group. Treatments were discontinued because of disease progression in 68·5% (146 patients) in the FOLFIRI group and in 66·2% (141) in the IRIS group, adverse events in 10·8% (23) and in 16·9% (36), and patient's refusal 1·9% (four) and 6·1% (13). 179 patients in the FOLFIRI group and 184 patients in the IRIS group needed a dose delay or dose reduction. Treatment after the trial (ie, treatment after failure of second-line regimen) was given to 159 (74·6%) patients in the FOLFIRI group and 147 (69·0%) in the IRIS group. As third-line treatment, an oxaliplatin-containing regimen was given to 58 (27·2%) patients in the FOLFIRI and 63 (29·6%) in the IRIS group. Molecularly targeted agents as treatments after the trial were used in 24 patients in the FOLFIRI group and 16 in the IRIS group.

As of Dec 31, 2008, collection of progression-free and overall survival data was cut off, with 389 confirmed events (194 FOLFIRI and 195 IRIS). Median follow-up was 12·9 months (IQR 11·5–18·2). Median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group. In the entire randomised population, the HR of progression-free survival in the IRIS group compared with the FOLFIRI group was 1·077 (95% CI 0·879–1·319, p=0·039). Similar results were seen in the per protocol population: median progression-free survival was 5·1 months in the FOLFIRI group and 5·7 in the IRIS group (HR 1·050, 95% CI 0·851–1·294).

The data on overall survival are preliminary because of short follow-up. 117 of the 213 patients in the FOLFIRI group and 110 of the 213 patients in the IRIS group died due to any cause. Median overall survival in the entire randomised population was 18·2 months in the FOLFIRI group and 19·5 months in the IRIS group (HR 0·909, 95% CI 0·699–1·181; figure 2). In the per protocol population, median overall survival was 18·1 months in the FOLFIRI group and 19·3 months in IRIS group (HR 0·896, 95% CI 0·685–1·172).

The overall response rate was 16·7% (one patient had a complete response, 28 patients had a partial response) of 174 patients with evaluable response data in the FOLFIRI group and 18·8% (one patient had a complete response, 33 patients had a partial response) of 181 in the IRIS group.

Figure 3 shows the results of subgroup analyses of progression-free survival. Although no interaction was identified between sex, age, histological type, or performance status and therapeutic effects of IRIS compared with FOLFIRI, a statistically significant interaction was noted between prior chemotherapy (with or without oxaliplatin) and therapeutic effects (p=0·030). In the subgroup of patients receiving prior chemotherapy with oxaliplatin, median progression-free survival was

5·7 months in the IRIS group and 3·9 months in the FOLFIRI group (adjusted HR 0·876, 95% CI 0·677–1·133), whereas in patients without prior oxaliplatin treatment it was 6·0 months and 7·8 months, respectively (HR 1·490, 95% CI 1·079–2·059). A similar tendency was noted in the overall survival (figure 4).

Table 2 lists major adverse events. In the two groups, the incidences of adverse events were not markedly different from those previously reported, and none of the adverse events were unexpected. Significantly more patients in the FOLFIRI group experienced grade three or four neutropenia than did those in the IRIS group (110 [52·1%] of 211 patients in the FOLFIRI group *vs* 76 [36·2%] of 210 in the IRIS group; p=0·0012); 33 (15·6%) of patients in the FOLFIRI group and 38 (18·1%) in the IRIS group experienced leucopenia (p=0·5178). The most common non-haematological toxicities were diarrhoea (10 [4·7%] in the FOLFIRI group *vs* 43 [20·5%] in the IRIS group; p<0·0001), anorexia (11 [5·2%] *vs* 23 [11·0%]; p=0·0329), nausea (nine [4·3%] *vs* four [1·9%]; p=0·2593), fatigue (seven [3·3%] *vs* 18 [8·6%]; p=0·0242), and febrile neutropenia (two [0·9%] *vs* 10 [4·8%]; p=0·0205), all at grade three (table 2). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.

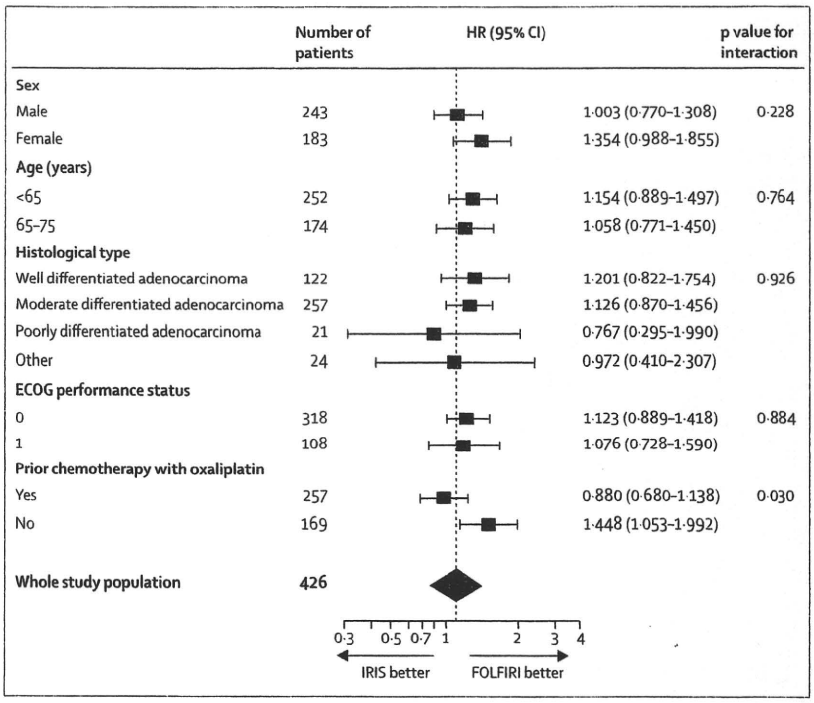

Figure 3: **Subgroup analysis of progression-free survival**
HR=hazard ratio.

Discussion

Our randomised study, comparing FOLFIRI and IRIS as second-line chemotherapy for patients with metastatic colorectal cancer, shows the non-inferiority of IRIS to FOLFIRI. Similar results were obtained in both the entire randomised population and in the more conservative per-protocol analysis. Response rates and overall survival were equivalent between the groups. To our knowledge, this is the first phase 3 trial that shows non-inferiority of oral fluoropyrimidine plus irinotecan therapy to FOLFIRI. From the point of convenience, there has been substantial demand for replacing infusional fluorouracil-based regimens with oral fluorouracil agents. Our study was not designed to collect specific data on working hours of clinicians or the quality of life of patients. However, unlike FOLFIRI, IRIS does not contain infusional fluorouracil and thus does not require a long infusion process, reducing the inconvenience to both patients and clinicians. Additionally, no infuser pump is needed, providing a great advantage to patients. Randomised studies comparing FOLFOX with capecitabine plus oxaliplatin (XELOX) in patients with metastatic colorectal cancer showed that XELOX was non-inferior to FOLFOX.[15,16] By contrast, Fuchs and colleagues[17] reported that progression-free survival with capecitabine plus irinotecan (CapeIRI; 5·8 months) was clearly inferior to that with FOLFIRI (7·6 months) as the first-line chemotherapy for metastatic colorectal cancer, and CapeIRI was associated with a higher incidence of gastrointestinal toxicities and hand-foot syndrome, resulting in discontinuation for reasons other than disease progression.

In our study, the incidence of grade three or worse diarrhoea, fatigue, febrile neutropenia, and anorexia were significantly higher in the IRIS group than the FOLFIRI group. In general, oral fluorouracil-derivative drugs have been shown to be associated with a higher incidence of diarrhoea.[15,17–19] This might also be applicable to S-1. It might be attributable to 2-week treatment with S-1 in IRIS compared with 2-day treatment with fluorouracil in FOLFIRI. However, there was no significant difference in the number of courses or dose intensity between groups. It is thought that all adverse events could be controlled by supportive care, treatment interruptions, or dose reduction, with little effect on treatment continuity. Of note, in the IRIS group, grade four diarrhoea was not detected and fewer of the patients enrolled towards the end of the study experienced grade three diarrhoea.

The incidence of fluorouracil-induced diarrhoea, especially by oral fluoropyrimidines, has been shown to be higher in non-Asian patients than Asian patients.[17,19–21] We speculate that IRIS therapy might also be less feasible in non-Asian patients; therefore, the optimum dose of S-1 in IRIS should be clarified for this population. The reported incidence of hand-foot syndrome due to fluoropyrimidine derivatives containing DPD inhibitors, such as S-1, was low in both Japanese and western trials.[22] In our study, grade three hand-foot syndrome, which is frequently noted with capecitabine-based regimens both in Japanese and non-Asian patients, was not noted in the IRIS group.

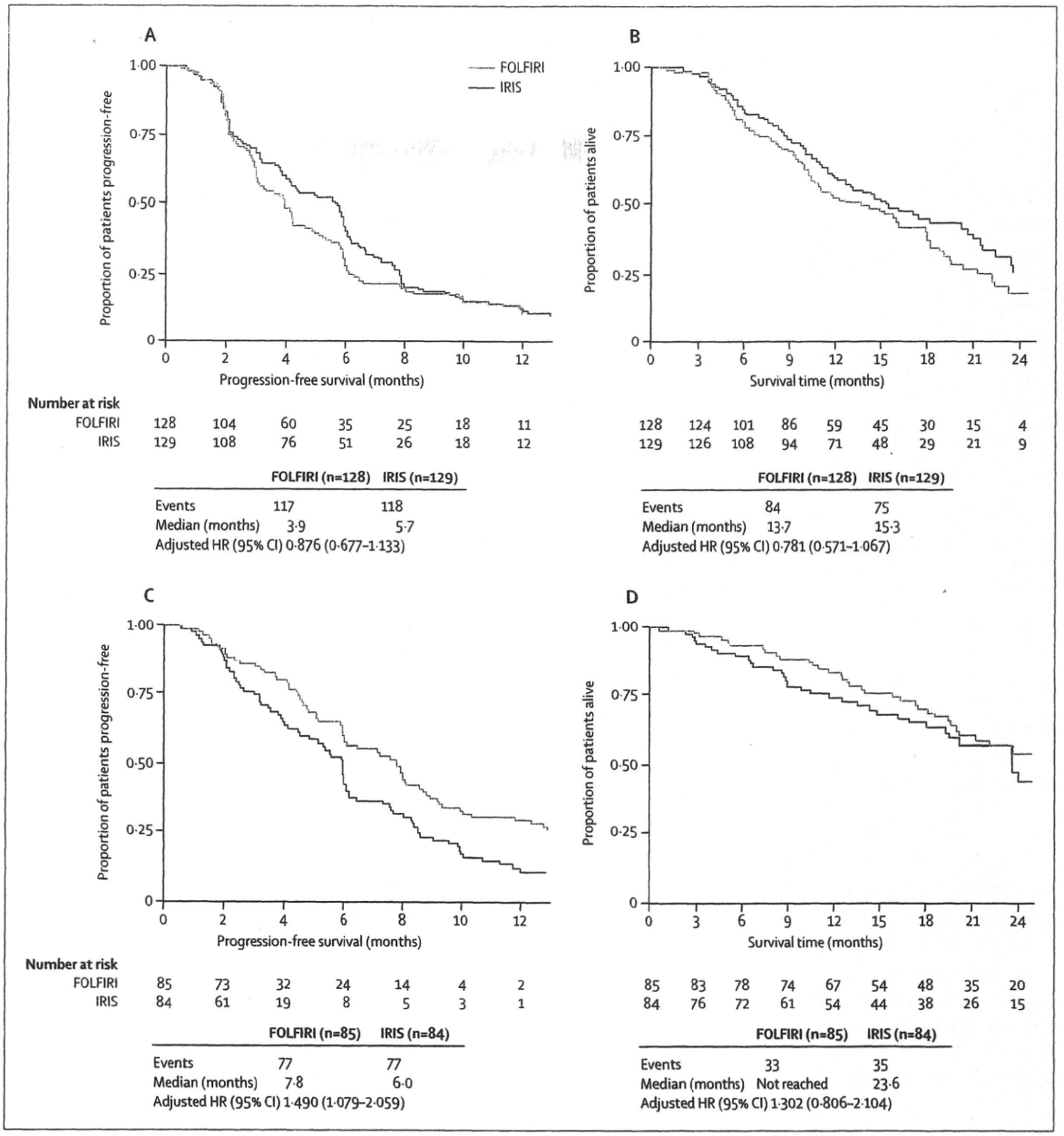

Figure 4: **Survival according to prior chemotherapy**
Progression-free survival with prior oxaliplatin (A). Overall survival with prior oxaliplatin (B). Progression-free survival without prior oxaliplatin (C). Overall survival without prior oxaliplatin (D). FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

When our trial was started, FOLFOX was already the standard first-line treatment worldwide, but because oxaliplatin had just been launched in Japan, patients who received prior chemotherapy regimens without oxaliplatin were also enrolled. In the subgroup that received prior oxaliplatin, the adjusted HR for progression-free survival of IRIS to FOLFIRI was 0·876 (95% CI 0·677–1·133) suggesting that IRIS was non-inferior to FOLFIRI after failure on oxaliplatin-containing regimens. In this subgroup, the median progression-free survival associated with IRIS was 5·7 months, and much better than the previously reported progression-free survival associated with FOLFIRI in patients who received prior chemotherapy with a fluoropyrimidine and oxaliplatin.[5,23] FOLFOX or FOLFIRI as the first-line chemotherapy and subsequent crossover in the second line is the most common treatment strategy for metastatic colorectal cancer, although there is no evidence of superiority of FOLFIRI over irinotecan alone. In Japan, the approved dose of irinotecan (150 mg/m^2, every 2 weeks) alone is lower than that in western countries, and monotherapy with irinotecan (350 mg/m^2, every 3 weeks) could not be used. Both IRIS

	FOLFIRI (n=211)			IRIS (n=210)			p value (grade 3–4)
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	
Neutropenia	179 (84·8%)	76 (36·0%)	34 (16·1%)	139 (66·2%)	54 (25·7%)	22 (10·5%)	0·0012
Leucopenia	170 (80·6%)	32 (15·2%)	1 (0·5%)	154 (73·3%)	32 (15·2%)	6 (2·9%)	0·5178
Anaemia	115 (54·5%)	13 (6·2%)	1 (0·5%)	156 (74·3%)	19 (9·0%)	2 (1·0%)	0·2221
Thrombocytopenia	63 (29·9%)	1 (0·5%)	1 (0·5%)	74 (35·2%)	0 (0·0%)	0 (0·0%)	0·4988
Diarrhoea	125 (59·2%)	10 (4·7%)	0 (0·0%)	167 (79·5%)	43 (20·5%)	0 (0·0%)	<0·0001
Fatigue	144 (68·2%)	7 (3·3%)	0 (0·0%)	153 (72·9%)	18 (8·6%)	0 (0·0%)	0·0242
Febrile neutropenia	3 (1·4%)	2 (0·9%)	0 (0·0%)	10 (4·8%)	10 (4·8%)	0 (0·0%)	0·0205
Mucositis or stomatitis	92 (43·6%)	1 (0·5%)	0 (0·0%)	102 (48·6%)	6 (2·9%)	0 (0·0%)	0·0677
Anorexia	129 (61·1%)	11 (5·2%)	0 (0·0%)	141 (67·1%)	23 (11·0%)	0 (0·0%)	0·0329
Nausea	111 (52·6%)	9 (4·3%)	0 (0·0%)	99 (47·1%)	4 (1·9%)	0 (0·0%)	0·2593

Data are number (%).

Table 2: **Safety analysis**

and FOLFIRI showed longer median progression-free survival than reported in trials of monotherapy with irinotecan.[3,22] Thus, irinotecan-based regimens, such as FOLFIRI and IRIS, delivered every 2 weeks, should be considered after FOLFOX failure, especially in Japan. By contrast, in the subgroup of patients previously treated without oxaliplatin, progression-free survival was longer in the FOLFIRI group than in the IRIS group (HR 1·490, 95% CI 1·079–2·059). In this subset, prior fluorouracil monotherapy (oral, bolus) had failed in some patients. For these patients, FOLFIRI might have greater efficacy than IRIS. Nonetheless, even in this subgroup, median progression-free survival in the IRIS group was 6·0 months and no worse than that previously reported for second-line chemotherapy in patients refractory to fluorouracil alone.[3,24–26]

In each of the subgroups stratified by use or non-use of oxaliplatin, no differences were identified in other patient characteristics between the two groups. There is no clearly understood reason for the interaction between the presence or absence of oxaliplatin and therapeutic effects in the two groups. We speculate that a different mode of fluorouracil administration in FOLFIRI compared with prior therapy might work more effectively than S-1 for the patients without prior therapy with oxaliplatin, and that S-1 might have some salvage effects in patients who received FOLFOX involving bolus and infusional fluorouracil.

Our data have some limitations. First, progression-free survival, the primary endpoint, was assessed on the basis of disease progression established by the investigator at each medical institution. Therefore, caution should be used when our results are compared with those of other studies in which progression-free survival was centrally assessed. Second, around 40% of the patients in this trial were not previously treated with oxaliplatin, since FOLFOX therapy was approved in Japan only just before the study was started. Because FOLFOX is now widely used as first-line chemotherapy in Japan, patients should be carefully selected when our overall results are used to apply IRIS therapy in the clinical setting. However, we believe that the findings from subgroup analyses suggest that IRIS was better than FOLFIRI in patients who received an oxaliplatin-containing regimen as first-line chemotherapy.

In conclusion, progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. IRIS therapy can be an additional treatment option for second-line chemotherapy in metastatic colorectal cancer.

Research in context

Systematic review

Before the study was initiated, we searched the PubMed database for relevant articles using search terms such as "metastatic colorectal cancer", "chemotherapy", "second line", and "phase 3". Based on the relevant articles obtained, the institutional review board reviewed the appropriateness as well as ethical and scientific aspects of the study, on which to base the approval of the study.

Interpretation

Our study demonstrates the non-inferiority of IRIS to FOLFIRI, one of international standard therapies for second-line chemotherapy of metastatic colorectal cancer; thus, IRIS is an option for second-line chemotherapy.

Contributors

IH, SM, NB, YS, HT, YK, MW, and KS, as a steering committee, participated in all phases of this study, including design and writing of the ancillary protocol, analysis, interpretation, and preparation of the report. All authors, with the exception of IH and SM, participated in data collection. SM undertook all analyses. All authors reviewed and helped revise the paper, and approved the submitted version. A list of participating institutions can be found in the webappendix.

See Online for webappendix

Conflicts of interest

KM has received payment for writing the report from Daiichi Sankyo and honoraria from Taiho and Yakult Honsha. NB has received a grant from Taiho; NB's institution has received grants from Taiho. YS has received honoraria from Taiho and Yakult Honsha; YS's institution has received board membership fees and grants from Daiichi Sankyo. AT has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha;

AT's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. SS has received honoraria from Yakult Honsha and lecture fees from Taiho; SS's institution has received grants from Taiho. HB has received board membership fees from Taiho and Daiichi Sankyo, and lecture fees from Taiho, Daiichi Sankyo, Yakult Honsha, and Wyeth; HB's institution has received grants from Taiho, Daiichi Sankyo, Yakult Honsha, Kyowa Hakko Kirin, and Wyeth. TS has received consulting fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin and Wyeth; TS's institution has received grants form Taiho. TD has received honoraria from Taiho, Wyeth, and Yakult Honsha, and lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; TD's institution has received grants from Taiho and Yakult Honsha. KI's institution has received grants from Taiho. TN has received honoraria from Taiho, Wyeth, and Yakult Honsha; TN's institution has received grants from Daiichi Sankyo. KY has received lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; KY's institution has received grants from Taiho. HT has received board membership fees from Daiichi Sankyo, consulting fees from Yakult Honsha, and honoraria from Taiho and Daiichi Sankyo. TE has received lecture fees from Kyowa Hakko Kirin, Taiho, Wyeth, and Yakult Honsha; TE's institution has received grants from Taiho and Yakult Honsha. ST's institution has received grants from Taiho. HK has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; HK's institution has received grants from Taiho and Daiichi Sankyo, HK's institution has received grants from Daiichi Sankyo. YK has received board membership fees from Daiichi Sankyo, Kyowa Hakko Kirin, Taiho, and Wyeth, and honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; YK's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. MW has received board membership fees, honoraria, and lecture fees from Taiho; MW's institution has received grants from Taiho. IH has received board membership fees from Taiho, and consulting fees, honoraria, and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin. SM has received board membership fees from Daiichi Sankyo, consulting fees and honoraria from Taiho and Daiichi Sankyo; SM's institution has received grants from Daiichi Sankyo. KS has received board membership fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Wyeth; KS's institution has received grants from Taiho.

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REPORT

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. © **2010 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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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 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.

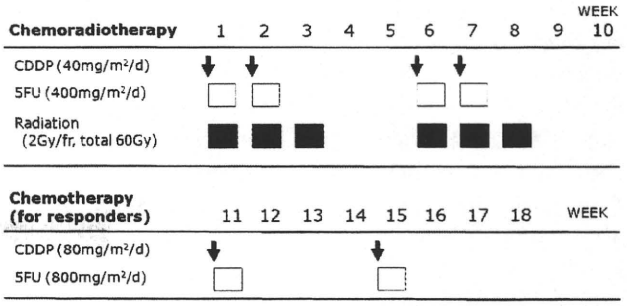

Fig. 1. Protocol scheme.

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

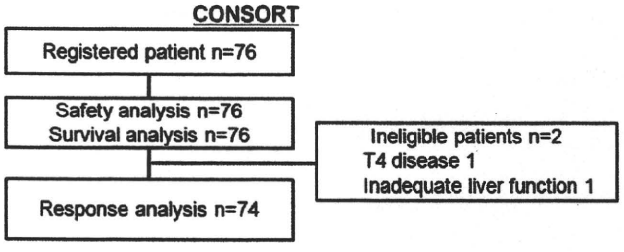

Fig. 2. Consolidated Standards of Reporting Trials diagram.

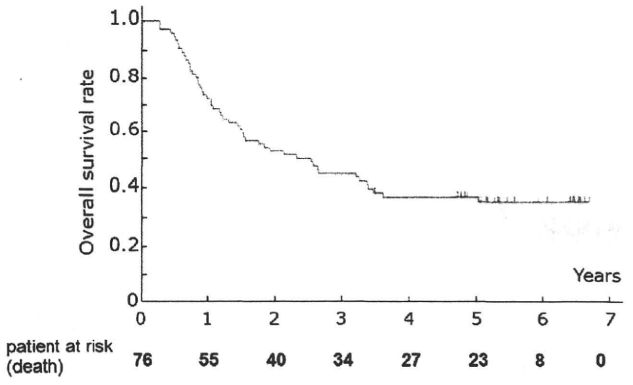

Fig. 3. Overall survival of the 76 patients enrolled in the study.

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.

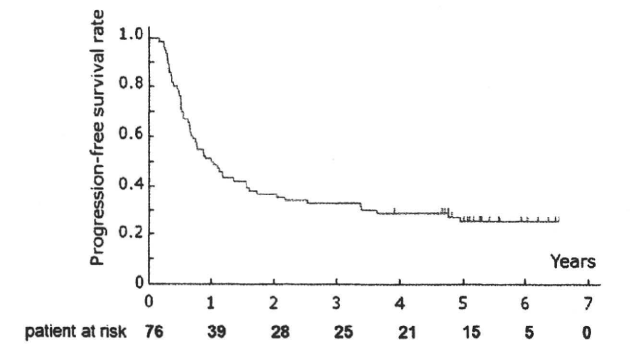

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

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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ORIGINAL ARTICLE

A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy

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Abstract
Purpose To evaluate the efficacy and safety of weekly paclitaxel (Taxol®) in patients with advanced or recurrent esophageal cancer.
Methods Fifty-three patients with recurrent or advanced esophageal cancer who had previously received platinum-based chemotherapy were treated with paclitaxel 100 mg/m^2 once weekly by 1-h infusion on days 1, 8, 15, 22, 29, and 36 of a 49-day cycle. Fifty-two patients were evaluable for efficacy and 53 for safety. Forty-one (77%) patients had recurrent, and 12 (23%) had advanced disease. Most patients (52/53) had squamous cell carcinoma, and one had adenocarcinoma.
Results A median of 2 cycles was delivered (range 1–8). The overall response rate was 44.2% (23/52; 95% confidence interval (CI) 30.5, 58.7%), with 4 patients (7.7%) achieving complete response. The median duration of response was 4.8 months, and median overall survival was 10.4 months. The most common Grade 3 or 4 adverse events were neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), and fatigue (9.4%). Adverse events resulted in treatment discontinuation in 34.0% of patients and dose reductions in 43.4%. There were no treatment-related deaths.
Conclusions Weekly paclitaxel demonstrated efficacy and manageable toxicity in patients with advanced or recurrent esophageal cancer and may be a treatment option for this population.

Keywords Esophageal cancer · Paclitaxel · Phase II study · Weekly infusion

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