In conclusion, excessive blood loss was found to be a prognostic determinant for survival after surgery for pancreatic cancer based on this analysis of patients at a large surgical center. As a treatment strategy for pancreatic cancer, methods to reduce blood loss should be considered an important focus and might be accomplished with continued innovation in surgical methods. There is no doubt that curative resection should be sought in all cases. From the surgical point of view, it is very important to successfully perform a curative resection and also reduce blood loss. Because pancreatectomy is one of the most complicated and challenging operations, there is still ample opportunity for surgeons to play a role in improving outcomes by pursuing sophisticated surgical techniques.

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ORIGINAL ARTICLE

Modified FOLFOX6 with oxaliplatin stop-and-go strategy and oral S-1 maintenance therapy in advanced colorectal cancer: CCOG-0704 study

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Abstract
Background A combination of fluorouracil and leucovorin (5-FU/LV) with oxaliplatin (FOLFOX) is an established first-line therapy for metastatic colorectal cancer (mCRC). However, the cumulative neurotoxicity of oxaliplatin often requires therapy to be discontinued while the patient is still responding. A strategy to stop FOLFOX, deliver 5-FU/LV as a maintenance therapy and reintroduce FOLFOX was found to be equivalent in terms of efficacy while neurotoxicity was substantially reduced. The aim of this study was to evaluate feasibility of a stop-and-go strategy with S-1, an oral fluoropyrimidine derivative, as a maintenance therapy administered between modified FOLFOX6 (mFOLFOX6) as a first-line treatment of mCRC.
Methods Thirty patients with untreated mCRC were treated with six cycles of mFOLFOX6 followed by maintenance therapy with oral S-1. Reintroduction of mFOLFOX6 was scheduled after four cycles of S-1 or upon tumor progression. The primary endpoint was duration of disease control (DDC).
Results Twenty-one of the 30 patients who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in 15 patients. Median DDC and progression-free survival were 9.3 and 7.9 months, respectively. The response rates and disease control rates were 40.0 and 86.6% for the initial mFOLFOX6, 23.8 and 57.1% for S-1 maintenance therapy and 20.0 and 73.3% for mFOLFOX6 reintroduction, respectively. Twenty-eight patients (93.3%) had peripheral neuropathy, but grade 3 neurotoxicity was observed in only 1 patient (3.3%).
Conclusion The planned oxaliplatin stop-and-go strategy with oral S-1 maintenance therapy was feasible as a first-line treatment for Japanese mCRC patients. Further prospective randomized control study is warranted.

Keywords Metastatic colorectal cancer · First-line chemotherapy · Oxaliplatin · Neurotoxicity · S-1

Introduction

The combination of fluorouracil and folinic acid (5-FU/LV) with oxaliplatin (FOLFOX) has been established as one of the standard first-line treatments for metastatic colorectal cancer (mCRC) [1]. However, the sensory neurotoxicity, which is an adverse event typically correlated to the cumulative dose of oxaliplatin, often requires discontinuation of oxaliplatin in patients who are still responding. Oxaliplatin-induced cumulative neurotoxicity has been reported in the range of 18–21% in the majority of trials [1–3].

Among various attempts to manage and prevent this adverse reaction, the planned oxaliplatin stop-and-go strategy with maintenance therapy by 5-FU/LV has been considered an appropriate option. Tournigand and de Gramont [4] showed the efficacy of modified FOLFOX-7 with infusional 5-FU/LV as a maintenance therapy in the OPTIMOX1 trial, and proceeded to give no maintenance therapy in the OPTIMOX2 trial [5]. These studies suggested that

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oxaliplatin could be stopped after six cycles without compromising the efficacy on the condition that maintenance therapy with 5-FU/LV was given.

Recently, some new oral fluoropyrimidine derivatives that can be given on an outpatient basis and thus avoid catheter-related problems have been introduced and their non-inferiority when compared with infusional 5-FU has been proven in numerous clinical trials [6–9]. S-1 is another oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil, CDHP is a dihydropyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyl transferase, reducing gastrointestinal toxicities [10, 11]. In addition, DPD inhibition in tumor cells has been suggested to contribute to anti-tumor effects since S-1 has been effective against various solid tumours with high DPD expression [11]. The response rate (RR) of S-1 as a single agent was promising at around 35% for mCRC [11, 12]. These results suggested that the efficacy of S-1 as a maintenance therapy might be comparable to that of infusional 5-FU/LV and that S-1 might also be more convenient for both patients and medical facilities.

The aim of this study was to evaluate modified FOLFOX6 (mFOLFOX6) with maintenance therapy by oral S-1 in patients with mCRC in the first-line setting.

Patients and methods

Patient selection

The study enroled patients with histologically confirmed unresectable metastatic adenocarcinoma of the colon or rectum, who had not previously received chemotherapy for metastatic disease. Patients who had been treated with adjuvant 5-FU-based chemotherapy were eligible provided they had remained disease-free for at least 6 months after the completion of adjuvant therapy. The other eligibility criteria included age of 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, bidimensionally measurable disease, a life expectancy of at least 3 months, adequate organ function (white blood cell count 3,000–12,000 cells per μL, platelet ≥100,000 per μL, aspartate aminotransferase (AST) ≤100 IU/L, alanine aminotransferase (ALT) ≤100 IU/L, total bilirubin ≤25.7 μmol/L (≤15 mg/L), and creatinine ≤106.1 μmol/L (≤12 mg/L)). Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhea; clinically evident gastrointestinal hemorrhage; and ascites or pleural effusion needing treatment. The protocol of this study was approved by the institutional review board or ethics committee of the participating institutions. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients who were entered into the study.

Treatment plan

Patients received mFOLFOX6 (consisting of a 2-h infusion of oxaliplatin at 85 mg/m^2 and l-LV 200 mg/m^2 followed by intravenous bolus of 5-FU at 400 mg/m^2 followed by a 46-h infusion of 5-FU at 2,400 mg/m^2, every 2 weeks) for six cycles. Treatment was continued until disease progression, unmanageable toxicity, withdrawal of consent, or until six treatment cycles were completed. Oral S-1 maintenance therapy was initiated for patients who were in a state of persistent objective response or stable disease (SD) after the six cycles of mFOLFOX6. S-1 (80 mg for patients with body surface area (BSA) <1.25 m^2; 100 mg for patients with BSA 1.25 < 1.5 m^2; 120 mg for patients with BSA ≥1.5 m^2) was administered orally in two divided doses for 28 days, followed by a 14-day treatment-free interval. In the event of disease progression or after a maximum of four cycles of S-1 treatment, mFOLFOX6 could be reintroduced. The reintroduced mFOLFOX6 was continued until progression, unacceptable toxicity, or patient's wish to terminate the treatment. Surgical treatment of the metastatic lesions was allowed in patients with sufficient objective response that rendered the lesions resectable.

Patient evaluation

Physical examination and laboratory tests were performed at baseline and repeated at least biweekly during treatment. Tumor size was assessed at the baseline (within 1 month before enrolment), after every four cycles of mFOLFOX6 therapy, and after every two cycles of S-1 therapy. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.

National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used to assess toxicity. Treatment was delayed until recovery when the white blood cell count fell below 3,000 cells per μL, platelets fell below 100,000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25.7 μmol/L, creatinine was higher than 106.1 μmol/L, and when the patient experienced diarrhea of grade 1 or greater, or other non-hematologic toxicities greater than grade 2. If a patient experienced either a grade 4 hematologic or a grade 3 or higher non-hematologic toxicity, the dose was decreased by one level at the subsequent treatment course.

Statistical considerations

The primary endpoint was duration of disease control (DDC), which was defined as progression-free survival (PFS), or, if mFOLFOX6 was reintroduced, addition of the initial PFS and the PFS of the reintroduction, except in the case of progression at the first evaluation after mFOLFOX6 reintroduction.

The secondary endpoint was PFS, overall survival (OS), RR (complete response (CR) and partial response (PR)) of each therapy, disease control rate (DCR) (CR, PR and SD) of each and safety.

The Kaplan–Meier method was used to calculate the distribution of DDC, PFS, and OS, and the log-rank test was used to compare the curves.

Results

Patient characteristics

Thirty patients were enrolled from November 2007 to December 2009. Baseline characteristics of the patients are presented in Table 1. The median age was 66 years (range 47–74 years). All patients had a performance status of 0 or 1.

Treatment diagram

Thirty patients were treated by initial mFOLFOX6 therapy. The oral S-1 maintenance therapy was initiated in 21 patients and mFOLFOX6 was reintroduced in 15 patients. A treatment diagram is presented in Fig. 1.

DDC, PFS and OS

After a median follow-up time of 26.9 months, 25 patients (83.3%) had disease progression, and 5 patients (16.7%) died of various causes. Median DDC, the primary endpoint, was 9.3 months (Fig. 2), and median PFS was 7.9 months (Fig. 3). Median survival time was not reached.

Initial mFOLFOX6 therapy

Thirty patients were treated by initial mFOLFOX6 therapy. The median number of cycles administered was six (range 3–6) and the median relative dose intensity (RDI) of oxaliplatin in initial mFOLFOX6 was 78%. The objective response was CR in one patient, PR in 11 patients, SD in 14 patients, and PD in 4 patients. The RR and DCR were 40.0 and 86.6%, respectively (Table 2). Surgical removal of the residual metastases could be performed after six cycles of mFOLFOX6 in 2 patients (6.7%).

Table 1 Patient characteristics

Characteristic	No.	%
Age (years)		
Median	66	
Range	44–74	
Sex		
Male	20	66.7
Female	10	33.3
WHO PS		
0	21	70.0
1	9	30.0
Primary site		
Colon	10	33.3
Rectum	20	67.7
Metastases		
Metachronous	22	73.3
Synchronous	8	26.7
Metastatic sites		
Liver	11	36.7
Lung	10	33.3
Peritoneum	6	20.0
Lymph nodes	5	16.7
Adjuvant chemotherapy		
Yes	16	53.3
No	14	46.7
Oxaliplatin	0	0
S-1	0	0

WHO World Health Organization, *PS* performance status

S-1 maintenance therapy

The oral S-1 maintenance therapy was initiated in 21 patients (70.0%). The median number of cycles and treatment duration of S-1 maintenance therapy were 2 cycles (range 1–4 cycles) and 3.6 months (range 1.4–6.3 months). The median RDI of S-1 was 100% (range 77–100%). The objective response was CR in one patient, PR in 4 patients, SD in 7 patients, and PD in 9 patients. RR and DCR were 23.8 and 57.1%, respectively (Table 2).

mFOLFOX6 reintroduction

mFOLFOX6 was reintroduced in 15 patients (50.0%). The median cycles of reintroduced mFOLFOX6 was 6 (range 2–6) and the median RDI of oxaliplatin was 77.4%. Reasons for no reintroduction were early progression of disease (1 patient), brain metastasis (1 patient), debasement of PS (1 patient), patient's preference for other treatment options (2 patients), and surgical resection of residual metastasis (1 patient). One patient had CR, 2 patients had PR, and 8

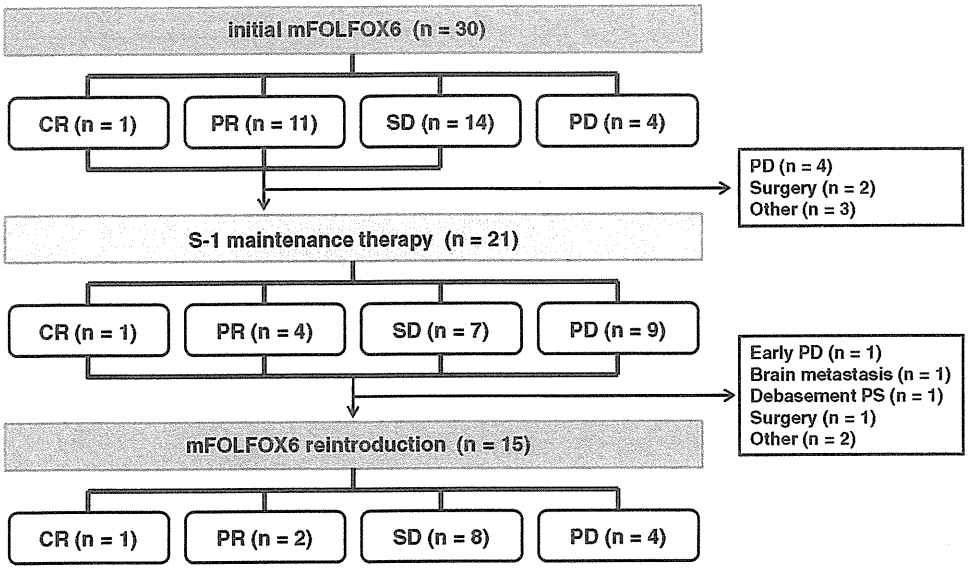

Fig. 1 Treatment diagram. Thirty patients were treated by initial mFOLFOX6 therapy. Twenty-one of the 30 patients (70.0%) who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in fifteen patients (50.0%)

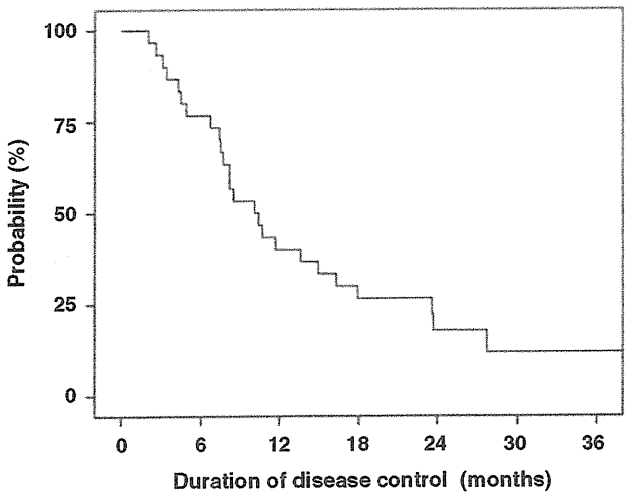

Fig. 2 Duration of disease control (DDC). After a median follow-up time of 26.9 months, 25 patients (83.3%) had disease progression. Median DDC, the primary endpoint, was 9.3 months

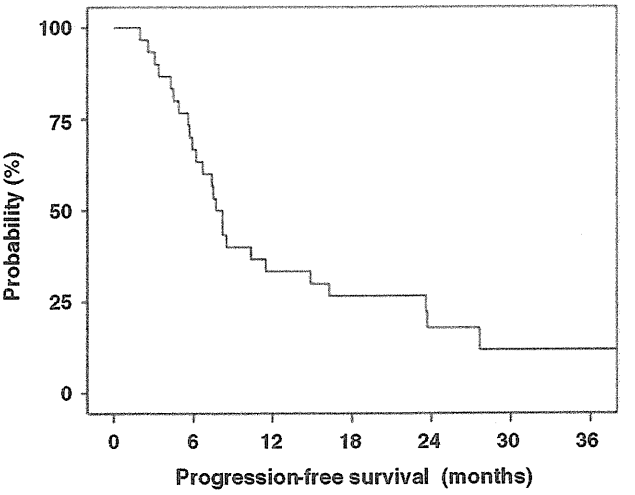

Fig. 3 Progression-free survival (PFS). Median PFS was 7.9 months

patients had SD. RR and DCR in reintroduced mFOLFOX6 were 20.0 and 73.3%, respectively (Table 2).

Second-line and subsequent therapy

After the study, 21 patients (70.0%) had received second-line chemotherapy; 16 patients (53.3%) had received an irinotecan-based second-line chemotherapy regimen. None of the patients had second-line therapy before progression; 6 patients (20.0%) received a second-line chemotherapy regimen with the addition of bevacizumab.

Adverse events

The most frequent toxicities during initial mFOLFOX6 chemotherapy were neutropenia (73.3%), thrombocytopenia (23.3%), anorexia (46.7%), nausea/vomiting (30.0%), diarrhea (16.7%) and mucositis (16.7%) (Table 3). The incidence of peripheral neuropathy during initial mFOLFOX6 chemotherapy was 86.7%; however, grade 3 neurotoxicity was observed in only one patient (3.3%).

The most frequent toxicities during S-1 maintenance therapy were neutropenia (42.9%), thrombocytopenia (38.1%), diarrhea (28.6%), anorexia (23.8%), hand–foot syndrome (19.0%) and mucositis (19.0%) (Table 3). The incidence of peripheral neuropathy decreased to 28.6%, with no patient suffering from grade 3 neurotoxicity after initiation of maintenance therapy (Fig. 4).

The most frequent toxicities during mFOLFOX6 reintroduction were neutropenia (53.3%), thrombocytopenia (15.0%), allergic reaction (33.3%), anorexia (20.0%), mucositis (13.3%) and nausea/vomiting (6.7%) (Table 3).

Table 2 Objective tumor response rates

Response	Initial mFOLFOX6 ($n = 30$)		S-1 maintenance ($n = 21$)		Reintroduced mFOLFOX6 ($n = 15$)	
	No.	%	No.	%	No.	%
CR	1	3.3	1	4.8	1	6.7
PR	11	36.7	4	19.0	2	13.3
SD	14	46.7	7	33.3	8	53.3
PD	4	13.3	9	30.0	4	26.7
RR	12	40.0	5	23.8	3	20.0
DCR	26	86.6	12	57.1	11	73.3

mFOLFOX6 modified FOLFOX6, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate (CR + PR), *DCR* disease control rate (CR + PR + SD)

Table 3 Frequency of common toxicities

Toxicity	Initial mFOLFOX6 ($n = 30$)		S-1 maintenance ($n = 21$)		Reintroduced mFOLFOX6 ($n = 15$)	
	All grade (%)	>Grade 3 (%)	All grade (%)	>Grade 3 (%)	All grade (%)	>Grade 3 (%)
Neutropenia	73.3	26.7	42.9	0	53.3	13.3
Thrombocytopenia	23.3	0	38.1	0	15.0	0
Anorexia	46.7	6.7	23.8	4.8	20.0	0
Nausea/vomiting	30.0	3.3	9.5	0	6.7	0
Diarrhea	16.7	3.3	28.6	9.5	0	0
Mucositis	22.3	0	19.0	0	13.3	0
Hand–foot syndrome	6.7	0	19.0	4.8	6.7	0
Allergy	3.3	0	0	0	33.3	20.0
Neurogenic	86.7	3.3	53.3	0	66.7	6.7

mFOLFOX6 modified FOLFOX6

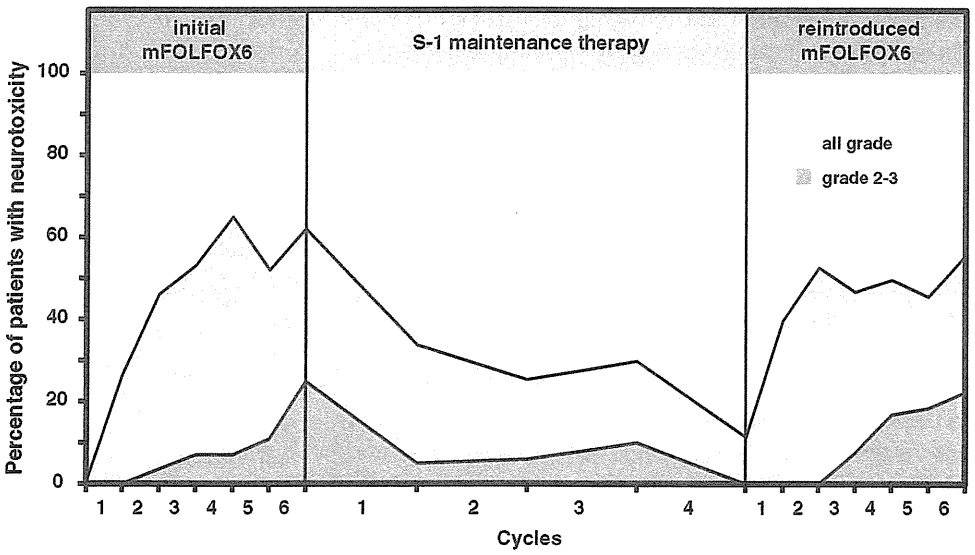

Fig. 4 Neurologic toxicity. The incidence of peripheral neuropathy during initial mFOLFOX6 chemotherapy was 86.7%; however, grade 3 neurotoxicity was observed in only one patient (3.3%). This incidence decreased to 28.6%, with no patients suffering from grade 3 neurotoxicity after initiation of S-1 maintenance therapy. After mFOLFOX6 reintroduction, peripheral neurotoxicity was observed in 66.7% of patients, but grade 3 neurotoxicity was observed in only one patient and did not require treatment discontinuation

Peripheral neurotoxicity was observed in 66.7% of patients after mFOLFOX6 reintroduction, but grade 3 neurotoxicity was observed in only one patient (6.7%) and did not require treatment discontinuation.

Discussion

In recent studies with the uninterrupted FOLFOX regimen, the median PFS was in the range of 8.2–9.0 months, and

severe neurotoxicity was observed in 18–21% of patients [1–4]. In the OPTIMOX1 trial, which evaluated the efficacy of oxaliplatin stop-and-go strategy, PFS and DDC were 8.7 and 10.9 months, respectively. Grade 3 sensory neuropathy was observed in 13.3% of patients. Oxaliplatin was reintroduced in 40.1% of patients and objective response or disease stabilization was observed in 69.4% of these patients [4]. With a median DDC of 9.3 months and a median PFS of 7.9 months, the current study showed that the stop-and-go strategy with mFOLFOX6, employing oral S-1 monotherapy as a maintenance therapy, achieved efficacy comparable to previous studies, while the incidence of severe neurotoxicity was greatly reduced. Grade 3 peripheral neurotoxicity was observed in only 3.3% during the initial mFOLFOX6 treatment. This incidence was reduced to 0% during S-1 maintenance therapy. After mFOLFOX6 reintroduction, 66.7% of patients had mild neurotoxicity, but grade 3 was observed in only one patient (6.7%) and did not require treatment discontinuation. The low incidence of severe neurotoxicity in this study was apparently due to the stop-and-go strategy.

In search of a convenient and well-tolerated treatment, S-1 was chosen to be tested as a maintenance therapy since this oral fluoropyrimidine is an effective alternative to intravenous 5-FU/LV for mCRC as well as being a promising alternative for use in the adjuvant setting in Japan. Median duration of S-1 maintenance therapy was 3.6 months (range 1.4–6.3 months) in the present study and adverse events were mild and typical of those observed with this agent. The RR (23.8%) and DCR (57.1%) were comparable to infusional 5-FU/LV regimens. Furthermore, S-1 maintenance therapy produced a 58.1% reduction in the incidence of peripheral neuropathy with no patient suffering from grade 3 toxicity. These results indicated that S-1 is useful in this setting.

mFOLFOX6 was reintroduced in 50% of patients and achieved disease control in 73.3% of the patients in our study. Only one patient developed grade 3 neurotoxicity after mFOLFOX6 reintroduction. In previous studies, the DCRs after reintroduction of oxaliplatin were similar and in the range of 45–73%. These findings suggest that the chemosensitivity to oxaliplatin is maintained despite an interruption by S-1, and adequate disease control can be expected after the reintroduction of FOLFOX.

Furthermore, the stop-and-go approach is not only a way to decrease oxaliplatin-induced neurotoxicity, but is also a new way to give chemotherapy with advantages in costs without deterioration in survival. In our strategy, S-1 maintenance therapy over 6 months costs approximately 3,700 US dollars, while mFOLFOX6 therapy for the same duration costs approximately 28,400 US dollars in Japan.

In summary, this study suggests that the oxaliplatin stop-and-go strategy with S-1 as a maintenance therapy is oncologically feasible and is associated with a very low incidence of grade 3 neurotoxicity. Although the number enroled was far too small for a definite conclusion, DDC and PFS were comparable to those usually reported in the treatment of mCRC patients. This study adds to a growing body of evidence showing the benefit of a 'stop-and-go' concept, and demonstrates the feasibility of S-1 as an alternative to be used as a maintenance therapy in this strategy.

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Conflict of interest No author has any conflict of interest.

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A Randomized Phase II Trial to Test the Efficacy of Intra-peritoneal Paclitaxel for Gastric Cancer with High Risk for the Peritoneal Metastasis (INPACT Trial)

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Owing to its peculiar pharmacological characteristics, paclitaxel attains substantial intra-peritoneal concentration for a prolonged period when delivered intra-peritoneally, and is active against peritoneal metastasis of ovarian cancer. It is also considered promising against disseminated gastric cancer. However, the fact that the intra-peritoneal paclitaxel has not been approved in Japan has rendered its evaluation by a formal clinical trial impossible. The authors designed a randomized phase II trial using the Kodo Iryo Hyoka system, a new system to legally test an yet unapproved mode of treatment. It is hoped that this trial will result in a breakthrough in the treatment of peritoneal carcinomatosis from gastric cancer.

Key words: paclitaxel – clinical trial – gastric cancer

TRIAL BACKGROUNDS AND RATIONALE

Curatively resected gastric cancer patients often suffer from recurrence as peritoneal carcinomatosis. This could be caused by cancer cells that had already been shed from the serosal surface at the time of surgery, sometimes detectable by examining the peritoneal washes, or those that were disseminated during surgical procedures. In addition to extensive irrigation of the peritoneal cavity (1), intra-peritoneal (IP) instillation of effective anticancer drugs could eliminate these cells to the extent that the recurrences could be prevented. Repeated IP administration of paclitaxel (PTX) has been shown to be safe and effective for disseminated ovarian cancer, another cancer type where peritoneal disease often turns out to be a major cause for disease failure (2). Since its efficacy when administered intravenously (DIV) against gastric cancer has been proved (3) and its potential advantage when given intra-peritoneally has been robustly shown pharmacologically (4,5), IP PTX has been considered promising also to eliminate peritoneal metastasis from gastric cancer.

Formal clinical trials to prove the efficacy of this approach have been hindered by the fact that the IP administration of PTX has not been approved by the Ministry of Health, Labour and Welfare in Japan. When using such drugs outside of the medical insurance system, all other expenses such as the cost of medical services at the outpatient clinic, including drugs such as steroids, H2 blockers and anti-emetics will have to be covered also by the individual researcher or the patient. The authors attempted to overcome this problem by making an official request to conduct a multi-institutional trial by using a system known as the 'Kodo Iryo Hyoka' system. Using this system, unapproved or experimental medical practice whose cost is covered by the individuals can be delivered simultaneously with general medical procedures that are covered by the insurance. To use this system, the study protocol will have to be scrutinized and approved by a committee appointed by the Ministry. Furthermore, a trial thus performed is expected to be designed so as to generate an evidence for future approval of

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the treatment by the Ministry. A one-arm single-institutional phase II trial to confirm the efficacy of a regimen that includes IP PTX (6) has already been approved and is ongoing using the 'Kodo Iryo Hyoka' system. To add further evidence in support of the IP treatment and to ultimately establish a basis for the future approval by the Ministry, a head-to-head comparison of IP and DIV of the same drug under the same schedule was considered mandatory. Since the patients so allocated will then have to be treated by IP PTX alone for a fixed period of time, patients who are deemed eligible for the trial had to have a significant risk to develop peritoneal carcinomatosis, while harbouring no gross lesions that immediately call for systemic administration of the anticancer drugs.

The authors held a few meetings to finally compile a protocol for a clinical trial to evaluate IP PTX, as described in the following section. The study is called INPACT, in which INPACT is an abbreviation for 'IP administration of chemotherapeutic agent'.

PROTOCOL DIGEST OF THE STUDY

Purpose

The purpose of this study is to show a prognostic impact of repeated IP of PTX over the DIV on the identical treatment schedule, among patients who are considered to have a high risk of developing peritoneal carcinomatosis. In the event of detecting a survival advantage, this study should be one of valuable evidence based on which to request the Ministry of Health, Labour and Welfare for approval of the IP administration. The establishment of various combinations incorporating IP PTX to combat all types of metastatic gastric cancer and a subsequent randomized trial to prove their survival benefits would then be expected.

Resources

Data centre services and statistical supervision are funded by a non-profit organization, the Epidemiological and Clinical Research Information Network (ECRIN), Kyoto, Japan. All treatments with the exception of PTX-administered IP have been approved as a general practice within the scope of general medical insurance. IP administration of PTX has been approved by the Ministry of Health, Labour and Welfare as of July 2010, exclusively for the participants of this trial, using the Kodo Iryo Hyoka system. Bristol- Myers Squibb has kindly agreed to supply PTX to be given intra-peritoneally.

Endpoints

The primary endpoint is the 2-year overall survival (OS) rate. The secondary endpoints are the incidence of adverse events, progression-free survival time, and OS time.

Eligibility for Participating in the Trial

Approval of the protocol by the institutional review board is a prerequisite to participate in the trial. In addition, each participating institution is requested to fill in and send an application form to the Ministry of Health, Labour and Welfare via Nagoya University to obtain final approval by the government to join the Kodo Iryo Hyoka system.

Eligibility Criteria for the Enrollment

Inclusion criteria for primary registration:

(i) Histologically confirmed adenocarcinoma of the stomach.
(ii) Either macroscopically defined as Type 3 with a diameter >8 cm or Type 4 (linitis plastica), or defined as the other macroscopic type, but is considered highly suspicious for serosal invasion or peritoneal seeding.
(iii) Patients without the following findings on computerized tomography: cervical or mediastinal lymphadenopathy, bulky metastasis to suprapancreatic or retroperitoneal lymph nodes, distant organ metastasis, thoracic effusion, ascites spreading beyond the pelvic cavity.
(iv) No previous history of chemotherapy or radiation.
(v) Eastern Cooperative Oncology Group performance status of 0 or 1.
(vi) Age ≥ 20.
(vii) Adequate organ function is defined as follows: a white blood cell count of 3000–12 000/m^3, neutrophil count of $>1500/m^3$, platelet count of $>100\,000/m^3$, AST and ALT ≤ 100 IU/l, total bilirubin ≤ 1.5, serum creatinin level ≤ 1.5 mg/dl, serum albumin level ≥ 3.0 g/dl.
(viii) Surgery planned within 1 month of registration.
(ix) Written informed consent.

Exclusion criteria for primary registration:

(i) Serious comorbidities include the following:
  (a) Ischemic heart disease and arrhythmia needing treatment.
  (b) Myocardial infarction within 6 months of onset.
  (c) Liver cirrhosis.
  (d) Interstitial pneumonitis.
  (e) Gastrointestinal bleeding in need of repeated blood transfusion.
  (f) Uncontrolled diabetes mellitus.
(ii) Bowel obstruction rendering treatment with oral drugs impractical.
(iii) Active synchronous cancer or disease-free metachronous cancer within 5 years of onset.
(iv) Signs of acute infection or inflammatory disease
(v) Systemic treatment with corticosteroids
(vi) Hypersensitivity to Cremophor EL.

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(vii) Women who are pregnant, contemplating pregnancy or amid breast-feeding.
(viii) Mental disorders which may affect ability or willingness to provide informed consent.
(ix) History of severe hypersensitivity to any drugs.
(x) History of alcoholic anaphylaxis.
(xi) Peripheral neuropathy.
(xii) Patients otherwise considered inappropriate for inclusion in the study.

Inclusion criteria for secondary registration:

(i) Considered resectable either at laparotomy or laparoscopy.
(ii) If the macroscopic type was not Type 3 with a diameter >8 cm or Type 4 (linitis plastica), peritoneal seeding or positive cytology of the peritoneal washes need to be confirmed during surgery.
(iii) Placement of the IP reservoir is possible.

Registration

Participating investigators are instructed to send an eligibility criteria report to the data centre at the non-profit organization ECRIN for the primary registration within 1 month of the scheduled surgery. Investigators are then requested to proceed to the secondary registration by telephone upon laparotomy or laparoscopy, when the eligibility criteria such as resectability, peritoneal metastasis and peritoneal washing cytology findings were confirmed. Patients are randomized during surgery to one of the two treatment groups by a centralized dynamic method using the following factors as balancing variables: macroscopical Type (Types 3 and 4/others), curability of surgery (R0 and R1/R2), age (<75 years/≥75 years) and institution. Follow-up data including compliance to the treatment, adverse reactions and survival are to be reported to the data centre through clinical report forms.

The first 10 cases are to receive the IP PTX exclusively as a feasibility test, which will be evaluated only for toxicity and will be not included in the survival analysis. If more than four successful IP deliveries are conducted in less than 5 of the 10 patients, the study will either be terminated or modified appropriately.

The study has been registered in the University hospital Medical Information Network (UMIN) as No. 000002957.

Treatment Methods

Patients enrolled in this study are randomized to receive one of the following regimens of chemotherapy after gastrectomy.

Group A: IP administration group:

PTX: 60 mg/m2 IP on the day of surgery (day 1) and on days 15, 22, 29, 43, 50 and 57. The dose of IP PTX is based on a phase I trial performed in the USA for ovarian cancer patients, and its safety when given weekly has been confirmed by a phase II trial (2).

Group B: Intravenous administration group:

PTX: 80 mg/m^2 DIV on the day of surgery (day 1) and on days 15, 22, 29, 43, 50, and 57.

These regimens of treatment are to be followed after 2–3 weeks by a standard systemic chemotherapy for advanced gastric cancer which, at the time the trial started, would be either S-1 monotherapy or a combination of S-1 and cisplatin (CDDP) (7). S-1 is generally recommended after R0/R1 resection and S-1/CDDP after R2 resection, but the selection is left to the discretion of the physician in charge. When patients randomized into Group A failed to receive IP chemotherapy for reasons other than allergic reaction to PTX, they are expected to continue with intravenous PTX according to the predetermined schedule, so that the subsequent systemic chemotherapy will be started at the same time as in other patients.

Study Design and Statistical Methods

The current study is a randomized phase II trial applying selection design as proposed by Simon et al. with selection probability of around 80% (8). The primary analysis in this study is aimed to select an appropriate treatment arm for further evaluation, and the sample size was calculated on the hypothesis that the 2-year OS rate of the DIV arm, estimated to be 30–40%, could be improved by 10% in the IP arm. The selection probability is estimated to be 82–83% when a total sample size is 80 and 84–85% when a sample size is 100. Since the first 10 cases will be treated by IP therapy as a feasibility phase and will be excluded from the survival analysis, the total sample size will be 90–110 and 50–60 patients will receive IP therapy.

Interim Analysis and Monitoring

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding efficacy and safety data. The first interim analysis will be performed at 1 year after registration of the last patient and DSMC will decide whether or not to publish the results based on futility analysis and safety data.

Funding

This study is supported, in part, by Epidemiological and Clinical Research Information Network (ECRIN). PTX for IP administration will be supplied by Bristol Myers Squibb.

Conflict of interest statement

Dr Mitsuru Sasako received lecture fee and donation for promotion of education and research from Taiho Pharmaceutical Co., Ltd.

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消化器内科，52(1)：48-54，2011

特集Ⅰ 胃癌化学療法

胃切除後の化学療法における課題*

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Key Words : gastric cancer, postoperative chemotherapy, intraperitoneal administration, drug delivery, cytoreductive surgery

まず手術を行うという考え方は時代遅れか

ティーエスワン(S-1)，irinotecan, taxane系抗癌剤が新薬として広く使用されるようになって以来，胃癌の化学療法は進歩したといわれている[1]．こうしたなか，根治切除が不能な胃癌の治療においては，(1)化学療法が奏効しないと結局は長期の生存は見込めない，(2)化学療法のみで長期生存が可能なケースが散見される，(3)各種の胃術後障害は化学療法の実施に悪影響を及ぼす，といった理由から，出血，狭窄などの症状がない限り手術療法を避ける考え方が一般的となってきた．また，遠隔転移を有する胃癌においては，肉眼や画像診断で捕捉不能な微小転移が高率に存在し，術後速やかに再燃するに違いないという考え方のもと，肉眼的に完全切除が可能でも外科治療には消極的な傾向がみられる．たとえば，同じ肝転移でも胃癌由来か大腸癌由来かで治療方針は大きく異なる場合があり，これは胃癌と大腸癌の生物学的特性の違いを物語っている．一方，造影CTを中心とする画像診断の目覚ましい進歩と，審査腹腔鏡の普及に伴い，術前stagingの精度に大きな向上が得られつつある[2]．ゆえに，開腹以前に手術適応なしと診断されるケースが増えてきた．

一方，胃癌はわが国では頻度の高い疾患であり，その切除術は消化器外科領域では基本的な手術の一つと位置づけられている．各臓器の学会で独自の高度技能医や専門医の制度をつくる動きがあるなか，胃癌学会では，このような一般的な疾患にまで専門医制度を設けては現場に混乱が起きるとの配慮のもと，専門医制度を設立する構想は出ていない．実際に，個人病院を含め，幅広い層の医師によって診療されている疾患であり，それだけに，胃癌の治療に携わるあらゆる医療機関で審査腹腔鏡が随時実施可能な態勢をとったり，高性能の画像診断装置を導入できるわけではない．高精度な診断に基づく正確なstagingをもとに，集学的治療の最初に術前補助化学療法を含む化学療法をもってくる戦略が十分に浸透するには，エビデンスとともに，胃癌を取り扱う医療機関の構造改革が必要かもしれない．現時点でどこの医療機関でも実施可能なのは，切除可能と診断されればまず手術を行い，予期せぬ転移・浸潤にはその場で善処し，

* Postoperative chemotherapy for optimally debulked gastric cancer.

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以後，適宜化学療法を行うというものである．この基本方針での現在の治療成績を把握し，その改善に努めるのも，わが国の実情を考えれば，重要な研究の一つと考えられる．

Optimally debulked gastric cancer という概念はありうるか

かねてより実地臨床においては，胃癌根治切除後の再発を防ぐために微小転移を叩く目的で補助化学療法が行われてきた[3]．しかし，術後補助化学療法についてのエビデンスがようやく得られたのは2006年のことで，Stage II, IIIの胃癌の術後に1年間のS-1療法を追加するかどうかのランダム化試験，ACTS-GCにおける適格基準を満たした全症例の中間解析で，3年生存率で試験の有効中止に値する差が認められた[4]．そして，この術後3年における生存率の差は術後5年の時点でも維持されていることが，2010年のEuropean Society of Medical Oncology学術集会で報告されたところである．S-1には一定頻度で微小転移を死滅させる効果があることが示されたと理解される．微小転移と粗大な病巣では抗癌剤の効果が異なるという理論[5]がある程度実証されたものと考えると，仮に遠隔転移を有する胃癌であっても，これを含めた肉眼レベルの全切除が無理なく可能でかつ術後に化学療法が行えるのであれば，手術も選択肢の一つになりうる．以前から化学療法がある程度有効であった卵巣癌においては，遺残する病巣がすべて径1cm未満となるように病巣をできる限り切除する手術がoptimal surgeryと定義され[6]，その状態はoptimally debulkedと称される．実際にはこうした減量手術の意義にも，1cmというカットオフ値にも異論はあるようだが，optimally debulkedであることを適格基準とした臨床試験が組まれるほど一般的な考え方となっている[7]．突飛かもしれないが，胃癌においてもoptimally debulkedという状態を設定できる時代が来ているのではないだろうか．卵巣癌と異なる点は，胃癌をoptimally debulkedと定義する際の遺残腫瘍の径が，現段階では肉眼的に捕捉可能なレベルにはないということである．こう考えると，化学療法の進歩ゆえに，新たに手術適応が生じる場合があるという，一見逆説的な現象が見えてくる．

腹腔洗浄細胞診は癌性腹膜炎および予後の優れた予知因子である．過去には細胞診陽性(CY1)症例の転帰は，肉眼的な腹膜転移を有する場合と同等であるとの報告が相次ぎ，胃癌取扱い規約第13版よりCY1であればStage IVと分類されるようになり，現行の14版でもこの扱いは続いている．したがって，CY1であれば手術適応から外れるという考え方もありうることになる．しかし，筆者らは関連病院を含むNPO法人CCOG[8]において，CY1を唯一の非治癒因子とする胃癌に対し，D2郭清を伴う標準的な胃切除術の術後にS-1を投与する第II相試験を行った．そして，48例を集積し，2年生存率46%，5年生存率20%という成績を得た[9](図1)．これは，この試験で独自においたhistorical controlを大幅に上回る成績であった．腹腔内に遊離している癌細胞そのものは機械的な洗浄で除去できる可能性があるが，CY1である以上，すでに腹膜表面に肉眼的には捕捉不能な大きさの腹膜転移を形成していると考えるべきであろう．そして，S-1は一定の確率でこの程度の規模の微小転移を死滅させることができるということになる．ここにきて，数多くの施設から，後向き研究ながら，CY1はStage IVのなかでは特段に予後の良いサブセットであり，手術適応がある旨が報告されるようになった．こうなると，CY1の胃癌にR1手術を行った場合などは，真っ先にoptimally debulkedな状態の一つにあげられるのではないだろうか．

Optimal debulkingの後に多剤併用療法は可能か

現時点で進行・再発胃癌で最長の生存期間が得られる化学療法はSPIRITS試験の結果S-1とcisplatin(CDDP)の併用療法と判明し，特にこれを行いにくい条件(腎機能障害等)がない限り，第一選択と考えられている[10]．進行・再発胃癌でエビデンスの得られたレジメンを次の段階で術後補助化学療法に流用し，癌の治癒率を高めるのがグローバルな研究戦略である．現実にStage III胃癌ともなれば，S-1による補助化学療法をもってしても予後がよいとは言い難く，より強力な術後補助化学療法が望まれている．とはいえ，

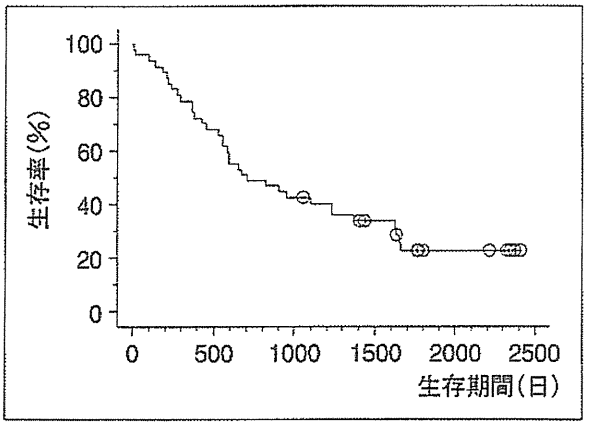

図1　CCOG0301(CY1症例に対する術後S-1単剤療法の第II相試験)で得られた生存曲線

S-1/CDDP療法を胃切除術後に行うには困難が予想された．筆者らはStage IV胃癌を対象とした胃切除後のS-1/CDDP療法の忍容性試験を前述のCCOGにて行ったが，5コース完遂例は31例中わずか7例，S-1, CDDPのプロトコール治療中のrelative drug intensity(5コースをプロトコールどおりに完遂した場合の薬剤量を100%とし，実際の投与量を比率で表したもの)はそれぞれ37%，40%と惨憺たるものであった[11]．有害反応のGradeや頻度はSPIRITS試験[10]と大きく変わるものではなかったが，同程度の有害反応ではあっても，胃切除後間もないという不利な状態においては，特に消化器毒性に対する忍容性が格段に低下する実情がうかがえた．Japan Clinical Oncology Group(JCOG)のStage IIIを対象とする忍容性試験では，この場合の1コース目をCDDP抜きで行い，2コース目からS-1/CDDP療法に入ることでコンプライアンスが明らかに改善することがつきとめられており，こうした戦略に加え，アプレピタント等の新規制吐剤を使用することで，術後に本レジメンを採用する道が残されている可能性は否定できない．しかし，現段階で術後にS-1/CDDP療法をしっかり行うことを前提とした戦略は立て難いのも事実である．なお，S-1/docetaxel療法であれば，消化器毒性が少ない分，よりすぐれた忍容性が示唆されている．ただし，進行・再発胃癌におけるエビデンスという点で，S-1/docetaxel対S-1のランダム化比較試験，START試験の結果を待たねばならない状況にある[12]．最終的に術後補助化学療法でS-1単剤を超える治療法が得られない場合には，optimally debulkedを含め，Stage IIを超える進行胃癌に対する標準治療はS-1/CDDPをはじめとする多剤同時併用療法による術前補助化学療法に移行し，手術後に化学療法を考えるという戦略は時代から取り残される可能性がある．もちろん，このためには，現在大型3型・4型胃癌を対象にJCOGで行われているような，術前補助化学療法の有無をランダム化比較する臨床試験によるエビデンスが必要である．

逐次併用という考え方

抗癌剤を用いた化学療法においては，一般的に単剤より多剤併用の方が腫瘍縮小効果が高いため，海外では補助化学療法においても2剤，3剤の同時併用の報告が多い．同時併用における薬剤の投与量については，各薬剤における単剤でのdose intensityをそのまま維持するのが理想であり，そのために用量制限毒性が重複しない組み合わせを選択するなどの工夫が必要とされる．しかし，現実には使用する薬剤の一部，またはすべてを減量しなければ，投与は事実上不可能である(分子標的治療薬はこの限りではない)．同じ多剤併用でも逐次併用の場合には，各薬剤をそれぞれの期間，full doseで投与可能である．Kobayashiらは，S-1を超える試みの一つとして，腹腔内への移行が良好で腹膜転移の治療に定評があり，消化器毒性の少ないpaclitaxel単剤による治療を先行させ，3か月後からS-1に切り替える逐次併用療法(図2)を考案し，その忍容性が良好であることを確認した[13]．S-1には比較的強い消化器毒性があり，ACTS-GCにおいて開始後3か月の段階で治療を継続できている症例は全体の89%であった[4]が，paclitaxelを先行させることでより高いコンプライアンスが期待されていた．逐次併用療法にS-1単剤を超える無病生存期間が得られることを検証することを主たる目的とするSAMIT試験(図3)は，すでに1,500例の集積を終え，現在追跡調査中である[14]．

補助化学療法の効果予測は可能か？

抗癌剤の感受性を左右する分子メカニズムとしては，1つの抗癌剤に多くの因子がさまざまな

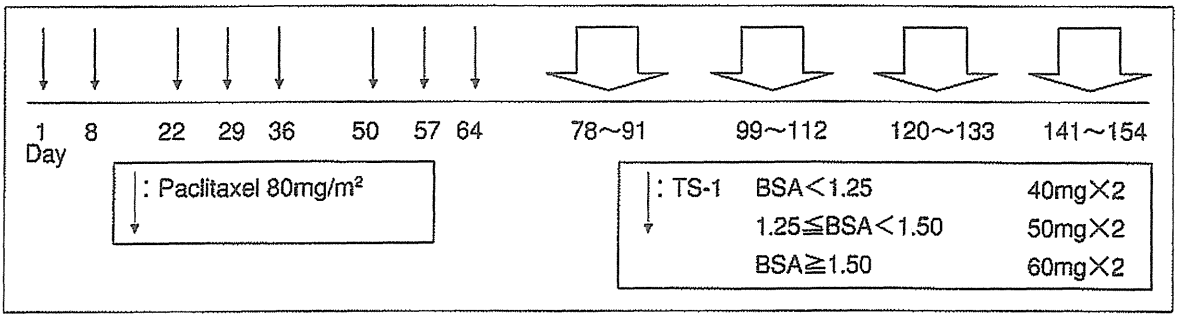

図2 Paclitaxel/ティーエスワン逐次併用による補助化学療法

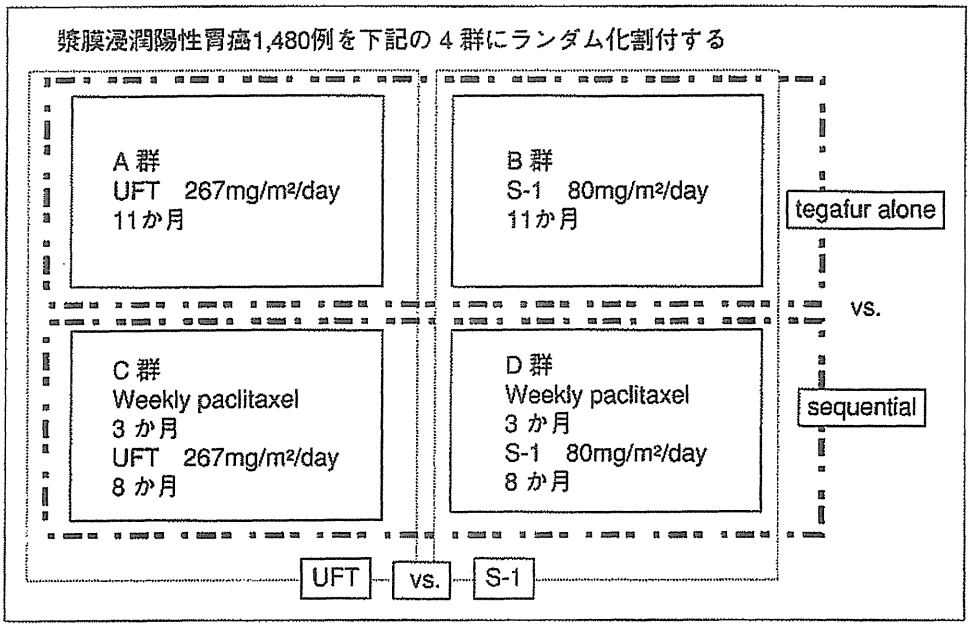

図3 SAMIT trialの研究デザイン(2×2 factorial design)
各群370例で，AB群(740例) vs. CD群(740例)の比較を行い，フッ化ピリミジンのみの3年無病生存率が40～50%，paclitaxelを追加することで48.1～57.4%に向上するとの仮説を検証する．さらに，BD群(S-1)がAC群(UFT)に非劣勢であることを証明することが可能である．

重要度で複雑に関係すると考えられ，分子標的治療薬のように単一の分子の発現や遺伝子変異の検討で効果予測を行うのは，困難と考えられている．抗癌剤感受性試験は抗癌剤を含む培養液中で外科切除標本から得た癌組織ないしは細胞を培養し，その増殖の抑制程度をもって感受性を評価するものである．古典的な方法であり，高価である上に技術的にも高度なものが要求されるが，感受性をつかさどる分子メカニズムについて知識が得られていなくても判定が可能である点が長所といえる．現在ではcollagen gel droplet embedded culture drug sensitivity test (CD-DST法)[15]，histoculture drug response assay(HDRA法)[16]などの方法が外注可能であり，Stage IV胃癌切除例を対象とする単一回の実施についてのみ保険適用となっている．ただし，保険点数が20,000点で，実際の検査価格の1/3以下であるため，その実施は事実上困難な状況にある．

KubotaらはStage III胃癌に補助化学療法を行った場合，HDRA法で感受性ありと判定された場合と感受性なしと判定された場合に，5年生存率において40%程度の差があることを報告している[17]．このデータをもとに，筆者らは，前述のSAMIT試験において5FUとpaclitaxelの感受性試験をCD-DST法で行い，その結果と生存期間の相関をみる付随研究を計画，実施した．TXLを使用した症例を60例集積し，追跡3年で「感受性あり」と「なし」の間に37%の差を検出するデザインであった．検体の鮮度等の問題で，感受性試験そのも

のの成功率は78％と，当初必要と考えた80％をやや下回ったが，166例が集積され，SAMITにおける生存期間のデータが得られ次第解析予定である．この検査を生かすには，まず手術を行って摘出標本で感受性を判定し，その結果を術後化学療法に反映させることになる．optimal debulkingに意義があるなら，その後の治療方針の決定に際し，一つの選択肢となりうる検査であり，今後の解析が待たれる．

腹腔内化学療法に未来はあるか

腹膜転移の治療を行う際に以前から注目されているのが腹腔内投与(IP)である．現時点でIPの保険適用がある薬剤はmitomycinやcyclophosphamideなど，今や胃癌には使用されない薬剤に限られている．また，90年代にはJCOGの手術単独群を対照群としたランダム化試験でCDDPのIPを含む術後補助化学療法が検証されたが，まったく無効であることが示された．しかし，この投与経路についての関心は根強く，最近では腹腔内で高濃度が維持されるtaxaneに注目が集まっている．taxaneは，CDDPとは異なり，IP後に血中に移行しにくく，腹水がある場合には高い腹水中濃度が長時間維持されることが知られている[18]．一方，IPされた薬剤が腹膜表面から垂直方向に浸透する距離には限りがある．Ohashiらはマウスの癌性腹膜炎モデルを用いてpaclitaxelのIPには経静脈投与(DIV)を大きく上回る効果があることを示すとともに，マウスの腹腔内に転移能を持つ細胞株を注入した直後と，一定時間が経過し腫瘍が増大した後では，IPの効果が大きく異なることをつきとめた[19]．時間の経過とともに増大した病巣には血管新生が起きており，もはやDIVでなければ薬剤の癌への移行が十分に得られないためである．

こうしたなか，optimally debulkedな状態の卵巣癌におけるランダム化比較試験で，paclitaxelとCDDPのIPを含むレジメンが，薬剤がすべてDIVで投与されるレジメンを上回る治療成績を示した[20]．胃癌におけるoptimally debulkedの状態がたとえばCY1と定義できるとすれば，遺残する腫瘍は微小であるため，ここでもIPに期待が持てそうである．問題は，paclitaxelのIP投与が保険適用ではないために，臨床試験を行うこともままならない点である．このため，筆者らは保険診療外であるIPをその他の診療と一緒に行っても，その他の診療については診療報酬が請求できるように，高度医療評価システムを用いて臨床試験を行うこととし，2009年から厚生労働省の担当者と相談を繰り返した．本制度を用いる場合，なんらかの形でエビデンスを残せる臨床試験としての運用が求められていた．そこでpaclitaxelのIPとDIVを直接比較し，IPが勝ることを示すことでこの投与法の認可を受けるというのが試験の目的となった．対象を腹膜転移を有する，あるいはそのリスクが高い症例とすることになるが，これらは通常測定可能病変を有さないので，エンドポイントは生存期間でしかあり得ない．このため，ランダム化試験の形でしか，IPのメリットを実証することはできないということになった．一方，IPについては当時他の抗癌剤治療との併用療法が確立されておらず，といって，保険未承認では第Ⅰ相試験を行うこともままならない．そこで，適格基準を満たす症例の胃切除術後にTXL単剤でのIP治療をしばらく行うことを試験治療とし，同一スケジュールでpaclitaxel DIV投与を行う群との比較を行うランダム化第II相試験とした(INPACT study, 図4)[21]．2年生存率においてIP群が10％上回るという仮説を証明するために90例の集積を目指すこととした．対象症例は術後2か月程度はIP療法のために抗癌剤の全身投与ができなくても許容されるような，腹膜転移治療の必要性が特段に高い症例に限る必要があり，また，そのためにも原発巣の切除は必須と考えられた．CY1症例，あるいは少量の腹膜播種がありこれを合併切除した症例(すなわち，optimally debulked gastric cancer)を理想的な対象症例と考えている．なお，IP群もDIV群もpaclitaxel終了後にS-1ないしはS-1/CDDPを行うこととなっており，DIV群については，上述のSAMIT試験における逐次併用療法に近似した治療法となる．すなわち，INPACT studyにおいては，IP療法と同時にpaclitaxel DIVとS-1/CDDPの逐次併用療法を開発することになる．

INPACT studyはようやくスタートの準備ができたところであり，筆者らの施設では登録可能である．しかし，90例程度の集積を要し，多施

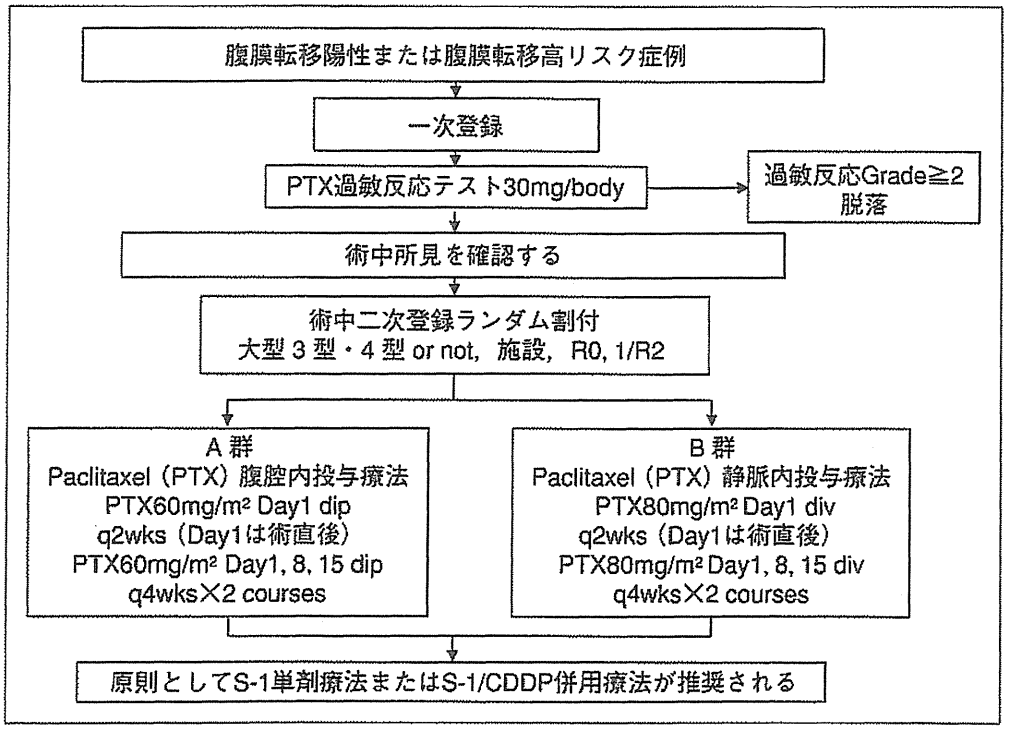

図4 INPACT study

設共同でなければ成り立たないが，参加施設はIRB審査への対応とともに，厚生労働省に高度医療評価制度における協力医療機関としての申請をしなければならない．書類作成などに膨大な手間と時間を与儀なくされるなか，参加希望者の根気が続くかどうかが，高度医療評価システムを利用して多施設で臨床試験を行う場合の最大の懸念事項である．

ま と め

本稿では，昔ながらの「まず切除してから考える」というコンセプトで治療を行った場合の，現在の到達点と問題点を示した．optimally debulked gastric cancerを語る上でCY1症例をモデルとした関係上，腹膜転移の治療が話題の中心となった．しかし，肉眼的な転移を肝切除で取りきった肝転移例もoptimally debulkedといえる可能性はあり，その場合は，肉眼や画像でとらえきれない肝内の微小転移が治療の標的となる．今のところS-1単剤による術後補助化学療法による肝転移再発の抑制効果についてはやや否定的な見方があり[4]，肝転移切除例をoptimally debulkedと呼ぶためには別の治療レジメンが必要かもしれない．いずれにしても，化学療法のみで胃癌が治癒する時代が来るまでは，胃切除術は進行胃癌の集学的治療の重要なパーツであり続ける．これを行う最適なタイミングについては，しっかりデザインされた臨床試験を積み重ねて検討する必要があろう．

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Current Organ Topics:

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Ⅳ. 腹膜播種陽性胃癌に対する化学療法

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はじめに

腹膜播種は胃癌が漿膜に浸潤すると急激に頻度が高くなる転移形式であり，しばしば切除不能の原因となる。また，進行胃癌の根治術後の再発形式としてもっとも頻度の高いものでもある[1]。しかし，腹膜播種に対する治療法の開発には様々な障害があり，高いニーズに見合ったエビデンスがコンスタントに得られてきたとは言い難い。化学療法の開発が困難な理由として，個々の病巣が小さく画像で捕らえにくく測定可能病変とみなされないため，奏効率をエンドポイントとする第Ⅱ相試験の対象とならない点があげられる。実際に奏効度を確認するのが困難であるため，客観性の高い治療成績の評価は困難である。そもそも，抗癌剤が第Ⅱ相試験の結果をもとに採用されていた時代には，臨床試験の対象は肝転移，リンパ節転移など測定可能病変を有する病変であったはずであり，ここで有効性が認められた薬剤が腹膜播種にも効くと考えるためには，肝転移を起こしやすい癌と腹膜転移を起こしやすい癌が同様の感受性を持つという前提が必要となる。実際には，肝転移と腹膜転移の両方を認める胃癌も決して珍しくはないものの，肝転移をきたしやすい胃癌と腹膜転移をきたしやすい胃癌では生物学的特性が異なる可能性はある。また，経口・経静脈投与された薬剤の腹腔内への移行性も腹膜播種の治療の成否を分ける要素であると考えられる。いずれにしても，過去に行われた胃癌化学療法の開発においては腹膜播種に対する効果の有無は度外視されがちであった。こうした中でもMTX/5FU併用療法[2]，タキサン系抗癌剤[3]など，経験的に腹膜転移治療に向いていると考えられ，使用されてきた治療法は存在する。しかし，腹膜播種陽性胃癌に対する化学療法をエビデンスに基づいて確立するには，これに対象を絞った臨床試験を実施する必要がある。そこで，わが国でいくつかの科学的な臨床試験が行われはじめたが，今のところ大きな成果は得られていない。例えば，腹膜播種に比較的有効とされていたMTX/5FU併用療法は，腹膜転移陽性胃癌237例を集積したランダム化比較試験JCOG0106で，5FU持続静注に対する優越性を示すことができなかった（ハザード比0.94）。

肝転移では腫瘍の縮小の確認が容易である分，化学療法の効果を実感する機会に恵まれることも多い。また，適応を絞って転移巣を切除した場合には，一定の頻度で治癒が得られる[4]。これに対して，腹膜転移の場合には，腹腔内洗浄細胞診によって確認されるような微小な転移巣からも必ずといってよいほど癌性腹膜炎に進展するため，P1症例とCY1症例の予後は同等に不良と報告されてきたほどである。こうした転移巣を切除によって治癒させようとするのは現実的ではなく，加えて腹膜転移に対する化学療法の治療効果についても悲観的に考えられがちであった。しかし，最近の臨床試験の結果から間接的に得られる知見をみると，必ずしも否定的な材料ばかりではないことに気付かされる。

まず，胃癌術後補助化学療法の効果を見たACTS-GC試験がある[5]。この試験の対象はStage Ⅱ，Ⅲの進行胃癌，すなわちCY0であった。それでも実際には微量の腹腔内遊離癌細胞が存在しうることはRT-PCRなどの手法により明らかになっており[6]，ACTS-GC試験登録例の中からも，腹膜転移再発例は多数みられている。ここで注目すべき点は，腹膜転移再発例がティーエスワン（S-1）群で手術単独群より少なかった点である（表1）[5]。同じ補助化学療法が血行性転移再発の抑制には寄与していなかったのと対照的であり，S-1には少量の腹腔内遊離癌細胞に対して一定の効果があることを示唆するデータである。さらに，CY1を唯一の非治癒因子とする症例に対するS-1単剤療法のデータも存在する[7]。2年生存率が46%と，歴史的対照に比較してはるかに良い治療成績であり，その後5年以上の長期生存例も確認できている（図1）。その他の報告も併せると，有効な抗癌剤が増えた現在では，CY1P0の治療成績はP1には勝る可能性が考えられ，腫瘍量が少ない腹膜転移であれば何とか制御が可能な時代が到来した感はある。

1．腹膜播種陽性胃癌に対する現時点での標準治療

胃癌に対する化学療法は，術後補助化学療法，術前補助化学療法，進行・再発胃癌に対する化学療法という3つのカテゴリーに分かれる。このうち，術後補助化学療

表1 ACTS-GCにおける初回再発形式[5]
S-1による術後補助化学療法で腹膜転移再発が抑えられた。

部位	S-1群 (n=529)	手術単独群 (n=530)	ハザード比 (95% CI)	p値
総計	133 (25.1%)	188 (35.5%)		
局所	7 (1.3%)	15 (2.8%)	0.42 (0.16～1.00)	0.05
リンパ節	27 (5.1%)	46 (8.7%)	0.54 (0.33～0.87)	0.01
腹膜	59 (11.2%)	84 (15.8%)	0.64 (0.46～0.89)	0.009
血行性	54 (10.2%)	60 (11.3%)	0.84 (0.58～1.21)	0.35

法においては，胃切除術後というQOLの著しく低下する時期に行う治療である点の配慮が必要である。術前補助化学療法においては，高度な腫瘍縮小効果が求められる。進行・再発胃癌に対する化学療法は，こうした制限に縛られることはないが，最大の全生存期間が得られる治療法であることが求められる。エビデンスに基づけば，JCOG9912試験[8]とSPIRITS試験[9]の結果，現在の進行・再発胃癌に対する標準治療はS-1とcisplatin（CDDP）の併用療法である。CDDPを使用できない場合はS-1単剤療法が標準治療となる。これは進行・再発胃癌全般に対するものであり，腹膜播種陽性胃癌に特化した標準治療は現段階では存在しない。しかし，SPIRITS試験のサブセット解析を見る限り，標的病変を有さない症例，あるいは腹膜転移例に対してS-1/CDDP療法が不利な要素はない。また，昨今，審査腹腔鏡により以前は開腹しなければ把握できなかったP1，CY1が開腹前に診断できるようになった。そして，このような場合に切除を行わずS-1/CDDP療法を行った上でsecond lookの審査腹腔鏡ないしは開腹を行うと，腹膜転移が消失したりCYが陰性化するなどして根治切除が行えるケースが稀ならずあることがわかってきた[10]。こうした化学療法は現時点では術前補助化学療法とは考えるべきではなく，あくまでも進行・再発胃癌に対する化学療法が奏効した結果，切除という選択肢が得られたと考えるのが妥当と思われる。切除した場合の長期の治療成績や，切除後の化学療法の是非等については，何ら結論は得られていない。以上より，腹膜播種陽性胃癌に対する現時点での標準治療は，S-1/CDDP療法を手術を前提とせずに行い，延命を目指すことであると言えよう。なお，経口摂取不能な場合には5FU/ロイコボリン静注か5FU持続静注療法を行うことになるが，これらにpaclitaxelを併用する方法も開発されている。

先般，HER2陽性胃癌において，trastuzumabにフッ化ピリミジンとCDDPに対する有意な上乗せ効果があることが報告された[11]。これは極めて重要な知見であるが，HER2陽性例には分化型の腺癌が多く，腹膜播種陽性胃癌の多くは該当しないと思われる。一方，START試験においては，S-1とdocetaxelの併用療法のS-1単剤に対する優越性は示されなかった。しかし，サブセット解析をみると，標的病変を有さない症例ではS-1/docetaxel療法が優勢であり，この中には腹膜播種陽性例も多く含まれると考えられる。S-1/CDDP療法との比較でS-1/docetaxel療法が優れている点は，高齢者においても同等の効果を持つ点であり，高齢者，腎機能の低下した症例，大量輸液が困難な症例などにはS-1/docetaxel療法も選択肢となりうると考えられる。

2．腹膜播種陽性胃癌に対する二次治療

わが国では胃癌に二次治療以降を行うのが常識となってきているが，腹膜転移の有無を問わず，二次治療が胃癌に有用であるかどうかを示すレベルの高い根拠は存在しない。こうした中，腹膜転移にはタキサン系薬剤が有効とされてきた。しばしば用いられているweekly paclitaxel療法については，他臓器の癌におけるweekly投与の用量より少ない点，保険適応となった用法・用量と異なる点などで批判的な見解もあるが，本療法におけるpaclitaxelの薬理動態を見る限りでは有効な血中濃度に達しているようである[12]。そして，その効果と安全性についての感触から多くの臨床家に支持されるに至っており[13]，community standardのひとつと考えられる。こうした背景から実施されるにいたったJCOG0407は，一次治療不応性腹膜転移例について，bolusと持続静注のうち一次治療で使用しなかった方の5FU basedの治療とweekly paclitaxel療法を比較するランダム化比較試験であり，weekly paclitaxel療法を安全で有望な治療と位置付けている。

3．腹膜播種陽性胃癌に対する腹腔内投与

先に述べたように，腹腔内への抗癌剤の移行は重要なポイントである。そこで，腹腔内に直接抗癌剤を投与する方法が考案された。古くはmitomycin Cの腹腔内投与があり，これについては経静脈投与とのランダム化比較などが行われ，腹腔内投与のみならず腹腔リザーバー挿入手技も保険適応となっている。しかし，腹腔内投与を