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ORIGINAL PAPER

Sequential chemotherapy with methotrexate and 5-fluorouracil for chemotherapy-naive advanced gastric cancer with disseminated intravascular coagulation at initial diagnosis

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Abstract
Purpose Advanced gastric cancer (AGC) rarely presents with disseminated intravascular coagulation (DIC) at the time of diagnosis before treatment with no current standard chemotherapy (CTx) regimen. However the prognosis is extremely poor without CTx. We investigated the effectiveness of sequential CTx with methotrexate and 5-fluorouracil (MF) in chemotherapy-naive AGC patients with DIC.
Methods We retrospectively examined AGC patients who received first-line CTx and selected those who were diagnosed with DIC before starting CTx to investigate clinical characteristics and responses.
Results From July 1999 to January 2007, 1,365 patients with unresectable or recurrent AGC received first-line CTx at the National Cancer Center Hospital in Tokyo, Japan. DIC was diagnosed in 22 (1.6%) patients (16 men and 6 women; median age, 56 years) and the performance status of all the patients was 1/2/3 = 9/10/3. Nineteen patients (86%) had histologically diffuse-type adenocarcinoma and 18 (82%) had bone metastasis. Patients received sequential MF every week until progressive disease was confirmed, with DIC improving in 17 (77%) patients. The median time-to-treatment failure for AGC and overall survival were 98 days [95% confidence interval (CI), range 50–146 days] and 154 days (95% CI, range 126–180 days), respectively. Grade 3 or greater toxicities consisted of neutropenia (4 patients, 18%), anemia (9 patients, 40%), thrombocytopenia (4 patients, 18%), and bilirubinemia (1 patient, 5%).
Conclusions MF was an effective and well-tolerated regimen for improving DIC in chemotherapy-naive AGC patients with DIC; however, the prognosis of the patients remained poor even with improved DIC parameters.

Keywords Gastric cancer · Disseminated intravascular coagulation · Chemotherapy · Methotrexate · 5-fluorouracil

Introduction

Disseminated intravascular coagulation (DIC) is a clinical condition in which various underlying diseases pathologically activate the coagulation system. DIC is characterized by multiple thrombi in microvessels (Levi and Ten Cate 1999; Sase et al. 2003). Subsequent microcirculation failure can induce organ injury, while exhaustion of coagulation factors and platelets induces a bleeding tendency. Underlying diseases causing DIC include hematological malignancies, infection, sepsis, and trauma. Solid tumors can be complicated by DIC (Al-Mondhiry 1975; Sallah et al. 2001), which occurs in approximately 10% of patients with solid tumors between the time of diagnosis and death (Okajima et al. 2000).

The prognosis of advanced gastric cancer (AGC) patients with DIC is extremely poor, and life expectancy without any intervention is only 1–3 weeks (Al-Mondhiry 1975; Sallah et al. 2001). DIC treatment includes chemotherapy (CTx) to control the underlying disease. However,

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only a few studies have examined the effectiveness of CTx for AGC with DIC (Chao et al. 2000; Hironaka et al. 2000; Huang et al. 2008; Tokar et al. 2006).

One of the standard systemic chemotherapeutic regimens for unresectable or recurrent gastric cancer is 5-fluorouracil (5-FU) combined with cisplatin (CDDP) (Kim et al. 1993; Koizumi et al. 2008). However, when AGC is complicated by DIC, the patient's systemic condition is often poor with accompanying thrombocytopenia. Anemia is often detected and may be caused by microhemolysis (Jiang et al. 1997; Tsuchiya et al. 1989). An increased bleeding tendency due to thrombocytopenia is also often observed. These abnormal bleeding conditions make CDDP administration to AGC patients with DIC difficult.

The rationale for the use of methotrexate (MTX) in combination with 5-FU (MF) is based on biochemical modulation. Pre-administered MTX inhibits purine synthesis, which causes elevated levels of intracellular phosphoribosyl pyrophosphate that facilitate 5-FU metabolism, thereby enhancing its antitumor effects (Cadman et al. 1979; Fernandes and Bertino 1980). The effectiveness of MF against various cancers, particularly metastatic colon cancer, has been studied worldwide. A meta-analysis of 5-FU monotherapy and MF confirmed the efficacy of MF for colorectal cancer (Advanced Colorectal Cancer Meta-Analysis Project 1994) as well as for other unresectable and recurrent gastric cancers (Konishi et al. 1994; Perez et al. 1998).

MF is associated with only mild hematologic and nonhematologic toxicities and thus this regimen has been administered to patients in poor general condition, including those with AGC-induced ascites or peritoneal dissemination (Hamaguchi et al. 2008; Konishi et al. 1999; Tahara et al. 2001; Yamao et al. 2004). Based on some reports, in Japan, MF is considered one of effective and safety regimens for AGC patients in poor general condition. A randomized phase III study of 5-FU continuous infusion versus MF in chemotherapy-naive gastric cancer patients with peritoneal metastasis is currently being conducted by the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group. In our hospital, we have been using MF as a first-line CTx for AGC patients with DIC.

In this study, we retrospectively investigated the therapeutic effects and toxicity of MF therapy in chemotherapy-naive AGC patients with DIC.

Patients and methods

Chemotherapy-naive AGC patients with DIC were identified among those receiving CTx for AGC at the National Cancer Center Hospital between July 1999 and January 2007. Chemotherapy-naive AGC patients included those with recurrent tumors for more than 6 months following completion of oral adjuvant fluoropyrimidine CTx. We analyzed patient background, treatment courses, response to MF therapy for DIC and AGC, time-to-tumor progression, and overall survival (OS). All study participants provided written consents before participating in the study.

Definition of DIC

We defined DIC according to the Japanese criteria issued in 1988 (Table 1) with individual patient scores based on underlying disease, bleeding symptoms, organ symptoms, and essential laboratory data, including elevated fibrin degradation product (FDP), decreased platelet count, decreased serum fibrinogen levels, and prolonged prothrombin times. DIC was diagnosed in patients with a total score of ≥ 7 points, and DIC was considered to improve when a patient's DIC score dropped to <5.

Chemotherapy regimen

MTX (100 mg/m^2) was administered intravenously by bolus infusion followed by a bolus infusion of 5-FU (600 mg/m^2) 3 h later. Six courses of leucovorin rescue (10 mg/m^2) were administered orally or intravenously every 6 h commencing 24 h following MTX administration.

Table 1 Diagnostic criteria of disseminated intravascular coagulation

Items/points	0	1	2	3
Basic disease	−	+		
Bleeding symptoms	−	+		
Organ symptoms	−	+		
FDP (mg/ml)	<10	≤10 to <20	≤20 to <40	≤40
Platelets ($\times 10^4$/mm^3)	<12	<8 to ≤12	<5 to ≤8	≤5
FIBG (mg/dl)	<150	<100 to ≤150	≤100	
PT (ratio)	<1.25	≤1.25 to <1.67	≤1.67	
Diagnosis	Total ≥7	Certain DIC		
	Total 6	Suspicion of DIC		
	Total ≤5	No DIC		

Disseminated Intravascular Coagulation Score of the Japanese Ministry of Health and Welfare in 1988

FDP fibrin degradation product, *FIBG* fibrinogen, *PT* prothrombin time

In an effort to prevent MTX-associated renal toxicities, acetazolamide (250 mg) was given intravenously immediately following MTX infusion, and sodium bicarbonate (33.3 mEq) was added to 500 ml of electrolyte solution and administered by drip infusion for urine alkalinization during the 3 h interval between MTX and 5-FU administrations. Treatment was repeated every week until progressive disease was observed in the patients.

Toxicity assessment

We evaluated each patient's physical examination records and laboratory tests at least every week during treatment, and a toxicity assessment was performed using the Common Terminology Criteria for Adverse Events version 3.0.

Evaluation of efficacy outcomes

Tumor response to CTx was assessed based on tumor reduction according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for patients with measurable lesions. This objective response was evaluated every 4–8 weeks using a computerized axial tomography scan. The time-to-treatment failure (TTF) was measured from initiation to the final day of CTx, and OS was measured from CTx initiation to either the last date of follow-up or death and was censored as of the last date of contact. The TTF and OS were estimated using the Kaplan–Meier method, and statistical analyses were performed using Dr. SPSS II for Windows 11.0.1J software (SPSS Japan, Inc., Tokyo, Japan).

Results

Patients

A total of 1,365 chemotherapy-naive patients received CTx for recurrent or unresectable AGC from July 1999 to January 2007; 22 (1.6%) of these patients, including 16 men and 6 women, were diagnosed with DIC.

The background data of the 22 patients are summarized in Table 2. The median age was 56 years (range 26–75 years), the performance status (PS) was ≥2 in 13 of 22 cases (59%), and many patients had a poor clinical condition. In terms of histological type, diffuse-type adenocarcinomas were identified in 19 patients (86%) and macroscopic type 3 or type 4 tumors were seen in 16 patients (73%). Bone metastasis was found in 18 patients (82%).

MF was administered to all 22 patients. The median number of doses was eight (range 1–17) with 15 of the 22 patients (68%) receiving four or more doses of MF. Treatment was terminated because of disease progression in 21 patients, but one patient was still on MF at the time of this study.

Table 2 Patient characteristics

Characteristics	No. of patients	
	(n = 22)	(%)
Sex		
Male	16	73
Female	6	27
Age, years		
Median	56	–
Range	26–75	–
Histology		
Intestinal type	3	14
Diffuse type	19	86
Macroscopic type of primary tumor		
Early	3	14
Type 2	1	5
Type 3	8	36
Type 4	8	36
Unknown	2	9
ECOG performance status		
1	9	41
2	10	45
3	3	14
Gastrectomy		
No	10	45
Yes	12	55
Metastatic site		
Bone	18	82
Lymph node	11	50
Liver	3	13
Peritoneum	2	9

ECOG Eastern Cooperative Oncology Group

Safety and toxicity

Toxicities related to MF are summarized in Table 3. Hematological toxicities ≥grade 3 included neutropenia in four patients [(18%) although neutropenia-induced fever was not observed], anemia in nine patients (41%), and thrombocytopenia in four patients (18%). In terms of non-hematological toxicities ≥grade 3, one patient (5%) showed an elevated bilirubin level. However, none of the patients exhibited symptoms of gastrointestinal toxicities such as nausea, vomiting, or diarrhea.

Therapeutic outcomes

DIC improvement with a DIC score <5 was observed in 17 patients (77%). Following MF administration, most of the patients showed improvement of hematological data within

Table 3 Toxicities of MF regimen (no. of patients)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥ 3 (%)
Leukopenia	4	5	1	1	2 (9)
Neutropenia	4	4	3	1	4 (18)
Anemia	2	2	4	5	9 (41)
Thrombocytopenia	0	0	1	3	4 (18)
Bilirubinemia	1	1	1	0	1 (5)
Elevated AST/ALT	6	1	0	0	0
Elevated Creatinine	4	0	0	0	0
Nausea	10	1	0	0	0

2 weeks. Changes in platelet count, an important indicator in DIC assessment, are shown in Fig. 1. Tumor response based on the RECIST criteria could be assessed in only nine of these patients, and three of them (33%) showed evidence of a partial response. Median TTF was 98 days [95% confidence interval (CI), range 50–146 days] and median OS was 154 days (95% CI, range 126–180 days) (Fig. 2).

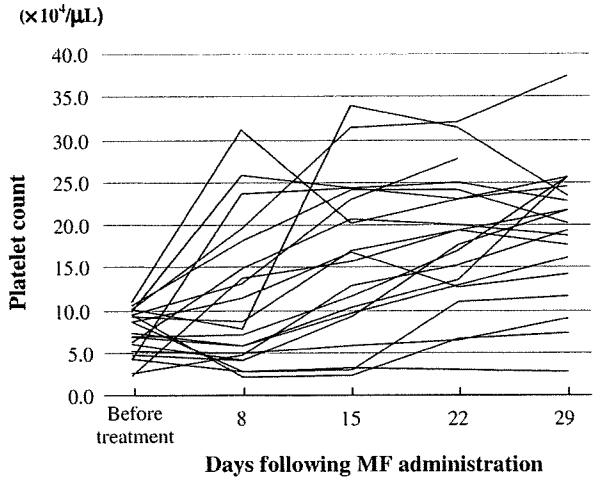

Fig. 1 Changes in platelet count during MTX + 5-FU

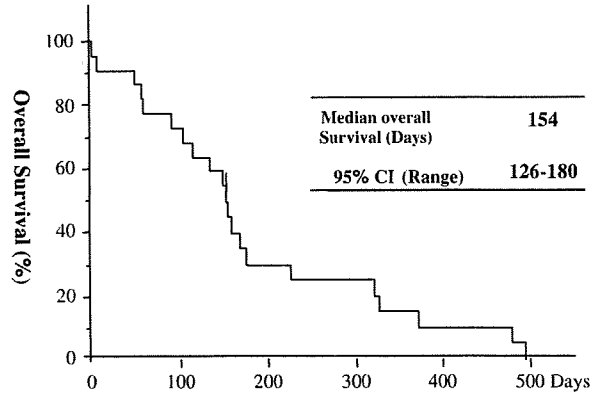

Fig. 2 Kaplan–Meier overall survival plot

Eleven of 17 patients (65%) whose DIC improved following MF administration later showed DIC recurrence at the time of disease progression. Despite MF administration, DIC showed no improvement in 5 of the 22 patients (23%). Weekly paclitaxel (PTX) was administered immediately as a second-line CTx to two of these five patients. Both responded to the PTX treatment, showing improvement in their DIC. Overall, CTx resulted in DIC improvement in 19 of 22 patients (86%). All patients who recovered from DIC were discharged and started outpatient chemotherapy. DIC showed no response to CTx in the remaining three patients (14%). One patient died of an acute subdural hematoma 2 days after starting MF, and another died of pulmonary carcinomatous lymphangiosis 8 days after starting MF. The third patient received MF four times. However, DIC showed no improvement, and the patient died from cancer progression 60 days after starting MF. We determined that these three patients were not treatment-related death but disease progression.

Discussion

To the best of our knowledge, this investigation is the largest single-institutional study of AGC complicated by DIC. Several other case series involving 6–19 patients (Chao et al. 2000; Hironaka et al. 2000; Huang et al. 2008; Tokar et al. 2006) are summarized in Table 4.

With respect to other solid tumors, DIC usually develops after diagnosis during the follow-up period; however, DIC can sometimes be detected during the initial diagnosis of metastatic gastric cancer (stage IV) or during recurrence after a curative surgical operation (Pasquini et al. 1995). In some patients, screening for DIC can lead to a diagnosis of AGC. There are several distinctive characteristics of AGC with DIC. In previous reports, relatively young patients were diagnosed with AGC with DIC. However, the patients in this study had a median age of 56 years. In terms of histological type, most of these patients had diffuse-type adenocarcinoma, ranging from 68 to 100%. Interestingly, there was a high frequency of bone metastasis or bone marrow involvement, ranging from 50 to 100%. In our study, bone

Table 4 Summary of case series previously reported

Author	Regimen	*n*	Median age (range)	Diffuse-type adenocarcinoma	Bone metastasis	DIC response	MST (weeks)
				No. of patients (%)	No. of patients (%)	No. of patients (%)	
Chao et al.	Weekly EEPFL	6	38 (36–71)	–	3 (50)	6 (100)	30
Hironaka et al.	MF	9	–	–	9 (100)	8 (89)	16
Tokar et al.	5-FU	6	48.5 (32–56)	6 (100)	–	5 (83)	14.5
Huang et al.	5-FU/Leucovorin	19	53 (31–72)	13 (68)	13 (68)	14 (74)	12
The present study	MF	22	56 (26–75)	19 (86)	18 (82)	17 (77)	22

DIC disseminated intravascular coagulation, *MST* median survival time, *EEPFL* etoposide and epirubicin and cisplatin and 5-FU, *MF* methotrexate and 5-fluorouracil

metastasis was diagnosed by bone scintigraphy and/or magnetic resonance imaging. Since such tests were performed only when symptoms were evident, the actual frequency of bone metastasis may have been higher. Although we did not conduct bone marrow tests, we suspect that most patients probably had bone marrow infiltration with the resultant bone marrow dysfunction leading to a predisposition to DIC development. In this case, AGC with DIC would be quite different from AGC without DIC.

When AGC is complicated by DIC, anti-cancer agents may not be used because of the poor general condition of the patient or the presence of thrombocytopenia and severe anemia. Unfortunately, the prognosis of untreated AGC with DIC is extremely poor, and patients generally live for only 1–3 weeks without CTx (Al-Mondhiry 1975; Okajima et al. 2000). Here, DIC improved in 19 of 22 patients following CTx with an OS of 167 days (95% CI, range 141–192 days), indicating that CTx was at least somewhat effective in treating AGC complicated by DIC. However, DIC showed no improvement in 3 of 22 patients, who died 2, 8, and 60 days following MF. Based on our analysis, we believe that MF provides a survival benefit for AGC patients with DIC. And 19 of 22 patients (86%) were discharged and continued outpatients chemotherapy, these data suggest that MF provide better QOL.

Several reports have been published examining the control of DIC by CTx in patients with AGC. Chao et al. administered etoposide, epirubicin, CDDP, and 5-FU to six AGC patients with DIC (Chao et al. 2000). Hironaka et al. (2000) administered MF to AGC patients with bone metastasis and reported DIC in nine of these patients. Tokar et al. reported that 5-FU administered alone and in combination with CDDP and epirubicin stopped the bleeding tendency in six AGC patients with DIC (Tokar et al. 2006). Finally, Huang et al. (2008) administered 5-FU and leucovorin to 19 AGC patients with DIC. Although each of these reports involved only a relatively small number of patients, the successful control of DIC by CTx was achieved in most patients. In our study, MF improved DIC in 17 of 22 patients (77%). Based on our results, AGC patients with DIC may respond favorably to CTx with accompanying improvement in DIC. However, even if DIC improves in these patients, their prognosis still appears to be worse than that of AGC patients without DIC.

One of the primary reasons for selecting MF is because of its mild toxicity (Hamaguchi et al. 2008; Konishi et al. 1999; Tahara et al. 2001; Yamao et al. 2004). However, the frequency of both anemia and thrombocytopenia as adverse events was higher in the present study patient group than in past clinical study patient groups. Anemia may have been caused by microhemolysis or the bleeding tendency associated with DIC. CTx improved thrombocytopenia (Fig. 1), and the other toxicities were mild and well-tolerated by the patients.

In conclusion, MF for the treatment of chemotherapy-naive AGC patients was an effective and well-tolerated regimen for improving DIC; however, the prognosis of the patients remained poor even with improvement in DIC parameters. Although this was a retrospective study where concrete conclusions based on our findings are not possible, the results are nonetheless significant in terms of their implications for clinical practice.

Conflict of interest statement We received no financial support for this study and report no conflicts of interest. Informed consent was obtained from all patients before initiating chemotherapy. This study was approved by the president of National Cancer Center Hospital.

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Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study

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Summary

Background The best chemotherapy regimen for metastatic gastric cancer is uncertain, but promising findings have been reported with irinotecan plus cisplatin and S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate). We aimed to investigate the superiority of irinotecan plus cisplatin and non-inferiority of S-1 compared with fluorouracil, with respect to overall survival, in patients with metastatic gastric cancer.

Methods We undertook a phase 3 open label randomised trial in 34 institutions in Japan. We enrolled patients aged 20–75 years or younger, who had histologically proven gastric adenocarcinoma, and randomly assigned them by minimisation to receive either: a continuous infusion of fluorouracil (800 mg/m² per day, on days 1–5) every 4 weeks (n=234); intravenous irinotecan (70 mg/m², on days 1 and 15) and cisplatin (80 mg/m², on day 1) every 4 weeks (n=236); or oral S-1 (40 mg/m², twice a day, on days 1–28) every 6 weeks (n=234). The primary endpoint was overall survival. Analyses were done by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00142350, and with UMIN-CTR, number C000000062.

Findings All randomised patients were included in the primary analysis. Median overall survival was 10·8 months (IQR 5·7–17·8) for individuals assigned fluorouracil, 12·3 months (8·1–19·5) for those allocated irinotecan plus cisplatin (hazard ratio 0·85 [95% CI 0·70–1·04]; p=0·0552), and 11·4 months (6·4–21·3) for those assigned S-1 (0·83 [0·68–1·01]; p=0·0005 for non-inferiority). Three treatment-related deaths occurred in the irinotecan plus cisplatin group and one was recorded in the S-1 group.

Interpretation S-1 is non-inferior to fluorouracil and, in view of the convenience of an oral administration, could replace intravenous fluorouracil for treatment of unresectable or recurrent gastric cancer, at least in Asia. Irinotecan plus cisplatin is not superior to fluorouracil in this setting.

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Introduction

Gastric cancer is the second leading cause of death from malignant disease worldwide.[1] The prognosis of unresectable or recurrent tumours is dismal: with best supportive care, median survival is about 4 months, and with chemotherapy it is around 8 months.[2–4]

During the early 1990s, several randomised trials for gastric cancer were undertaken of anthracyclines, mitomycin C, fluorouracil, methotrexate, and cisplatin.[5–13] At that time, the standard treatment for this malignant disease had not been established. When planning our current trial, no meta-analysis had been published of chemotherapy for advanced gastric cancer. Data from three phase 3 trials did not show a survival benefit of fluorouracil plus cisplatin over fluorouracil alone.[11–13] We reported previously that fluorouracil plus cisplatin caused more toxic effects and did not extend survival compared with continuous infusion of fluorouracil alone, despite a higher response rate and longer progression-free survival.[13] We concluded that continuous infusion of fluorouracil would be a standard arm in any subsequent phase 3 study.

In the late 1990s, new antitumour agents were developed for gastric cancer. In a phase 2 trial, combination chemotherapy with irinotecan plus cisplatin showed a response rate of 59% and median survival time of 322 days with grade 4 neutropenia (57%) and grade 3 or 4 diarrhoea (20%).[14] These efficacy measures were the best compared with those of other phase 2 trials. Although this regimen showed substantial toxic effects, they were deemed manageable, with dose reduction in some patients.

S-1 is a new oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate. Data of two phase 2 studies of S-1 alone[15,16] showed a response rate of 45% and 2-year survival of 17%, in association with 5% or lower frequencies of grade 3 or 4 toxic effects. Furthermore, treatment could be administered on an outpatient basis.

With these findings in mind, we planned a three-arm phase 3 study of two pair-comparisons. On behalf of the gastrointestinal oncology study group of Japan Clinical Oncology Group (GIOSG/JCOG), we aimed to investigate

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superiority of irinotecan plus cisplatin, and non-inferiority of S-1, compared with continuous infusion of fluorouracil for metastatic gastric cancer.

Methods

Patients

We undertook a three-arm, phase 3, randomised trial in 34 institutions in Japan. We used the following eligibility criteria to screen patients for inclusion: histologically proven gastric adenocarcinoma; unresectable or recurrent disease; adequate self-supported nutritional intake; age-range 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; no history of chemotherapy, radiation therapy, or both (however, adjuvant chemotherapy with an oral fluoropyrimidine other than S-1, not exceeding 1-year duration, completed more than 6 months before entry, was allowed); preserved organ functions; white-blood-cell count of $3 \cdot 0$–$12 \cdot 0 \times 10^9$/L; number of platelets 100×10^9/L or more; aspartate aminotransferase and alanine aminotransferase concentrations of 99 U/L or less; total bilirubin 25·65 μmol/L or lower; creatinine concentration 132·6 μmol/L or less; and creatinine clearance of 50 mL/min or faster. Having a target lesion or lesions according to response evaluation criteria in solid tumours was not mandatory. We excluded patients with severe peritoneal metastasis such as ileus or sub-ileus, ascites beyond the pelvic cavity, or narrowing of the colon detected by barium enema.

All eligible patients provided written informed consent to participate. The study was approved by the institutional review board of every participating institution. The JCOG data and safety monitoring committee (standing committee) monitored patients' safety, adverse events, and progress of the trial.

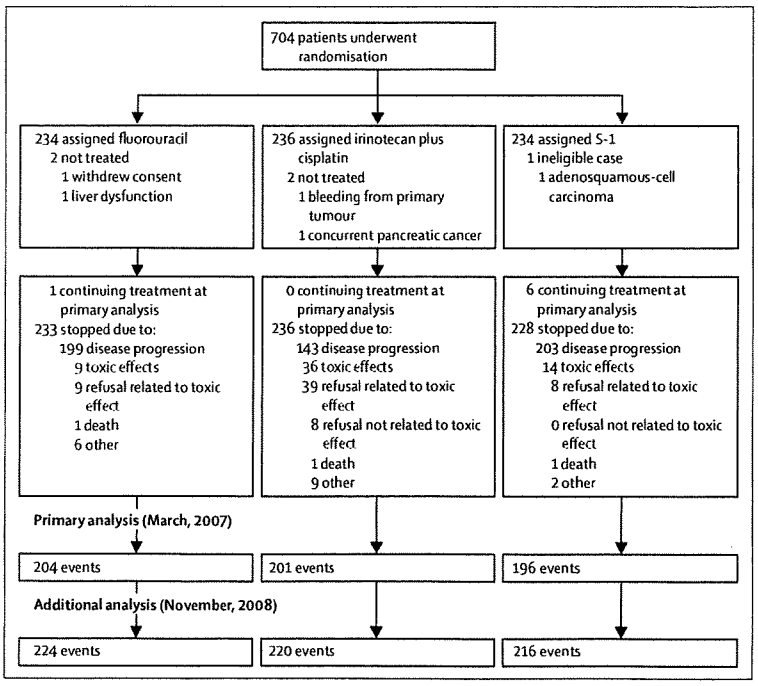

Figure 1: Trial profile

Randomisation and masking

We communicated patient's details to the data centre by fax or telephone. Staff in data centre entered these details into the computer to check eligibility, complete registration if appropriate, and randomly allocate the patient to a treatment group. Staff at the JCOG data centre randomly assigned every patient to either continuous infusion of fluorouracil, irinotecan plus cisplatin, or S-1, using the minimisation method,[17] with an algorithm (concealed to the investigators) that balanced institution, ECOG performance status (0, 1, or 2), and previous treatment (none, curative surgery alone, curative surgery and adjuvant chemotherapy). The treatment allocation was then communicated to the appropriate investigator by fax or telephone. The investigators participating in this trial treated their patients and took care of them all through the clinical course. Because the three treatment methods studied were quite different, the treatment allocation could not be masked from the investigators or patients. All data in case-report forms were sent to the JCOG data centre and checked by central data managers.

Procedures

Patients assigned fluorouracil received 800 mg/m² daily as a continuous infusion for 5 days, repeated every 4 weeks. Those assigned irinotecan plus cisplatin received an infusion of 70 mg/m² irinotecan on days 1 and 15 and 80 mg/m² cisplatin as a drip infusion on day 1 with adequate hydration, repeated every 4 weeks. After six cycles, the same dose of irinotecan alone was continued every 2 weeks. Individuals assigned S-1 received 40 mg/m² twice a day orally for 4 weeks, followed by a 2-week rest.

We delayed every treatment cycle until non-haematological toxic effects had recovered to grade 1 or lower, body temperature was 38°C or less, white-blood-cell count was $3 \cdot 0$–$12 \cdot 0 \times 10^9$/L, platelets were 100×10^9/L or more, aspartate aminotransferase and alanine aminotransferase concentrations were 99 U/L or less, total bilirubin was 25·65 μmol/L or lower, and creatinine concentration was 132·6 μmol/L or less. We reduced the treatment dose if, during the previous cycle, one of the following events had arisen: grade 4 leucopenia (less than $1 \cdot 0 \times 10^9$/L); thrombocytopenia (less than $10 \cdot 0 \times 10^9$/L); haemoglobin (less than 65g/L); grade 3 or higher non-haematological toxic effect; irinotecan not given on day 15; or S-1 or fluorouracil administration was suspended. The dose of cisplatin was reduced if the amount of creatinine was 106·1–132·6 μmol/L. We discontinued treatment if disease progression was diagnosed clinically or by imaging, if a serious adverse

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event arose, if a treatment cycle was delayed due to an adverse event continuing for longer than 2 weeks, if an adverse event meant a subsequent dose reduction was needed after the first reduction, if the patient refused treatment, or if judged necessary by the treating doctor for other reasons.

We did physical examinations and laboratory tests at least once every 2 weeks, and we assessed all adverse events according to the National Cancer Institute's common toxicity criteria (version 2.0). The JCOG data and safety monitoring committee reviewed serious adverse events and judged whether an adverse event was attributable to treatment. We assessed tumour response every 2 months according to RECIST (version 1.0). CT and endoscopic images of responders taken every 2 months independently of the treatment schedule were reviewed centrally at a trial group meeting; reviewers were unaware of treatment allocations at this time. We calculated response rates without interval confirmation.

The primary endpoint was overall survival. Secondary endpoints were time to treatment failure, non-hospitalised survival, adverse events, and response rate in patients with target lesions. We measured overall survival from the date of randomisation to the date of death and censored at the date of last contact for a surviving patient. We calculated progression-free survival to the date disease progression was detected, or death, and censored at the date on which progression-free status was verified. We deemed time to treatment failure to be the date when the doctor decided to discontinue treatment for any reason, and we censored at the date of last contact. We calculated non-hospitalised survival by subtracting the sum of all days in hospital from overall survival.

Statistical analysis

We estimated 6-month and 1-year survival with a continuous infusion of fluorouracil as 50% and 30%. The initial sample size was 450 in total, which allowed detection of a 10% increase in overall survival for irinotecan plus cisplatin and a 5% margin of non-inferiority for S-1, with a study-wide one-sided α level of 0·05 and a power of 70% for each pair comparison. Non-inferiority with a 5% margin corresponds to a hazard ratio of 1·16. We adjusted for multiplicity due to two pair-comparisons with the Bonferroni method, with a one-sided α level of 0·025 for each comparison keeping a study-wide α error of 0·05. We planned an interim analysis when 300 patients had been accrued, using the O'Brien and Fleming type α spending function.

We calculated 1-year survival for all randomised patients when initial accrual was almost complete and it was much higher than anticipated. Therefore, in March, 2005, we recalculated the sample size along with an increase of power from 70% to 80%, and the final sample size was 690. To raise statistical efficiency, we amended the method for adjustment of multiplicity in February, 2007, to that of Holm.[18] According to Holm's method, the pair with the largest difference is compared at first with an α of 0·025 and, if significant, then the other is compared with an α of 0·05. If non-inferiority of S-1 is confirmed, superiority is tested with the same significance level. We planned these amendments in a masked way and they were approved by the data and safety monitoring committee before the primary analysis.

We did the primary analysis in March, 2007, of all randomised patients, based on data up to 1 year after the last patient was enrolled. We analysed overall survival with the stratified log-rank test, and we estimated every hazard ratio (HR) with stratified Cox's proportional-hazards model. We did these stratified analyses with the balancing factors used for randomisation, except for institution. For analyses of progression-free survival, time to treatment failure, and non-hospitalised survival, and for subgroup analyses, we used the log-rank test and estimated the hazard ratio with the Cox model, assuming a common baseline hazard without balancing factors. All subgroup analyses were exploratory and details were not prespecified in the protocol. We revised the protocol to undertake additional analyses of overall survival, progression-free survival, and non-hospitalised survival after 2 years of follow-up, in November, 2008.

	Fluorouracil (n=234)	Irinotecan plus cisplatin (n=236)	S-1 (n=234)
Age (years)	63·5 (57–69)	63 (59–68)	64 (58–69)
Sex (male)	176	180	175
ECOG performance status			
0	152	151	151
1	79*	81	80
2	3	4	3
Surgery			
Unresectable	189	190	188
Recurrent	45	46	46
Previous adjuvant chemotherapy	1	1	1
Macroscopic type†			
0	5	5	5
1, 2	63	73	68
3, 4, 5	164	155	161
Histological type‡			
Intestinal	111	102	110
Diffuse	121	134	124
Target lesions§	175	181	175
Metastatic sites			
0, 1	103	100	102
≥2	131	136	132
Peritoneal metastasis	87	76	69

Data are median (range) or number of patients, with the exception of age (median; IQR). *Includes one patient who underwent random allocation as ECOG performance status 1, but was later found to be 0. This patient was treated as performance status 1 in all analyses. †Japanese classification of gastric carcinoma; no data available for two patients assigned fluorouracil and three assigned irinotecan plus cisplatin. ‡Assessed with Lauren classification; no data available for two patients assigned fluorouracil and for one in the S-1 arm with adenosquamous-type cancer. §Assessed with the RECIST; target lesions larger than double the size of a CT slice.

Table 1: **Baseline characteristics**

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We did all analyses by intention to treat using SAS version 9.1. Unless otherwise specified, we present one-sided p values for superiority. This study is registered with ClinicalTrials.gov, number NCT00142350, and UMIN-CTR, number C000000062.

For UMIN-CTR see http://www.umin.ac.jp/ctr

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 13, 2000, and Jan 20, 2006, 704 patients underwent randomisation: 234 were allocated continuous infusion of fluorouracil, 236 irinotecan plus cisplatin, and 234 S-1 (figure 1). Baseline characteristics were well balanced between the three treatment groups (table 1). Nearly all individuals had an ECOG performance status of 0 or 1. Only one patient in every group had received previous adjuvant chemotherapy. About 75% (531/704) of participants had a target lesion or lesions.

Table 2 shows adverse events recorded within 6 months. For patients assigned continuous infusion of fluorouracil, grade 3 or 4 adverse events with frequencies greater than 10% were haemoglobin (<80 g/L) and anorexia. For individuals assigned irinotecan plus cisplatin, grade 3 or 4 leucopenia and neutropenia had the highest frequencies and were associated with febrile neutropenia and infection with neutropenia. Frequencies of grade 3 or 4 adverse events in patients assigned S-1 were similar to those seen with continuous infusion of fluorouracil, except for a higher rate of diarrhoea. Three treatment-related deaths were reported in the group assigned irinotecan plus cisplatin and one in the S-1 group.

	Fluorouracil (n=232)*	Irinotecan plus cisplatin (n=234)*	S-1 (n=234)
Leucocytes (<2·0×10⁹/L)	0	97 (41)	2 (1)
Neutrophils (<1·0×10⁹/L)	3 (1)†	152 (65)	13 (6)
Haemoglobin (<80 g/L)	36 (16)	92 (39)	30 (13)
Febrile neutropenia	0	22 (9)	0
Infection with neutropenia	0	18 (8)	1 (<1)
Infection without neutropenia	9 (4)	9 (4)	13 (6)
Aspartate aminotransferase (≤99 U/L)	11 (5)	6 (3)	11 (5)
Alanine aminotransferase (≤99 U/L)	8 (3)	6 (3)	8 (3)
Bilirubin (≤25·65 μmol/L)	7 (3)	3 (1)	10 (4)
Creatinine (≤132·6 μmol/L)	0	5 (2)	2 (1)
Hyponatraemia	15 (6)‡	53 (23)	12 (5)‡
Fatigue	4 (2)	24 (10)	12 (5)
Anorexia	29 (13)	77 (33)	29 (12)
Diarrhoea	1 (<1)	21 (9)	18 (8)
Nausea	16 (7)	48 (21)	13 (6)
Stomatitis	7 (3)	0	4 (2)
Hand-foot syndrome	0	0	3 (1)
Neuropathy—motor	0	1 (<1)	2 (1)
Neuropathy—sensory	0	1 (<1)	0
Treatment-related death§	0	3 (1)	1 (<1)

Data are number of patients (%). *Two patients were not treated in each group. †Data for one patient not available. ‡Data for two patients not available. §Judged by data and safety monitoring committee.

Table 2: **Adverse events (grade 3 or higher) recorded within 6 months**

At the time of the primary analysis (March, 2007), 601 (85%) events had been recorded (figure 1). Median overall survival in patients assigned continuous infusion of fluorouracil was 10·8 (IQR 5·7–17·8) months, in individuals allocated irinotecan plus cisplatin it was 12·3 (8·1–19·5) months, and in those assigned S-1 it was 11·4 (6·4–21·3) months. Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·85 [95% CI 0·70–1·04]; p=0·0552). Non-inferiority of S-1 to a continuous infusion of fluorouracil was confirmed (0·83 [0·68–1·01]; p=0·0005), but S-1 was not superior to fluorouracil (p=0·0336; one-sided α=0·025).

At the time of the additional analysis (November, 2008), the number of events had risen to 660 (94%; figure 1). Actual 2-year overall survival was 14% in patients assigned continuous infusion of fluorouracil, 18% in individuals allocated irinotecan plus cisplatin, and 21% in those assigned S-1 (figure 2). Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·82 [95% CI 0·68–0·99]; p=0·0194), whereas S-1 was non-inferior to fluorouracil (0·83 [0·68–1·00]; p=0·0002 for non-inferiority, p=0·0233 for superiority). All HR calculated by multivariate analyses with baseline factors were essentially the same as those measured by univariate analyses (data not shown).

The median time to treatment failure was 2·3 (IQR 1·4–5·4) months for patients assigned continuous infusion of fluorouracil, 3·7 (1·9–5·6) months for those allocated irinotecan plus cisplatin (HR 0·85 [95% CI 0·71–1·02]; p=0·0430), and 4·0 (2·0–6·3) months for individuals assigned S-1 (0·73 [0·61–0·88]; p=0·0004). More than 85% of patients who were allocated either continuous infusion of fluorouracil or S-1 discontinued treatment because of disease progression; a third of those allocated irinotecan plus cisplatin stopped because of toxic effects (figure 1). Median non-hospitalised survival was 7·2 (IQR 2·7–13·3) months for individuals assigned continuous infusion of fluorouracil, 9·5 (4·9–15·7) months for those allocated irinotecan plus cisplatin (0·81 [0·67–0·97]; p=0·0115), and 9·3 (4·2–18·0) months for those assigned S-1 (0·77 [0·63–0·92]; p=0·0025).

Second-line chemotherapy was given to 194 (83%) patients assigned continuous infusion of fluorouracil, 183 (78%) allocated irinotecan and cisplatin, and 173 (74%) assigned S-1 (data not available for 31 individuals). Of those assigned continuous infusion of fluorouracil, 70 crossed over to irinotecan plus cisplatin and 20 moved to S-1. Of those allocated irinotecan plus cisplatin,

127 moved to S-1 and seven to continuous infusion of fluorouracil. Finally, of those in the S-1 arm, two patients crossed over to continuous infusion of fluorouracil and 68 moved to irinotecan plus cisplatin.

Median progression-free survival was 2·9 (IQR 1·7–5·7) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·2) months for those allocated irinotecan plus cisplatin (HR 0·69 [95% CI 0·58–0·83]; p<0·0001), and 4·2 (2·2–7·1) months for individuals assigned S-1 (0·77 [0·64–0·93]; p=0·0027; figure 2). In patients with a target lesion or lesions, response rates were 9% (15/175) for those assigned continuous infusion of fluorouracil, 38% (68/181) for those allocated irinotecan plus cisplatin, and 28% (49/174, data not available for one patient) for individuals assigned S-1. In this subgroup, median progression-free survival was 2·2 (1·4–5·3) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·1) months for those allocated irinotecan plus cisplatin (0·56 [0·45–0·69]; p<0·0001) and 3·8 (2·0–5·6) months for those assigned S-1 (0·80 [0·65–0·98]; p=0·0174).

Findings of exploratory subgroup analyses of overall survival (figure 3) showed favourable results for S-1 compared with continuous infusion of fluorouracil for all subgroups except recurrent cases. In the subgroup with target lesions, median survival was 9·0 (IQR 5·4–15·2) months for patients assigned continuous infusion of fluorouracil (n=175), 12·1 (8·1–19·0) months for those allocated irinotecan plus cisplatin (n=181; HR 0·73 [0·59–0·91]; p=0·0022), and 10·5 (5·6–19·2) months for those assigned S-1 (n=175; 0·84 [0·68–1·05]; p=0·0590). In the subgroup without target lesions, median survival was 13·5 (7·9–23·4) months for patients assigned continuous infusion of fluorouracil (n=59), 14·4 (9·0–20·7) months for those allocated irinotecan plus cisplatin (n=55; 1·12 [0·76–1·65]; p=0·7219), and 18·1 (10·5–26·6) months for those assigned S-1 (n=59; 0·79 [0·53–1·16]; p=0·1101).

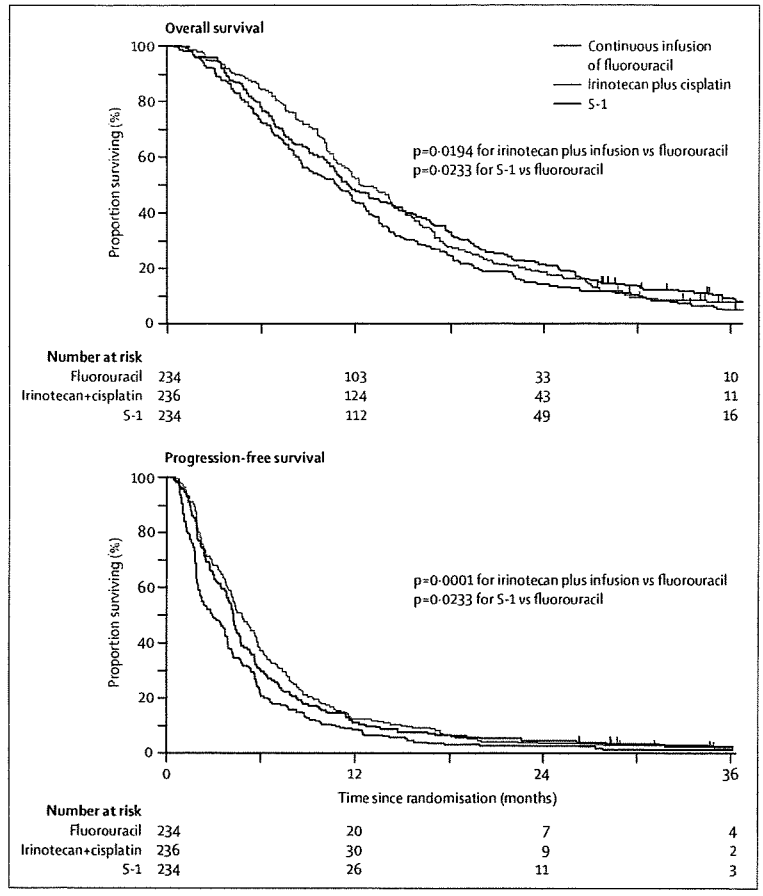

Figure 2: **Survival curves of all randomised patients (November, 2008)**

Discussion

Our findings show that S-1 is non-inferior to continuous infusion of fluorouracil with respect to overall survival. Although S-1 was not superior with respect to overall survival at the primary analysis, patients assigned S-1 had a 7% higher 2-year overall survival rate than those allocated a continuous infusion of fluorouracil. Furthermore, other measures of effectiveness of S-1, such as response rate and progression-free survival, were better than those obtained with continuous infusion of fluorouracil. These findings for S-1 are consistent with those reported in two phase 3 trials containing an S-1 alone arm.[19,20] Drug development for gastric cancer has been focused on replacement of intravenous fluorouracil with oral agents.[21,22] Taken together with our findings, S-1 might have some advantages over continuous infusion of fluorouracil.

Any new treatment, even if non-inferior to standard treatment, should have some benefits, such as for quality of life, cost, or safety. In our study, compared with continuous infusion of fluorouracil, S-1 was associated with almost equivalent safety and longer non-hospitalised survival. Additionally, in Japan, the cost of S-1 (about ¥76000 per month [about US$834]) is cheaper than that of continuous infusion of fluorouracil (about ¥140000 per month [US$1537]). In view of the effectiveness, safety, convenience, and cost, continuous infusion of fluorouracil could be replaced by S-1 for first-line chemotherapy of metastatic gastric cancer.

Findings of a meta-analysis of chemotherapy for advanced gastric cancer[23] indicated that survival was slightly better with combination chemotherapy than with a single agent. In the SPIRITS trial,[19] in which S-1 plus cisplatin was compared with S-1 alone for recurrent or unresectable gastric cancer, the combination showed a survival benefit over S-1 alone. In a previous study by us,[13] fluorouracil plus cisplatin could not prolong survival compared with a continuous infusion of fluorouracil, and our findings in this current study suggest that S-1 is non-inferior to continuous infusion of fluorouracil. Therefore, these data support the rationale for S-1 to be a control arm in the SPIRITS trial.[19] Several studies of

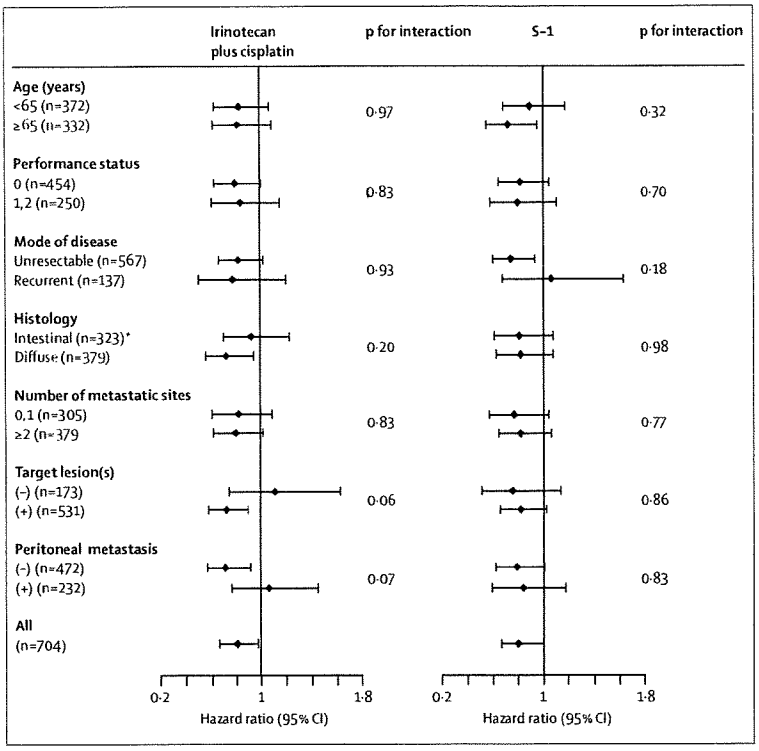

Figure 3: **Forest plot of subgroup analyses**
For every analysis, continuous infusion of fluorouracil is compared with irinotecan plus cisplatin (left) and S-1 (right). *Unknown types were excluded from the analysis.

combination chemotherapy based on S-1 plus cisplatin, including molecular target agents, are ongoing.

Toxic effects of S-1 have been reported to be more severe in individuals from the USA than in Asian patients, resulting in different recommended doses in these populations.[24,25] Since similar discrepancies in toxic effects have been noted with tegafur and uracil,[26] ethnic variations would seem to be a factor with these dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines. In a trial from China,[27] S-1 plus cisplatin was superior to continuous infusion of fluorouracil plus cisplatin. Outside Asia,[28] despite differences in dose and schedule of S-1 from Asian trials, S-1 plus cisplatin was associated with fewer toxic effects, had slightly better survival, and showed non-inferiority compared with fluorouracil plus cisplatin. S-1 plus cisplatin, with an equitoxic dose to fluorouracil plus cisplatin, should be investigated in European and North American populations.

The toxic effects of irinotecan plus cisplatin were the most severe of the three treatment groups in our study, and the rate of treatment failure due to toxic effects was the highest, resulting in a shorter time to treatment failure than that obtained with S-1. In the subgroup with target lesions, of the three treatment groups, irinotecan plus cisplatin showed the best response rate, progression-free survival, survival within 1 year, and overall survival. In North America, divided doses of irinotecan and cisplatin have been investigated,[29] which are associated with a similar response rate to, and fewer toxic effects than, the regimen in our study. Since control of toxic effects of irinotecan plus cisplatin is a big problem, divided doses of irinotecan and cisplatin should be investigated in future phase 3 trials.

Some chemosensitivity-related markers have been suggested to be prognostic factors for irinotecan plus cisplatin treatment.[30] Expression of specific chemosensitivity-related genes is currently being investigated in patients enrolled in our study, and preliminary data suggest that dihydropyrimidine dehydrogenase expression could be a predictive marker for whether irinotecan plus cisplatin or S-1 (plus cisplatin) would be the better treatment in a given patient.[31] We postulate that some populations would benefit from irinotecan plus cisplatin even though chemotherapy regimens containing irinotecan have not shown a survival benefit in phase 3 trials.[20,32] Because clinical behaviour and pathogenesis of gastric cancer are heterogeneous, treatment strategies tailored for optimum chemotherapy according to a patient's clinical and genetic background should be established in the near future, and irinotecan plus cisplatin could then serve as one of the options.

Although median progression-free survival of S-1 and irinotecan plus cisplatin in our study were similar to those reported in other phase 3 trials, median overall survival was somewhat extended.[21,22,32–34] Moreover, median progression-free survival—both in this study and in our previous phase 3 trial[13]—was 2 months for patients who received continuous infusion of fluorouracil. Overall survival of patients with target lesions in this current study was about 2 months longer than that reported by us previously. The proportion of patients who received second-line chemotherapy in our study was more than 70%, which is higher than in our previous study (53%).[13] Since irinotecan and taxanes were approved in the late 1990s in Japan, available active agents for subsequent chemotherapy differed between this current study and our previous study. We postulate that second-line chemotherapy might have contributed to the favourable overall survival in this study, although a survival benefit of second-line chemotherapy has not yet been clarified.

Contributors

NB, HF, and SY wrote the protocol and designed the trial based on discussion with, and agreement from, all authors. All authors (except SY and HF) recruited patients to the study. HF directed the data centre. SY and HF did the statistical analysis. NB wrote the report with revisions from all other authors.

Conflicts of interest

The authors declared no conflicts of interest.

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トピックス

I. がん薬物療法の展開
4. 固形癌の標準的薬物療法
2) 消化器癌

坂下　博之　　白尾　国昭

要　旨

消化器癌の本邦における標準治療は，欧米の標準治療と必ずしも一致していないところがあるものの，近年徐々に国際レベルでの標準化がはかられつつある．切除不能・再発症例での本邦での標準治療は食道癌では5-FU＋CDDP，胃癌はS-1＋CDDP，大腸癌はFOLFOX＋bevacizumab or FOLFIRI＋bevacizumabとされている．その他食道癌では5-FU＋CDDPの術前化学療法，胃癌では術後化学療法としてS-1，大腸癌の術後では5-FU/LV，UFT/LV，もしくはcapecitabinが標準治療として行われている．最近では分子標的薬が用いられるようになり，cetuximabをはじめ個別化医療への方向性も含めてその効果が期待されている．

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Key words：食道癌，胃癌，大腸癌，分子標的薬

はじめに

本稿では食道癌，胃癌，大腸癌，小腸癌および消化管間葉腫瘍（GIST）の標準的な薬物療法について述べる．固形癌の標準的な薬物療法については，切除不能もしくは再発癌における治療と術前術後補助化学療法に分けられる．術前術後補助化学療法については，手術方法，技術の問題もあり，必ずしも欧米のエビデンスが受け入れられない面がある．また承認薬剤の問題があり，欧米でのエビデンスがありながら本邦では使えない薬剤も存在する．本稿では，現在の日本の臨床現場における標準治療を概説する．

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1. 食道癌の薬物療法

日本と欧米では食道癌の組織型別頻度が異なること（欧米では腺癌が多く，日本をはじめとするアジアでは扁平上皮癌が多い），また手術方法が異なることなどより，日本では欧米の臨床試験の結果をそのまま受け入れる方向になく，我が国独自のエビデンスを追加した形で標準治療が検討されている．以下，本邦における標準治療法について，病期別に概説する．

1) I期

臨床病期I期の中で内視鏡的粘膜切除術の絶対的適応は進達度が上皮内ないし粘膜固有層以浅のもので，かつ周在性が2/3以下の症例である．内視鏡的粘膜切除の対象とはならない症例に対しては食道切断術が標準治療であるが，化学放

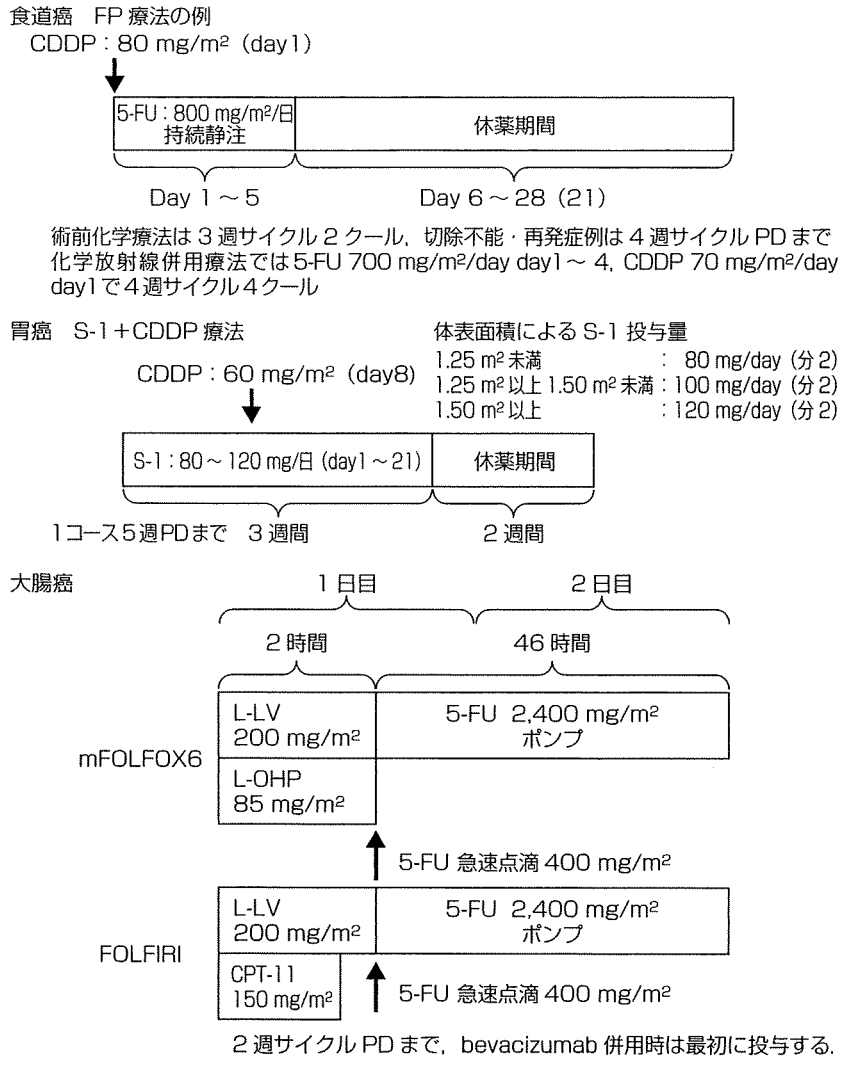

図 1．化学療法のレジメの実際
PD：progressive disease

射線療法は有望なオプションとして認識されている．JCOG(Japan Clinical Oncology Group)9708による臨床病期I期に対する臨床試験の成績が報告され，化学療法はFP療法（5-FU＋CDDP（cisplatin））（図 1），放射線は総線量 60 Gyで，5 年生存率 76% と，食道切断術の成績 70～75% と比べて遜色のない成績であった．これを受けて現在比較試験（JCOG0502）が進行中であり，今後臨床病期I期に対する化学放射線療法は，食道切断術に代わって標準治療となる可能性がある．

2）II期，III期（T4 を除く）

（1）術前または術後の補助療法

切除可能な症例においてはまず手術療法が検討される．欧米では，手術単独群，術前化学療法群，術前化学放射線療法群の無作為化比較試験のメタアナリシスの結果より，術前化学放射線療法が一般的となっている．本邦ではT4 を除く臨床病期II期，III期症例を対象にしたJCOG 9204（手術単独vs術後FP療法群）の結果で術後補助化学療法群が勝るという結果に引き続き，

補助化学療法（FP療法2コース）を術前に実施する群と，術後に実施する群との無作為比較試験（JCOG9907）が行われ，術前群のほうが，PFS（progression free survival），5年生存率ともに上回るという結果を得た[1]．以上より，現在本邦ではT4を除く臨床病期II期，III期における標準治療はFP療法（図1）2コースによる術前化学療法と認識されている．

（2）根治的化学放射線療法

臨床病期II期，III期の切除可能例を対象とした根治的化学放射線療法（FP療法＋放射線60 Gy）の臨床試験JCOG9906では，5年生存割合が37%であったのに対して[2]，JCOG9907の術前化学療法＋手術群における5年生存率は60%であり，耐術性に問題のある患者以外では，依然として標準治療は術前化学療法＋手術と考えられている．根治的化学放射線療法の症例ではCR（complete response）症例でも約半数に局所再発が認められ，化学放射線療法後のsalvage surgeryを組み合わせることで治療成績の向上を目指す動きもある．また，化学放射線療法のレジメンを米国RTOG（Radiation Oncology Group）と同様のFP高用量，放射線照射法（休止期間をおかずに50.4 Gy）で行う試みもなされている．

3）T4，M1（LYM）症例

周囲臓器への浸潤を伴う局所高度進行型切除不能III期例や，頸部や腹部のリンパ節転移（M1Lym）を有するIV期の進行例では，化学放射線療法（FP療法＋放射線療法）が行われており，生存期間中央値で約9〜10カ月というものである．手術では術死や術後合併症の頻度が高いなど成績が悪いこともあって，食道切除術と化学放射線療法の無作為試験はないが，食道切除術に代わって化学放射線療法が実地臨床でも広く用いられるようになっている．ただし，T4症例では大出血や穿孔などの危険性も高いため注意が必要である．

4）IV期（M1（LYM）を除く），再発症例

標準治療として確立したものはないが，FP療法（図1）が汎用されている．しかし，化学療法での延命効果を示すエビデンスがないため，現状では姑息的治療の位置づけである．また，docetaxelも用いられるが，FP療法無効例での2次治療として単剤で用いられることが多い．

2. 胃癌の薬物療法

1）切除不能再発癌

術後再発例や遠隔転移例や拡大手術の適応のないIV期に対する化学療法として行われる．

（1）1次治療

現在，胃癌の1次化学療法として，全世界で認められた標準治療は確立していない．我が国では，5-FU単独療法が標準治療のひとつと考えられていた．その後，2007年に我が国で開発された新薬であるS-1を用いた第3相試験の結果が発表となった．1つ目は，5-FU単独療法とS-1単剤，CPT-11＋CDDP併用療法の3群における比較試験（JCOG9912）である[3]．生存期間において，S-1単剤療法は5-FU単剤に比べて非劣性であることが証明された．一方，CPT-11＋CDDPの生存期間中央値（MST 12カ月）は，3群の中で1番良好であったが，5-FU群（MST 10.8カ月）に比べて優越性を示すことができなかった．以上の結果から，S-1単独療法は5-FU単剤療法と同等以上の効果があり，副作用も少なく，さらには経口薬であり外来治療が可能となることから，標準治療のひとつとみなすことができると結論された．2つ目はS-1単独療法とS-1＋CDDP併用療法との比較試験（SPIRITS試験）である[4]．全生存期間において，S-1＋CDDP併用療法のS-1単独に対する優位性が示された（MSTはそれぞれ13.0カ月vs 11.0カ月，PFSはそれぞれ6.0カ月vs 4.0カ月）（図2）．副作用はCDDP群のほうが強かったが，日常診療でおこなっていくうえで十分耐用可能であり，S-1＋CDDP療法（図1）が本邦での標準治療と位置づけられた．

一方米国ではDTX（docetaxel）＋CDDP＋5-

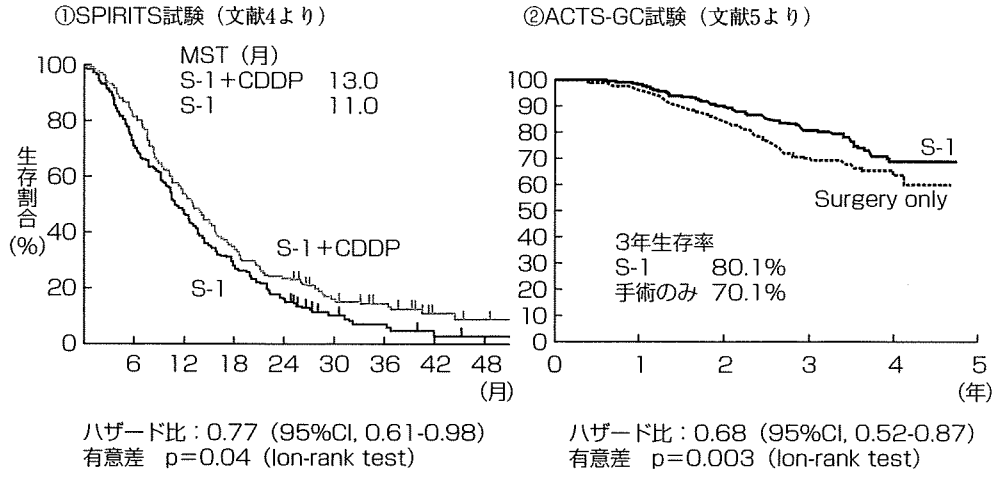

図2. 胃癌の大規模試験の生存曲線

FU（DCF）療法とFP療法の比較試験（TAX325試験）が行われた．DCF療法群で2年生存率，PFSが良好であり，DCF療法が標準治療とされたが，発熱性好中球減少症が高度であるなど，副作用が強く，普及はしていない．

欧州では，epirubicin＋CDDP＋5-FU（ECF）療法のCDDPをoxaliplatin（OHP）に，5-FUをcapecitabinに置き換えた比較試験(REAL-2試験)が行われた．EOX療法群（epirubicin＋OHP＋capecitabin）で奏効率，全生存期間とも優れた傾向であった．このレジメは外来化学療法を可能にするものではあるが，我が国ではOHPとcapecitabinは胃癌において保険承認されていない．

以上より，国内外での標準治療は確立していないが，国内の2つの臨床試験の結果から本邦ではS-1＋CDDP併用療法が1次治療の標準治療と考えられるようになった．なお，2009年のASCO-GI（American Society of Clinical Oncology-The Gastrointestinal Cancers Symposium Meeting）において，海外でのS-1＋CDDP併用療法の大規模比較試験（FLAGS試験）によりS-1＋CDDPのFP療法に対する優越性は示せなかったという結果が報告されたが（生存曲線ではS-1＋CDDPが上回っていた），利便性と毒性の低さもあり，現在でも日本ではS-1＋CDDPが標準治療とみなされている．

（2）2次治療以降

いくつかの臨床試験が行われているが，2次治療そのものの有用性についての十分なエビデンスは確立していない．胃癌に対して感受性の高い薬剤として5-FU系，CDDP系，Taxan系，CPT-11系が挙げられるが，2次治療以降は一旦耐性となった薬剤を使わないという原則に基づき治療を変えてゆくことが一般的である．現在2次治療においてはTaxan系薬剤とCPT-11のいずれかを用いるかが議論されているところである．なお，一定以上の腹膜転移例において，CPT-11は毒性が重篤化する危険性があるため使用しづらく，weekly paclitaxelが用いられることが多い．

2）術後補助化学療法

胃癌では，最近まで術後補助化学療法の有用性は認められず，手術単独が標準的であった．しかし，2007年のASCO-GIにおいて，II期（T1を除く）/III期症例における胃癌治癒切除症例に対する，S-1投与群（術後1年間）と手術単独の第III相試験（ACTS-GC）の結果が報告され，術後補助化学療法としてS-1単剤を1年間内服した群の3年生存率は80.1%と，手術単独群70.1%に比べ，明らかな延長が認められた(図2)[5]．以上の結果から，現時点でのII期/III期の根治切除

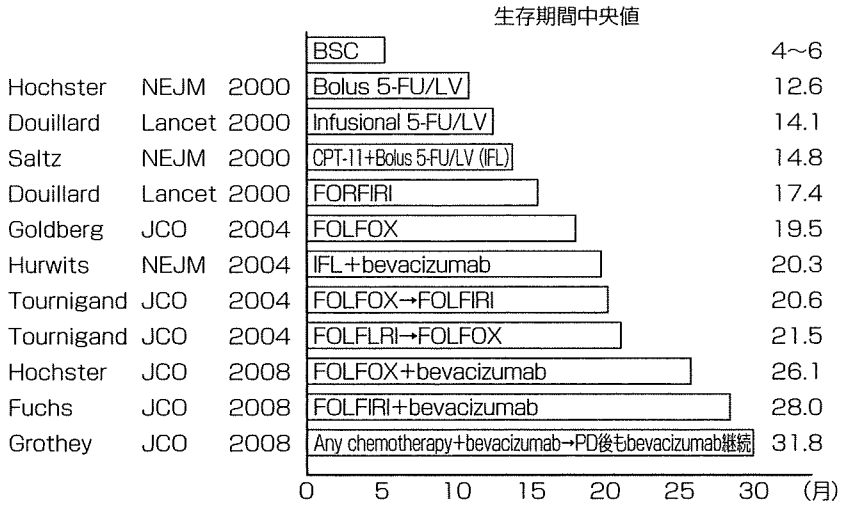

図3. 大腸癌の化学療法の進歩による生存期間の延長

例に対する国内での標準治療は，S-1の術後1年間の内服であると考えられるようになった．

3. 大腸癌の薬物療法

1) 切除不能・転移性癌

切除不能・転移性癌においてはここ数年の分子標的薬を含んだ全身化学療法の進歩により，生存期間の延長やQOL（quality of life）の改善がおおいに認められるようになり，MSTも20カ月を超えるようになった（図3）．大腸癌のキードラッグである5-FU，L-OHP，CPT-11と分子標的薬であるbevacizumabとcetuximabの組み合わせが行われており，すべてを使い切るような治療戦略をたてることが重要であるとされている．また，リザーバーを用いた外来治療が可能になったことが特徴である．大腸癌では化学療法の原則からはずれて，無効となった薬剤を再度組み合わせを変えて使うことがあることと，遠隔転移例でも治癒を目的とした手術が行われることが特徴である．化学療法後転移巣が縮小した場合，治癒切除の可能性もあるため外科医と相談が必要であるが，適応についてはまだ確立されていない．

本邦でも欧米と同様にFOLFOX療法やFOLFIRI療法，副作用等のためそれらの治療が出来ない場合には5-FU/LVにbevacizumabを加える治療が現在1次治療として行われている（図1）．欧米では5-FUの替わりにcapecitabinを用いるXELOX療法も用いられるが，本邦では使用できない．FOLFOXとFOLFIRI療法はFOLFOXとFOLFIRIとの投与順序を交差させるGERCOR V308試験では同等であるとされた．そのため日常診療ではどちらを先に用いても良いと思われる[6]．ただ，各々のレジメンでは副作用の発現頻度に違いがあり，FOLFOXではL-OHPによるアレルギー反応，末梢神経障害が極めて特徴的であり，FOLFIRIでは下痢などの消化管毒性や脱毛が特徴的である．そのため，患者の状況に応じて選択し，2次治療ではFOLFOX，FOLFIRI療法のうち初回で使わなかったものを，3次治療ではEGFR（上皮細胞増殖因子受容体）陽性例でCPT-11＋cetuximabやcetuximab単独の治療がおこなわれている．FOLFOX療法は外来投与の利便性からFOLFOX6が，さらに神経毒性の点でL-OHPの量を減量したmFOLFOX6が一般的に用いられている．

bevacizumabは血管内皮増殖因子（VEGF）を

ターゲットとしたキメラ型ヒト化マウスモノクローナル抗体である血管新生阻害薬である．初回治療例を対象としたAVF2107 g試験においてIFL療法（5-FU/LV/CPT-11）にbevacizumabを上乗せすることで，PFSの中央値を4.4カ月，OSの中央値を4,7カ月延長させることが示された．さらに，1次治療におけるFOLFOX4/XELOX療法へのbevacizumabの上乗せ効果（NO16966試験），mFOLFOX6療への上乗せ効果（TREE試験）[7]が証明された．また，2次治療ではE3200試験によりFOLFOX4療法への上乗せ効果（MST，PFS）が証明された．なお，1次治療に続き，2次治療でもbevacizumabを継続すべきかについてはBRiTE試験でその有効性を示唆する結果が報告され，現在第3相試験（ML18147）が行われている．3次治療としては効果が認められなかった．bevacizumabの併用により高血圧，蛋白尿，動静脈血栓症，消化管穿孔，出血，創傷治癒遅延，可逆性後白質脳症症候群，infusion reactionなどの有害事象が起こることが知られており，注意しながら投与する必要がある．

cetuximabはヒトマウスキメラ型化モノクローナル抗体であり，上皮細胞増殖因子受容体（EGFR）阻害薬である．CPT-11抵抗性のEGFR陽性患者に対して行われたBOND-1試験で，cetuximab単独群とcetuximab＋CPT-11併用群の比較が行われた[8]．この試験で，cetuximab＋CPT-11併用群が高い奏効率と良好なPFSを示した（奏効率はそれぞれ10.8% vs 22.9%，PFSはそれぞれ1.5カ月vs 4.1カ月）．同様にCPT-11の治療歴がなくフッ化ピリミジン系薬剤もしくはL-OHPに抵抗性のEGFR陽性患者を対象としたEPIC試験ではFOLFIRI単独群に比べ奏効率，PFSにおいてcetuximab＋FOLFIRI併用群の優越性が確認された．

もう1つの重要な試験は，CPT-11，L-OHP，フッ化ピリミジン系薬剤に不応または耐容不能のEGFR陽性転移性大腸癌における，3次治療としてのcetuximab単独群とbest supportive care（BSC）を比較するNCIC CTG CO.17試験である[9]．この試験では奏効率，PFSだけでなく，生存期間でcetuximab単独群の優越性を示した（生存期間の中央値で1.5カ月の延長）（図4）．国内で同様に行われたCPT-11に不応となった患者に対するcetuximab＋CPT-11の第2相試験（EMR62202-049試験）では奏効率30.8%，PFS4.1カ月と海外試験とほぼ同様の成績が得られた．

一方，未治療の転移性大腸癌を対象としたCRYSTAL試験でもFOLFIRI＋cetuximabはFORFILI単独に比べRR（response rate），PFSの改善がみられた．また，OPUS試験ではFOLFOXにおいても同様に併用効果が確認されているが，統計学的有意差は認めていない．ただし，興味深いことに先のNCIC CTG CO.17試験，CRYSTAL試験，OPUS試験でのretrospectiveな解析結果で，*KRAS*遺伝子がwild typeである患者ではcetuximabの上乗せ効果を認めたが，mutationのある患者では上乗せ効果は認められなかったという報告がなされた（図4）[10]．この結果大腸癌の化学療法において*KRAS*遺伝子がcetuximab治療のmolecular markerとなることを意味しており，実際に米国では*KRAS*遺伝子がwild typeのみcetuximabを投与することが推奨されているが，本邦では2009年4月現在*KRAS*遺伝子変異検査は保険承認されていない．さらにEGFRのシグナルの伝達経路のさらに下流である*BRAF*遺伝子についても同様なことがいえる可能性が示唆されている．一方で，各種臨床試験においてEGFRの発現の程度と奏効率には相関を認めておらず，現在では免疫染色によるEGFRの発現の有無は臨床的には意義がないと考えられている．また，PACCE試験やCAIRO-2試験ではbevasizmabと抗EGFR抗体薬の併用で良好な結果は得られていない．cetuximabの有害事象としてざ瘡様皮疹が特徴的で，これは治療効果予測因子とされている．その他infusion reactionや間質性肺炎が有害事象として報告されている．

以上切除不能・転移性癌においては1st line