3/4 anemia, leukocytopenia, and neutrocytopenia was 4, 4, and 10%, respectively [9]. Anemia, leukocytopenia, and neutropenia were also reported as AEs for patients treated with imatinib; the incidence of grade 3/4 anemia, leukocytopenia, and neutropenia in a large Phase III study was 2.0, 1.4, and 4.8%, respectively [6]. The only hematological toxicity of motesanib was anemia (grade 2, 3%; grade 3, 6%). Despite long-term exposure to motesanib, hematological toxicities were mild. Motesanib may therefore present an alternative treatment option for patients who experienced neutrocytopenia or thrombocytopenia after treatment with imatinib or sunitinib.

To evaluate the potential effect of gastrectomy on motesanib disposition, the motesanib PK profiles from patients with a history of gastrectomy were compared with those who did not have prior gastrectomy. Median t_{max} values occurred earlier in patients with gastrectomy on both days 1 and 29, suggesting faster absorption in patients with a history of gastrectomy. Since gastrectomy impacts the gastric emptying rate and the absorption rate resulting in increase in C_{max}, these findings should be considered in the following clinical trials.

The current treatment options for patients with GIST after treatment failure with imatinib and sunitinib are limited to best supportive care and investigative therapies. This study shows that in Japanese patients with advanced GIST motesanib is well tolerated, and, although an objective tumor response was observed in only one patient, motesanib may have an impact on survival in a retrospective analysis. However, focusing on other clinically meaningful measures, such as the Choi criteria [13] that incorporating tumor density and small changes in tumor size as revealed by CT scanning, is more important than focusing on the tumor response rate, which may fail to identify a potentially effective therapy [14, 15]. Randomized, well-controlled studies with time to progression or survival as the primary endpoints of efficacy will be needed to identify agents for which a tumor regression effect is not anticipated. Results from such studies will help in making an informed decision of whether or not to continue the clinical development of such agents in GIST.

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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.

Funding Taiho Pharmaceutical Co Ltd and Daiichi Sankyo Co Ltd.

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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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]

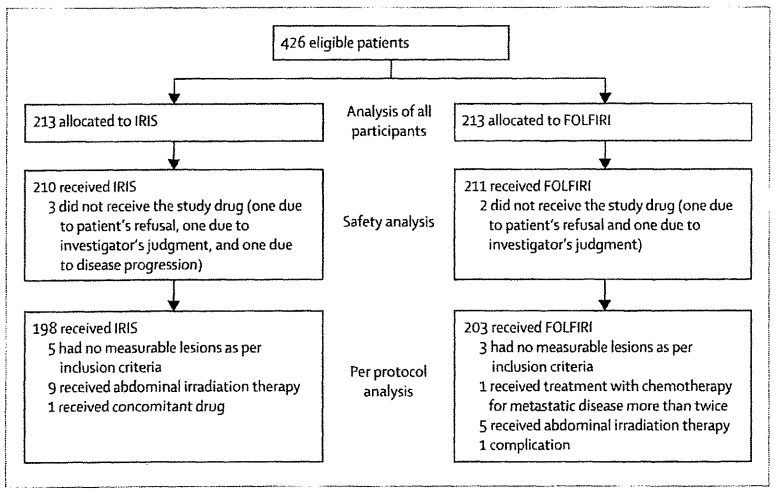

Figure 1: Trial profile

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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 100000 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).

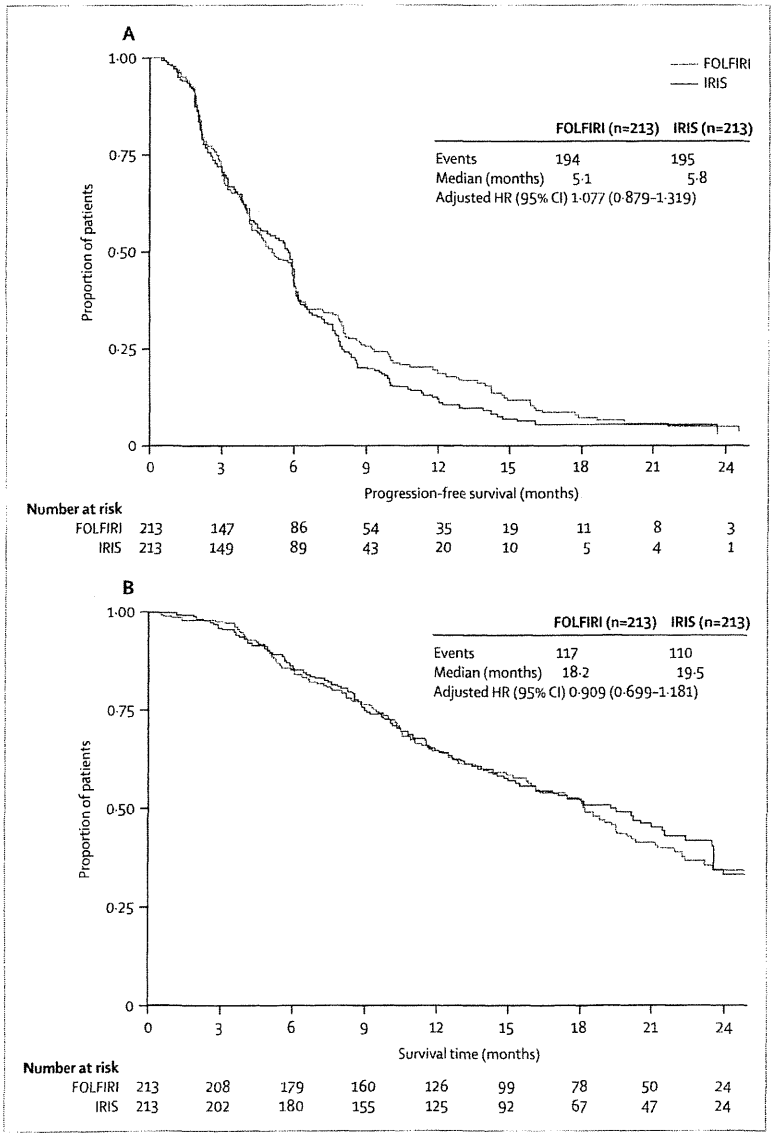

Figure 2: **Progression-free survival (A) and overall survival (B)**
FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

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.

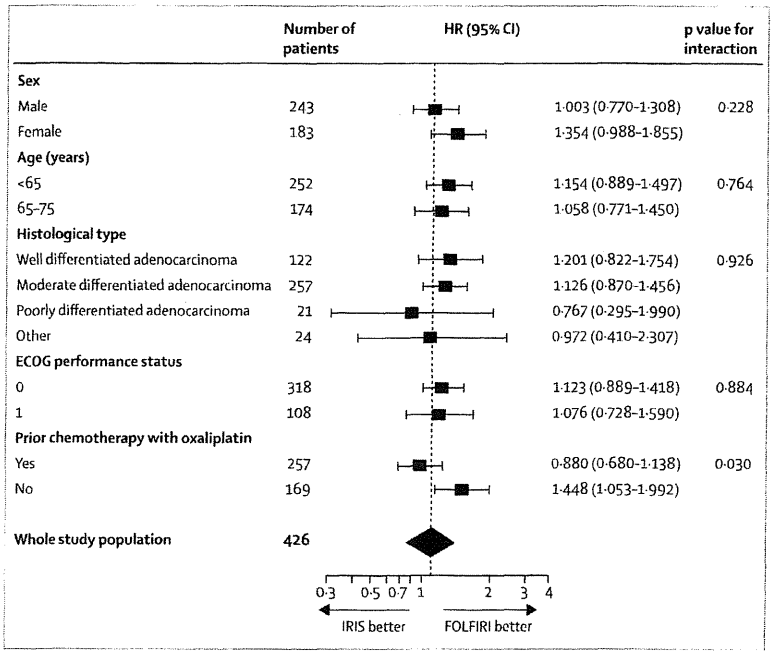

Figure 3: **Subgroup analysis of progression-free survival**
HR=hazard ratio.

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.

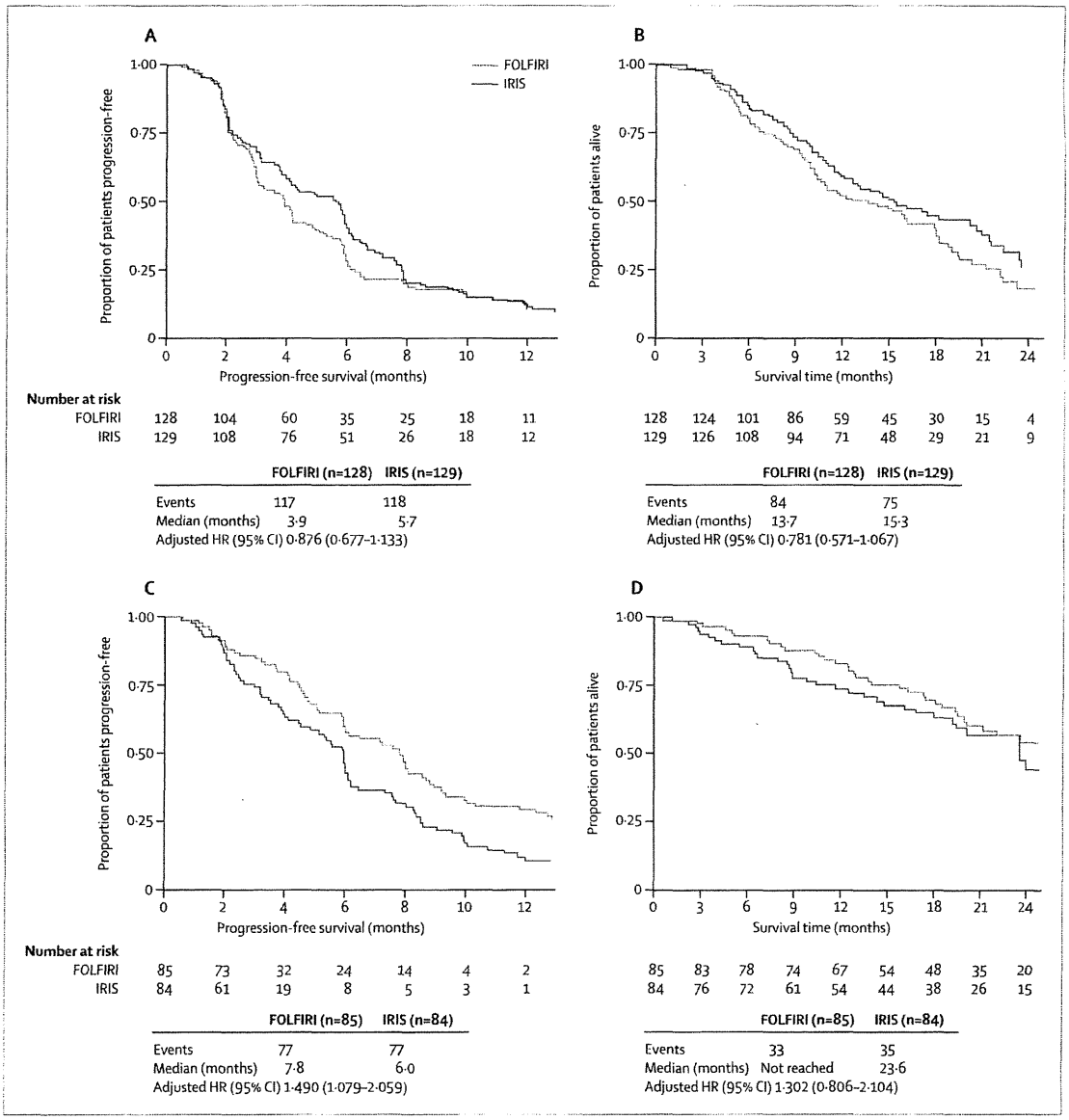

Figure 4: **Survival according to prior chemotherapy**
Progression-free survival with prior oxaliplatin (A). Overall survival with prior oxaliplatin (B). Progression-free survival without prior oxaliplatin (C). Overall survival without prior oxaliplatin (D). FOLFIRI=infusional fluorouracil, folinic acid, 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

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	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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A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study)

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Abstract

Aims: Clinically serosa-positive (T3–4) gastric cancer has a poor prognosis. This phase II trial explored the feasibility and safety of preoperative chemotherapy followed by D2 or D3 gastrectomy in this type of gastric cancer.
Methods: Patients with T3–4 gastric cancer received one course of S-1 (80 mg/m^2 daily for 3 weeks) and cisplatin (60 mg/m^2 on day 8) chemotherapy and then underwent D2 or D3 gastrectomy with curative intent. Primary endpoint was toxicities.
Results: Of 50 patients enrolled, 49 were eligible and received the treatment protocol. Chemotherapy-related toxicities were mild; grade 3 neutropenia in 2 patients, anorexia in 3, and nausea in 2, and no grade 4 toxicities. Clinical response was achieved in 13 of 34 evaluable patients. Of the 49 patients, 39 underwent D2 or D3 dissection. There was no surgical mortality. Operative morbidity occurred in 5 of 49 patients, including pancreatic fistula in 1 and abdominal abscess in 2.
Conclusion: This multi-modality treatment seems to be feasible and safe for T3–4 gastric cancer.

Keywords: Gastric cancer; Chemotherapy; Surgery; Phase II

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe.[1] Complete resection is essential for cure,[2] and because more than half of T3 and T4 tumors have metastasized to lymph nodes along the major branch arteries or in the para-aortic area, complete resection has involved D2 or D3 dissection in Japan.[3,4] However, despite resection of these tumors with curative intent, prognosis has been limited.[5] To improve the survival of these patients, new treatment strategies must be developed.

Most clinical trials of postoperative adjuvant chemotherapy have failed to prove a survival benefit.[6] However, a large phase III trial recently demonstrated that adjuvant chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M ostat potassium) significantly improved survival after D2 curative

Abbreviations: CF, 5-FU plus cisplatin; ECF, triplet chemotherapy of CF plus epirubicin; DCF, CF plus docetaxel; JACCRO, Japan Clinical Cancer Research Organization; WBC, white blood cell count; PLT, platelet count; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase; RECIST, response evaluation criteria in solid tumors; JCOG, Japan Clinical Oncology Group.

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gastrectomy in Japanese patients with T2N+ or T3 disease.[7] Based on this, D2 surgery and postoperative S-1 chemotherapy has been established as a standard treatment in Japan. Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for T3 tumors was not satisfactory.

Preoperative chemotherapy followed by extended surgery has some theoretical benefits when compared with postoperative chemotherapy.[8] If bulky tumors are reduced in size by chemotherapy, complete tumor removal could theoretically be easily achieved by extended surgery. If distant micrometastases are eliminated by chemotherapy, complete resection by extended surgery may improve survival and result in cure in some cases. However, preoperative chemotherapy followed by extended surgery has not been confirmed in phase III trial.

A high response rate and relatively low toxicity are required for preoperative chemotherapy, because target tumors are resectable or marginally resectable and the patients must receive potentially curative surgery after chemotherapy. Combined chemotherapy with S-1 plus cisplatin is an attractive regimen for preoperative chemotherapy for gastric cancer. A previous phase II trial of this regimen in metastatic gastric cancer reported a high response rate of 76% and acceptable toxicities.[9] Recently, a Japanese phase III trial of chemotherapeutic regimens for metastatic gastric cancer (SPIRITS trial) demonstrated that S-1 plus cisplatin led to significantly longer median overall survival than S-1 alone (13 months vs. 11 months).[10] Moreover, in the recent international phase III trial (FLAGS), S-1 plus cisplatin had lower toxicity but achieved equally overall survival compared with 5-FU plus cisplatin (CF) (Ajani JA, et al. presented at the 2009 Gastrointestinal Cancers Symposium). Triplet chemotherapy of CF plus epirubicin (ECF) or CF plus docetaxel (DCF) is effective but more toxic than CF.[11]

However, the influence of preoperative chemotherapy on D2 or D3 surgery has not been fully evaluated, although D2 and D3 gastrectomy are safe procedures in Japan.[12] Unlike D0 or D1 surgery, D2 or D3 gastrectomy involves nodal dissection along the pancreas, which can cause pancreatic fistula or abdominal abscess. These complications can be lethal and might be increased by preoperative chemotherapy. The effect of preoperative chemotherapy on surgical mortality or morbidity with these procedures has not been fully clarified. Recently, preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 dissection was tested in phase II trial to evaluate the efficacy and toxicity in Japan.[13] However, this trial has been terminated due to high treatment-related death during the accrual. A safe and effective regimen before extended surgery has yet to be reported.

The Japan Clinical Cancer Research Organization (JACCRO) therefore, conducted a multi-institutional phase II trial (JACCRO GC-01) to evaluate the feasibility and safety of preoperative chemotherapy with S-1 plus cisplatin followed by curative D2 or D3 gastrectomy for clinically serosa-positive (T3–4) gastric cancer.

Patients and methods

Eligibility criteria

Eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) stage clinically assessed as T3–4, N0–N3 which is classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma,[14] and M0; (3) age 20–75 years; (4) Eastern cooperative oncology group (ECOG) performance status 0–1; (5) no prior therapy; (6) sufficient organ function [white blood cell count (WBC) 4000–12,000 mm^3, platelet count (PLT) >100,000/mm^3, glutamic oxaloacetic transaminase (GOT) <80 IU/l, glutamic pyruvic transaminase (GPT) <80 IU/l, total bilirubin <1.5 mg/dl, alkaline phosphatase (ALP) < two times greater than upper limit of normal, creatinine <1.2 mg/dl, creatinine clearance >60 ml/min, and hemoglobin >8.0 g/dl]; and (7) written informed consent. Clinical diagnosis was based on gastric fiberscopy, upper gastrointestinal series, computed tomography, and ultrasonography. Serosal invasion of the primary tumor was evaluated by computed tomography. Endoscopic ultrasonography or diagnostic laparoscopy was not mandatory, because these remain outside of routine preoperative examinations in Japan. Exclusion criteria were (1) severe co-morbidities; (2) active and acute bleeding from the digestive tract; (3) insufficient oral intake; (4) synchronous or previous malignancy other than carcinoma *in situ*; and (5) contraindications to S-1 or cisplatin. All patients provided informed consent before registration and were registered centrally at the JACCRO Data Center by means of the online Flexible licence assisted data server (FLADS) system. The JACCRO Data Center conducted the data management, central monitoring, and statistical analysis.

Preoperative chemotherapy

On the basis of previous reports S-1 (80 mg/m^2) was given orally every day for 3 weeks and cisplatin (60 mg/m^2) was administered intravenously on day 8 as one course.[9,10] If the patient had a WBC of 2000/mm^3 or lower, neutrophil count of 1000/mm^3 or lower, PLT of 75,000/mm^3 or lower, diarrhea or mucositis of grade 3 or higher, GOT or GPT of grade 2, or serum creatinine of grade 1, chemotherapy was postponed until recovery from these adverse events and the next dose of S-1 was reduced to 70 mg/mm^2. For diarrhea or mucositis of grade 1, chemotherapy was postponed until recovery. In the case of GOT and/or GPT of grade 3 or higher or serum creatinine of grade 2 or higher, chemotherapy was terminated. If the patient had cardiac or neurologic toxicities, chemotherapy was postponed until recovery from these toxic effects and confirmation of their cause. For any other adverse events of grade 2 or higher, chemotherapy was postponed until recovery. If the chemotherapy was postponed but the toxicities had not resolved within 21 days, the chemotherapy was terminated after this period.

Surgery

Tumor resectability was assessed after completion of chemotherapy. Resection criteria were (1) R0 resection was anticipated by D2 or extended D2 gastrectomy; (2) sufficient organ function (WBC $>3000/mm^3$, neutrophils $>1000/mm^3$, PLT $>100{,}000/mm^3$, GOT <100 IU/l, GPT <100 IU/l, creatinine <1.5 mg/dl); and (3) no active infection. Patients who fulfilled these criteria were treated by D2 or D3 gastrectomy with curative intent between two and four weeks after finishing chemotherapy. The precise procedure of D2 and D3 dissection has been reported previously.[12,15] Combined resections of adjacent organs were permitted when these procedures were indispensable for curative resection.

Treatment defined by the protocol

The treatment protocol was defined as completed when a patient received preoperative chemotherapy and underwent R0 resection by gastrectomy with D2 or D3 dissection. The treatment protocol was stopped when: (1) response was evaluated as progressive disease during chemotherapy; (2) the patient did not meet the criteria for surgery after chemotherapy; (3) the patient underwent surgery after chemotherapy but this took the form of exploratory laparotomy, bypass, or non-R0 resection; (4) the patient refused further participation; or (5) the doctor recommended stopping the protocol. After the treatment protocol was stopped, any treatment was allowed and postoperative adjuvant therapy was not defined.

Endpoints

Primary endpoint was toxicities. Secondary endpoints included response rate and overall survival.

Evaluation

The response rate was evaluated only in patients with measurable lesions; Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used[16] and response to chemotherapy was evaluated by external review committee. Adverse reactions during chemotherapy were evaluated by National Cancer Institute – Common Toxicity Criteria Version 2.0.[17]

Statistical hypothesis

As it is difficult to predict the occurrence of severe adverse events or treatment-related deaths and to calculate sample size, feasibility and safety was evaluated in calculated sample size based on the response rate to be required in this setting. A Simon optimal two-stage design[18] was used to calculate the sample size, assuming an anticipated response rate of 50% and a threshold response rate of 30% with 10% alpha error and 10% beta error. Using this design, if at least 8 objective responses were observed among 22 patients in the first stage, an additional 24 patients would be recruited to the second stage. Taking into account tumors without measurable lesions and patients not fulfilling the eligibility criteria, sample size was determined to be 50. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC). This phase II trial was approved by the JACCRO Protocol Review Committee and the institutional review board of each of the 8 JACCRO institutions involved.

Results

Patients

Between February 2004 and January 2005, 50 patients were enrolled and the study was terminated. During the accrual, unpredicted severe adverse events or treatment-related death was not observed. One of these patients declined to participate, while the other 49 were eligible and received the treatment protocol. Table 1 shows patient demographics and tumor characteristics. Clinically apparent nodal disease was observed in 40 patients.

Preoperative chemotherapy and toxicities

Of all 49 eligible patients, 3 did not receive cisplatin because of S-1-related toxicity. The average proportion of actual dose to proposed dose was 94% (2219.2 mg/2348.6 mg) for S-1 and 94% for cisplatin (87.8 mg/

Table 1
Patient demographics and pre-treatment tumor characteristics (all eligible patients, $n = 49$).

Age (median, range)	62, 20–73
Sex (male/female)	36/13
PS (0/1)	46/3
Macroscopic type	
1	4
2	6
3	24
4	14
5	1
Histologic type	
Differentiated	17
Undifferentiated	31
Miscellaneous	1
Depth of tumor invasion	
T3	44
T4	5
Nodal status[a]	
N0	9
N1+, perigastric	17
N2+, along major branch arteries	12
N3+, para-aortic	11

[a] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

92.0 mg). Adverse events during chemotherapy are shown in Table 2. There were no grade 4 and a few grade 3 toxicities.

Clinical response

Clinical response could be evaluated in 34 patients who had enlarged lymph nodes as target lesions as defined by RECIST criteria. There were 13 responders (all showed partial response); 18 patients had stable disease and 3 had progressive disease. Thus, 13 of 34 evaluable patients demonstrated a clinical response (38%) with a 95% confidence interval from 22% to 56%.

Surgery

All of the 49 patients who completed chemotherapy underwent surgery. Surgical findings are shown in Table 3. Three patients underwent exploratory laparotomy due to massive peritoneal dissemination, and 7 underwent palliative D0 or D1 resection due to peritoneal dissemination or extended lymph node metastasis. Curative resection was intended for the remaining 39 patients; D2 was performed in 27 and D3 in 12. Thus, D2 or D3 was performed in 39 of all eligible 49 patients. Consequently, R0 resection was performed in 38 patients, R1 in 1 due to positive peritoneal cytology, and R2 in 7 due to peritoneal dissemination or extended lymph node metastases (Table 3). Thus, the proportion of R0 resections was 78% (38 of all eligible 49 patients), with a 95 per cent confidence interval from 66% to 89%.

Surgical morbidity and mortality

Surgical complications are shown in Table 4. There was no operative mortality. On the other hand, operative morbidity was observed in 5 of the 49 patients including pancreatic fistula in 1 and abdominal abscess in 2. No anastomotic leakage was observed and no patients required re-operation for morbidity.

Table 2
Adverse events during chemotherapy in all eligible patients ($n = 49$).

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	48	0	1	0	0
Neutrophils	38	4	5	2	0
Hemoglobin	40	7	2	0	0
Platelets	48	0	1	0	0
Total bilirubin	48	1	0	0	0
GOT	46	2	1	0	0
GPT	47	1	1	0	0
ALP	46	3	0	0	0
BUN	45	0	4	0	0
Urine creatinine	47	1	1	0	0
Urine protein	47	1	1	0	0
Anorexia	33	8	5	3	0
Nausea	37	6	4	2	0
Vomiting	42	3	4	0	0
Diarrhea	45	3	1	0	0
Pigmentation	45	3	1	0	0

Table 3
Surgical findings in all operated patients ($n = 49$).

Type of surgery	
Proximal gastrectomy	1
Distal gastrectomy	18
Total gastrectomy	27
Exploratory laparotomy	3
Dissection ($n = 46$)[a]	
D0	4
D1	3
D2	27
D3	12
Combined resection	
Spleen	13
Pancreas	4
Gall bladder	8
Spleen + pancreas	2
None	22
Operation time (minutes)	
Median, range	232, 25–590
Blood loss (ml)	
Median, range	342, 0–2760

[a] Three missing cases were exploratory laparotomy.

Pathological response

Details of pathological data are shown in Table 5. A total of 18 patients were diagnosed as pathological T1 or T2 disease. The pathological response rate in resected patients, defined by the degeneration/necrosis area $\geq 1/3$, was 39%. On the other hand, nodal status, which was classified by 2nd English Edition of Japanese Classification of Gastric Carcinoma, was evaluated in 39 patients who underwent D2 or D3 gastrectomy. Pathological N0 was observed in 8 patients.

Overall survival

Survival time was estimated in all 49 patients who were eligible. Median follow-up period was 31 months from 27 to 38 months. The overall survival curve is shown in Fig. 1. The three-year survival rate was 43.0% with a 95% confidence interval from 35.6% to 50.3%.

Discussion

This multi-institutional phase II prospective trial demonstrated neither treatment-related death nor severe adverse

Table 4
Surgical complications in all operated patients ($n = 49$).

	Number of patients	%
Anastomotic leakage	0	0
Pancreatic fistula	1	2
Abdominal abscess	2	4
Pneumonia	0	0
Ileus	0	0
Wound infection	1	2
Renal dysfunction	1	2

Table 5
Pathological results.

Depth of tumor invasion ($n = 46$[a])			
T1		3	
T2		15	
T3		19	
T4		9	
Nodal status[b] ($n = 39$[c])			
	D2	D3	D2/D3
N0	7	1	8
N1	12	3	15
N2	6	4	10
N3	2[d]	4	6

[a] Three missing cases were exploratory laparotomy.
[b] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]
[c] Ten missing cases included exploratory laparotomy in 3, palliative D0 in 4 and palliative D1 gastrectomy in 3.
[d] Two cases were determined by a few lymph nodes of N3 dissected in addition to D2 dissection.

events by preoperative chemotherapy of S-1 plus cisplatin followed by extended surgery, suggesting that this multimodality treatment was safe and feasible.

Surgical mortality

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

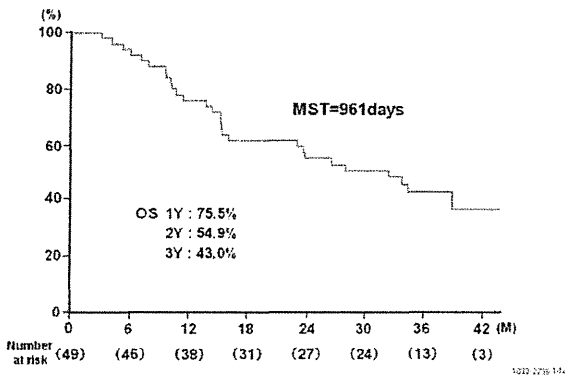

Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

Pancreas-related surgical morbidity

Pancreatic fistula is the major specific complication after D2 or greater extended surgery. In this study, pancreatic fistula was observed in 1 patient and abdominal abscess in 2 patients. As no apparent anastomotic leak was found in the latter 2 patients, the abdominal abscess might have been caused by pancreatic fistula. Thus, pancreatic fistula might have been a complication in a maximum of 3 of 49 patients in the present study, a proportion almost equivalent to that found in the JCOG 9501 phase III trial.[12] In that trial, tumors were diagnosed as T2–T4, N0–N2, and P0 by surgical findings.[12] In the present study, on the other hand, all tumors were clinically diagnosed as T3–T4. Moreover, 11 of the present patients had clinically apparent N3 disease. Hence, although the tumors were more advanced in this study, the rate of pancreatic fistula was not increased by preoperative chemotherapy with S-1 plus cisplatin. On the other hand, pancreatic fistula was observed in 12.2% in JCOG 0001 trial consisting of CPT-11 plus cisplatin followed by D3 dissection.[13] Toxic regimen could increase the rate of pancreatic fistula.

Overall surgical morbidity

In the present study, overall surgical morbidity was 5 of 49 which was slightly lower than the 20.9% to 28.1% observed in the JCOG 9501 trial.[12] In particular, anastomotic leakage and re-operation were not observed in this study, while rates of these events were 1.9% and 2.7%, respectively, in the JCOG 9501 study.[12] Thus, operative morbidity did not increase with the present preoperative chemotherapy regimen. In the MAGIC trial, morbidity was similar in both arms of the trial; 45.3% in the surgery alone group and 45.7% in chemotherapy group.[19] Because our preoperative chemotherapy was performed only short term, operative morbidity appears not to increase even after D2 or D3 surgery.

Chemotherapy-related toxicities

Chemotherapy-related toxicities were relatively mild in this study. There were no grade 4 toxicities and only a few grade 3 toxicities including neutropenia, anorexia, and nausea. In the SPIRITS trial,[10] grade 3/4 bone marrow suppression was more frequently observed when compared with the present trial. Chemotherapy was limited to one course in this study while it continued until disease

progression in the SPIRITS trial, which would explain the difference in the toxic profile between the two studies. Our results may also suggest that mild toxicities led to high compliance with this chemotherapy regimen and low morbidity and mortality of D2 or D3 resection.

Response to the chemotherapy

The present study achieved a relatively high response rate of 38%, which was almost the same as observed in the pathological response of the primary tumor. Previous trials in metastatic gastric cancer have demonstrated that response rate was 76% in a phase II trial[9] and 54% in the SPIRITS phase III trial.[10] The response rate in this study was slightly lower, which may be attributable to only one course of chemotherapy being administered in the present study. In the MAGIC phase III trial, three courses of ECF chemotherapy were performed preoperatively.[19] Considering the low toxicities of one course of S-1 plus cisplatin and the low mortality and morbidity of subsequent extended surgery, an additional two or three courses of this chemotherapy should be evaluated in another phase II study.

Survival

In the present study, all patients were clinically diagnosed with T3 or T4 disease before entry and overall 3-year survival rate was 43.0%. It has been reported that clinical diagnosis of T3–T4 was accurate in 74.4% in clinical T3 tumors and 87.0% in clinical T4 tumors.[5] M0 was evaluated by computed tomography and diagnostic laparoscopy was not mandatory in this study, therefore, peritoneal metastases may not be excluded in this series.[22] Retrospective analyses of Cancer Institute Hospital of Japan have reported 5-year survival rates of 25.3% and 1.8% in pathological T3 and T4 with any N, respectively.[5] In this series of patients, the 3-year survival rate was 43% despite that R0 resection was only performed in 77.6%. Although it may be difficult to compare these survival rates, our results appear to be worthy of further investigation using the same strategy.

Conclusion

In conclusion, preoperative chemotherapy with one course of S-1 plus cisplatin followed by gastrectomy with D2 or D3 dissection seems to be feasible and safe for clinically serosa-positive (T3–4) gastric cancer.

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Conflict of interest

No authors have any conflict of interest.

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Recent Advances in Chemotherapy for Advanced Gastric Cancer in Japan

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Abstract
In the early 1990s, a combination of 5-fluorouracil (5-FU) and cisplatin was widely adopted to treat advanced gastric cancer; however, no survival advantage over single-agent 5-FU was confirmed by the results of randomized trials conducted over a long period. Recently developed agents such as irinotecan, taxanes (docetaxel), and new oral fluorouracil (S-1) have yielded more promising results, with a response rate of over 50% and a median survival time of over 10 months in combination studies. These newer combination regimens were investigated in various randomized phase III studies to clarify if the newer-generation regimens provided a survival advantage over the older-generation regimens. Based on the findings of a large randomized study, S-1 has become standard in the adjuvant setting after D2 dissection curatively resected stage II and III gastric cancer. This article reviews the recent advances in gastric cancer chemotherapy, especially in Japan.

Key words Gastric cancer · Chemotherapy · Standard chemotherapy

Introduction

Gastric cancer (GC) is the most common malignancy in Japan. In 1998, more than 100000 new cases were reported[1] and by 2015, it is anticipated that this number will have climbed to nearly 150000.[2] The only potentially curative treatment for GC is surgical resection of all of the gross and microscopic disease; however, recurrence is common, both in regional and distant sites. The standard treatment for advanced or relapsed gastric cancer (AGC) is chemotherapy, aimed at prolonging survival.

Until about 10 years ago, there were few medical oncologists in Japan, and gastrointestinal surgeons played the part of oncologists in designing cancer chemotherapy for patients with gastric or colorectal carcinomas. The educational systems for medical oncologists were initiated by the Japan Society of Medical Oncology (JSMO). However, from 2005 to 2007 only 205 specialists in medical oncology passed the JSMO examination. The JSMO predicts that 80 medical oncologists will be initiated into the system each year, but this will be insufficient to cover all patients who have AGC. Thus, surgeons must continue to treat their patients with AGC oncologically in Japan. Our aim in writing this review is to make surgeons aware of the widely used regimen or standard chemotherapy for GCs, because we expect them to be able to treat their AGC patients effectively and safely.

Anticancer Drugs for AGC

One of the most widely studied single-agent chemotherapies is the antimetabolite, 5-fluorouracil (5-FU), which confers response rates of approximately 20%.[3,4] Tumor antibiotics (mitomycin C, doxorubicin, and epirubicin), heavy metals (cisplatin and carboplatin), taxanes (paclitaxel and docetaxel), and camptothecins (irinotecan and topotecan) have also been evaluated in the treatment of AGC and afford response rates ranging from 5% to 30%.[5–7] Newer fluorinated pyrimidines such as the 5-FU prodrug, UFT (uracil and tegafur), and 5-FU derivatives such as S-1, are of particular interest since they can be administered orally and allow for mimicking of conventional infusional therapy.

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Is Chemotherapy Effective Against AGC?

Several combination chemotherapeutic regimens have been evaluated for their efficacy and tolerability in the treatment of AGC. They often achieve adequate response rates with variable toxicity in previously untreated AGC patients. Compared with the best supportive care, the median survival with combination chemotherapy appears to be increased by 2 months or longer.[8,9]

Standard Chemotherapy for AGC in Western Countries

In Western countries, FAM (5-FU/adriamycin/mitomycin C), FAMTX (5-FU/adriamycin/methotrexate), ELF (etoposide/leucovorin/5-FU), and CF (cisplatin/5-FU) regimens have been compared in several studies. In consideration of their moderate activity, we do not recommend that any of the evaluated regimens be regarded as the standard treatment. In a prospective, randomized phase III study, Waters et al.[10] compared a combination of epirubicin, cisplatin, and 5-FU (ECF) with FAMTX in previously untreated patients with AGC. This ECF regimen resulted in significantly higher response rates (46% vs 21%), median survival (8.7 vs 6.1 months), and 2-year survival rates (14% vs 5%), and is the de facto standard treatment for AGC in Europe.

In a randomized phase III study (TAX325), Moiseyenko et al.[11] compared the efficacy and safety of cisplatin and 5-FU (CF) vs docetaxel, cisplatin, and 5-FU (TCF) as front-line therapy in patients with metastatic or nonresectable AGC. The final analysis revealed that the addition of docetaxel to CF resulted in significantly higher response rates (37% vs 25%, for TCF and CF, respectively). Time-to-progression, the primary study endpoint, was significantly higher in the TCF-treated patients than in the CF-treated patients (5.6 months vs 3.7 months, respectively; $P < 0.0004$). At the time of this interim analysis, the observed difference in median overall survival favored TCF over CF (9.2 vs 8.6 months, respectively; $P = 0.0201$). The common severe toxicities associated with TCF and CF included stomatitis (20.8% and 27.2% of subjects, respectively), lethargy (21.3% and 17.9%), diarrhea (20.4% and 8.0%), nausea (15.8% and 18.8%), vomiting (14.9% and 18.8%), and febrile neutropenia or neutropenic infection (30% and 13.5%). Based on the results of the TAX325 trial, TCF is regarded as standard chemotherapy in the United States.

Japan Clinical Oncology Group (JCOG) 9205

Until the early 1990s there was no standard chemotherapy in Japan, although 5-FU infusion, CF, and uracil-tegafur, and mitomycin C (UFTM) regimens were widely employed in the clinical setting. In a three-arm, large randomized phase III trial, Ohtsu et al.[12] compared 5-FU with CF and with UFTM. They found 5-FU to be equal to or better than UFTM in terms of response and survival. Although CF achieved a better response rate and progression-free survival (PFS) than 5-FU monotherapy, there was no difference in overall survival between these two arms (7.3 and 7.1 months for CF and 5-FU, respectively). 5-FU monotherapy remained as a reference arm in the next phase III trial of the JCOG group.

New Anticancer Agents

S-1 consists of a 1:0.4:1 molar ratio mixture of tegafur and two 5-FU-modulating substances: gimeracil (5-chloro-2,4-dihydroxypyrimidine, CDHP) and oteracil (potassium oxonate). Sakata et al.[13] investigated the efficacy of S-1 as a single chemotherapeutic agent in AGC patients in a late phase II study. Four cycles of S-1 were administered twice a day to 51 patients at a dose of 80 mg/m^2 per day. One complete response (CR) and 24 partial responses (PRs) were observed, with an overall response rate of 49%. The median survival time (MST) achieved by S-1 in a phase II study was 8 months and it was generally well tolerated, the major toxicities including anemia, leukopenia, granulocytopenia, diarrhea, malaise, and proteinuria.

Boku et al.[14] reported a phase II trial of cisplatin/CPT-11 combination chemotherapy involving 44 patients with AGC by the JCOG. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and CPT-11 was administered at a dose of 70 mg/m^2 on days 1 and 15 every 4 weeks. They reported 1 CR and 20 PR, with an overall response rate of 48.0%, and an MST of 9 months. The grade 4 major toxicities with this combination were leukopenia (9.0%), neutropenia (57.0%), thrombocytopenia (2.0%), and anemia (5.0%).

JCOG 9912 Trial

The JCOG conducted another three-arm, randomized phase III trial in 1999 (the JCOG 9912 trial), evaluating the superiority of cisplatin/CPT-11 over the reference arm 5-FU, and the noninferiority of S-1 to 5-FU. The MSTs achieved by 5-FU, cisplatin/CPT-11, and S-1 were 10.8 months, 12.3 months, and 11.4 months,

respectively. Survival was not significantly better with cisplatin/CPT-11 vs 5-FU ($P = 0.055$); however, the non-inferiority of S-1 vs 5-FU was confirmed ($P < 0.001$). Subsequently, S-1 has been widely used in Japan as the standard and first-line chemotherapy for AGC.

Combination Chemotherapy with S-1

The efficacy of combination chemotherapy with S-1 in AGC has been assessed in a number of phase I/II studies. Cisplatin at a dose of 60 mg/m^2 on day 8 was combined with S-1 for 3-weeks-on and 2-weeks-off.[15] Treatment was repeated every 5 weeks, unless disease progression was observed. The subjects of this trial were 19 AGC patients, and the incidences of severe (grade 3/4) hematological and nonhematological toxicities were 15.8% and 26.3%, respectively, but all cases were manageable. The response rate was 74% (14/19; 95% confidence interval, 54.9–90.6), and the MST was 383 days.

Komatsu et al.[16] reported the results of a phase I/II study with CPT-11 and S-1 (IRIS) in AGC patients. S-1 was given orally twice a day for 14 days, and CPT-11 was administered as a 90-min intravenous infusion on days 1 and 15. This regimen was repeated every 4 weeks. Fifteen patients were registered in the phase I study and 9 were added to the phase II study. Most of the nonhematological toxicities were classified as grade 2 or lower, except for grade 3 nausea and grade 3 level 2 dermatitis. The hematological toxicities consisted of grade 4 neutropenia in one patient at level 1 and level 2 in phase I, and grade 4 neutropenia in 4 patients at level 2 in phase II. All of these patients recovered after the drug was suspended. These side effects were tolerable, and the overall response rate was 54.2%. The MST achieved with this regimen was 581 days.

Yoshida et al.[17] performed a phase I study and a phase II study of docetaxel in combination with S-1 in patients with AGC. In the phase I study, neutropenia and leukocytopenia were the dose-limiting toxicities (DLTs). The recommended dose (RD) was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 3 weeks. In the phase II study, the response rate was 52.1% and the MST was 434 days. The most common severe toxicities were neutropenia (18.5%), leukopenia (12.3%), anemia (2.6%), stomatitis (10.4%), anorexia (6.3%), and nausea (6.3%). Yamaguchi et al.[18] reported a phase I/II study of docetaxel in combination with S-1. During dose escalation, G3 infection without neutropenia was the DLT. The RD was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 4 weeks. The response rate was 45.7%, the MST was 14.2 months, and the PFS was 4.3 months. The most common severe toxicities were neutropenia (67.4%), leukopenia (41.3%), anemia (21.7%), anorexia (21.7%), nausea (6.5%), and stomatitis (6.5%).

Phase III Trials of S-1 Monotherapy vs S-1 in Combination

Based on the results obtained in the above phase II studies, three large randomized phase III studies, the SPIRITS trial, the TOP-002 trial, and the JACCRO GC03 trial, were conducted independently to compare data with that of S-1 monotherapy. In the SPIRITS trial,[19] chemotherapy-naïve patients with AGC were randomly assigned to receive either S-1 plus cisplatin or S-1 alone. In the patients assigned to receive S-1 plus cisplatin, the S-1 (40–60 mg depending on the patient's body surface area) was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 cisplatin was given intravenously on day 8, followed by a 2-week rest period within a 5-week cycle. Patients assigned to receive S-1 alone were given the same dose of S-1 twice daily for 4 consecutive weeks, followed by a 2-week rest period, within a 6-week cycle. The primary endpoint was overall survival and the secondary endpoints were PFS, proportion of responders, and safety. Of the 305 patients enrolled, 7 were ineligible or withdrew consent, 148 patients were assigned to the S-1 plus cisplatin group, and 150 were assigned to the S-1 alone group. Median overall survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (13.0 vs 11.0 months, respectively; hazard ratio, 0.77; 95% confidence interval, 0.61–0.98; $P = 0.04$). The PFS was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (median PFS, 6.0 months vs 4.0 months, respectively; $P < 0.0001$). Moreover, of the 87 patients with target tumors, assigned to receive S-1 plus cisplatin, 1 showed a CR and 46 showed a PR (total response rate, 54%), and of the 106 patients with target tumors, assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total response rate, 31%). Grade 3 or 4 adverse events including leukopenia, neutropenia, anemia, nausea, and anorexia were reported in the group assigned to S-1 plus cisplatin rather than in the group assigned to S-1 alone. There were no treatment-related deaths in either group. Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1/CPT-11) vs S-1 for AGC.[20] Patients with previously untreated AGC were randomized to Arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or Arm B (IRIS: oral S-1,

80mg/m^2 on days 1–21; and intravenous irinotecan, 80mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. Treatment was continued unless disease progression or unacceptable toxicity was observed. The primary endpoint was overall survival and the secondary endpoints were 1-year survival, response rate, and toxicity. As a result, 326 patients were randomized to Arm A (162 patients) or Arm B (164 patients), with a final 315 evaluable patients (160 in Arm A and 155 in Arm B). The patients' characteristics were well balanced in the two groups. By the end of the trial, 247 events (78%) had been observed. Although the MST of the Arm A patients was 318 days (95% confidence interval, 286–395) and that of the Arm B patients was 389 days (95% confidence interval, 324–458), Arm B did not show significant superiority to Arm A (log-rank test P = 0.23; hazard ratio = 0.86). The 1-year survival rates were 44.9% in Arm A and 52.0% in Arm B. The response rates were significantly different, being 26.9% in Arm A vs 41.5% in Arm B (chi-square test; P = 0.035) in 187 RECIST (Response Evaluation Criteria In Solid Tumors) evaluable patients. The most common grade 3/4 toxicities in Arm A vs Arm B were neutropenia (10.6% vs 27.1%), diarrhea (5.6% vs 16.1%), anorexia (18.8% vs 17.4%), nausea (5.6% vs 7.1%), and vomiting (1.9% vs 3.2%). Based on this trial, IRIS achieved MST and was better tolerated; however, IRIS did not show significant superiority to S-1 alone in terms of the overall survival. Thus, IRIS could not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1/docetaxel combination is ongoing through the JACCRO GC03 trial.[21] This study is a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients are randomly assigned to receive 3-week cycles of Treatment Arm A (docetaxel and S-1) or 6-week cycles of Treatment Arm B (S-1 only). The primary objective of the study is to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only) in patients with AGC. The secondary objectives are to assess the time to tumor progression (TTP), defined as the time from randomization to the date of first documentation of progressive disease (PD); to determine the clinical response (RR = response rate), defined as the sum of the CR and PR according to the RECIST; and to evaluate the safety of the two regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this has been exceeded, with 628 patients from 103 centers confirmed in September 2008. The first author of this review is a principal participating investigator in this trial, the results of which will be available in 2010.

Future Perspectives of Standard Chemotherapy

If the results of the S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC. A triplet of the S-1/cisplatin/docetaxel combination is expected as the next candidate of the standard regimen.[22] The replacement of heavy metals from cisplatin to oxaliplatin in the combination with S-1 is also expected. Some molecular target agents have already been investigated for AGC. These agents of the new generation are expected to make revolutionary progress in chemotherapy for unresectable or recurrent GCs.

Second-Line Chemotherapy

Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy, but there is no established regimen for patients with AGC failing to respond to, or with progression after, first-line chemotherapy. Although there are some phase III studies ongoing, the treatment of S-1 refractory GC remains controversial with regard to whether S-1 should be continued as a second-line. After the successful adjuvant S-1 results (ACTS-GC trial),[23] the same problem will arise in patients receiving adjuvant S-1 for recurrence. The JACCRO GC05 trial is a randomized phase II/III trial of second-line chemotherapy comparing CPT-11 monotherapy with the S-1/CPT-11 combination for S-1 refractory GC. We expect that the results of this study will resolve the controversy.

Neoadjuvant Chemotherapy (NAC)

Japanese surgeons can control N2 lymph node metastasis by standard gastrectomy with D2 dissection. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Tumors with H0, P0, T3, T4, or N3 are most suitable for this therapy. The downstaging of lymph node metastasis of N3 or over to controllable N2 is the main target of NAC. Other distant metastasis, such as hepatic, lung, or peritoneal dissemination, is usually treated by chemotherapy first, and is not a target of NAC. S-1/cisplatin is widely used for the NAC regimen based on the high response rate reported in a phase II trial.[15] Randomized controlled phase III studies are needed in conjunction with accurate staging of the disease by laparoscopy. The results of histopathologic examination of resected materials following preoperative chemotherapy are thought to be an indicator of chemosensitivity in the postoperative adjuvant setting.

As yet, there is no clear evidence of the utility of NAC for GC, but its benefits will be proved soon by randomized controlled trials.

Adjuvant Chemotherapy

Before 2004, no positive results of adjuvant chemotherapy for curatively resected GC were reported. In the United States, the INT-0116 showed that adjuvant chemoradiation prolonged survival and relapse-free survival.[24] However, most of the patients in this study underwent D0 or D1 surgery, whereas only 10% underwent D2 lymphadenectomy. The European MAGIC trial, performed mainly in the United Kingdom, showed that perioperative and postoperative chemotherapy with ECF significantly prolonged overall survival and progression-free survival. In that study, D2 surgery was not the standard procedure, as it is in Japan. Comparisons of adjuvant chemotherapy vs surgery alone after D2 surgery in Japan were not positive.

In 2007, Nakajima et al.[25] reported positive results of adjuvant UFT based on the NSAS GC trial. In this trial, patients with TNM (tumor node metastasis) stage T2 N1-2 GC were randomly assigned to undergo surgery alone or to undergo surgery followed by postoperative UFT 360 mg/m^2 per day orally for 16 months. However, this trial was terminated before the target number of patients had been reached as accrual was slower than expected, with 190 patients registered and 95 randomized to each group. Nevertheless, after a median follow-up of 6.2 years, the overall and relapse-free survival rates were significantly higher in the surgery+chemotherapy group (hazard ratio for overall survival 0.48, $P = 0.017$; hazard ratio for relapse-free survival 0.44, $P = 0.005$). Furthermore, in 2007 Sakuramoto et al.[23] reported the success of adjuvant S-1 chemotherapy in patients with curatively resected GC. Patients with stage II or III GC who underwent gastrectomy with D2 dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the surgery+S-1 group, S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg/m^2 of oral S-1 per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. There were 529 patients assigned to the surgery+S-1 group and 530 patients assigned to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of independent data and the safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the surgery+S-1 group had a higher overall survival rate than the surgery-only group ($P = 0.002$). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the surgery+S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the surgery+S-1 group vs the surgery-only group was 0.68 (95% confidence interval, 0.52–0.87; $P = 0.003$). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute), which were relatively common in the surgery+S-1 group, were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%). It was concluded that S-1 is an effective adjuvant treatment for patients who have undergone a D2 dissection for locally advanced GC.

Conclusions

1. The standard regimen now used for AGC in Japan is the S-1/cisplatin combination, and we are awaiting the trial results about S-1/docetaxel combination chemotherapy. If the results of this S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC.
2. Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy after refractory S-1, but there is still no standard second-line regimen until ongoing phase III results are reported.
3. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Downstaging of N3 (or more) lymph node metastasis to controllable N2 is the main target of NAC.
4. The standard chemotherapy for T2 N1-2 GC after D2 dissection is adjuvant UFT, and that for stage II, III GC after D2 dissection is adjuvant S-1.

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