Ishiguro et al. BMC Cancer 2012, 12:281
http://www.biomedcentral.com/1471-2407/12/281

BMC Cancer

STUDY PROTOCOL Open Access

Study protocol of the SACURA trial: a randomized phase III trial of efficacy and safety of UFT as adjuvant chemotherapy for stage II colon cancer

Megumi Ishiguro[1], Hidetaka Mochizuki[2], Naohiro Tomita[3], Yasuhiro Shimada[4], Keiichi Takahashi[5], Kenjiro Kotake[6], Masahiko Watanabe[7], Yukihide Kanemitsu[8], Hideki Ueno[2], Toshiaki Ishikawa[9], Hiroyuki Uetake[9], Shigeyuki Matsui[10], Satoshi Teramukai[11] and Kenichi Sugihara[1*]

Abstract

Background: Adjuvant chemotherapy for stage III colon cancer is internationally accepted as standard treatment with established efficacy, but the usefulness of adjuvant chemotherapy for stage II colon cancer remains controversial. The major Western guidelines recommend adjuvant chemotherapy for "high-risk stage II" cancer, but this is not clearly defined and the efficacy has not been confirmed.

Methods/design: SACURA trial is a multicenter randomized phase III study which aims to evaluate the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment after surgery for stage II colon cancer in a large population, and to identify "high-risk factors of recurrence/death" in stage II colon cancer and predictors of efficacy and adverse events of the chemotherapy. Patients aged between 20 and 80 years with curatively resected stage II colon cancer are randomly assigned to a observation group or UFT adjuvant therapy group (UFT at 500–600 mg/day as tegafur in 2 divided doses after meals for 5 days, followed by 2-day rest. This 1-week treatment cycle is repeated for 1 year). The patients are followed up for 5 years until recurrence or death. Treatment delivery and adverse events are entered into a web-based case report form system every 3 months. The target sample size is 2,000 patients. The primary endpoint is disease-free survival, and the secondary endpoints are overall survival, recurrence-free survival, and incidence and severity of adverse events. In an additional translational study, the mRNA expression of 5-FU-related enzymes, microsatellite instability and chromosomal instability, and histopathological factors including tumor budding are assessed to evaluate correlation with recurrences, survivals and adverse events.

Discussion: A total of 2,024 patients were enrolled from October 2006 to July 2010. The results of this study will provide important information that help to improve the therapeutic strategy for stage II colon cancer.

Trial registration: ClinicalTrials.gov NCT00392899.

Keywords: Colon cancer, Stage II, Adjuvant chemotherapy, UFT, Risk factor, Predictive factor, Prognostic factor, Surgery-alone, Randomized controlled trial, Japan

* Correspondence: k-sugi.srg2@tmd.ac.jp
[1]Department of Surgical Oncology, Tokyo Medical and Dental University, Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Full list of author information is available at the end of the article

Background

In Japan, colorectal cancer is the second most common cancer following stomach cancer, and the third most fatal cancer following lung cancer and stomach cancer [1]. Postoperative adjuvant chemotherapy has been demonstrated to improve the outcome in stage III colon cancer and is internationally accepted as standard treatment. On the other hand, no consensus has been reached on the usefulness of adjuvant chemotherapy for stage II colon cancer.

A meta-analysis using the studies C-01 to C-04 of the National Surgical Adjuvant Breast & Bowel Project (NSABP) [2] showed that adjuvant chemotherapy significantly decreased the risk of recurrence/death in both Dukes' B and C. However, other pooled analysis or large population database review revealed no statistically significant additive survival benefit of adjuvant therapy including 5-FU + leucovorin exclusively in stage II colon cancer [3,4].

In Japan, Sakamoto et al. [5] reported the results of the meta-analysis that adjuvant therapy with oral 5-FU drugs (without concomitant use of leucovorin) contributed to significant improvement in recurrence-free survival (RFS) and overall survival (OS) in stage II colon cancer. UFT (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is one of the most widely used oral 5-FU agent as adjuvant chemotherapy for colorectal cancer in Japan. UFT is a combination drug of tegafur and uracil at a molar ratio of 1:4 and is characterized by long maintenance of a high 5-FU concentration level converted from tegafur in blood/tumors due to inhibition of degeneration of 5-FU by uracil. In the randomized controlled trial (RCT) comparing 2-year adjuvant therapy using UFT (400 mg/body) with observation without adjuvant therapy in 289 patients after surgery for stage II/III colon and rectal cancer [6], the 5-year RFS was significantly better in the UFT group. However, the analysis exclusively for colon cancer (160 patients) revealed no significant difference (77.4% in the UFT group, 74.0% in the observation group, $p = 0.71$). In the RCT comparing 1-year adjuvant therapy using UFT (400 mg/m^2/day) with observation without adjuvant therapy in 610 patients after surgery for stage III colon and rectal cancer [7], 1-year treatment with UFT was well tolerated and significantly improved the RFS and OS in rectal cancer, while the analysis for 332 patients with colon cancer showed no significant difference in both the 5-year RFS (71.3% in the UFT group, 69.6% in the observation group, $p = 0.56$) and OS.

Although both of the abovementioned two RCTs [6,7] failed to demonstrate an additive effect, 1- or 2-year postoperative adjuvant therapy with UFT alone has often been used for stage II colon cancer in clinical practice in Japan, because of its good feasibility [8] and low-cost. The Japanese Study Group for Postoperative Follow-up of Colorectal Cancer reported that the 5-year survival rate of 1,262 patients with stage II colon cancer who underwent surgery between 1977 and 2000 was 82.1% [9]. Given such a good outcome, it is necessary to clarify in a larger population whether postoperative adjuvant treatment with UFT alone has an additive effect on stage II colon cancer compared with observation only.

On the other hand, the reports using a large-scale database disclosed that stage II colon cancer included subpopulations with different prognosis [9,10]. The major Western guidelines recommended to select the "high-risk group of recurrence" in stage II colon cancer and to give postoperative adjuvant chemotherapy. The NCCN guidelines of 2012 [11] lists T4 lesions, number of lymph-nodes examined <12, perforation, lymphovascular involvement, poorly differentiated histopathology, and perineural invasion as high-risk factors, while the ASCO guidelines of 2004 [12] lists inadequately sampled nodes, T4 lesions, perforation, and poorly differentiated histology as factors for considering for adjuvant chemotherapy in stage II colon cancer. In addition to these, high CEA is listed as high-risk factor in the ESMO guidelines [13]. Recently, the biomarker studies have proposed new risk factors for recurrence/prognosis.

It seems appropriate to use adjuvant chemotherapy for a subgroup with poor prognosis in stage II colon cancer. However, the definition of "high-risk stage II" is not clear yet, and the efficacy of adjuvant chemotherapy for those patients has not been demonstrated. We therefore conducted the SACURA trial (Surgical Adjuvant Chemotherapy with UFT for Curatively Resected Stage II Colon Cancer), a multicenter phase III RCT to verify the efficacy of adjuvant chemotherapy for curatively resected stage II colon cancer in a large population through evaluating the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment, and to identify "high-risk factors of recurrence" in stage II colon cancer and predictors of efficacy and adverse events (AEs) of the chemotherapy.

Methods/design

The design of study

This study is a multicenter randomized phase III trial, in which patients with curatively resected stage II colon cancer are randomly assigned to either the observation group or UFT adjuvant therapy group (Figure 1). The primary endpoint is disease-free survival (DFS), and the secondary endpoints are OS, RFS, and incidence and severity of AEs. Superiority of adjuvant therapy with UFT compared to observation without any adjuvant therapy

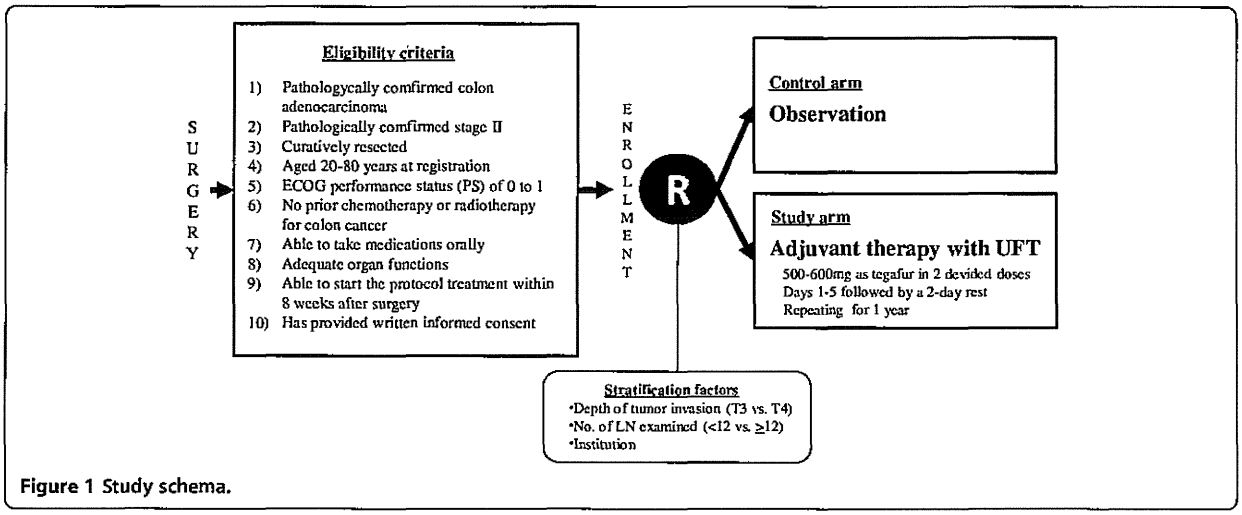

Figure 1 Study schema.

is evaluated. As an additional translational study, the surgical specimens are collected for histopathological and biomolecular assessments.

Enrollment and allocation

Eligible patients are enrolled at the Translational Research Informatics Center using a web-based system. Patients are randomly assigned, in a 1:1 ratio, to either an observation group or UFT adjuvant therapy group, using minimization by introducing a random element with a 0.8 assignment probability [14], balanced on the following stratification factors: depth of tumor invasion (T3 vs. T4), number of lymph-nodes examined (<12 vs. ≥12) and institution (Figure 1). Treatment assignment is not masked from the investigators and patients.

The main eligibility criteria are as follows:

Inclusion criteria

1) Histologically confirmed stage II colon cancer
2) Histologically confirmed adenocarcinoma
3) Has undergone curative surgery
4) Age: 20–80 years
5) ECOG performance status: 0–1
6) No prior chemotherapy or radiotherapy for colon cancer
7) Able to take medications orally
8) Adequate organ functions as listed below (at ≤14 days prior to enrollment)
   i) Leukocytes: 3,500/mm^3 to 12,000/mm^3
   ii) Neutrophil: ≥ 1,500/mm^3
   iii) Hemoglobin ≥ 9.0 g/dL
   iv) Platelet count ≥ 100,000/mm^3
   v) Total bilirubin ≤ 2.0 mg/dL
   vi) Aspartate aminotransferase (AST), alanine aminotransferase (ALT): ≤ 100 IU/L
   vii) Creatinine: ≤1.5 mg/dL
9) Able to start the protocol treatment within 8 weeks after surgery
10) Has provided written informed consent

Exclusion criteria

1) Other active malignancies (i.e. diagnosed within 5 years) (Tis colorectal cancers are allowed to enroll)
2) Hereditary colorectal cancer
3) Severe comorbidities:
   i) Severe postoperative complication
   ii) Uncontrollable diabetes mellitus
   iii) Uncontrollable hypertension
   iv) Myocardial infarction within 6 months
   v) Unstable angina pectoris
   vi) Cirrhosis or liver failure
   vii) Interstitial pneumonia, pulmonary fibrosis, or severe emphysema
   viii) Psychiatric disorder
4) Concern about pregnancy
5) The investigator considers the patient not suitable for the study

Protocol treatment

Assigned treatment is started within 8 weeks after surgery.

Observation group

Patients are followed-up without adjuvant treatment, according to the schedule defined in the study protocol for 5 years until recurrence, other malignancy or death is confirmed (Figure 2).

UFT adjuvant therapy group

UFT is given at a dose of 500–600 mg/day as tegafur in 2 divided doses after meals for 5 days, followed by a

2-day rest [8]. This one-week cycle is repeated for one year. During protocol treatment, clinical findings and laboratory values are evaluated every month.

Protocol treatment is started and continued when the patients fulfill the following criteria: leukocytes ≥3,000/mm^3, platelets ≥100,000/mm^3, AST and ALT ≤100 IU/L, total bilirubin ≤2.0 mg/dL, no greater than grade 2 anorexia, nausea, vomiting, or diarrhea. If the criteria for starting/continuing treatment are not met, treatment is postponed or temporarily suspended until AEs improve to meet the criteria. And then, treatment is resumed at one dose level lower (−200 mg). The dose can be reduced if the physician judges that dose reduction is necessary. Once the dose has been reduced, it is not to be subsequently re-increased.

Protocol treatment is discontinued in the cases as follows: treatment fails to be resumed within 29 days after being postponed or temporarily suspended (the planned drug rest is not included), the physician judges that the protocol treatment is difficult to continue due to AEs, recurrence or other malignancies develop, the patient requests discontinuation of protocol treatment, and the patients withdraw informed consent.

After the completion of protocol treatment, patients are followed-up following the same schedule as for the observation group (Figure 2) until recurrence, other malignancy or death is confirmed.

Evaluation of treatment delivery and adverse events

Treatment delivery (UFT adjuvant therapy group only)

Physicians report the treatment delivery via a web-based case report system, including the followings: daily dose, drug compliance*, temporary suspension (+/-), number of days of suspension, reason for suspension, dose reduction (+/-), etc.

* The drug compliance for each 3 months period is defined as the ratio of the dose actually taken to the prescribed dose, and is classified to the following 4 categories: 1) ≥90% taken, 2) ≥75% to <90% taken, 3) ≥50% to <75% taken, and 4) <50% taken.

Safety profile (both groups)

The types and severities of AEs from the start of protocol treatment to 30 days after the last administration are evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The most severe grade of each AE is reported every 3 months. The following AEs are required to be reported as "priority survey items": leukocytes, hemoglobin, platelets, total bilirubin, AST, ALT, stomatitis, anorexia, nausea, vomiting, diarrhea, rash/desquamation, hyperpigmentation, and fatigue.

Statistical background

Definition of endpoint

The primary endpoint of this study is DFS, and the secondary endpoints are OS, RFS, and incidence and

	At enrollment	Time after surgery: 3 months	6 months	9 months	12 months	1y3m	1y6m	1y9m	2y	2y3m	2y6m	2y9m	3y	3y6m	4y	4y6m	5y	5y after final enrollment
Patient characteristics	●																	
General/clinical findings	●	●	●	●	●													
Hematology/ Serum chemostry	●	●	●	●	●													
Adverse events		●	●	●	●													
Treatment delivery/compliance		○	○	○	○													
Tumor marker (CEA, CA19-9)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Colonoscopy or Barium enema exam.		✱			●								●				●	
Abdominal CT or US			●		●		●		●		●		●	●	●	●	●	
Chest CT or X-ray			●		●		●		●		●		●	●	●	●	●	
CRF submission	●				●				●				●					●

● : Indicates mandatory items. ○ : Indicates mandatory for UFT group only.
✱ : To be performed if preoperative examinations of the proximal colon are inadequate.
□ : To be performed mandatory at least every month in UFT group.

Figure 2 Observation, examination, and report schedule.

severity of AEs. DFS is defined as the time to recurrence, other malignancies or death, whichever comes first. Patients alive and free of recurrence or other malignancies are censored at time of last follow-up. RFS is defined as the time to recurrence or death. Patients alive and free of recurrence are censored at time of last follow-up. The intervals are calculated from the date of enrollment.

Definition of target sample size

In two clinical studies conducted in Japanese patients with colon cancer in the 1990's, the 5-year DFS rate in patients without adjuvant chemotherapy was 74.3% (Dukes' B) [15] and 74.0% (Dukes' B and C) [6]. Given a recent improved surgical outcome, it was assumed that the 5-year DFS rate would be 80% in the control group (observation group). With an expected 5-year DFS rate of 85% (hazard ratio: 0.729) in the study treatment group (UFT adjuvant therapy group), a two-sided significance level of 5%, and a power of 90%, the necessary sample size was calculated to be 970 patients per group according to the method described by Shoenfeld et al. [16]. A target sample size of 1,000 patients per group (a total of 2,000 patients in two groups) was determined in consideration of a 3% excluded rate.

Analysis plan

The primary analyses are done on an intent-to-treat basis. The survival curves (DFS, OS, and RFS) are estimated by the Kaplan-Meier method, and the stratified log-rank test, stratified by the depth of tumor invasion and the number of lymph-nodes examined, are used to test the null hypothesis that the respective curves are equal between the two groups. The hazard ratio is estimated using a stratified proportional hazard model. A two-sided significance level of 5% is used. Subgroup analyses are performed according to sex, age, depth of tumor invasion, and number of lymph-nodes examined for comparison between the two groups.

The treatment delivery in the UFT adjuvant therapy group is summarized. The incidence of AEs between two groups is compared with the Fisher's exact test.

An interim analysis of the efficacy is planned at 3 years after enrollment of the last patient. For the primary endpoint (DFS), the significant levels in interim and final analyses are determined according to α spending function (the O'Brien-Fleming type) to keep the overall type I error at 5%.

Additional translational study

The assessments shown in Figure 3 are made in paraffin-embedded thin sections of surgical specimens from primary tumors to evaluate the correlation with recurrences, survivals and AEs. The details of methods and analytical procedures will be reported separately.

Ethical matters

This study is conducted in accordance with the "Declaration of Helsinki" and "Ethical Guidelines for Clinical Research," and has been approved by the Institutional Review Boards of each participating institute. Written informed consent is obtained from all patients before enrollment.

Discussion

This study is conducted to prospectively evaluate adjuvant chemotherapy for stage II colon cancer in terms of the efficacy, safety and feasibility in a large population.

1) Analysis of mRNA expression of enzymes related to nucleic acid metabolism, folic acid metabolism, and tumor progression
   - TS (thymidylate synthase)
   - DPD (dihydropyrimidine dehydrogenase)
   - TP (thymidine phosphorylase)
   - OPRT (otate phosphoribosyl transferase)
   - FPGS (folylpolyglutamate synthetase)
   - VEGF (vascular endothelial growth factor)
   - COX-2 (cyclooxygenase-2)

2) Analysis of microsatellite instability (MSI) and chromosomal instability (i.e., 18qLOH)

3) Evaluation of histopathological factors in HE-stained specimens
   - tumor budding
   - extent of the poorly differentiated component
   - Crohn's-like lymphoid reaction
   - fibrotic cancer stroma etc.

Figure 3 Items included in additional translational study.

According to the Japanese "Guidelines for the Treatment of Colorectal Cancer" [17] published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), adjuvant chemotherapy is recommended for stage III colorectal cancer. However, in line with the major Western guidelines [11-13], the JSCCR guidelines states that adjuvant chemotherapy for stage II colon cancer is considered for patients with a "high-risk factor of recurrence" after adequate informed consent, although the efficacy of adjuvant chemotherapy for stage II colon cancer is not clearly demonstrated and "high-risk stage II" is not clearly defined. No definite conclusion has been reached on this clinically important issue, probably for the following reasons: 1) large number of patients would be required to evaluate the efficacy of adjuvant chemotherapy for stage II colon cancer because of good surgical outcome; and 2) no high-quality RCT for stage II colon cancer alone has been conducted.

The SACURA trial is a RCT in patients with curatively resected stage II colon cancer, evaluating whether 1-year adjuvant treatment with UFT improves the DFS and OS compared with observation without adjuvant treatment (superiority study). Between October 2006 and July 2010, a total of 2,024 patients were enrolled from the 270 institutes. In Japan, complete mesocolic excision with central vascular ligation (D3 dissection) [17-19] is the standard surgery for colon cancer. The institutions which met the conditions that the member of the JSCCR, more than 80 colorectal cancer surgery each year and D3 dissection as routine surgery were selected for the study to insure the quality of the study.

In the present study, the observation group is used to investigate the clinicopathological high-risk factors for recurrence, and the UFT adjuvant therapy group is used to evaluate the effect of adjuvant therapy on the patients with those "high-risk factors". These assessments will provide useful information to determine the indication of adjuvant therapy for patients with stage II colon cancer.

New reliable risk factors of recurrence other than routine items in histopathological examination are expected. The present study evaluates the following histopathological markers as promising prognostic factors for stage II colorectal cancer: tumor budding [20], extent of the poorly differentiated component [21], Crohn's-like lymphoid reaction [22], and fibrotic cancer stroma [23]. This is the first study to evaluate those new possible prognostic histopathological markers prospectively using a large sample size.

In recent years, risk classification for recurrence/prognosis and prediction of efficacy to chemotherapy based on the biomolecular profiles are intensively studied. The meta-analysis reported that MSI-high stage II colorectal cancer was characterized by a lower recurrence rate and better prognosis, compared with MSI-low and microsatellite-stable stage II colorectal cancer [24]. On the other hand, the pooled analysis disclosed that adjuvant chemotherapy with 5-FU drugs for MSI-high colorectal cancer resulted in poorer OS than those of patients without the chemotherapy [25], indicating that MSI may be interesting as a predictor of efficacy to 5-FU based chemotherapy. Deletion or loss of heterozygosity (LOH) of the long arm of chromosome 18 (18q) is considered as an indicator of chromosomal instability [26,27], which can be related to carcinogenesis and tumor progression. In the PETACC-3 molecular study [28], both the univariate and multivariate analyses in 420 patients without adjuvant chemotherapy after surgery for stage II colon cancer revealed that 18qLOH was a significant factor for poor prognosis and that MSI-high was a significant factor for good prognosis. In the present study, MSI and 18qLOH are evaluated in more patients collected prospectively than those in the PETACC-3 study.

The efficacy and AEs of 5-FU drugs may be related to 5-FU-related enzymes in blood or tumor [29,30]. In Japan, several oral 5-FU drugs with differing mechanisms of action have been frequently used, but few prospective studies with a large sample size about this issue have been conducted. In the present study, the tumor mRNA expression levels of enzymes related to nucleic acid metabolism, folic acid metabolism, and tumor progression are measured to evaluate the correlation with the prognosis and AEs to identify predictors of efficacy and safety. In the future, it is expected that oral 5-FU drugs can be used in personalized ways based on differences in the appearance of these enzymes.

In conclusion, the SACURA trial is a large, multicenter phase III RCT intended to demonstrate the efficacy and safety of postoperative adjuvant therapy in patients with stage II colon cancer by showing the superiority of 1-year adjuvant treatment with UFT to observation without any adjuvant treatment. The results will identify 1) "high-risk stage II" colon cancer, 2) predictors of efficacy and AEs of adjuvant chemotherapy with 5-FU drugs and 3) subgroup benefited from adjuvant chemotherapy, and will contribute to establish an improved therapeutic strategy for stage II colon cancer.

Abbreviations

AEs: Adverse events; MSI: Microsatellite instability; OS: Overall survival; RCTs: Randomized controlled trials; RFS: Recurrence-free survival; DFS: Disease-free survival; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; JSCCR: Japanese Society for Cancer of the Colon and Rectum; LOH: Loss of heterozygosity.

Competing interest

SACURA trial (BRI_CC0501, BRI_CC0502) was conducted by "Foundation for Biomedical Research and Innovation, Translational Research Informatics Center" with funding from Taiho Pharmaceutical Co. Ltd., Japan.

MI has received consulting fees from Taiho Pharmaceutical Co. Ltd., Bristol-Myers Squibb and Merck Serono Co. Ltd; honoraria from Taiho, Chugai Pharmaceutical Co. Ltd., and Yakult Honsha Co. Ltd.
HM has received consulting fees from Otsuka Pharmaceutical Factory, Inc. and Sysmex Co.; honoraria from Taiho, Chugai, Yakult Honsha, Daiichi Sankyo Co. Ltd., Astellas Pharma Inc.
NT has received research funding from Taiho, Chugai, and Yakult Honsha; honoraria from Taiho, Chugai, Takeda Pharmaceutical Co. Ltd., Merck Serono.
YS has received honoraria from Taiho, Chugai and Yakult Honsha.
KT has received honoraria from Taiho and Takeda.
KK has received consulting fees from Taiho and Chugai; honoraria from Taiho, Chugai, Bristol-Myers, Merck Serono and Otsuka.
MW has received research funding from Taiho, Chugai, Yakult Honsha, Johnson and Johnson K. K. and Covidien Japan Co. Ltd.
YK has received honoraria from Taiho and Chugai.
H. Ueno has received honoraria from Taiho, Chugai, Yakult Honsha, Bristol-Myers and Daiichi Sankyo.
TI has received research funding from Taiho; honoraria from Chugai.
H. Uetake has received consulting fees, research funding, and honoraria from Taiho, Chugai, Takeda, Bristol-Myers and Merck Serono.
SM has no competing interest.
ST has received consulting fees from Taiho, Daiichi Sankyo and Solasia Pharma K. K.; research funding from Daiichi Sankyo, Yakult Honsha and Kureha Co. Ltd.; honoraria from Daiichi Sankyo.
KS has received consultant fees, research funding and honoraria from Taiho, Chugai, Takeda, Yakult Honsha, Daiichi Sankyo, Bristol-Myers, Merck Serono, and Pfizer Co. Ltd.

Authors' contributions

MI, as a task manager, participated in entire coordinating of the study, data collection, data analysis, data interpretation, and writing of the manuscript. HM, NT, YS, KT, KK, MW, YK, and KS, as a steering committee, participated in all phases of this study, including design and writing of the protocol, data collection, data analysis, data interpretation, and preparation of the manuscript. H. Ueno, TI, and H. Uetake, as a steering committee for additional translational study, carried out the molecular and pathological evaluation, and participated in all phases of this study, including design and writing of the protocol, data collection, data analysis, data interpretation and preparation of the manuscript. SM and ST, as a chief of statistical analysis, participated in statistical setting of study design and data analysis. All authors reviewed and approved the final manuscript.

Authors' information

No relevant information.

Acknowledgement

We are grateful to all of the patients and the co-investigators for their cooperation in SACURA trial. The authors also thank the following additional investigators for their contributions to this trial: Yasuyo KUSUNOKI, Fumie KINOSHITA and Naoko KASHIWAGI in data management, Akinori OGASAWARA, Yuri UEDA and Syuichiro SUGIMOTO as the project office staff, Yoko TAKAGI, Aiko SAITO and Sachiko KISHIRO in preparating thin slice sections of tumors and extracting DNA, Yasuyo OKAMOTO as the additional translational study office staff, and Masanori FUKUSHIMA, M.D., Ph.D. as a director of Translational Research Informatics Center.

Author details

[1]Department of Surgical Oncology, Tokyo Medical and Dental University, Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. [2]Department of Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan. [3]Department of Surgery, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. [4]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. [5]Department of Surgery, Cancer and Infectious Diseases Center Komagome Hospital, 18-22, Honkomagome 3-chome, Bunkyo-ku, Tokyo 113-8677, Japan. [6]Department of Surgery, Tochigi Cancer Center, 4-9-13 Yonan, Utsunomiya, Tochigi 320-0834, Japan. [7]Department of Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0375, Japan. [8]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan. [9]Department of Translational Oncology, Tokyo Medical and Dental University, Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. [10]Department of Data Science, the Institute of Statistical Mathematics, 10-3 Midori-cho, Tachikawa, Tokyo 190-8562, Japan. [11]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, 54 Shogoin-kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan.

Received: 17 February 2012 Accepted: 21 June 2012
Published: 7 July 2012

References

1. *Cancer statistics in Japan*. 2010 http://www.fpcr.or.jp/publication/statistics.html
2. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H: **Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04).** *J Clin Oncol* 1999, 17:1349–1355.
3. **Efficacy of adjuvant fluorouracil and folinic acid in colon cancer: International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators.** *Lancet* 1995, 345:939–944.
4. Schrag D, Rifas-Shiman S, Saltz L, Bach PB, Begg CB: **Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer.** *J Clin Oncol* 2002, 20:3999–4005.
5. Sakamoto J, Ohashi Y, Hamada C, Buyse M, Burzykowski T, Piedbois P: **Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials.** *J Clin Oncol* 2004, 22:484–492.
6. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A: **Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial.** *Langenbecks Arch Surg* 2002, 386:575–581.
7. Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y: **Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC).** *Cancer Chemother Pharmacol* 2011, 67:587–596.
8. Sadahiro S, Ohki S, Yamaguchi S, Takahashi T, Otani Y, Tsukikawa S, Yamamura T, Takemiya S, Nagasaki H, Nishiyama K, Fukushima T, Hiki Y, Yamaguchi S, Kumada K, Shimada H, Mitomi T, Makuuchi H: **Feasibility of a novel weekday-on/weekend-off oral UFT schedule as postoperative adjuvant chemotherapy for colorectal cancer.** *Cancer Chemother Pharmacol* 2000, 46:180–184.
9. Higuchi T, Sugihara K: **Complete mesocolic excision (CME) with central vascular ligation (CVL) as standardized surgical technique for colonic cancer: a Japanese multicentre study [abstract].** *Dis Colon Rectum* 2010, 53:176.
10. Sobin LH, Gospodarowicz MK, Wittekind C: *TNM Classification of Malignant Tumours*. 7th edition. New York: Wiley-Blackwell; 2009.
11. NCCN Clinical Practice Guidelines in Oncology: *Colon cancer version 2*. 2012. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
12. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, Haller DG: **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004, 22:3408–3419.
13. Van Cutsem E, Oliveira J: **Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up.** *Ann Oncol* 2008, 19(Suppl 2):ii29–ii30.
14. Pocock SJ, Simon R: **Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial.** *Biometrics* 1975, 31:103–115.
15. Watanabe M, Nishida O, Kunii Y, Kodaira S, Takahashi T, Tominaga T, Hojyo K, Kato T, Niimoto M, Kunitomo K, Isomoto H, Ohashi Y, Yasutomi M: **Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5 -fluorouracil and uracil/tegafur.** *Int J Clin Oncol* 2004, 9:98–106.
16. Schoenfeld DA, Richter JR: **Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint.** *Biometrics* 1982, 38:163–170.

17. Japanese Society for Cancer of the Colon and Rectum: *JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer*. Tokyo: Kanehara & Co., Ltd; 2010.
18. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P: **Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon.** *J Clin Oncol* 2010, 28:272–278.
19. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, Sugihara K, Quirke P: **Understanding optimal colonic cancer surgery. Comparison of Japanese D3 resection and European complete excision with central vascular ligation.** *J Clin Oncol* 2012, 30:1763–1769.
20. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC: **Tumour 'budding' as an index to estimate the potential of aggressiveness in rectal cancer.** *Histopathology* 2002, 40:127–132.
21. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Kajiwara Y, Sato T, Shimazaki H, Hase K, Talbot IC: **Histological grading of colorectal cancer: a simple and objective method.** *Ann Surg* 2008, 247:811–818.
22. Graham DM, Appelman HD: **Crohn's-like lymphoid reaction and colorectal carcinoma: a potential histologic prognosticator.** *Mod Pathol* 1990, 3:332–335.
23. Ueno H, Jones AM, Wilkinson KH, Jass JR, Talbot IC: **Histological categorisation of fibrotic cancer stroma in advanced rectal cancer.** *Gut* 2004, 53:581–586.
24. Des Guetz G, Schischmanoff O, Nicolas P, Perret GY, Morere JF, Uzzan B: **Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis.** *Eur J Cancer* 2009, 45:1890–1896.
25. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, French AJ, Kabat B, Foster NR, Torri V, Ribic C, Grothey A, Moore M, Zaniboni A, Seitz JF, Sinicrope F, Gallinger S: **Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer.** *J Clin Oncol* 2010, 28:3219–3226.
26. de la Chapelle A: **Microsatellite instability.** *N Engl J Med* 2003, 349:209–210.
27. Walther A, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D: **Genetic prognostic and predictive markers in colorectal cancer.** *Nat Rev Cancer* 2009, 9:489–499.
28. Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, Topham C, Tabernero J, Andre T, Sobrero AF, Mini E, Greil R, Di Costanzo F, Collette L, Cisar L, Zhang X, Khayat D, Bokemeyer C, Roth AD, Cunningham D: **Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3.** *J Clin Oncol* 2009, 27:3117–3125.
29. Koizumi W, Tanabe S, Azuma M, Ishido K, Nishimura K, Sasaki T, Nakatani K, Higuchi K, Nakayama N, Katada C: **Impacts of fluorouracil-metabolizing enzymes on the outcomes of patients treated with S-1 alone or S-1 plus cisplatin for first-line treatment of advanced gastric cancer.** *Int J Cancer* 2010, 126:162–170.
30. Ichikawa W, Takahashi T, Suto K, Yamashita T, Nihei Z, Shirota Y, Shimizu M, Sasaki Y, Hirayama R: **Thymidylate synthase predictive power is overcome by irinotecan combination therapy with S-1 for gastric cancer.** *Br J Cancer* 2004, 91:1245–1250.

doi:10.1186/1471-2407-12-281
Cite this article as: Ishiguro *et al.*: Study protocol of the SACURA trial: a randomized phase III trial of efficacy and safety of UFT as adjuvant chemotherapy for stage II colon cancer. *BMC Cancer* 2012 12:281.

Trastuzumab for a Patient With Heavily Pretreated Gastric Cancer Plus Massive Ascites and Ovarian Metastasis

Kohei Shitara,[1] Yasushi Yatabe,[2] Tomoya Yokota,[1] Daisuke Takahari,[1] Takashi Shibata,[1] Takashi Ura,[1] Yozo Satoh,[3] Yasuhiro Kodera,[4] Kei Muro[1]

[1]*Department of Clinical Oncology*
[2]*Department of Pathology*
[3]*Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Aichi, Japan*
[4]*Department of Surgery II, Nagoya University Graduate School of Medicine, Nagoya, Japan*

CASE REPORT

A 42-year-old female with a chief complaint of anorexia and abdominal fullness was diagnosed with gastric cancer and referred to our hospital in September 2008. Her oral intake was decreased to one-third of her normal intake. She was the mother of three children and had no significant past medical history. On physical examination, her abdomen was distended with fluid. Her ECOG performance status was 2. Gastroduodenoscopy revealed diffuse infiltration of gastric cancer with the appearance of linitis plastica. Pathological examination showed poorly differentiated adenocarcinoma (Figure 1A) with a signet-ring-cell carcinoma component. Computed tomography (CT) scan revealed massive ascites, thickened gastric wall, and bilateral ovarian metastases.

Beginning in October 2008, chemotherapy with weekly 5-fluorouracil, and methotrexate was administered as first-line chemotherapy. After three chemotherapy cycles, her abdominal distension and oral intake improved. Although the same regimen was continued for one additional month on an outpatient basis, the patient was again admitted in December 2008 with anorexia and abdominal distension due to increased ascites, which necessitated routine twice weekly paracentesis. She refused peritoneovenous shunt placement.

Second-line chemotherapy using paclitaxel was administered four times, with no tumor or ascites response. However, following chemotherapy with docetaxel and intraperitoneal cisplatin injection, there was a decrease in her ascites, and the patient could be discharged.

In April 2009, she was readmitted with fatigue, anorexia, and increased ascites. Paracentesis showed hemorrhagic ascites, which required twice weekly drainage, and she also required weekly transfusions. After two cycles of chemotherapy with triweekly pemetrexed, there was transient response, with a decrease in ascites that changed from hemorrhagic to serous.

In June, the patient's general status worsened, with frequent vomiting caused by gastrointestinal stenosis, massive ascites, and enlarged ovarian metastases (Figures 2A–B). Additionally, she also developed dyspnea with dry cough, and lymphangitic pulmonary metastases of the right lower lung were suspected (Figure 3A). Since she and her family strongly desired additional chemotherapy, the HER2 status of her gastric cancer biopsy specimen was evaluated by immunohistochemistry (IHC; HercepTest™, DAKO, Copenhagen, Denmark) and was found to be strongly positive (3+) (Figure 1B) in accordance with high gene amplification of *HER2* (red signal, Figure 1C).

Because of her deteriorated performance status, trastuzumab monotherapy was initiated (4 mg/kg first dose, then 2 mg/kg weekly). A percutaneous transesophageal gastrostomy was also performed. After three cycles, her dyspnea improved (Figure 3A). After six administrations of trastuzumab, the volume of ascites was

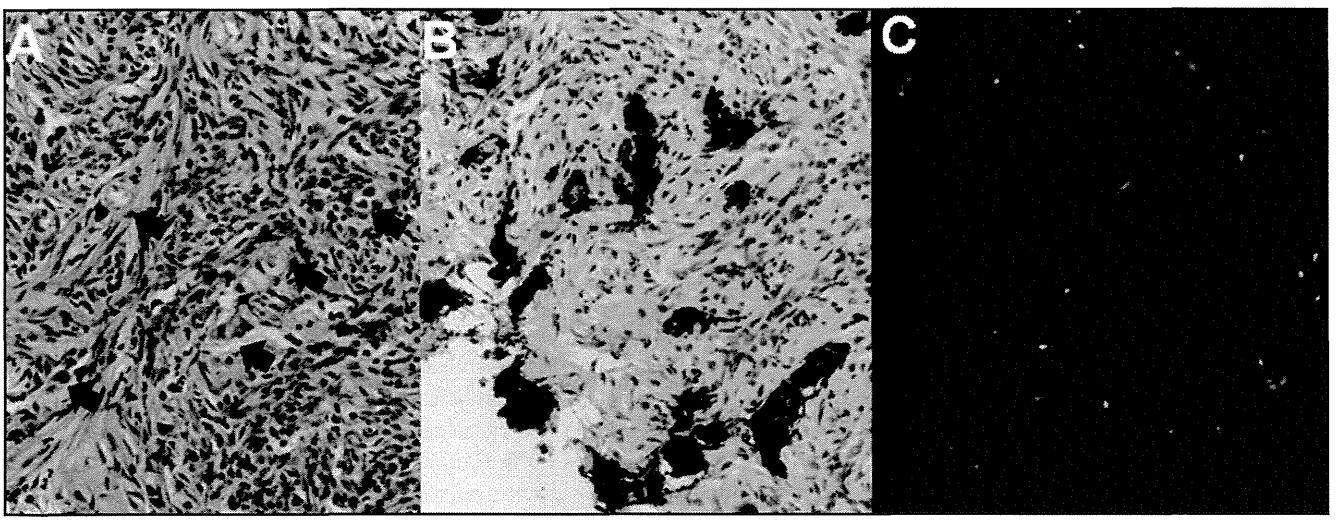

Figure 1. Pathological specimen of the primary gastric cancer. (A) Endoscopic biopsy specimen showed poorly-differentiated adenocarcinoma cells (arrows). (B) HER2 status was evaluated by IHC (HercepTest), and was found to be strongly positive (3+). (C) High gene amplification of HER2 was also seen by FISH (red signal).

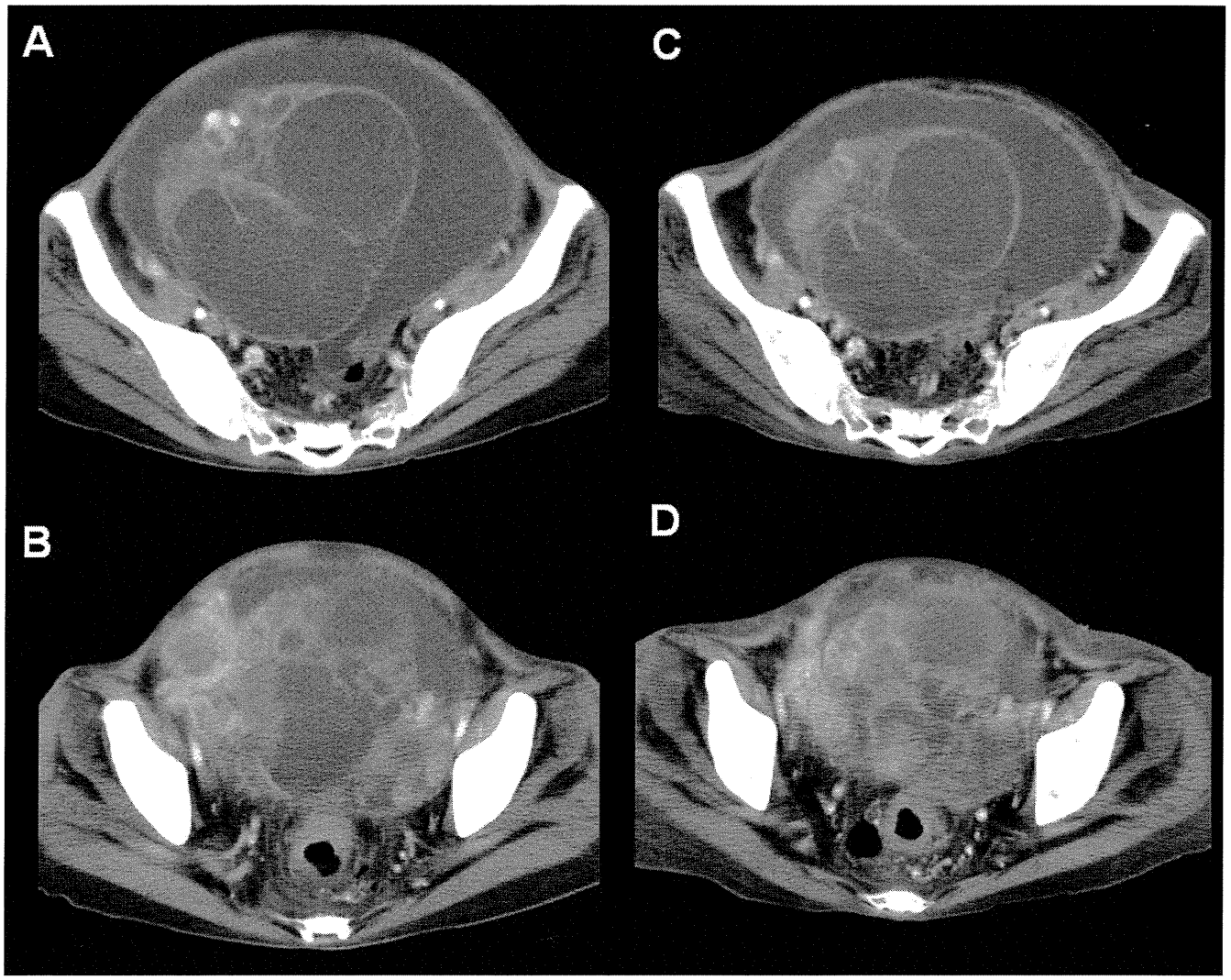

Figure 2. CT scan before and on trastuzumab monotherapy. (A–B) CT scans before treatment showed large ovarian metastasis with ascites. (C–D) CT scans after 6 administrations of trastuzumab showed that her ovarian tumors were slightly reduced.

decreased, and the frequency of paracentesis was reduced from twice to once weekly. A CT scan showed that her ovarian tumors were slightly reduced (Figures 2C–D). No apparent trastuzumab toxicity was observed, and her performance status was maintained for two and a half months. Trastuzumab monotherapy was continued for 3 months until the patient became icteric in September 2009, 11 months after the first admission and 9 months since routine paracentesis was begun. Best supportive care was offered thereafter.

DISCUSSION

Trastuzumab, a recombinant, human–mouse chimeric monoclonal IgG1k antibody that specifically targets HER2 protein, has improved survival in HER2-positive breast cancer patients. In the first pivotal trial of breast cancer, trastuzumab plus paclitaxel or an anthracycline improved overall survival by a hazard ratio of 0.80 (95% confidence interval [CI], 0.64–1.0, $P = .046$) compared with chemotherapy alone.[1] In another trial, trastuzumab plus docetaxel also improved breast cancer survival compared with chemotherapy alone.[2] After these results, trastuzumab-containing chemotherapy became the standard of care for breast cancer patients with HER2 overexpression.[3]

Because HER2-positive gastric cancers have been reported, the efficacy of trastuzumab for HER2-positive gastric cancer has also been anticipated. The ToGA study[4] comparing 5-fluorouracil plus cisplatin with or without trastuzumab showed improved survival in the trastuzumab arm with a hazard ratio for death of 0.74 (95% CI, 0.60–0.91, $P = .0,046$). In contrast to breast cancer, HER2 amplification revealed by fluorescence in situ hybridization (FISH) was seen in gastric cancers with IHC results of 0 or 1+ by modified HercepTest. Therefore, when survival analysis in the TOGA study was limited to HER2 cancers that were 2–3+ by IHC and FISH-positive, the reduction in risk of death became more apparent (HR 0.65; 95% CI, 0.51–0.83). No apparent increase in toxicity was seen in the trastuzumab arm[4]; therefore combination chemotherapy using trastuzumab may become the standard of care for HER2-positive gastric cancer and has been approved in the United States for this indication.

In the TOGA study screening data,[5] the HER2-positive rate was higher in gastroesophageal junction cancer (33.2%) than in gastric cancer (20.9%). In addition, the diffuse type had a lower positive rate (6%) than the intestinal type (34%) of gastric cancer. However,

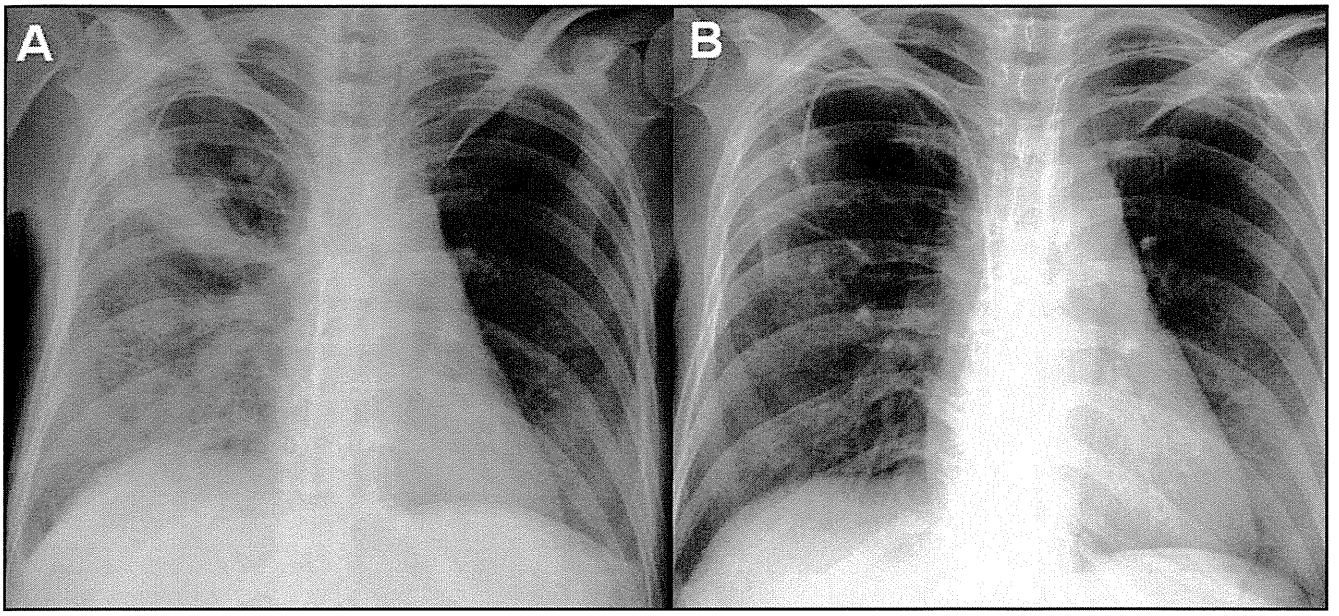

Figure 3. Chest x-ray before and on trastuzumab monotherapy. (A) Lymphangitic pulmonary metastases of right lower lung were suspected. (B) Abnormal finding improved with trastuzumab.

as confirmed by experience with our patient, although patients with diffuse-type gastric cancer are frequently HER2 negative, HER2 status of all gastric cancer types should be evaluated.

Because the ToGA study included chemonaive patients with gastric cancer, the benefit or efficacy of chemotherapy using trastuzumab for patients pretreated with chemotherapy is not currently known. In addition, the antitumor effect of trastuzumab monotherapy is not known. However, trastuzumab monotherapy has been shown to be active with a response rate of 15% in pretreated breast cancer (18% for 3+ IHC),[6] although this is a slightly lower response rate than for monotherapy in chemonaive breast cancer (35% in 3+ IHC),[7] and trastuzumab monotherapy has been adopted for patients who are not considered suitable for cytotoxic chemotherapy.[3]

In summary, this case was instructive for the following reasons: (1) trastuzumab monotherapy was feasible in this heavily pretreated patient with gastric cancer plus massive ascites, (2) trastuzumab and sufficient supportive care were effective in improving the cancer-related symptoms in this patient, (3) although chemotherapy using trastuzumab may become standard first-line chemotherapy for patients with HER2-positive gastric cancer, trastuzumab may even be effective in the salvage setting.

REFERENCES

1. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783–792, 2001
2. Marty M, Cognetti F, Maraninchi D, et al: Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 23:4265–4274, 2005
3. NCCN Clinical Practice Guidelines in Oncology. *Breast Cancer* ver. 2, 2009
4. Van Cutsem E, Kang Y, Chung H, et al: Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol* 27:4265–18s, 2009 (suppl; abstr LBA4509)
5. Bang Y, Chung H, Xu J, et al: Pathological features of advanced gastric cancer (GC): relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. *J Clin Oncol* 27:4265–15s, 2009 (suppl; abstr 4556)
6. Cobleigh MA, Vogel CL, Tripathy D, et al: Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 17:2639–2648, 1999
7. Vogel CL, Cobleigh MA, Tripathy D, et al: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 20:719–726, 2002

Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Address correspondence to: Kohei Shitara, MD, Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Aichi, Japan. Phone: 81-52-762-6111; Fax: 81-52-752-8390; E-mail: Kouheis0824@yahoo.co.jp

4. 腹膜播種病変に対する腹腔内化学療法－臨床における効果－

Intraperitoneal chemotherapy for peritoneal metastasis from gastric carcinoma: Clinical benefits

名古屋大学大学院医学系研究科消化器外科学　小寺　泰弘
Yasuhiro Kodera
（教授）

Summary

胃癌では，転移再発形式として頻度の高い腹膜転移の制御が重要である。抗癌剤の局所濃度を上昇させ，最大限の効果を得るには，腹腔内投与が合理的と思われ，過去にはシスプラチンの投与が試みられたが，十分な効果は示されなかった。近年，腹腔内投与時の薬理動態からパクリタキセル（PTX）が有望と考えられており，実際に，この薬剤の腹腔内投与と経静脈投与をS-1と組み合わせた併用療法（東大レジメン）が第Ⅱ相試験において胃癌腹膜転移例に対してきわめて良好な治療効果を示した。PTXの腹腔内投与には保険適応がないが，現在，切除可能胃癌を対象としたPTX腹腔内投与vs経静脈投与と，非切除例を対象とした東大レジメンvs S-1/シスプラチン療法の2件のランダム化試験が，高度医療評価制度を利用して行われている。その成果としてPTX腹腔内投与が保険収載され，実地臨床で腹膜転移の制御を目的に使用可能となることに期待したい。

Surgery Frontier 19(2)：41-45，2012

Key Words

胃癌，癌性腹膜炎，腹膜転移，腹腔内化学療法，腹腔内投与

胃癌腹膜転移は根治切除後に最も多くみられる再発形式であるのみならず，診断時にすでに同時性にみられる場合も少なくない。癌の浸潤が漿膜面に到達し，ここからはがれた癌細胞が腹腔内に播種するというのがその主な発生機序とされる。このような遊離癌細胞は，腹腔内洗浄液の細胞診で検出可能であり，胃癌取扱い規約では洗浄細胞診陽性はCY1と記載され，ほかに非治癒因子を認めなくてもStage Ⅳとなる。現実に，肉眼的に腹膜転移を認める場合（P1）と同等に予後不良であることが，多数の施設から報告されている。胃癌治療ガイドラインによれば，Stage Ⅳの胃癌は根治手術の適応とはならない。

腹膜転移は胃癌のほかに，卵巣癌でもしばしばみられる転移形式である。興味深いことに，卵巣癌では洗浄細胞診が陽性でも肉眼的な腹膜転移を認めなければStage Ⅰであり，肉眼的な転移を認めても，径1 cm未満の病巣以外を（すなわち，主だった転移巣を）切除できればoptimally debulked cancerとされ，化学療法で一定の治療成績を見込めるとする見解がある。すなわち，化学療法がよく効く癌であるため，胃癌では意義が少ないと考えられてきた減量手術（debulking surgery）

◆メモランダム◆

保険適応と高度医療評価制度

現在，胃癌に使用されている薬剤の腹腔内投与は保険適応ではない。腹腔内投与を研究費で，ほかの医療行為を保険でまかなうと混合診療となる。しかし，全治療を研究費でまかなうとコストがかかりすぎるので，臨床試験は実施できない。高度医療評価制度においては，厚生労働省に申請し承認を受けた新規治療法を特定の医療機関で行う場合，新規治療法のコストは自費や研究費で補い，ほかの医療行為は保険診療として研究を進めることができる。

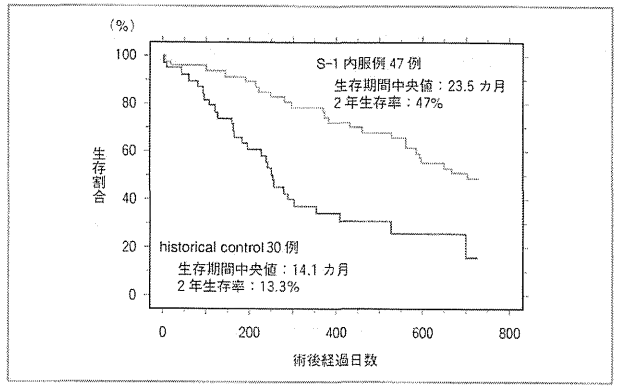

図 1　CY1 症例に対する胃切除後 S-1 療法の治療成績 historical control との比較
〔文献 1 より一部改変引用〕

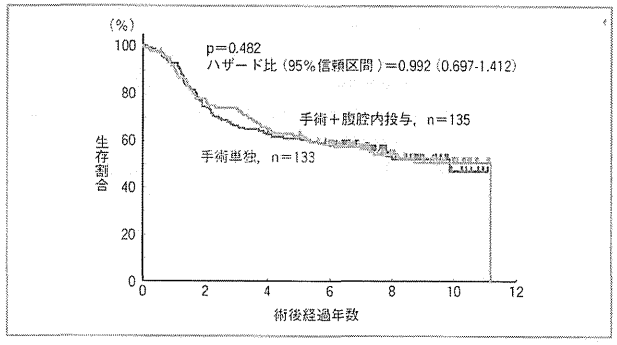

図 2　洗浄細胞診陰性・漿膜浸潤陽性胃癌に対する CDDP IP を含む術後補助化学療法を検証するランダム化試験 JCOG9206-2
〔文献 2 より一部改変引用〕

に意義が認められ，顕微鏡レベルの遺残については必ずしも悲観する必要はないようである。胃癌においても化学療法が奏効するようになれば，減量手術の意義が再浮上する可能性がある。

現実に筆者らは CY1 以外に非治癒因子を認めない胃癌（ただし，少量の腹膜転移であれば，胃切除と同時にすべて切除できれば適格とした）に定型手術を施行したうえで S-1 を投与する第Ⅱ相試験を行い[1]，過去の報告を大幅に上回る 47％という 2 年生存率を得ている（図 1）。また，現在進行・再発胃癌の標準治療となっている S-1 とシスプラチン（CDDP）の併用療法も，腹膜転移例に相性がよいようである。

CY0 で治癒切除がなされた漿膜浸潤陽性胃癌に対する手術当日の CDDP の腹腔内投与（intraperitoneal administration ： IP）を含む補助化学療法が，JCOG の第Ⅲ相試験で検証されたが，大方の予想に反し手術単独群と全く同等の成績しか得られなかった（図 2）[2]。術後に行われる 1 コースの 5FU/CDDP と，その後の UFT による補助化学療法のコンプライアンスが不良であったのも一因とされているが，少なくとも手術当日の CDDP の IP はほぼもれなく行われていたはずであり，少なくともこれについては全く効果がなかったものと考えられる。IP された CDDP は血中への移行がきわめて良好で，腹腔内に短時間しかとどまらないため，単回投与での局所への効果には限界があったものと思われる。なお，臨床試験が行われた当時も現在も CDDP の腹腔内投与は保険適応ではない。したがって，本臨床試験を JCOG で実施できたのは時代背景の相違という以外に説明の術はない。本臨床試験の結果をかんがみても，現在わが国で CDDP の IP を実地臨床として行うべきではない。近年，韓国の単施設での第Ⅲ相試験において，CDDP の単回投与を含む補助化学療法が，これを含まない補助化学療法に比し有意に良好な生存期間を得たとの報告があり，長期観察でも有意差は維持されていることが 2012 年の Gastrointestinal Cancers Symposium で報告された。しかし，CDDP IP 投与群では，手術当日にマイトマイシン C も投与され，術後にカペシタビン / CDDP 療法が行われ（CDDP IP 非投与群はカペシタビン単剤），さらにそのコース数も多いなど，IP 以外にも両群間に多数の相違点があるため，本試験の結果をもって CDDP 単回投与の失地を回復することはできないと考えられる。

わが国で IP が再度注目を集めたのは，腹腔内投与時の薬理動態ゆえに腹腔内投与に適していると考えられる（図 3）タキサンが使用されるようになってからである。しかし，タキサンの IP が保険適応でないことから，手順を踏んで用量設定試験などを行うのは事実上不可能であった。ただ，米国では卵巣癌を対象にパクリタキセル（PTX）の IP の臨床試験が多数行われており，ここでは週に 1 度単剤での投与を行う場合の至適投与量が 60 mg/m^2 に設定されていた。筆者らは，高度医療評価制度を用いて PTX の IP を検証する臨床試験を計画した。単回投与では物足りないため，腹腔リザーバーを挿入し，術後 10 週間にわたり PTX の IP のみの治療を行うこととした。このため，エビデンスのある術後 S-1 療法を遅らせても倫理的に問題が少ないと思われる，特段に腹膜転移再発のリスクの高い症例（スキルス胃癌の根治切除例，CY1 症例，同時性の P 因子を同時に完全切除した症例，微量の P 因子が遺残した症例）を対象とした。そして，手術当日を含む計 7 回の PTX の IP を試験アームとし，同一スケジュールで PTX の点滴静脈注射（DIV）を reference とするランダム化第Ⅱ相試験，INPACT 試験を開始するに至った[3]（図 4）。プロトコール治療後は根治度に応じ，S-1 単剤ないしは S-1/CDDP 併用療法を継続すること

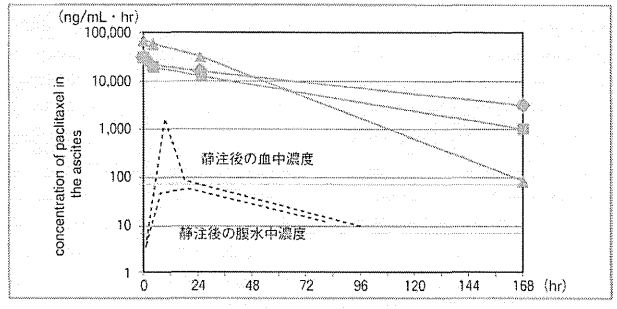

図 3　腹腔内投与された PTX の薬理動態
腹水を有する 3 症例に PTX 60 mg/m^2 を腹腔内投与した場合の腹水中濃度の推移を実線で示す。点線は，腹水を有する症例に PTX 60 mg/m^2 を経静脈投与した場合の血中濃度と腹水中濃度を superimpose したものである。

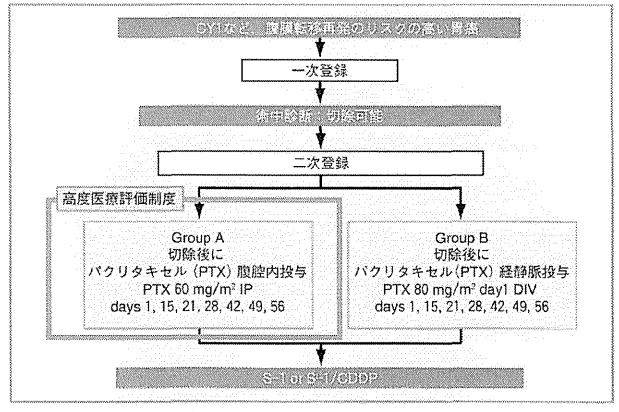

図 4　INPACT 試験（多施設共同ランダム化第Ⅱ相試験）

としている。DIV 投与群に割り付けられ PTX 終了後に S-1 単剤に移行する場合にも，術後 S-1 単独療法に代わる新たな補助化学療法の候補として第Ⅲ相試験（SAMIT 試験）で検証中である PTX/S-1 の逐次併用療法と同様の治療法となり，有用な治療法である可能性は秘めている。また，S-1/CDDP 療法は胃切除後すぐに行うには毒性が強く，忍容性に乏しいとされている[1]が，1 コース目に CDDP をスキップすれば，2 コース目からは導入可能であることが示唆されている。INPACT 試験の DIV 群で S-1/CDDP 療法を行う場合には，術後早期には PTX を使用し，時間が経過してから S-1/CDDP 療法を導入することになり，胃切除後に S-1/CDDP 療法を行う手段のひとつとして期待される。INPACT 試験は，2012 年 1 月現在，目標症例数の 25％に相当する症例集積を得ている。

一方，切除不能な同時性腹膜転移例や再発症例を対象に，Ishigami らは独自に校費負担で S-1 内服，PTX DIV，PTX IP を併用する新たなレジメン（東大レジメン）の第 1 相試験を行い，推奨用量を設定した[5]。すでに確立されている S-1/PTX 療法（S-1 は 80 mg/m^2 で 2 週間内服・1 週間休薬，PTX は 50 mg/m^2 で day 1，8 に点滴静注）に PTX IP を追加するかたちのレジメン（図 5）であるため，IP の用量は 20 mg/m^2 と少ない設定となったが，IP によって圧倒的に高い腹腔内濃度が得られる薬理動態を考慮すれば，本用量でも十分に効果が見込まれた。引き続き行われた第Ⅱ相試験では，高度な腹膜転移例（旧取扱い規約における P3 症例が主体）を対象としたにもかかわらず，1 年生存率は 78％，洗浄細胞診が 86％で陰性化するなど，驚異的な治療成績が得られ，腹膜転移例に対するきわめて有望なレジメンと位置付けられた（図 5）[6]。筆者らも P3 症例 5 例にこれを行い，うち 2 例で P 因子の消失を確認し，conversion surgery に至っている。現在，東大レジメン対 S-1/CDDP の第Ⅲ相試験 PHOENICS 試験が同じく高度医療評価制度を用いて行われており，同時性腹膜転移を有する切除不能例を対象に症例集積中である。

さらに，Ishigami らは S-1 既治療例（S-1 による補助化学療法後再発例を含む）を対象に PTX と CDDP の併用腹腔内化学療法を開発し[7]，第Ⅰ相試験で PTX DIV，PTX IP，CDDP IP の biweekly の推奨用量がおのおの 80 mg/m^2，20 mg/m^2，25 mg/m^2 に設定された。これも現段階では高度医療評価制度か校費負担によってのみ検証が可能な治療法であるが，先に述べたランダム化試験からエビデンスが得られることにより，PTX IP が保険収載されこうした治療法の検証が容易となり，IP 法の開発が加速することに期待したい。

以上，PTX の腹腔内投与は有望な治療法であり，単剤，および併用の両面から，臨床試験による検証が行われている。

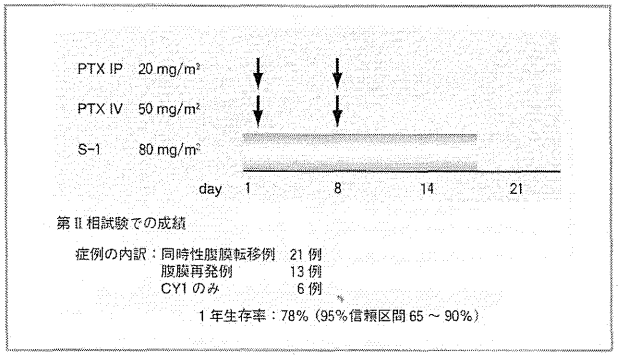

図 5　東大レジメンの内容と治療成績

文　献

1）Kodera Y, Ito S, Mochizuki Y, et al：A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). Eur J Surg Oncol 35：1158-1163, 2009
2）Miyashiro I, Furukawa H, Sasako M, et al：Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone：final results of the Japan Clinical Oncology Group trial JCOG9206-2. Gastric Cancer 13：212-218, 2011
3）Kodera Y, Imano M, Yoshikawa T, et al：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). Jpn J Clin Oncol 41：283-286, 2011
4）Kodera Y, Ishiyama A, Yoshikawa T, et al：A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703). Gastric Cancer 13：197-203, 2010
5）Ishigami H, Kitayama J, Otani K, et al：Phase I pharmacokinetic study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer. Oncology 155：142-146, 2009
6）Ishigami H, Kitayama J, Kaisaki A, et al：Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol 21：67-70, 2010
7）Ishigami H, Kitayama J, Kaisaki S, et al：Phase I study of biweekly intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel for gastric cancer with peritoneal metastasis. Oncology 79：269-272, 2010

Gastric Cancer (2012) 15:335–337
DOI 10.1007/s10120-012-0156-3

SHORT COMMUNICATION

Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study

Yasuhiro Kodera · Seiji Ito · Yoshinari Mochizuki · Norifumi Ohashi · Chie Tanaka · Daisuke Kobayashi · Hiroshi Kojima · Takanori Matsui · Ken Kondo · Michitaka Fujiwara

Received: 8 March 2012 / Accepted: 17 March 2012 / Published online: 21 April 2012

Abstract
Background In gastric cancer patients who have positive results for peritoneal lavage cytology the disease is defined as CY1, and classified as stage IV, and this population has generally suffered a dismal outcome. For this population, we had conducted a phase II trial, with the 2-year survival rate as the primary endpoint, to test the strategy of D2 dissection followed by chemotherapy with single-agent S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium). Forty-eight patients were enrolled, of whom 47 were found to have been eligible for analysis. The 2-year survival rate of 46 % exceeded our expectations.
Methods Further follow up was conducted to confirm whether radical surgery could be recommended for the CY1 population.
Results The 5-year overall and relapse-free survival rates were 26 and 21 %, respectively.
Conclusions Gastrectomy with curative intent could be considered for patients with CY1 disease provided they are scheduled to receive effective postoperative chemotherapy.

Keywords Gastric cancer · S-1 · Cytologic examination · Peritoneal carcinomatosis

Introduction

Stage IV gastric cancer is generally considered incurable and this population is usually ineligible for radical surgery. Treatment options for this population, recommended by the Japanese Guidelines, are chemotherapy, radiotherapy, palliative surgery and palliative care medicine [1]. However, several case series suggest that the possibility of cure cannot be ignored in some carefully selected populations of stage IV patients, given the improvements in multimodal treatment [2–4]. Patients with free cancer cells in the peritoneal cavity could constitute such a population. Detection of free cancer cells by peritoneal lavage cytology predicts the risk of peritoneal carcinomatosis with high specificity [5]. When cancer cells are detected, the positive cytology status is designated as CY1 by the *Japanese classification of gastric carcinoma, 2nd English edition* [6]. Patients with CY1 status are classified as stage IV even in the absence of macroscopic evidence of peritoneal seeding. Whether this population should be treated radically or palliatively has been an issue for debate [7].

For the Chubu Clinical Oncology Group

Y. Kodera (✉) · N. Ohashi · C. Tanaka · D. Kobayashi · M. Fujiwara
Department of Surgery II, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
e-mail: ykodera@med.nagoya-u.ac.jp

S. Ito
Department of Gastroenterological Surgery, Aichi Cancer Center Chuo Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Japan

Y. Mochizuki
Department of Surgery, Komaki Municipal Hospital, 1-20 Jobushi, Komaki, Japan

H. Kojima · T. Matsui
Department of Surgery, Aichi Cancer Center Aichi Hospital, 18 Ketsumachi Aza Kuriyado, Okazaki, Japan

K. Kondo
Department of Surgery, Nagoya Medical Center, 4-1-1, Sannomaru, Naka-ku, Nagoya, Aichi, Japan

The outcome in CY1 patients has been reported to be poor in the East as well as in the West [8, 9], but the recent introduction of novel anticancer agents has changed the picture to some extent. We conducted a phase II trial, named CCOG0301, exploring D2 dissection followed by treatment with 1 M tegafur–0.4 M gimestat–1 M otastat potassium (S-1), in which 48 patients were registered, of whom 47 were eligible for analysis, and we achieved a two-year survival rate of 46 %, which exceeded the initial expectations [4]. The choice of a sample size of 50 patients in this study had been based on the hypothesis that the two-year survival rate would be 36 % and the lower limit of the 90 % confidence interval would exceed 23.5 %, which was the upper limit of the 90 % confidence interval for the historical controls whose two-year survival rate had been 13.3 %. While this phase II trial was ongoing, a pivotal phase III trial comparing postoperative adjuvant S-1 monotherapy with treatment by surgery alone in patients with stage II/III gastric cancer turned out to show positive results for the S-1 monotherapy arm. Moreover, the incidence of relapse, as peritoneal carcinomatosis, was found to be significantly lower in the S-1 monotherapy group [10]. This finding suggests that S-1 is effective against microscopic residual disease in the peritoneal cavity that is undetectable by peritoneal lavage cytology, and also suggests the potential of S-1 to control micrometastases in the peritoneal cavity. Encouraged by these findings, we were motivated to follow the patients for longer, to see what proportion of the patients who were entered in the CCOG0301 trial were actually cured, in order to reconsider the indication for curative surgery in patients with CY1 disease.

Patients and methods

Forty-seven patients who were registered between February 2002 and July 2006 for the CCOG0301 study underwent further follow up (for a median of 2,337 days or until death) to evaluate the long-term outcome.

Characteristics of the patients who were enrolled in the CCOG0301 study

Eligible patients had to meet all of the following criteria: (1) a confirmed diagnosis of gastric adenocarcinoma and age less than 80 years; (2) gastrectomy with systemic D2 lymphadenectomy performed (splenectomy could be omitted at the discretion of the surgeons); (3) no distant metastasis, with the exception of minimal peritoneal deposits that were completely resected; (4) no prior treatment besides surgery; (5) positive cytologic results for cancer cells on examination of peritoneal washings (CY1); and (6) adequate organ function [4]. Of the 47 eligible patients, 7 patients had peritoneal deposits, which were co-resected at surgery. Seven patients were intraoperatively confirmed to have invasion to adjacent organs (T4), and 38 others had serosal invasion. All but five patients were confirmed to have nodal involvement on pathological examination; six patients had metastasis to the paraaortic lymph nodes [4].

Treatment protocol of the CCOG0301 study

The interval from surgery to the start of therapy was not to exceed 6 weeks. Patients received S-1 at an oral dose of 40 mg per square meter of body-surface area twice daily for 4 weeks, followed by 2 weeks without chemotherapy. Patients with a body-surface area of less than 1.25 m^2 received 80 mg daily; those with a body-surface area of 1.25 m^2 to less than 1.5 m^2 received 100 mg daily; and those with a body surface area of 1.5 m^2 or greater received 120 mg daily. This 6-week cycle was repeated in an outpatient setting under medical supervision until disease progression, unacceptable adverse events, or the patient's withdrawal of consent. Adequate dose modification and changes in the treatment schedule were conducted, as described previously [4, 10].

Disease status was assessed once every 3 months on the basis of serum tumor markers and at least once every 6 months by computed tomography (CT) scanning for the first 2 years. Follow-up visits including a CT scan were performed once every 6 months until the patients were considered disease-free at 5 years after the surgery.

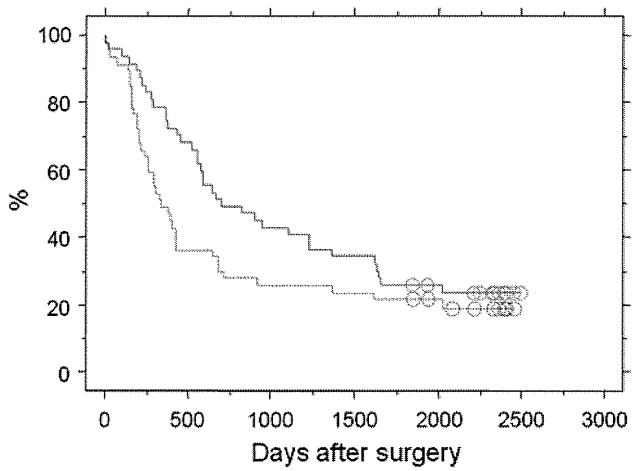

Fig. 1 Overall survival (*solid line*) and relapse-free survival (*dotted line*) of patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy

Results

Overall survival and relapse-free survival from the day of surgery are shown in Fig. 1. Median overall survival time was 705 days, and relapse-free survival time was 376 days. The 2- and 5-year survival rates were 46 and 26 %, respectively, and the 5-year relapse-free survival rate was 21 %. The most frequent pattern of disease recurrence was peritoneal carcinomatosis, occurring in 29 patients (62 % of all patients enrolled). Other patterns of recurrence were hepatic in 4 patients, lymphatic in 4, locoregional in 2, pulmonary in 1, and osseous in 1. Three patients died of disease other than gastric cancer, at 5, 1371, and 2023 days after surgery. Details on treatment compliance, dose intensity, and toxicity have been reported previously [4].

Conclusions

Patients with CY1 disease with no other non-curative factors could be indicated for surgery with curative intent, provided adequate chemotherapy is given. Although post-operative treatment with S-1, now a standard of care for stage II/III gastric cancer, remains as an option, further trials are warranted to decide on the optimal chemotherapeutic regimen and whether to deliver it before or after surgery.

References

1. Japanese Gastric Cancer Association. Gastric cancer treatment guidelines. 3rd ed. Kanehara: Shuppan (in Japanese); 2010.
2. Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol. 2007;95:534–9.
3. Koga R, Yamamoto J, Ohyama S, Saiura A, Seki M, Seto Y, et al. Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. Jpn J Clin Oncol. 2007;37:836–42.
4. Kodera Y, Ito S, Mochizuki Y, Kondo K, Koshikoawa K, Suzuki N, et al. A phase II study of radical surgery followed by post-operative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). Eur J Surg Oncol. 2009;35:1158–63.
5. Leake P-A, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systemic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer. 2012 (in press).
6. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma: 2nd English edition. Gastric Cancer. 1998;1:10–24.
7. Okabe H, Sakai Y. Gastrectomy for patients with positive peritoneal cytology: comments on the article "Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients". Ann Surg Oncol. 2011;18:S211–4.
8. Kodera Y, Yamamura Y, Shimizu T, et al. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. J Surg Oncol. 1999;72:60–4.
9. Mezhir JJ, Shah MA, Jacks LM, Brennan MF, Coit DG, Strong VE. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol. 2010;17:3173–80.
10. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387–93.

BMC Cancer

STUDY PROTOCOL Open Access

A randomized phase II trial to elucidate the efficacy of capecitabine plus cisplatin (XP) and S-1 plus cisplatin (SP) as a first-line treatment for advanced gastric cancer: XP ascertainment vs. SP randomized PII trial (XParTS II)

Akira Tsuburaya[1*], Satoshi Morita[2], Yasuhiro Kodera[3], Michiya Kobayashi[4], Kohei Shitara[5], Kensei Yamaguchi[6], Takaki Yoshikawa[1], Kazuhiro Yoshida[7], Shigefumi Yoshino[8] and Jun-ichi Sakamoto[9]

Abstract

Background: On the basis of international clinical trials, capecitabine plus cisplatin (XP) as a first-line treatment of advanced gastric cancer is considered a global standard regimen. However, the usefulness of XP as compared with S-1 plus cisplatin (SP), which is considered standard therapy in Japan, has not yet been assessed.

Methods/design: This is a multicenter randomized phase II trial to elucidate the efficacy of XP as compared with SP for first-line treatment of advanced gastric cancer. Patients with unresectable metastatic or recurrent gastric cancer, 20–74 years of age and human epidermal growth factor 2 (HER2)-negative status, will be assigned in a 1:1 ratio to receive either S-1 40 mg/m^2 bid for 21 days plus cisplatin 60 mg/m^2 (day 8) every 5-week cycle or capecitabine 1000 mg/m^2 bid for 14 days plus cisplatin 80 mg/m^2 (day 1) every 3-week cycle. Patients will be also asked to the analysis of tumor tissues for translational investigations. The Primary endpoint is progression-free survival and secondary endpoints are overall survival, time to treatment failure, tumor response rate and safety. These comparisons will also be evaluated in terms of biomarkers. Planned sample size is 100 (50 in each arm), which is appropriate for this trial.

Discussion: Fluoropyrimidine plus cisplatin combination is the standard regimen of the first line treatment for advanced gastric cancer. Both S-1 and capecitabine are the prodrug of 5-FU but differ from their process of metabolism. Result of this trial and translational research will provide the important clues to prepare the individualized therapy for advanced gastric cancer in the near future.

Trial registration: ClinicalTrials.gov Identifier NCT01406249

Keywords: Biomarker, Capecitabine, Cisplatin, Clinical trial, Gastric cancer, S-1

* Correspondence: tuburayaa@kcch.jp
[1]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, 241-0815, Yokohama, Asahi-ku, Japan
Full list of author information is available at the end of the article

Background

Gastric cancer is the fourth most common malignancy in the world (988 602 cases in 2008, 7.8% of total) and the second leading cause of cancer death (737 419 deaths, 9.7% of total) [1]. For the treatment of advanced or recurrent gastric cancer (AGC), the most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine (5-fluorouracil or oral fluoropyrimidine) plus a platinum agent with or without docetaxel or anthracyclines [2-6].

S-1 is an oral anticancer drug composed of the 5-fluorouracil (5-FU) prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7,8]. In a phase III trial (SPIRITS trial) that compared S-1 alone to S-1 plus cisplatin (SP), SP showed a significantly longer overall survival (OS; 13 months vs. 11 months; HR = 0.77, 95% CI 0.61–0.98, p = 0.04) and longer progression-free survival (PFS; 6.0 months vs. 4.0 months; HR = 0.57, 95% CI 0.44–0.73, p < 0.0001) [4]. Therefore, SP is now considered to be one of the standard first-line regimens for AGC in Japan.

Capecitabine is also an oral fluoropyrimidine, which is metabolized primarily in the liver and converted in tumor tissues to 5-FU by the enzyme thymidine phosphorylase (TP), which is associated in higher concentrations in tumor cells than in normal cells [9]. Kang and colleagues evaluated the non-inferiority of capecitabine plus cisplatin (XP) compared with 5-FU plus cisplatin (FP). The median PFS showed significant non-inferiority (5.6 months vs. 5.0 months; HR = 0.81, 95% CI 0.63–1.04, P < 0.001) [5]. On the basis of these results, XP is now considered one of the standard treatments of AGC [10], and XP was adopted as the reference arm in two recent global studies of molecular targeting agents [11,12]. However, data is scarce with respect to XP treatment in Japanese patients, and also the usefulness of XP as compared with SP has not yet been assessed.

As another issue, these 2 types of oral fluoropyrimidine show some different characteristics in the mechanisms of their antitumor effect. A subset analysis of the FLAGS trial showed that S-1 seemed to be better than 5-FU in the subgroup with diffuse-type gastric cancer [6]. This result was consistent with the results of a subset analysis of the JCOG9912 trial, which showed that S-1 was better than 5-FU in patients with diffuse-type gastric cancer or with gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD), with diffuse-type tumors associated more commonly than intestinal type with high DPD [13]. This result was expected, since S-1 consists of tegafur, otastat potassium, and gimestat which is a potent competitive inhibitor of DPD. Capecitabine is transformed to 5-FU in several steps, to be finally converted by TP as above [9]. A phase II trial in Japan showed that response rate (RR) was significantly higher (Fisher's exact test, $p = 0.028$) in patients with TP-positive and DPD-negative tumors (60%, 6/10) than in the remaining patients (13%, 2/15) [14]. In contrast, high expression of TP is reported to be negatively associated with efficacy of 5-FU or S-1 in gastric cancer [15,16].

On the basis of the above reports, histological type (diffuse or intestinal) and biomarkers (TP, DPD, and others) may be candidates to select whether S-1 or capecitabine be used for each patient, although validation with a randomized study is necessary. We planned the current clinical trial to elucidate the efficacy of XP and SP for the first-line treatment of AGC. This comparison will be also evaluated in terms of several biomarkers.

Method/design

Study objective

This randomized phase II trial is planned to elucidate the efficacy of SP and XP and also to explore predictive or prognostic biomarkers with additional research. This trial protocol has been approved by the Institutional Review Board (IRB) of each participating institution and the Kanagawa Cancer Center.

Study endpoints

Primary endpoint is PFS and secondary endpoints are OS, RR, time to treatment failure (TTF), and incidence of adverse events (safety).

Eligibility criteria

Inclusion criteria

(i) Histologically confirmed gastric adenocarcinoma with unresectable metastatic or recurrent disease
(ii) Lesions confirmed by imaging no more than 28 days before registration (not required for measurable lesions as defined in RECIST version 1.1)
(iii) No previous chemotherapy or radiotherapy. However, prior adjuvant chemotherapy is allowed if more than 6 months has passed since the end of adjuvant chemotherapy
(iv) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
(v) Life expectancy of at least 3 months after registration
(vi) Written informed consent
(vii) Between the ages of 20 and 74 years at the time informed consent is obtained
(viii) Adequate major organ function including:
(a) Neutrophil count: ≥1500/mm^3
(b) Platelet count: ≥10.0 × 10^4/mm^3
(c) Hemoglobin: ≥9.0 g/dL
(d) AST, ALT: ≤2.5 × upper limit of normal (ULN) in each institution (≤5 times in cases of metastases to liver)
(e) ALP: ≤2.5 × ULN in each institution (≤5 times in cases of metastases to liver, and ≤10 times in cases of metastases to bone)

(f) Total bilirubin: ≤1.5 × ULN in each institution
(g) Creatinine clearance: ≥60 mL/min (as estimated by Cockcroft-Gault equation)

Exclusion criteria

(i) HER2- positive status
(ii) Previous history of fluoropyrimidine therapy within 6 months prior to registration
(iii) Previous treatment with platinum agents within 12 months prior to registration
(iv) Previous treatment with cisplatin more than total dose of 120 mg/m^2
(v) Previous history of serious hypersensitivity to fluoropyrimidines or platinum agents
(vi) Previous history of adverse reactions suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency
(vii) More than 1 cancer at the same time or more than 1 cancer at different times separated by a 5-year disease-free interval. However, multiple active cancers do not include carcinoma *in situ* or skin cancer which is determined to have been cured as a result of treatment.
(viii) Obvious infection or inflammation (pyrexia ≥38.0°C)
(ix) Active hepatitis
(x) Heart disease that is serious or requires hospitalization, or history of such disease within the past year
(xi) Having a complication that is serious or requires hospitalization (intestinal paralysis, intestinal obstruction, interstitial pneumonia or pulmonary fibrosis, poorly controlled diabetes mellitus, renal failure, liver disorders, or hepatic cirrhosis)
(xii) Being treated or in need of treatment with flucytosine, phenytoin, or warfarin potassium
(xiii) Chronic diarrhea (watery stools or ≥4 times/day)
(xiv) Active gastrointestinal bleeding
(xv) Body cavity fluids requiring drainage or other treatment
(xvi) Clinical suspicion or previous history of metastasis to brain or meninges
(xvii) Women who are pregnant, breastfeeding, or potentially (hoping to become) pregnant
(xviii) Unwillingness to practice contraception
(xix) Poor oral intake
(xx) Psychiatric disorders which are being, or may need to be, treated with psychotropics
(xxi) Otherwise determined by investigators or site principal investigators to be unsuitable for participation in study

Registration

Physicians or coordinators will send a Case Registration Form to the data center (Epidemiological and Clinical Research Information Network, ECRIN) with all the required items filled out. Enrollment has started from July 2011.

Startification

Eligible patients will be randomized to either Arm-A (SP treatment) or Arm-B (XP treatment) by dynamic allocation via a centralized randomization method using 5 stratification factors as balancing variables:

(i) baseline ECOG Performance Status (0–1/2)
(ii) measurable lesion (yes/no)
(iii) prior adjuvant chemotherapy (yes/no)
(iv) histopathological classification (intestinal/diffuse)
(v) institution.

Statistical analysis

PFS has been set as the primary endpoint and is defined as the time from date of registration until the date that progression is determined or the date of death for any reason, whichever is sooner. "Progression" will be evaluated on the basis of Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [17]. More information about the definition of PFS and Progression are pre-specified (Table 1).

The primary objective of this trial is to evaluate the PFS of SP and XP as the first-line treatment for advanced gastric cancer. The 24-week progression-free rate (PFR) will be estimated for each group, calculating point estimates and 2-sided 90% confidence intervals. The 2-sided 90% confidence interval of the difference between the 2 groups will be also estimated. Exploratory analysis will be done to test the null hypothesis that PFS is equal in both groups. Cumulative PFS curves will be constructed as time-to-event plots by the Kaplan-Meier method.

With respect to secondary endpoints, efficacy endpoints OS and TTF will be evaluated according to the method of analysis of the primary endpoint. Overall response rate (RR) is defined as the proportion of patients with complete response (CR) or partial response (PR) by RECIST out of the patients with measurable lesions, and the chi-square test will be used to compare the 2 groups. The 2-sided 95% confidence interval of the difference between the 2 groups will also be estimated. For the analysis of safety, Fisher's exact test will be used if necessary, and the exact confidence intervals for the binomial distribution will be estimated.

Sample-size calculation

Assuming a threshold 24-week PFR of 40% and an expected 24-week PFR of 55% (clinically promising), and a 1.5-year registration period and a 1.5-year follow-up period, 49 patients are required in each group to ensure a 1-sided alpha of 5% and statistical power of 90%. Assuming that the 24-week PFR of the biomarker-positive (any FU-related enzyme or expression of intestinal type) population