INTRODUCTION

Robust adjuvant chemotherapy for stomach cancer has not yet been established. For resectable T2–T4 tumors, surgery remains the sole standard treatment in Japan. Recently opened Japanese trials also reported contradictory results: no benefit for cT3 tumors (JCOG9206) (1) and 54% risk reduction in 4 year survival for T2N1-2 tumors (NSAS-GC) (2). Most of these trials were not designed or failed to accumulate adequate number of patients, thus these bunch of underpowered studies are not able to show any definite answer. However, meta-analyses of those RCTs always suggest significant prognostic benefit of post-operative chemotherapy also in Japan.

In the United States, Macdonald et al. (3) reported a large RCT (INT116) comparing surgery versus surgery + post-operative 5-FU + LV + radiation with median survival of 27 months and 36 months, respectively ($P < 0.001$). This pivotal study has not yet been substantially appreciated in Japan due to the differences in lymph node dissection (D2 10%, D1 36% and D0 54% in the INT116, whereas D2 is standard in Japan).

Japan has pursued unique approach for decades using oral chemotherapy for post-operative adjuvant chemotherapy. Among them UFT (tegafur and uracil) has been most widely used in both clinical trials and general clinical practice (4). Recently, UFT has been gradually replaced by S1 (tegafur, 5-chloro-2,4-dihydroxyypyridine and oxonic acid) because of its high response rates. For Stages II and III stomach cancer, a large industry-driven clinical trial, ACTS-GC, comparing surgery alone versus surgery + S1 had finished accruing over...
1000 patients by the end of 2004 and the result will be disclosed by 2010. However, no comparison between UFT and the new agent S1 has been and is going to be done in clinical trials.

Paclitaxel has already been used extensively as one of key drugs for ovarian cancer, breast cancer and lung cancer (5,6). In advanced stomach cancer, it also achieved rather high response rate of 23.4% and median survival of 303 days by a triweekly administration (6). Paclitaxel has several unique characteristics as follows: (i) non-cross resistant to 5-FU; (ii) active with poorly differentiated carcinoma; (iii) good transition from the blood to the peritoneal cavity; and (iv) relatively low incidence of gastrointestinal toxicities (6,7,8). In addition, based on dose-dense hypothesis by Norton–Simon, enhancement of response rate and reduction in most of the toxicities with weekly administration has been reported.

As post-operative treatment for patients with T3–4 gastric cancer, sequential use of paclitaxel and S1 was safe and well tolerated in a multicenter Phase II trial (9). In this study, adjuvant treatment for curatively resected gastric cancer with paclitaxel, S1 and their combined sequential administration is proposed to be examined installing UFT as an active control for T3–4 gastric cancer.

**PROTOCOL DIGEST OF THE STUDY**

**OBJECTIVE**

A randomized Phase III trial with two-by-two factorial design was planned to elucidate survival benefit of sequential use of paclitaxel followed by oral fluoropyrimidines in comparison with fluoropyrimidines alone, and to compare the most commonly used two oral fluoropyrimidines, UFT and S1. Its protocol was approved by the Protocol Review Committee of the Japan South West Oncology Group (JaSWOG).

**RESOURCES**

Research grant from the Kyoto University EBM center and the non-profit organization: Epidemiological and Clinical Research Information Network (ECRIN).

**ENDPOINTS**

The primary endpoint is disease-free survival (DFS) and the secondary endpoints are incidence of adverse events, overall survival and proportion of patients who completed the protocol treatment.

**ELIGIBILITY CRITERIA**

Tumors are staged according to the 13th edition of the Japanese Gastric Cancer Classification (10).

Inclusion criteria for the first registration are as follows:
(i) Histologically proven adenocarcinoma of the stomach.
(ii) Clinical and surgical findings of T3 or T4, N0-2, P0, M0.
(iii) Underwent macroscopically curative gastrectomy with D2 or comparable lymphadenectomy.
(iv) No earlier chemotherapy or radiotherapy.
(v) Age ranging between 20 and 80.
(vi) Preoperative ECOG performance status 0–1.
(vii) Sufficient organ functions before chemotherapy.
(viii) Able to start chemotherapy between 14 and 56 days after surgery.
(ix) Without synchronous or metachronous cancer (synchronous multiple cancers in the stomach included).
(x) Written informed consent.

Exclusion criteria for the first registration are as follows:
(i) Serious complications
(a) Ischemic heart disease and arrhythmia which require treatment.
(b) History of myocardial infarction in 6 months.
(c) Liver disease under treatment.
(d) Pneumonitis or lung fibrosis in need for oxygen therapy.
(e) Gastrointestinal bleeding in need for repeated blood transfusion.
(f) Psychological disease which require treatment.
(g) Diabetes mellitus under treatment.
(h) Bowel obstruction or ileus.
(i) Medical history of allergy or hypersensitivity to any drugs
(ii) Hypersensitivity to Cremophor EL
(iii) Acute inflammation
(iv) Pregnancy
(v) Synchronous malignancies that may affect survival or adverse events
(vi) Patients judged inappropriate for the study by the physicians.

Inclusion criteria for the second registration are as follows:
(i) Recovered from or no operative complications.
(ii) Oral food intake possible.
(iii) Laboratory data: WBC ≥3000/mm³ and ≤12 000/mm³; neutrocyes ≥1500/mm³; platelets ≥100 000/mm³; hemoglobin ≥8.0 g/dl; albumin ≥3.0 g/dl; GOT ≤100 IU; GPT ≤100 IU; bilirubin ≤1.5 mg/dl; creatinine ≤1.5 mg/dl.

**REGISTRATION**

Within 35 days after operation, the physician or coordinator send an eligibility criteria checking report form to the data center at the EBM cooperative research center in the Kyoto University after confirming the patient’s data for the first registration. Then upon fulfilling the criteria for the second registration between 14 and 56 days after operation, the corresponding physician or coordinator send the same checking form to the data center. Eligible patients are randomized to one of arms A, B, C and D by a centralized dynamic method using macroscopic tumor size (<8 cm/≥8 cm in maximum diameter), nodal status (N0/N1–2) and institution as balancing variables. The accrual has started since August 2004.
TREATMENTS METHODS

Group A: UFT alone (control)
UFT 267 mg/m²/day daily for 4 weeks, every 4 weeks ×6

Group B: S1 alone
S1 80 mg/m²/day daily for 2 weeks, every 3 weeks ×8

Group C: Paclitaxel—UFT sequential
Paclitaxel 80 mg/m² Day 1, 8 for the first 3 weeks ×1
       Day 1, 8, 15 every 4 weeks ×2
       14 day interval
UFT 267 mg/m²/day daily for 4 weeks, every 4 weeks ×3

Group D: Paclitaxel—S1 sequential
Paclitaxel 80 mg/m² Day 1, 8 for the first 3 weeks ×1
       Day 1, 8, 15 every 4 weeks ×2
       14 day interval
S1 80 mg/m²/day daily for 2 weeks, every 3 weeks ×4

FOLLOW-UP

During the protocol treatment patients are checked up weekly to monthly by physical and blood examination. During and after finishing the protocol treatment in the study, physical check for recurrence and measurement of tumor markers, CEA and CA19-9, are performed every 3 month for 3 years. Abdominal CT or US is performed every 3 months in the first 2 years and every 6 months in the following year. Chest X-ray is taken every 6 months for 3 years. The registered patients will be followed for their status of recurrence and living for 3 years after the last patient is accrued.

STUDY DESIGN AND STATISTICAL METHODS

Two separate research hypotheses (i) the superiority of sequential use of paclitaxel followed by oral fluoropyrimidines to fluoropyrimidines (UFT/S1) alone and (ii) the non-inferiority of S1 to UFT were evaluated in terms of DFS benefit.

The sample size was calculated on the basis that 3 year DFS rate was expected to be in between 40 and 50% for the fluoropyrimidines alone group, and both accrual and follow-up intervals were 3 years. In case the effect of reducing the incidence of disease recurrence in the sequential regimen group is assumed to be 80% that for the fluoropyrimidines alone group (risk reduction 20%), 3 year DFS rate was estimated to be in between 48.1 and 57.4%.

In case 3 year DFS rate for the fluoropyrimidines alone group is 50%, the least number of patients to provide the 90% power necessary to confirm the superiority of a group was calculated to be 708 per group for a two-sided 5.0% significance level test. Taking loss of follow-up ~5% into account, the number of patients to be accrued was set at 370 per treatment arm (1480 in total). Furthermore, given the number of patients, 88% statistical power is retained to prove the non-inferiority for the upper limit at a 95% confidence interval for the hazard ratio of S1 compared with UFT was lower than the upper equivalence margin, 1.25. The significance levels for both inferences are set at 5.0%. In other words, we do no statistical adjustment to control the overall type I error rate when analysing the two separate hypotheses in the two-by-two factorial study design. In addition, no interim analysis is planned in terms of the primary endpoint (DFS).

Statistical analysis will be performed on an intention-to-treat basis. Cumulative DFS curves are constructed as time-to-event plots by the Kaplan–Meier method (11). Differences between the curves are tested for significance using stratified log-rank statistics and are estimated for non-inferiority using the hazard ratio produced by the Cox regression model (12). Both analyses are carried out by accounting for tumor size (<8 cm/≥8 cm) and N factor (0/1–2) as strata. Assessment of interaction among the treatments is done to examine the independence of the two research hypotheses using the Cox model including a corresponding interaction term as an explanatory variable. Furthermore, exploratory analyses using Cox regression models are performed to compare treatment effects on the primary endpoint between arm A and arm C, between arm B and arm D, between arm A and arm B, and between arm C and arm D. Similar analysis will be performed for overall survival. Adverse events and compliance of the protocol treatment will be compared using the chi-square test.

PARTICIPATING INSTITUTIONS

Approximately 250 Japanese institutions and hospitals participate in the trial to enroll patients in Japan.

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References