A Phase I/II Trial of Chemoradiotherapy Concurrent with S-1 plus Mitomycin C in Patients with Clinical Stage II/III Squamous Cell Carcinoma of Anal Canal (JCOG0903: SMART-AC)

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A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus mitomycin C in patients with clinical Stage II/III squamous cell carcinoma of the anal canal was started in Japan. The aim of this trial is to determine the recommended dose of S-1 combined with a fixed dose of mitomycin C plus radiotherapy in Phase I and to evaluate the efficacy and safety in Phase II. The primary endpoint for the Phase II part of this study is the proportion of 3-year event-free survival, in which the following are defined as events: disease progression, residual tumor at the end of chemoradiotherapy, colostomy or death, whichever comes first. Secondary endpoints are progression-free survival, proportion of complete response and adverse events. In the Phase II part of this study, a total of 65 patients will be enrolled from 42 institutions over 6 years.

Key words: anal canal cancer – chemoradiotherapy – S-1 – mitomycin C – radiotherapy

INTRODUCTION

Anal canal cancer is extremely rare in Japan: only 313 patients died of it in 2007 (1). In the USA, it is also a relatively rare disease: there were 5290 patients (~2 per 100 000) in 2009 (2). However, the incidence in the USA has doubled over the last 30 years and is expected to increase in the future. Considering the current situation in the USA, the incidence of anal cancer might rise in Japan.

For Stage II/III squamous cell carcinoma of the anal canal, there have been no clinical trials comparing surgery and concurrent chemoradiotherapy (CRT); however, CRT has been recognized as the standard treatment globally. This is because squamous cell carcinoma of the anal canal is sensitive to CRT and CRT can preserve the anal function, and residual or recurrent tumor can be safely resected by salvage surgery. The combination of 5-fluorouracil (5-FU) plus mitomycin C (MMC) concurrent with radiotherapy has shown better outcomes than radiotherapy alone or 5-FU with radiotherapy. Recently, two Phase III trials failed to show the superiority of 5-FU plus cisplatin over 5-FU plus MMC (3,4). On the basis of these results, 5-FU plus MMC is considered as the current standard regimen of CRT.

S-1 is an oral fluoropyrimidine, for which non-inferiority to 5-FU was reported in gastric cancer (5). In addition, it was reported that S-1 enhanced the effect of radiotherapy in vivo model (6). Oral drugs are clearly more convenient than parenteral preparations. If the combination of S-1 plus MMC has similar efficacy to 5-FU plus MMC, we can regard S-1 plus MMC as the new standard treatment.

The first aim of this study is to determine the recommended dose (RD) of S-1 in Phase I because we have no experience of CRT concurrent with S-1 plus MMC. The second aim of this study is to evaluate the efficacy and safety in Phase II. After the present study, we have not planned a Phase III study comparing 5-FU and S-1 because there are only a few anal cancer patients in Japan. In the
survey of the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG), there were only 59 eligible patients over the last 5 years (7). When the proportion of 3-year event-free survival (EFS), which is the primary endpoint of this study, is proven to be satisfactory, we can regard this combined treatment as the new standard treatment for Stage II/III squamous cell carcinoma of the anal canal, which means that this study is a non-randomized confirmatory study.

The Protocol Review Committee of the JCOG approved this study protocol in January 2010 and the study was initiated in February 2010. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000003237 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGESTS OF JCOG 0903

OBJECTIVES

PHASE I PART

To evaluate the maximum tolerated dose and dose-limiting toxicities (DLTs) to determine the RD of S-1 in combination with a fixed dose of MMC plus radiation therapy in patients with Stage II/III squamous cell carcinoma of the anal canal.

PHASE II PART

To evaluate the efficacy and safety of combination CRT with S-1 plus MMC in patients with Stage II/III squamous cell carcinoma of the anal canal.

STUDY SETTING

A multi-institutional open-label Phase I/II trial.

RESOURCES

This study is supported by Grants-in-Aid for Cancer Research (20S-3, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

ENDPOINTS

PHASE I PART

The primary endpoint is the number of patients with DLT. The secondary endpoint is the incidence of adverse events.

PHASE II PART

The primary endpoint is the proportion of 3-year EFS in all eligible patients, including the patients who received the level of RD in the Phase I part. EFS is defined from the date of registration to the date of death from any cause, first evidence of disease progression, evaluated as non-complete response (CR) at the second evaluation after CRT, undergoing colostomy or first evidence of second primary cancer, whichever comes first. It is censored at the last follow-up day when the patient is alive without any events. The definition of EFS is identical to that in RTOG9811.

The secondary endpoints are the proportion of CR, progression-free survival, EFS, overall survival, colostomy-free survival and incidence of adverse events. Progression-free survival is defined from the date of registration to the date of disease progression or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of progression. Colostomy-free survival is defined from the date of registration to the date of undergoing colostomy or death from any cause.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

For inclusion in the study, patients are required to fulfill all of the following criteria:

(i) Lesion located in the anal canal by endoscopic evaluation
(ii) Histologically proven squamous cell carcinoma or basaloid carcinoma
(iii) Clinical Stage II/III (TNM-UICC 6th, 2002)
(iv) Phase I part: aged 20–75 years old, Phase II part: aged 20–80 years old
(v) ECOG performance status of 0 or 1
(vi) Having measurable lesion is not mandatory
(vii) No previous therapy against anal canal cancer except simple colostomy 7 days or more before registration
(viii) Neither previous chemotherapy, CRT nor radiotherapy against any cancer
(ix) Sufficient oral intake
(x) Adequate organ functions
(xi) Written informed consent

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria:

(i) Simultaneous or metachronous (within 5 years) double cancers, with the exception of intramucosal tumor curable with local therapy
(ii) Patients requiring the administration of phenytoin or warfarin potassium
(iii) Pregnant or lactating women or women of childbearing potential
(iv) Psychosis
(v) Requiring systemic steroid medication
(vi) Serum HBs antigen-positive
(vii) Anti-HIV antibody-positive
(viii) Uncontrollable diabetes mellitus or continuous use of insulin
(ix) Uncontrollable hypertension
(x) Unstable angina, heart failure or with a history of myocardial infarction within 6 months
(xi) Interstitial pneumonitis, lung fibrosis or severe emphysema
(xii) Active bacterial or fungal infection
(xiii) Body temperature over 38°C

**REGISTRATION**

After confirmation of fulfillment of the eligibility criteria, registration is made by telephone or fax to the JCOG Data Center.

**TREATMENT METHODS**

**CHEMOTHERAPY**

Combined CRT consists of S-1, MMC and radiotherapy. S-1 is orally administered twice per day from days 1 to 14 and days 29 to 42. There are three dose levels of S-1 in the Phase I part of this study: 40, 60 and 80 mg/m²/day. The RD of S-1 is determined in the Phase I part and the RD is administered in the Phase II part of this study. MMC is infused on days 1 and 29 with a fixed dose, 10 mg/m²/day.

**RADIOTHERAPY**

Radiotherapy is delivered with megavoltage (≥6 MV) X-rays using a multiple-field technique. Patients receive 1.8 Gy/day of radiation for 5 days per week from the initiation of chemotherapy, and the total radiation dose is 59.4 Gy. Three-dimensional computed tomography (CT) simulation is required. The clinical target volume (CTV) includes the primary tumor plus 1–2 cm craniocaudally and 0.5–1 cm circumferentially, the metastatic lymph node and regional lymph nodes. The regional lymph nodes include the mesorectum with pararectal lymph nodes, sacral, internal iliac, obturator, external iliac and inguinal lymph nodes. Planning target volume (PTV) is defined as CTV plus 0.5–1 cm margins for uncertainty. After PTV has been treated up to a dose of 36.0 Gy, an additional dose of 23.4 Gy is given to a reduced irradiation volume, including only primary tumor and metastatic lymph nodes with margins, for a total dose of 59.4 Gy.

**DOSE ESCALATION METHOD**

In the Phase I part of this study, there are three dose levels of S-1 as follows: Level 1 at 40 mg/m²/day, Level 0 at 60 mg/m²/day and Level 1 at 80 mg/m²/day. Level 0 is the starting dose, and initially three patients are administered. The schema of dose escalation is shown in Fig 1.

**DEFINITION OF DLT**

DLT is defined by the following criteria. The observation period of DLT is between the date of initiating CRT and the date of 14 days after the last radiotherapy. Severity of toxicity is assessed according to the Common Terminology Criteria for Adverse Events v 3.0 (CTCAE v3.0).

(i) Grade 4 neutrophils lasting ≥8 days
(ii) Grade 4 platelets
(iii) Grade 3 febrile neutropenia lasting ≥4 days
(iv) Grade 3 infection with Grade 3 or 4 absolute neutrophil count (ANC) lasting ≥4 days
(v) Grade 3 infection with normal ANC lasting ≥4 days
(vi) Grade 3 diarrhea lasting ≥3 days despite supportive care
(vii) Grade 4 non-hematologic toxicity except for dermatitis chemoradiation, alkaline phosphatase, γ-glutamyltranspeptidase, hyperglycemia, hypercalcemia, hypocalcemia, hypernatremia, hypomagnesemia, hypophosphatemia, cholesterol and hypertriglyceridemia,
(viii) Unable to receive S-1 ≥15 times per course
(ix) Delay of starting the second course for ≥8 days
(x) Unable to complete the protocol treatment within 66 days from the initiation of CRT

**EFFECTIVENESS EVALUATION AND FOLLOW-UP**

All patients are assessed at 8 and 12 weeks after the end of CRT by abdominal and pelvic CT, pelvic magnetic resonance imaging (MRI) and colonoscopy. We classify as CR of overall response if both of the following criteria are met: no cancer cells are detected by biopsy from the primary site and no tumors are detected by CT, MRI and colonoscopy. Overall responses at both 8 and 12 weeks after the end of CRT are evaluated as CR; we define the best overall response as CR. When overall response is evaluated as first CR at 12 weeks after the end of CRT, the additional evaluation for confirmation will be performed at 16 weeks after the end of CRT.

Salvage surgery is recommended when disease progression is observed before the evaluation, the best response is non-CR at 12 or 16 weeks after the end of CRT or local recurrence is found after CRT.

Adverse events are evaluated at least every week during protocol treatment using CTCAE v3.0. After protocol treatment, patients are followed up every 4 months for 3 years and every 6 months for 5 years.

**STUDY DESIGN AND STATISTICAL ANALYSIS**

This study is a Phase I/II trial to determine the RD of S-1 in combination with a fixed dose of MMC plus radiotherapy in the Phase I part and to evaluate the efficacy and safety in the Phase II part.
The sample size in the Phase II part of this study is 65, including the RD level in the Phase I part. This sample size provides 80% power under the hypothesis of the expected value of the primary endpoint of 75% and the threshold value of 60% using one-sided testing at a 5% one-sided significance level. To test the hypothesis, % 3-year EFS estimated by the Kaplan–Meier method and its confidence interval (CI) by Greenwood’s formula are used.

S-1 is expected to be more toxic than 5-FU, but we expect that the frequency of neutropenic fever, which is the clinically meaningful toxicity, will be almost equivalent (<20%). On the other hand, the convenience for the patients will be increased by using S-1. Therefore, we consider CRT concurrent with S-1 plus MMC as an equivalently toxic and more convenient regimen. When the lower limit of 90% CI with % 3-year EFS is above 60% and the safety profiles are as low as expected, we can conclude that the CRT concurrent with S-1 plus MMC is the new standard treatment for anal cancer.

**INTERIM ANALYSIS AND MONITORING**

In the Phase II part of this study, we planned an interim analysis once during the trial when 25 patients are registered. The aim of interim analysis is to evaluate the futility. When the upper limit of 90% CI with % 1-year EFS is below 75%, this study will be discontinued.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate the study progress and to improve the study quality.

**PARTICIPATING INSTITUTIONS**

The participating institutions (from north to south) are as follows: Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital and Cancer Center, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center Hospital, Jyuntendo Urayasu Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keio University Hospital, Tokyo Medical and Dental University Hospital, Kitasato University East Hospital, Kanagawa Cancer Center, Yokohama Municipal Citizen’s Hospital, Kitasato University School of Medicine, Showa University Northern Yokohama Hospital, Niigata Cancer Center Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fuji Health University, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka Medical College, Sakai Municipal Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College of Medicine, Hiroshima University Hospital, Hiroshima City Hospital, National Hospital Organization Shikoku Cancer Center, Kurume University School of Medicine, and Oita University Faculty of Medicine.

*Institutions that participated from the Phase I part.
Conflict of interest statement

None declared.

References