LVと比較して5-FU/LV＋bevacizumabはgrade 3以上の高血圧が多くみられた以外は安全に使用できたとされている[14]．

消化器がんの化学療法の分野で，高齢者への治療法を検討する機会はますます増加している．しかし，高齢者の消化器がん患者に対する化学療法の前向きな臨床試験の成績はほとんどなく，大規模臨床試験のサブグループ解析からその傾向を垣間みることができるのみである．しかし，4つの臨床試験のpooled analysisでは，70歳以上の大腸がん患者のFOLFOX4療法において若年者よりも好中球減少症と血小板減少が有意に多かったが，奏効率や生存期間といった有効性では差はなかったとされている[15]．しかしながら，これら臨床試験の症例はかなり選択された症例であり，高齢者ではとくに腎機能の低下に気をつける必要がある[16]．通院化学療法に際しては，かかりつけ医や訪問診療，訪問看護によるサポートも重要と考えられる．とくに高齢者では副作用を正確に聞き取り，支持療法を迅速に開始することが大切である．

高齢者の消化器がんの放射線治療

消化器がんの放射線治療は主に食道がんにおいて行われる．放射線治療単独より，化学放射線療法のほうが治療効果が優れていることは知られている[17]．75歳以上あるいは80歳以上の食道がん患者に化学放射線療法が安全に行えた報告もあるが，適応は慎重に考えるべきであろう[18][19]．化学療法には5-FUと白金製剤が用いられることが多い．白金製剤の中でもcisplatinは腎毒性が問題となるため，水分負荷が必要である．一方，nedaplatinは腎毒性が少ないため水分負荷がさほど必要でなく，高齢者に有用な可能性がある．よって，高齢者には緩和的放射線療法が行われる傾向にある．とはいっても，放射線照射単独の治療でも循環器や呼吸器への晩期毒性が懸念される．リスクを減らすために放射線量の変更，多門照射，狭い照射範囲での治療などが試みられている．

ま と め

高齢者の消化器がん患者は臓器機能にばらつきが大きいため，標準治療を設けることは難しい．総合的なQOLやPSなどを考慮して，担当医が症例ごとに治療法を選択することが多いのが現状である[20]．今後，高齢者の消化器がん患者はますます増加すると予想されることから，高齢者の身体状態を評価するツールなどの開発が期待される．

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Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study)

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Background: The efficacy and safety of oxaliplatin combined with S-1 (SOX regimen) for unresectable advanced or recurrent gastric cancer were investigated.

Patients and methods: Oxaliplatin was administered i.v. (100 mg/m^2) on day 1, while S-1 was administered orally (80 mg/m^2/day, b.i.d.) for 14 days followed by a 7-day rest. This schedule was repeated every 3 weeks.

Results: Among 55 patients enrolled, one patient received oxaliplatin for the other study, and three patients were considered unsuitable against the inclusion criteria. Accordingly, 51 patients were assessable for efficacy. The response rate was 59%, and the disease control rate was 84%. The median progression-free survival time was 6.5 months, the 1-year survival rate was 71%, and the median survival time was 16.5 months. In 54 patients assessed for safety, the major grade 3/4 toxic effects were neutropenia (22%), thrombocytopenia (13%), anemia (9%), anorexia (6%), fatigue (6%), and sensory neuropathy (4%).

Conclusion: These findings indicate that SOX regimen with oxaliplatin at a dose of 100 mg/m^2 is feasible and shows promising efficacy against advanced gastric cancer.

Key words: advanced gastric cancer, oxaliplatin, phase II, S-1, SOX

original article

introduction

Chemotherapy for advanced gastric cancer was proven to be superior to best supportive care in terms of survival and quality of life [1–3]. Phase III studies have been carried out to compare epirubicin/cisplatin/5-fluorouracil (5-FU) with 5-FU/doxorubicin/methotrexate, cisplatin/5-FU with docetaxel/cisplatin/5-FU, and 5-FU/cisplatin with capecitabine/cisplatin [4–6]. On the basis of the results of these studies, advanced gastric cancer is mainly treated with combination chemotherapy that includes fluoropyrimidine derivatives and platinum compounds.

Oxaliplatin is a third-generation platinum compound that was developed to improve tolerability and ease of administration compared with cisplatin [7]. The non-inferiority of oxaliplatin-based regimens to cisplatin-based regimens was demonstrated in the Revised European-American Lymphoma (REAL)-2 phase III study [8]. In addition, the result of phase III study comparing 5-FU/leucovorin/cisplatin with 5-FU/leucovorin/oxaliplatin showed that oxaliplatin was at least as effective as cisplatin [9].

S-1 is an orally active prodrug of 5-FU that contains tegafur (which is continuously metabolized to 5-FU) blended with two modulators, gimeracil and potassium oxonate [10]. In Japan, advanced gastric cancer is mainly treated with S-1 alone or S-1 combined with other drugs. The SPIRITS phase III study demonstrated the superiority of S-1 plus cisplatin to S-1 alone [11]. The S-1 plus cisplatin regimen was also investigated by the FLAGS phase III study carried out in Western countries, which demonstrated that S-1 plus cisplatin was at least as effective as 5-FU plus cisplatin and less toxic [12].

We conducted a multicenter phase II study to evaluate the efficacy and safety of the combination regimen of S-1 and oxaliplatin (SOX regimen) in advanced gastric cancer as first-line therapy.

patients and methods

patients' eligibility

The following criteria were used to enroll patients for the present study. All patients had unresectable advanced or recurrent gastric cancer excluding the esophagus and gastroesophageal junction, confirmed by histological or

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cytological examination. They had survived at least 4 weeks if extended or standard surgery had been carried out (or at least 2 weeks after minor surgery) and were able to take oral drugs. They were aged ≥20 years, had an Eastern Cooperative Oncology Group performance status (PS) of zero to two, and were expected to survive for at least 2 months. In general, they had not received prior chemotherapy, but those who had completed postoperative adjuvant therapy at least 180 days before enrollment were eligible. They had at least one measurable lesion according to RECIST guidelines [13]. They also had adequate bone marrow function (hemoglobin level ≥ 80 g/l, white blood cell count of 3–12 × 10^9/l, neutrophil count ≥ 1.5 × 10^9/l, and platelet count ≥ 100 × 10^9/l), liver function (total bilirubin ≤ 1.5 × the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × the institutional upper limit of normal, and alkaline phosphatase ≤ 2.5 × the institutional upper limit of normal), and renal function (serum creatinine level ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min). All patients provided written informed consent.

This study was carried out in accordance with the Helsinki declaration and Good Clinical Practice guidelines and was approved by the institutional review boards of all participating medical institutions.

treatment plan

Oxaliplatin was administered i.v. at a dose of 100 mg/m^2 on day 1. S-1 was administered orally at a dose of 80 mg/m^2/day b.i.d. for 14 days (from the evening on day 1 until the morning on day 15), followed by a 7-day rest period in the 3-weekly schedule. Treatment was repeated until there was disease progression, unacceptable toxicity, or withdrawal of consent.

In the event of grade 4 neutropenia or febrile neutropenia or grade 3 diarrhea or stomatitis, the doses of oxaliplatin and S-1 were reduced by one dose level from the next cycle. If grade 2 sensory neuropathy not recovering by the end of the cycle or grade 3 sensory neuropathy occurred, the dose of oxaliplatin was reduced by one dose level from the next cycle after recovering to grade 2 or less. If grade 2 thrombocytopenia continued ≥8 days after the scheduled day for starting the next cycle or if platelet transfusion was required, oxaliplatin was reduced by one dose level from the next cycle. Oxaliplatin and S-1 could be reduced by two dose levels, but treatment was discontinued if subsequent reduction was indicated. The doses of oxaliplatin and S-1 could be reduced by 25 mg/m^2 and 10–30 mg/day, respectively, for each level. Treatment was discontinued if grade 4 diarrhea, stomatitis, or sensory neuropathy occurred, if grade 3 sensory neuropathy failed to recover by the time when the next cycle was scheduled, if grade 2 thrombocytopenia continued ≥15 days after the scheduled day for starting the next cycle, or if the rest period of S-1 was over 21 days.

evaluation

The data on the patients' characteristics, a 12-lead electrocardiogram, computed tomography (CT) scans, and tumor marker levels (CA19-9 and carcinoembryonic antigen) were obtained within 14 days of enrollment, while hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out within 7 days before enrollment. During the study, hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out every week until the end of the fourth cycle and subsequently every 3 weeks. CT scans were carried out and tumor markers were measured every 6 weeks (every 2 months after the best overall response was achieved).

Responses were evaluated according to the RECIST guidelines. To confirm partial response (PR) (30% or greater decrease in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions) or complete response (CR) (disappearance of all target and nontarget lesions together with normalization of tumor marker levels), tumor measurements were repeated no <4 weeks after objective response was firstly obtained. Responses were assessed by the independent review committee. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Progression-free survival (PFS) was the time from treatment initiation to first documentation of disease progression detected by the review committee or death from any cause (censored at second-line chemotherapy). Time-to-treatment failure (TTF) was the time from treatment initiation to discontinuation of treatment, first documentation of disease progression by the review committee, or death from any cause. Toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events V3.0.

statistical analysis

The primary end point was the response rate (RR), while the secondary end points were OS, PFS, TTF, and safety. The required sample size was calculated to be at least 49 patients on the null hypothesis of the RR of ≤40% versus the alternative hypothesis of the RR of >60%, power 80%, and α 2.5% (one sided). The 95% confidence interval (CI) was calculated for the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–Meier method. Safety was analyzed in all patients who received at least one dose of study medication.

The cut-off date for RR, PFS, TTF, and safety was 27 May 2008, while that for OS was 13 July 2009.

results

patients' characteristics

Fifty-five patients were enrolled from April to December in 2007. Among them, one patient who received oxaliplatin for the other study by mistake was excluded from all analyses. Three other patients were excluded from efficacy analysis because of prior chemotherapy (methotrexate), severe interstitial pneumonia, or absence of measurable lesions (one patient each). Accordingly, 51 patients formed the efficacy analysis set (Table 1), while 54 patients were analyzed for safety. The median age of the 51 patients was 63 years (range 30–77 years) and the PS was zero or one in 50 patients. Prior adjuvant chemotherapy with S-1 had been carried out in one patient, while 50 patients had received no prior chemotherapy.

treatment

At the data cut-off date, treatment was ongoing in eight patients. The major reasons for discontinuation of treatment in 46 patients were disease progression (63%), adverse events (28%), and withdrawal of consent (2%).

The median number of treatment cycles was 6.0 (range 1–16+). The median dose intensity was 88 mg/m^2/3 weeks for oxaliplatin and 867 mg/m^2/3 weeks for S-1, and the median relative dose intensity was 87.5% and 85.7%, respectively. The median total dose was 600 mg/m^2 for oxaliplatin and 5966 mg/m^2 for S-1.

efficacy

The response was assessed as PR, stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions), and progressive disease (PD) in 30, 13, and 5, respectively, of the 51

Table 1. Patients' profile (n = 51)

Characteristic	No. of patients	%
Median age, years (range)	63 (30–77)	
Sex		
Male	34	67
Female	17	33
ECOG PS		
0	32	63
1	18	35
2	1	2
Disease status		
Advanced	47	92
Recurrent	4	8
Primary tumor		
No	12	24
Yes	39	77
Prior adjuvant chemotherapy		
No	50	98
Yes	1	2
Histology		
Diffuse	35	69
Intestinal	16	31
Sites of metastasis		
Lymph nodes	41	80
Liver	23	45
Lung	9	18
Peritoneum	7	14
Other	9	18
No. of metastases		
1	22	43
≥2	29	57

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Objective response to treatment (n = 51)

Response	No. of patients	% (95% CI)
CR	0	0
PR	30	59
SD	13	26
PD	5	10
Not evaluable	3	6
Overall response rate	30	59 (44.2–72.4)
Disease control rate (CR + PR + SD)	43	84 (71.4–93.0)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients in the efficacy analysis set (three were not assessable). The RR was 59% (95% CI 44.2% to 72.4%) and the disease control rate (CR + PR + SD) was 84% (95% CI 71.4% to 93.0%) (Table 2).

The median follow-up period was 16.5 months as of 13 July 2009. The median survival time (MST) was 16.5 months (95% CI 13.2–22.3 months) (Figure 1), median PFS was 6.5 months (95% CI 4.8–11.2 months) (Figure 2), and median TTF was 4.8 months (95% CI 4.0–5.6 months). The patients who received

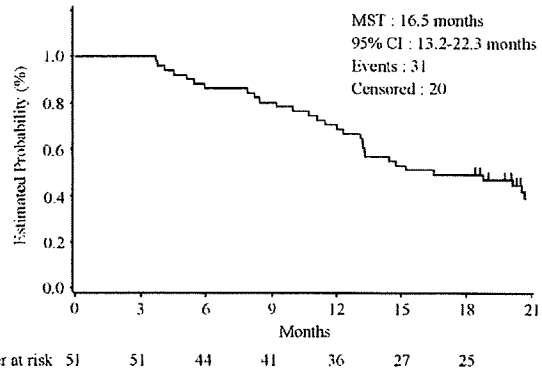

Figure 1. Kaplan–Meier estimates of overall survival (n = 51).

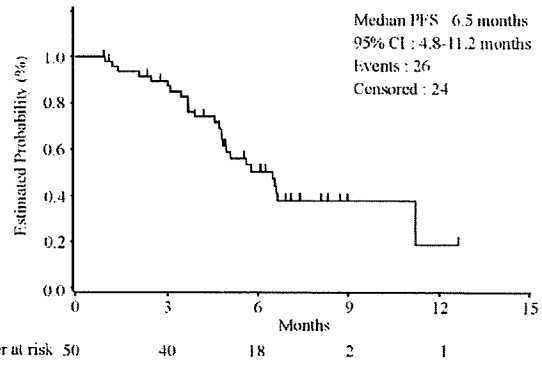

Figure 2. Kaplan–Meier estimates of progression-free survival (n = 50).

the second-line chemotherapy without PD were censored at the date of image examination immediately before the second-line chemotherapy in PFS analysis. The 1-year survival rate was 70.6% (95% CI 58.1% to 83.1%).

Forty-one of the 46 patients (89%) who discontinued treatment received second-line chemotherapy. One patient (2%) with PR underwent surgery and pathological CR was observed.

safety assessment

Grade 3/4 toxicity occurred in 33 of the 54 patients (61%) in the safety analysis set. Grade 3/4 leukopenia, neutropenia, thrombocytopenia, anemia, anorexia, and fatigue were noted in 2 (4%), 12 (22%), 7 (13%), 5 (9%), 3 (6%), and 3 patients (6%), respectively (Table 3). The median onset of thrombocytopenia in all grades was after 42 days and the nadir platelet count was seen at 113 days. The median time from the nadir to grade 0 or platelet count of treatment initiation was 15 days and the duration of thrombocytopenia in all grades was 21 days. Sensory neuropathy was observed in 48 patients (89%), but grade 3/4 neuropathy occurred only in two patients (4%). The median cumulative dose of oxaliplatin associated with sensory neuropathy of any grade was 150 mg/m^2 (grade 1: 150 mg/m^2, grade 2: 900 mg/m^2). There were no treatment-related deaths.

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Table 3. Toxicity of therapy (n = 54)

Toxicity (CTCAE)	No. of patients (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3/4
Hematological						
Leukopenia	15 (28)	16 (30)	2 (4)	0	33 (61)	2 (4)
Neutropenia	3 (6)	15 (28)	12 (22)	0	30 (56)	12 (22)
Thrombocytopenia	25 (46)	9 (17)	7 (13)	0	41 (76)	7 (13)
Anemia	14 (26)	14 (26)	4 (7)	1 (2)	33 (61)	5 (9)
Non-hematological						
Nausea	27 (50)	10 (19)	1 (2)	0	38 (70)	1 (2)
Vomiting	15 (28)	4 (7)	0	0	19 (35)	0
Diarrhea	17 (32)	4 (7)	1 (2)	0	22 (41)	1 (2)
Anorexia	21 (39)	16 (30)	2 (4)	1 (2)	40 (74)	3 (6)
Fatigue	24 (44)	14 (26)	2 (4)	1 (2)	41 (76)	3 (6)
Rash	13 (24)	2 (4)	0	0	15 (28)	0
Pigmentation	20 (37)	2 (4)	0	0	22 (41)	0
Hand–foot syndrome	12 (22)	2 (4)	0	0	14 (26)	0
Stomatitis	20 (37)	1 (2)	0	0	21 (39)	0
Increased creatinine	3 (6)	0	0	0	3 (6)	0
Febrile neutropenia	0	0	1 (2)	0	1 (2)	1 (2)
Sensory neuropathy	35 (65)	11 (20)	2 (4)	0	48 (89)	2 (4)

CTCAE, Common Terminology Criteria for Adverse Events V3.0.

discussion

Advanced gastric cancer is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several recent large-scale phase III studies have shown that the RR ranges from 25% to 54%, median PFS from 2.9 to 7 months, and MST from 8.6 to 13 months [5, 6, 8, 9, 11, 14]. Unfortunately, these results are not satisfactory. In Japan, S-1 plus cisplatin is considered to be the standard treatment for advanced gastric cancer on the basis of the results of two phase III studies: the JCOG9912 study demonstrated non-inferiority of S-1 to i.v. infusion of 5-FU [14] and the SPIRITS study showed that S-1 plus cisplatin was superior to S-1 alone [11]. In the SPIRITS study, the RR, median PFS, and MST achieved with S-1 plus cisplatin were 54%, 6.0 months, and 13 months, respectively. However, more frequent incidences of grade 3/4 adverse events were reported as compared with S-1-alone group, and the combination regimens with improved safety are expected.

With the present SOX regimen, the RR was 59%, median PFS was 6.5 months, 1-year survival was 70.6%, and MST was 16.5 months, indicating similar efficacy to that of S-1 plus cisplatin. The excellent result of our SOX regimen in MST may be explicable by good PFS and feasible safety profile, which enabled patients to receive the second-line chemotherapy in the high proportion (89%). The efficacy of SOX regimen was also comparable with epirubicin and oxaliplatin plus capecitabine in the REAL-2 study (1-year survival rate of 47% and MST of 11.2 months) [8], which demonstrated that oxaliplatin was as effective as cisplatin combined with epirubicin and 5-FU or capecitabine.

Comparison of safety between the present SOX regimen and S-1 plus cisplatin that were reported previously [11] indicates a lower incidence of grade 3/4 toxicity with SOX regimen than S-1 plus cisplatin for leucopenia (4% versus 11%), neutropenia (22% versus 40%), anemia (9% versus 26%), anorexia (6% versus 30%), and nausea (2% versus 11%). The incidence of grade 3/4 thrombocytopenia was higher with SOX regimen (13% versus 5%). Sensory neuropathy is a characteristic toxicity of oxaliplatin, and 89% of the patients receiving SOX regimen had neuropathy, but only 4% had severe (grade 3/4) neuropathy. These results indicate that SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety.

Yamada et al. [15] reported that the treatment was discontinued at high frequency (28%) due to prolonged thrombocytopenia when metastatic colorectal cancer patients were treated with S-1 plus 130 mg/m^2 of oxaliplatin. This discontinuation was supposed to be caused by the geniality of dose reduction criteria which allowed the reduction of oxaliplatin only in case of occurrence of grade 3 or more toxicity in terms of thrombocytopenia. The incidence of thrombocytopenia was 93% in all grades and 28% in grade 3/4, resulting in low median relative dose intensity of S-1 74.6% and that of oxaliplatin 82.8%. Zang et al. [16] also reported the study of SOX regimen with 130 mg/m^2 of oxaliplatin in patients with metastatic colorectal cancer. In their study, the treatment was interrupted in cases of grade 2 or higher toxicity until the recovery to grade 0 or 1, and the doses of oxaliplatin and S-1 were reduced after a second occurrence of grade 2 toxicity. As a result, the incidence of thrombocytopenia was 13% in grade 3/4, and the median relative dose intensity of oxaliplatin and S-1 was 82% and 82%, respectively. In this study, we used 100 mg/m^2 dose of oxaliplatin as SOX regimen for advanced gastric cancer to decrease the incidence of thrombocytopenia considering the possible bleeding from the primary tumor and to maintain the dose intensity of S-1, which have been demonstrated to a key drug against advanced gastric cancer as a single agent. In this new regimen, the incidence of

thrombocytopenia was 13% in grade 3/4 without reducing the antitumor activity. The median relative dose intensity of oxaliplatin and S-1 was 87.5% and 85.7%, respectively, indicating that the treatment was carried out as scheduled in most of patients in this study.

In conclusion, SOX regimen with oxaliplatin at a dose of 100 mg/m^2 was effective and well tolerated in patients with advanced gastric cancer. SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. Further investigation of this SOX regimen is expected.

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disclosure

All authors declared no conflicts of interest.

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Review article

Combination therapy with S-1 and irinotecan (CPT-11) for advanced or recurrent gastric cancer

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Abstract
S-1 and irinotecan (CPT-11) are active agents against gastric cancer. Some preclinical studies have demonstrated the theoretical background of combination therapy with S-1 and CPT-11 for gastric cancer. Based on these findings, several phase I/II studies of this combination therapy, which has been proposed as a candidate of standard treatment for advanced or recurrent gastric cancer in Japan, have been conducted. Although there were slight differences in the administration schedules of the combination therapy with S-1 and CPT-11 in these phase II studies, the response rates were more than 50%, and the median survival time (MST) exceeded 1 year. Also, good safety profiles were reported. These results warranted a further, phase III, study to define the efficacy of the combination in improving survival. In a phase III study (GC0301/TOP 002 trial), the response rate, the 1-year survival rate, and the MST in the arm with combination therapy of S-1 and CPT-11 were better than these parameters in the S-1 monotherapy arm. However, at 1.5-year follow-up, the overall survival (OS) in the combination therapy of S-1 and CPT-11 arm did not exceed that in the S-1 monotherapy arm [P = 0.23; hazard ratio (HR), 0.89]. As 22% of the patients were censored, further follow-up is needed to determine the OS with more precision. But, of note, in the SPIRITS trial, combination therapy with S-1 and cisplatin (CDDP) significantly prolonged OS compared to S-1 monotherapy (P = 0.037; HR, 0.77), suggesting that CPT-11 may not be the best partner to use in combination with S-1 at present.

Key words Gastric cancer · Irinotecan · S-1 · Combination chemotherapy

Introduction

S-1, an oral 5-fluorouracil (FU) derivative developed in Japan in 1999, consists of tegafur (FT) and two modulators, 5-chloro-2, 4-dihydroxypyridine [CDHP; a potent dihydropyrimidine dehydrogenase (DPD) inhibitor] and potassium oxonate (OXO; an orotate phosphoribosyl transferase inhibitor), at a molar ratio of 1:0.4:1, with the two modulators added in order to enhance antitumor effects via increasing the blood 5-FU concentration and reducing digestive toxicity [1, 2]. Two late phase II studies demonstrated the efficacy of single-agent therapy with S-1 for gastric cancer; the response rates were 49% (25/51) and 44% (19/43), respectively; these rates being high for single-agent anticancer therapy [3, 4]. In addition, S-1 is an oral preparation, and this route may be advantageous for patients undergoing chemotherapy. Thus, in Japan, single-agent therapy with S-1 has been emphasized as a standard treatment for advanced or recurrent gastric cancer. In 2007, the Japan Clinical Oncology Group (JCOG) presented the results of a randomized phase III study (JCOG 9912) including S-1 monotherapy at the annual meeting of the American Society of Clinical Oncology (ASCO); the efficacy of S-1 showed significant noninferiority to that of 5-FU alone. S-1 was recognized as a potent oral antitumor agent [5].

Irinotecan (CPT-11) is also an antitumor agent developed in Japan; its action mechanism involves the inhibition of topoisomerase I [6]. Concerning the efficacy of CPT-11 monotherapy for advanced gastric cancer, the response rates were 19.0% (4/21) and 18.4% (14/76), respectively, in early and late phase II studies in Japan [7, 8]. This agent may be useful for treating advanced or recurrent gastric cancer. Various combination therapies incorporating CPT-11 have been studied in clinical trials in Japan, especially combinations with cisplatin (CDDP) and S-1, and the potent antitumor effects of these combinations have been confirmed [9–13]. Based on these results, two randomized phase III studies were conducted in Japan. In this article, I focus on combination therapy with S-1 and CPT-11 for advanced or recurrent gastric cancer, and review the results of phase

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I/II clinical studies of combination therapy with S-1 and CPT-11 that were conducted in Japan [10–13]. In addition, I discuss the current and future perspectives of this combination therapy, based on the results of a randomized phase III study (S-1 vs S-1 + CPT-11; GC0301/TOP 002) reported at the Gastrointestinal Cancer Symposium in 2008 [14].

Theoretical background of combination therapy with S-1 and CPT-11 in gastric cancer

The action mechanism of fluoropyrimidines differs from that of CPT-11, and animal experimental studies have demonstrated the effects of fluoropyrimidine and CPT-11 combination therapy [15]. In colorectal cancer patients, combination therapy with CPT-11 and 5-FU (such as FOLFIRI regimen) was effective [16, 17]. In gastric cancer patients, the combination of fluoropyrimidines and CPT-11 may also be useful. Takiuchi et al. [18] reported that S-1 plus CPT-11 showed an augmented antitumor effect against 5-FU-resistant tumors with high thymidylate synthase (TS) activity, compared to CPT-11 alone and S-1 alone in an experimental study. A potential mechanism of this effect was suggested by the significant reduction in TS activity observed in tumors with high TS activity following CPT-11 administration (Fig. 1) [18]. Ichikawa et al. [19] investigated the mRNA expression of TS and a 5-FU-metabolizing enzyme, DPD, in their series, and indicated that many patients with low-level TS expression responded to S-1 alone, whereas a high proportion of patients with S-1-resistant tumors (some of whom had high-level TS-expression) responded to the combination of S-1 and CPT-11. On the other hand, both Takiuchi et al. [18] and Ichikawa et al. [19] reported that there was no relationship between high or low DPD mRNA expression and tumor response to either S-1 monotherapy or to combination therapy with S-1 and CPT-11. Fluoropyrimidines are a mainstay of palliative treatment for advanced or recurrent gastric cancer. S-1 has a theoretical advantage over 5-FU in terms of having antitumor activity that appears to be independent of the level of DPD expression, suggesting that S-1 should be active in tumors expected to be resistant to 5-FU on the basis of high DPD expression. Moreover, the combination of S-1 and CPT-11 should also be active in tumors expected to be resistant to S-1 monotherapy on the basis of high TS expression. Based on this theoretical background, several phase I/II clinical studies of combination therapy with S-1 and CPT-11 were conducted.

Phase I/II clinical studies of combination therapy with S-1 and CPT-11

The results of the main phase I/II studies of combination therapy with S-1 and CPT-11 in patients with advanced or recurrent gastric cancer in Japan are summarized in Table 1. Komatsu et al. [10] conducted a phase I study to estimate the maximum tolerated dose (MTD) of CPT-11 on days 1 and 15, given in combination with S-1, administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of each 4-week cycle. Fifteen patients were treated with increasing dose levels of CPT-11, as follows: CPT-11, 100 mg/m^2 (level 1); 125 mg/m^2 (level 2); and 150 mg/m^2 (level 3). All the patients were found to be assessable for drug safety. If level 3 was tolerated, this dose became the

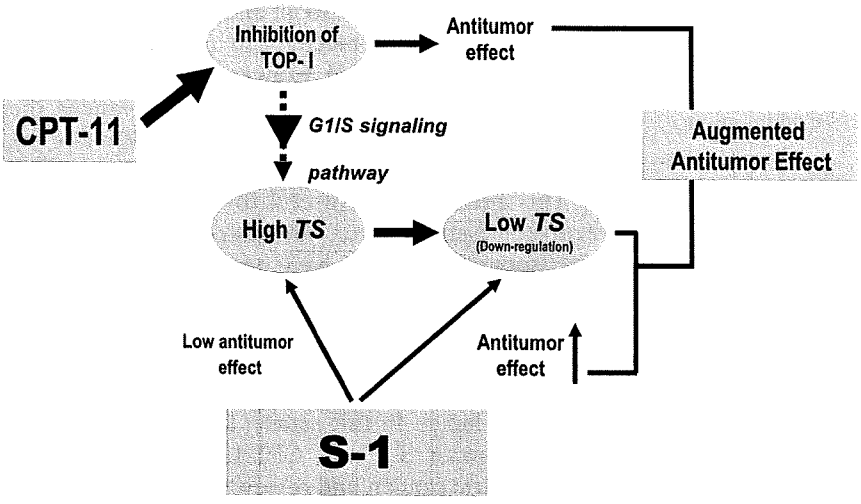

Fig. 1. Possible interaction between irinotecan (*CPT-11*) and S-1, which consists of tegafur and two modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP; a potent dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (OXO; an orotate phosphoribosyl transferase inhibitor), at a molar ratio of 1: 0.4: 1.
TOP-I, Topoisomerase I; *TS*, thymidylate synthase

Table 1. Phase I/II clinical studies of combination therapy with S-1 and CPT-11 in Japan

Dose (mg/m^2 per day)		Number of cases		Recommended dose (RD; mg/m^2)	Response rate (phase II)	Median survival time (MST; days)	Toxicity profile with RD (grade 3≤ ; %)		Author
CPT-11	S-1	Phase I	Phase II						
Level 1: 100	80	6	—	Level 2: 125	54% (13/24)	581	Neutropenia	60	Komatsu [10] (2006)
Level 2: 125	80	6	24[a]				Anemia	7	
Level 3: 150	80	3	—				Diarrhea	7	
							Nausea/Vomiting	27	
							Dermatitis	7	
Level 1: 40	80	6	—	Level 3: 80	48% (11/23)	394	Leukopenia	4.3	Takiuchi [11] (2005)
Level 2: 60	80	3	—				Neutropenia	8.7	Uedo [12] (2007)
Level 3: 80	80	4	23[a]				Anemia	8.7	
Level 4: 100	80	6	—				Diarrhea	4.3	
							Anorexia	4.3	
Level 1: 70	80	3	—	Level 2: 80	61% (31/51)	444	Leukopenia	12	Inokuchi [13] (2006)
Level 2: 80	80	7	51[a]				Neutropenia	14	
Level 3: 90	80	3	—				Anemia	3	
Level 3: 100	80	3	—				Thrombocytopenia	2	
							Anorexia	10	
							Nausea	7	
							Vomiting	5	
							Alopecia	10	

[a] Includes cases registered with the phase I trial

recommended dose in combination with S-1, because the maximum approved dose of CPT-11 alone in Japan is 150 mg/m^2. S-1, with dosage determined on the basis of the body surface area (BSA), was given orally for 2 weeks at the following doses: 40 mg (BSA < 1.25 m^2), 50 mg (BSA ≥ 1.25 to < 1.5 m^2), or 60 mg (BSA ≥ 1.5 m^2) twice daily (standard dose in Japan), followed by 2 weeks without treatment. Even at level 3, the MTD was not reached. However, at level 1, marked bone marrow suppression was noted in 1 patient. Therefore, the Efficacy and Safety Committee recommended that the recommended dose (RD) of CPT-11 should be established as 125 mg/m^2. In a phase II study, 24 patients with measurable lesions were enrolled. A total of 91 cycles were administered (median, 5.9 cycles). The response rate was 54% (13/24), and the median survival time (MST) was 581 days. The main grade 3 or higher side effects included neutropenia (60%) and nausea/vomiting (27%).

Takiuchi et al. [11] conducted a phase I study to determine the MTD and RD of CPT-11, given on days 1 and 15 in combination with S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–21 of each 5-week cycle. Nineteen patients were treated with increasing dose levels of CPT-11, as follows: CPT-11, 40 mg/m^2 (level 1); 60 mg/m^2 (level 2); 80 mg/m^2 (level 3); and 100 mg/m^2 (level 4). No dose-limiting toxicity (DLT) was observed at either level 1, 2, or 3. At dose level 4, three of six patients exhibited DLTs in the first course; one of the three patients had grade 3 diarrhea, and the other two patients had grade 3 rash; all three skipped the second administration of CPT-11 on day 15 because of delayed resolution of grade 2 leukopenia. The RD of CPT-11 in combination with S-1 was the dose of 80 mg/m^2 at level 3 according to the protocol definitions [11]. In a phase II study, 23 patients were enrolled to investigate the efficacy and safety of the combination. The response rate, median time to progression (TTP), and MST were 47.8% (11/23), 210 days, and 394 days, respectively. The incidence of grade 3 or 4 hematological and nonhematological toxicities was 17.4% and 8.4%; the toxicities included neutropenia (8.7%), anemia (8.7%), diarrhea (4.3%), anorexia (4.3%), and nausea/vomiting (4.3%); the incidences of severe toxicities were generally low [12].

Inokuchi et al. [13] conducted a phase I study to estimate the MTD of CPT-11, given on days 1 and 8 in combination with S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14, followed by 2 weeks' rest. The cycle was repeated every 4 weeks. The doses of CPT-11 investigated were 70, 80, 90, and 100 mg/m^2. At 100 mg/m^2, DLT was noted in two of three patients. Initially, the RD was established as 90 mg/m^2. According to subsequent follow-up data, grade 4 bone marrow suppression was observed at 90 mg/m^2 in all three patients in the second course. Therefore, the RD was finally established as 80 mg/m^2. In a phase II study, 51 patients were registered to estimate the efficacy and safety of the CPT-11 and S-1 combination. The response rate and MST were 61% (31/51) and 444 days, respectively. Grade 3 or higher side effects were neutropenia (14%), anorexia (10%), nausea (7%), and vomiting (5%) [13].

Although there were slight differences in the administration schedules, these phase II studies showed response rates of more than 50% and MSTs exceeding 1 year when a CPT-11 and S-1 combination was given as first-line treatment in patients with advanced or recurrent gastric cancer. In terms of toxicity profiles, the administration schedule employed by Takiuchi et al. [11] was considered to be more acceptable than the schedules reported by Komatsu et al. [10] and Inokuchi et al. [13]. Based on these results, a randomized phase III trial has been conducted to evaluate the efficacy of combination therapy with S-1 and CPT-11 in improving survival, compared with that of S-1 monotherapy, for advanced or recurrent gastric cancer (GC0301/TOP 002).

Current status and future perspectives of combination therapy with S-1 and CPT-11

The results of the GC0301/TOP 002 (S-1 vs S-1 + CPT-11) trial were announced by Imamura et al. [14] at the Gastrointestinal Cancer Symposium in 2008. The primary endpoint was overall survival (OS), and the secondary endpoints were time to treatment failure, 1-year survival rate, response rate, and safety. The follow-up period was 1.5 years. In patients evaluable according to the response evaluation criteria in solid tumors (RECIST), the response rates were 26.9% in the S-1 monotherapy arm and 41.5% in the combination therapy of S-1 and CPT-11 arm, with the difference being statistically significant ($P = 0.035$). The 1-year survival rate was 44.9% in the S-1 monotherapy arm and 52.0% in the combination therapy of S-1 and CPT-11 arm. In the two arms, the main grade 3 or higher side effects consisted of neutropenia (S-1 vs S-1 + CPT-11; 10.6% vs 26.6%), diarrhea (S-1 vs S-1 + CPT-11; 5.6% vs 15.8%), anorexia (S-1 vs S-1 + CPT-11; 9.9% vs 15.8%), nausea (S-1 vs S-1 + CPT-11; 3.7% vs 7.0%), and vomiting (S-1 vs S-1 + CPT-11; 0.6% vs 2.5%). The incidences of severe toxicity were slightly higher in the combination of S-1 and CPT-11 arm, but the toxicity was tolerable in both arms. The MST in the S-1 monotherapy arm was 318 days and that in the combination of S-1 and CPT-11 arm was 389 days; however, at 1.5-year follow up, the OS in the combination of S-1 and CPT-11 arm did not significantly exceed that in the S-1 monotherapy arm [*P*

= 0.23; hazard ratio (HR) = 0.89]. It was concluded that, considering that 68 patients (22%) were censored (mainly due to unexpectedly long survival times in both arms), further follow-up would be needed to confirm the OS with more precision.

On the other hand, as it was announced — at the annual meeting of ASCO in 2007 (SPIRITS trial) — that combination therapy with S-1 and CDDP significantly prolonged OS compared to S-1 monotherapy, it seems that CPT-11 may not be the best partner in combination with S-1 at present [20]. In a previous study comparing CPT-11 plus 5-FU/folinic acid (IF) with 5-FU plus CDDP (FP), OS in the IF arm did not exceed that in the FP arm, leading to the conclusion that IF would be the treatment choice for patients in whom CDDP administration is not possible for some reason [21]. In addition, in the JCOG 9912 trial reported by Boku et al. [5] in 2007, at the annual ASCO meeting, combination therapy with CPT-11 and CDDP did not show statistically significant superiority to 5-FU monotherapy, in terms of OS. Therefore, at present, no CPT-11-based regimens can be recommended as first-line treatment for advanced or recurrent gastric cancer. However, the report of the GC0301/TOP002 trial is not a final result, and further follow-up of the censored cases is still underway. In the near future, the final report of this trial should help us to resolve the question of the use of CPT-11 for treating gastric cancer.

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大阪医大誌　68, 1：52～53

2008大腸癌化学療法のトピック　～抗EGFR抗体～

瀧　内　　比呂也

大阪医科大学化学療法センター

近年ドラッグラグが社会問題となっていた大腸癌化学療法は，本年の抗EGFR抗体セツキシマブの臨床導入を機に，ついに欧米と同様の治療を展開できるところまできた。今後は国内での臨床試験の更なる充実により，海外に向けて発信できるエビデンスを作ることが重要と考えられる。セツキシマブは一次治療から三次治療まで，また単剤での使用から化学療法との併用まで幅広く有効性が示されているが，KRASを始めとするバイオマーカーについて興味深い報告がなされている。特にKRASの変異型を有する症例にはセツキシマブの効果が全く期待できないとの報告が2008ASCOのプレナリーセッションでなされ，その事実が様々なトライアルでもretrospectiveに確認されている。これは大腸癌化学療法における本年度最大のトピックである。

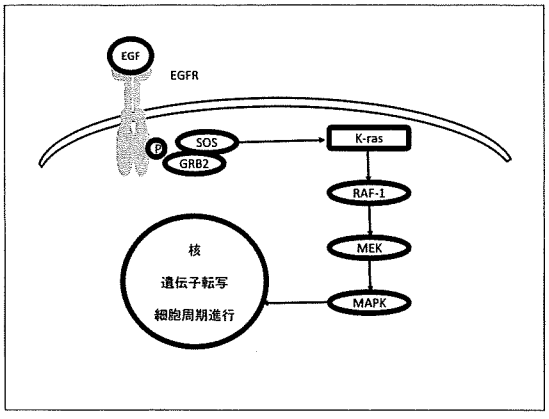

図1　上皮成長因子受容体(EGFR)からのシグナル伝達
リガンド結合ドメインにEGFが結合すると，EGFRあるいは他のHERファミリー受容体と二量体を形成し，細胞内の受容体型チロシンキナーゼ(tyrosine kinase, TK)ドメインで自己リン酸化が起こり，引き続いて下流へのシグナル伝達が起こる。このシグナル伝達には多数の経路の関与が考えられており，細胞のがん化と深く関連している経路がRas-mitogen-activated protein kinase (MAPK)経路である。

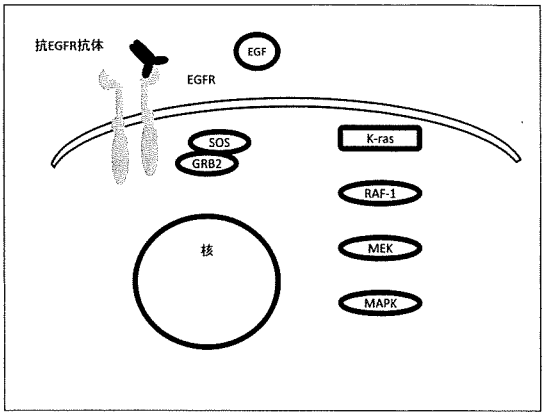

図2　抗EGFR抗体によるシグナル抑制
セツキシマブはリガンド結合ドメインに直接結合して二量体の形成を阻害する。その結果TKドメインでの自己リン酸化が抑制され，下流へのシグナル伝達を抑制することにより抗腫瘍効果を発揮する。

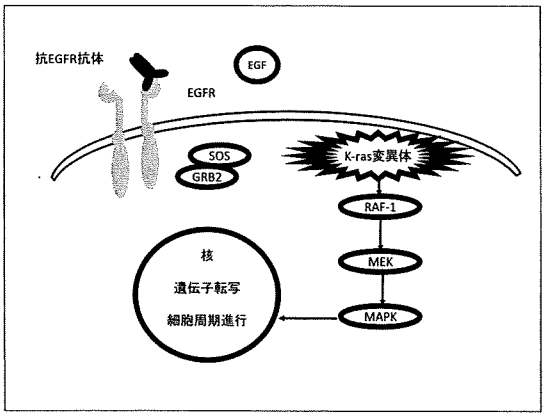

図3　K-ras変異体による恒常的シグナル
*Ras*遺伝子の変異が起こると，Ras変異体が形成され，上流からのシグナル伝達のコントロールは失われてしまう。

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●特 集● セカンドライン化学療法・分子標的治療の進歩

胃癌におけるSecond-Line化学療法・分子標的治療の進歩

瀧内比呂也*

〔*Jpn J Cancer Chemother* **36**(5): 717-720, *May*, 2009〕

The Progress of Second-Line Chemotherapy and Molecular Targeting Agents in Gastric Cancer: Hiroya Takiuchi (*Cancer Chemotherapy Center, Osaka Medical College*)

Summary

According to the results of Japanese phase Ⅲ trials recently reported such as JCOG 9912 and SPIRITS, there was a remarkable improvement in median survival time compared to the previous phase Ⅲ study (JCOG 9205). Many newer agents were used, such as taxane and irinotecan, which were absent during JCOG 9205. Using these agents as a second-line treatment may lead to improved survival. However, there is no evidence of a randomized control trial of second-line treatment. At present, several study groups are conducting randomized control trials to establish a standard for second-line therapy. However, there are several issues regarding the study design, especially a control arm. In future trials, we should exchange information among study groups to discuss the important issues involved. On the other hand, molecular targeting agents that have shown activity in other tumor types such as trastuzumab, bevacizumab, cetuximab, and lapatinib are under investigation in global randomized control trials. In these trials, patients from Japan and Korea account for more than half of the enrollees. The number of international studies is increasing, and the role of east Asian countries will be more important in this field. **Key words:** Advanced gastric cancer, Chemotherapy, Second-line, Molecular targeting agents, **Corresponding author:** Hiroya Takiuchi, Cancer Chemotherapy Center, Osaka Medical College, 2-7 Daigaku-cho, Takatsuki, Osaka 569-0801, Japan

要旨 最近わが国から相次いで報告された無作為化比較試験の生存期間中央値が，以前に報告されている試験結果のそれと比べて明らかに延長している。その一因としてsecond-line化学療法の寄与も大きいことが指摘されている。残念ながら現在までのところsecond-lineに関するRCTの報告はいまだ一つもなく，second-lineにおける標準的治療は存在しない。現在多くの臨床試験グループがsecond-lineの無作為化比較試験を実施しており，標準的治療の確立が期待されている。その一方でこれら臨床試験における問題点も明らかとなり，わが国全体の問題として解決すべき点もある。さらに，わが国において他癌腫で効果が確認されている分子標的治療薬が国際共同治験として検証されており，その結果に大きな期待が寄せられている。今後，分子標的治療薬の開発において，東アジア諸国の役割は重要性を増していくものと思われる。

最近報告された二つの無作為化比較試験（RCT）のJCOG9912試験ならびにSPIRITS試験により，わが国における切除不能進行・再発胃癌に対する標準的治療法が確立されたといっても過言ではない[1,2]。また1990年代に行われたJCOG9205試験における生存期間中央値（MST）と比べると，JCOG9912試験におけるMSTは明らかに延長している。その一因としてsecond-line化学療法の寄与も大きいことが指摘されている。残念ながら現在までのところsecond-lineに関するRCTの報告はいまだ一つもなく，これらは推論にしかすぎない。本稿では，最近報告された臨床試験結果から，いわゆるsecond-line化学療法の進歩と考えられている部分にフォーカスを当て，それが真実なのか，はたまた単なるわれわれの思い込みにすぎないのかを論じることにする。また，最近わが国も参加・計画している分子標的治療の国際共同治験の開発状況も併せて紹介する。

Ⅰ．JCOG9205試験とJCOG9912試験

Japan Clinical Oncology Group（JCOG）で行われたJCOG9205試験は，JCOG9912試験の一つ前に行われた

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0385-0684/09/¥500/論文/JCLS

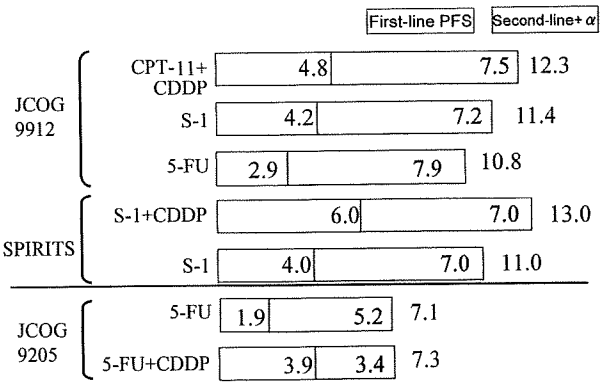

図 1 わが国における無作為化比較試験における first-line の無増悪生存期間（PFS）と second-line 以降の生存期間

試験である。1992 年に開始されたこの試験は，当初 5-FU vs 5-FU＋CDDP vs UFT＋MMC の 3 群比較であった。しかし中間解析の結果，UFT＋MMC が 5-FU を上回ることができない可能性が高いことが明らかとなり，中間解析以降，試験の対象から外された。そして最終的にこの試験は，5-FU vs 5-FU＋CDDP の 2 群比較となり，5-FU＋CDDP が 5-FU 単独を全生存期間で上回ることができなかったことが報告されている[3]。その時の 5-FU の MST は 7.1 か月で，無増悪生存期間（PFS）の中央値は 1.9 か月であった。この結果から単純な引き算をすると，second-line 以降の MST が 5.2 か月となる。引き続き行われた JCOG9912 試験では，再度 5-FU をコントロールにおいて試験が行われた。JCOG9912 試験における 5-FU の MST は 10.8 か月で，無増悪生存期間（PFS）の中央値は 2.9 か月であった。この結果に対し，同様の引き算をすると second-line 以降の MST が 7.9 か月となる（図 1）。同じ臨床試験グループで行われた試験で，異なる時代の 5-FU に関する生存期間のデータが得られた。しかも新しい試験における 5-FU の second-line 以降の MST が 2.7 か月延長していることになる。この事実が，わが国における second-line 化学療法の進歩を示す根拠として取り上げられることも多い。

JCOG9912 試験における 5-FU の second-line 以降の MST が 2.7 か月延長した理由として二つの理由が考えられる。まず second-line 以降の有効薬剤が JCOG9205 試験当時より増えたことがあげられる。JCOG9205 試験における second-line での使用薬剤は，CDDP や MTX などのいわゆる old generation drug であった。一方，JCOG9912 試験では second-line として taxane や irinotecan といった new generation drug が主に使用されており，それら薬剤の違いが 2.7 か月の差となったと考えられている。その一方で別の角度から，JCOG9205 試験と JCOG9912 試験における second-line への移行率の違いにも目を向ける必要もあろう。JCOG9205 試験における 5-FU の second-line への移行率は約 57％だったのに対して，JCOG9912 試験での 5-FU の second-line への移行率は約 81％と約 24％も増加していた。その second-line への移行率の差が，この 2.7 か月の差になったと考えられないことはないのか，慎重に見極める必要がある。

Ⅱ．Second-line 化学療法は進歩したのか？

JCOG9205 試験と JCOG9912 試験の second-line への移行率において 24％もの差が生じた理由の一つとして，両試験の対象患者に違いがあった可能性に留意すべきである。すなわち JCOG9205 試験が行われていた当時は，わが国における臨床試験の拡がりは今ほどではなく，登録された患者も現在われわれが臨床試験に登録する患者と比べると，病状の進んだ症例が数多く登録されていた可能性がある。なぜなら今回の JCOG9912 試験では，少なくとも中等度および高度腹膜播種症例が除外されていたからである。よって JCOG9912 試験では second-line への移行率も全体としてよくなり，second-line 以降の生存も延長したと考えられなくもない。

現在までのところ胃癌における second-line 治療の意義を証明した RCT は存在しない。またわが国で使用頻度の高い paclitaxel や irinotecan といった薬剤の，second-line における質の高い第Ⅱ相試験のデータも存在しない。よってわが国の方向性を見誤らないためにも，ベースラインのエビデンスを押さえておく必要がある。現在わが国において，初回治療でフッ化ピリミジン系薬剤に治療抵抗性となった腹膜転移を有する患者を対象にして，best available 5-FU と second-line として使用頻度の高い weekly paclitaxel との探索的な無作為化第Ⅱ相試験（JCOG0407 試験）が行われている。すでに 100 例の目標症例集積も終了して最終解析結果を待っている状況である。この試験において，best supportive care を想定した best available 5-FU に対して，仮に weekly paclitaxel の全生存期間がよい傾向を示さなかった場合，われわれは new generation drug に対する幻想をみていたと結論付けてもいいのかもしれない。second-line におけるベースラインのエビデンスを押さえるためにも JCOG0407 試験の結果に注目している。

現在数多くの分子標的治療薬が開発され，胃癌領域における開発も盛んになってきた。それらの多くは，国際共同治験として開発が進められている。second-line のエビデンスがないので，特に新薬開発においてはその薬剤の効果を確かめる方法として，best supportive care をコントロールアームとした試験がいくつも計画されて

表 1　わが国で実施中の second-line 化学療法の臨床試験

研究 ID	研究内容	相	集積目標	状況
OGSG0701	CPT-11 vs PTX vs S-1 併用群 (S-1/CPT-11 vs S-1/PTX)	r-P Ⅱ	120	active
CCOG0701	weekly PTX vs S-1＋weekly PTX	r-P Ⅱ	80	active
GI-0801 (TCOG)	CPT-11 vs CPT-11/CDDP for S-1-refractory	Ⅲ	130	active
GC-05 (JACCRO)	S-1 vs S-1/CPT-11	Ⅱ/Ⅲ	300	active
TRICS (ECRIN)	CPT-11/CDDP vs CPT-11	Ⅲ	200	active
WJOG4007	PTX vs CPT-11	Ⅲ	220	active

表 2　わが国で現在行われている国際共同治験一覧（胃癌）

国際共同治験名	検証される分子標的治療薬	First or second-line	相	予定患者数	現状
ToGA	trastuzumab	first	Ⅲ	374	On-going（集積終了）
AVAGAST	bevacizumab	first	Ⅲ	760	On-going（集積終了）
EXPAND	cetuximab	first	Ⅲ	870	On-going
LOGIC	lapatinib	second	Ⅲ	260	On-going

いる。特に mTOR inhibitor である RAD001（everorimus）は，わが国で行われた第Ⅱ相試験によって胃癌に対する POC が得られた薬剤であり，best supportive care をコントロールにした国際共同治験が間もなく開始される予定である。

Ⅲ．わが国における second-line 化学療法の臨床試験

現在わが国においては，表1に示すようないくつもの second-line の臨床試験が進行中である。大阪消化管がん化学療法研究会（OGSG）において，S-1 単独または S-1/CDDP 併用療法に抵抗性となった進行・再発胃癌に対する second-line の無作為化比較第Ⅱ相試験を実施している。試験の目的は S-1 failure 後の second-line chemotherapy の確立を目指して，現在の community standard である weekly paclitaxel に対する irinotecan の生存期間延長効果，および単独療法（paclitaxel，irinotecan）に対して S-1 を上乗せすることによる生存期間延長効果を探索的に検討する試験である。また同じ対象で，中部臨床腫瘍研究機構（CCOG）では weekly paclitaxel vs S-1/paclitaxel 併用療法の無作為化比較第Ⅱ相試験が実施中である。その一方で，わが国における様々な臨床試験グループによってほぼ同じ患者群を対象とした RCT がいくつも行われている。西日本がん研究機構（WJOG）では S-1 単独または S-1/CDDP 併用療法に抵抗性となった進行・再発胃癌に対する二次治療の無作為化比較第Ⅲ相試験（weekly paclitaxel vs irinotecan）が行われている。日本がん臨床試験推進機構（JACCRO）では irinotecan vs S-1/irinotecan 併用療法の無作為化比較第Ⅲ相試験が行われている。これらの試験は二次治療における S-1 継続の意義を検証するデザインとなっている。また疫学臨床試験研究支援機構（ECRIN）と東京がん化学療法研究会（TCOG）はともに irinotecan vs irinotecan/CDDP 併用療法の無作為化比較第Ⅲ相試験を実施している。これらの試験は，一次治療や術後補助化学療法として S-1 単独が使用された場合に，irinotecan を second-line として選択する場合のベストレジメンを検証する試験である。

Ⅳ．わが国における second-line 化学療法の臨床試験における問題点

これら second-line 化学療法に関する検証的な RCT おいて，試験によってコントロールアームが異なっていることは大きな問題である。WJOG の試験では weekly paclitaxel の MST を 5 か月，irinotecan に 50%の全生存期間の上乗せを期待するデザインとなっている。その一方 JACCRO では，irinotecan の MST を 5 か月と仮定し，S-1/irinotecan の MST を 7 か月と仮定して，症例設定がなされている。同じく ECRIN でも，irinotecan の MST を 5 か月，irinotecan/CDDP 併用の MST を 8 か月と仮定して，症例設定がなされている。WJOG の試験アームの irinotecan が，JACCRO や ECRIN の試験ではコントロールアームになっており，もしすべての試験が negative に終わった時のデータ解釈はたいへん難しいものがある。限りあるリソースを有効利用して，いち

早く患者サイドに標準的治療を届けるためには，各臨床試験グループの情報共有が今後よりいっそう必要となろう。

V．胃癌における分子標的治療薬の開発状況と今後

現在他癌腫で効果が確認されている bevacizumab（AVAGAST trial），cetuximab（EXPAND trial），trastuzumab（ToGA trial），lapatinib（LOGIC trial）などが国際共同治験として検証されている（表2）。これら試験のなかで，AVAGAST trial および ToGA trial は症例集積も終了し，解析結果を待っている状況である。これらの分子標的治療薬の有用性が確認されれば，さらなる胃癌治療の発展に大きく寄与することは間違いない。またこれら試験における登録患者の半数近くは，わが国および韓国からの症例である。今後，分子標的治療薬の開発において，胃癌患者数の多い東アジア諸国の役割は，ますます重要性を増していくものと思われる。

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胃がん Part2

胃がんの治療各論

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はじめに

胃がんに対する化学療法の目的はおのおのの進行度(病期)によって異なる．StageⅡ～Ⅲにおける術後補助化学療法のおもな目的はがんの再発予防である．また，根治手術ができないstageⅣの進行・再発がんに対する化学療法の目的は延命である．しかし実際にこれらの目的が達成できているかどうかを証明することは困難であったが，新規抗がん剤の開発により，stageⅡ～Ⅲ胃がんに対する術後補助化学療法の有用性が明らかとなり，stageⅣ進行・再発胃がんに対しても新たな標準治療が確立された．本稿では化学療法の適応となる病期ごとの標準治療について述べる．ただし術前補助化学療法の意義はまだはっきりせず，実験的治療として位置づけられているため，今回は割愛した．

1. 病期分類と予後

わが国では胃癌取扱い規約（日本胃癌学会編；2009年中に第14版刊行予定）による病期分類が用いられており，T（腫瘍の胃壁深達度）およびN（リンパ節転移程度）の組み合わせで病期が決定される．予後のよいものからstageⅠ～Ⅳに分けられ，腹膜や遠隔臓器（肝臓・肺など）転移がある場合はstageⅣであり通常根治手術はきわめて困難な状態と考えられている（表❶）[1]．それぞれの進行度における5年生存率はstageⅠ：約90%，Ⅱ：約70%，Ⅲ：約30～50%とされている．さらに，根治手術ができないstageⅣや術後再発症例で診断時に全身状態が良好な場合の生存期間中央値は10～13ヵ月と考えられる．

2. 治療

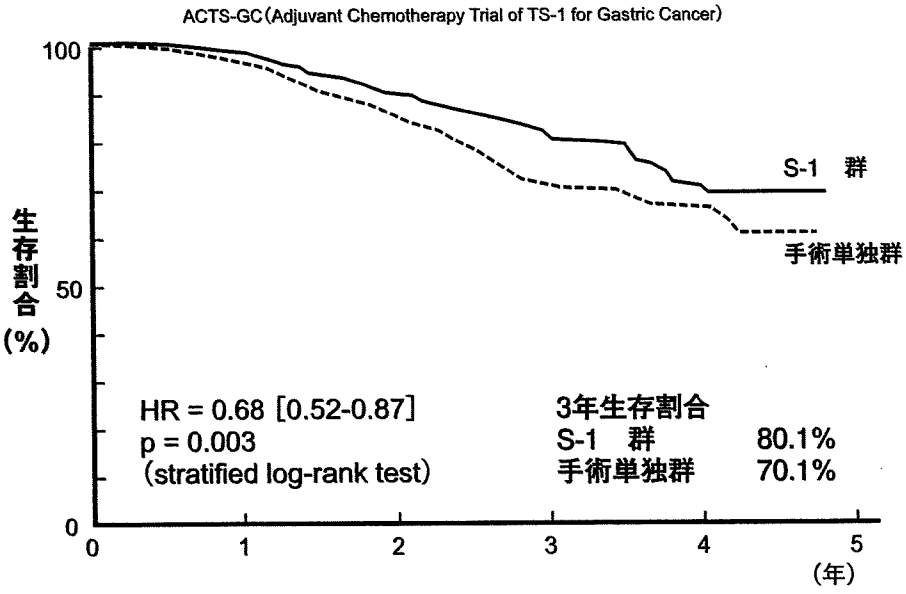
1) 術後補助化学療法

StageⅠの症例は内視鏡治療や手術単独治療で十分な効果が得られるため，通常術後補助化学療法はおこなわれない．一方，stageⅡ/Ⅲの症例に関しては，術後補助化学療法の検討が数多くされてきた．しかし，手術単独治療より有用な治療法の開発は困難をきわめ，2004年に日本胃癌学会から発行された胃癌治療ガイドライン〔第2版〕(2009年3月第3版発行）によれば，胃がん術後補助化学療法の適応条件として「臨床

表❶ 胃がんの進み具合（病期，ステージ）

深さ・転移 ＼ リンパ節	リンパ節への転移がない	胃に接したリンパ節に転移がある（1群）	胃を養う血管に沿ったリンパ節に転移がある（2群）	さらに遠くのリンパ節に転移がある（3群）
胃の粘膜から粘膜下層までの深さである（T1）	IA	IB	Ⅱ	Ⅳ
胃の表面にがんが出ていない，筋層あるいは漿膜下層まで（T2）	IB	Ⅱ	ⅢA	
漿膜を超えて胃の表面に出ている（T3）	Ⅱ	ⅢA	ⅢB	
胃の表面に出たうえに，他の臓器にもがんが連続している（T4）	ⅢA	ⅢB		
肝，肺，腹膜など遠くに転移している	Ⅳ			

（胃癌治療ガイドラインの解説（一般用），日本胃癌学会 編，金原出版[1]より一部改変引用）



図❶ stageⅡ/Ⅲの胃がんに対するS-1を用いた術後補助化学療法
(Sakuramoto S *et al*, 2007[2]より改変引用)

表❷ 根治手術不能進行・再発胃がんに対する化学療法の無作為化比較試験(化学療法 vs 無治療)

報告者	症例数	治療	生存期間中央値(ヵ月)	P値
Pyrhönen[4] (フィンランド)	41	FEMTX 無治療	12 3	<0.01
Murad[3] (ブラジル)	40	FAMTX 無治療	9 3	<0.01
Glimelius[5] (スウェーデン)	18	(E) LF 無治療	10 4	<0.02
Scheithauer[6] (オーストリア)	37	ELF 無治療	7.5 4	<0.02
全体	136	化学療法群 BSC	10 3~4	

FEMTX:フルオロウラシル・エピルビシン・メトトレキサート
FAMTX:フルオロウラシル・ドキソルビシン・メトトレキサート
ELF :エトポシド・フルオロウラシル・ロイコボリン

試験においてのみ実施すべきである.」とされている. しかし, その後大規模な術後補助化学療法の比較試験(ACTS-GC)の成績が発表され, 日常臨床での胃がん術後の治療戦略も大きく様変わりした[2]. この試験はstageⅡ/Ⅲ胃がん患者に対するS-1による補助化学療法群と, 手術単独群の比較試験である. S-1群において, S-1投与は術後1年間内服投与とした. 治療レジメンはS-1 80mg/m²/日を4週間経口投与し, その後2週間休薬する計6週間のコースをくり返しおこなった. 2001年10月~2004年12月までに529例がS-1群に, 530例が手術単独群に割り付けられた. 3年全生存率はS-1群で80.1%, 手術単独群で70.1%であった(**図❶**)[2]. この試験は術後補助化学療法の有用性を, 手術単独群と比較して証明したはじめての大規模比較試験であり, この発表を受けて現在はstageⅡ/Ⅲの胃がん術後補助化学療法はS-1の1年間投与が標準治療と考えられている.

2) 根治手術ができない進行・再発胃がんに対する化学療法

・化学療法をおこなうことが延命に寄与するのか?

以前から根治手術ができない進行・再発胃がんに対する化学療法が本当に延命につながるのか否かについては明らかではなかった. 一般的には, 腫瘍縮小効果が高い治療法ほど延命につながるであろうという推測のもと, さまざまな抗がん剤の併用療法が試されてきた. 1990年代に入り化学療法施行群と無治療群との比較試験の結果がいくつか報告されたが[3], いずれの試験においても化学療法施行群が無治療群にくらべて生存期間を延長する(生存期間中央値:9~12ヵ月 vs 3~4ヵ月)ことを示すものであった(**表❷**)[3]~[6]. こ