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Randomized Controlled Trial Comparing Gastrectomy Plus Chemotherapy with Chemotherapy Alone in Advanced Gastric Cancer with A Single Non-curable Factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01

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A randomized controlled trial has started in both Japan and Korea to evaluate the role of gastrectomy in the management of incurable advanced gastric cancer (AGC). Patients with AGC diagnosed as having a single non-curable factor are randomized to gastrectomy plus chemotherapy or chemotherapy alone. Surgeons at 33 specialized centers in Japan and at 15 high-volume hospitals in Korea will recruit 330 patients. Primary end-point is overall survival, and secondary end-points are progression-free survival and adverse events associated with either gastrectomy or chemotherapy.

Key words: gastrectomy – chemotherapy – advanced gastric cancer – non-curable factor – randomized controlled trial

INTRODUCTION

The prognosis of advanced gastric cancer (AGC) patients with non-curable factors, such as hepatic and peritoneal metastases, is poor and most of them die within 1 year. For these patients, the role of gastrectomy remains controversial. However, gastrectomy is the preferred procedure for these patients, even in the absence of any symptoms such as bleeding and stenosis, based on the results of retrospective studies showing that the procedure confers a survival benefit. In the literature (1–9), overall survival of 8.0–12.2 months is reported with gastrectomy compared with 2.4–6.7 months without gastrectomy, and the survival benefit of gastrectomy is obtained only in patients with a single non-curable factor. Obviously, there should be enormous selection bias in these data, generally speaking in favor of surgical patients. Furthermore, chemotherapy alone has recently shown, for the first time, a median survival time over 1 year in AGC deemed incurable (10). These situations warrant a prospective randomized controlled trial designed to investigate the role of gastrectomy in AGC with a single non-curable factor. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the following protocol on 18 December 2007, and the study was activated on 4 February 2008.

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PROTOCOL DIGEST OF THE JCOG0705/KGCA01

Purpose

The purpose of this trial was to investigate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in clinically stage IV AGC with a single non-curable factor, in terms of survival benefit and safety associated with gastrectomy or chemotherapy.

Study Setting

The study was a multi-institutional (33 specialized centers in Japan and 15 high-volume hospitals in Korea) randomized controlled trial.

Resources

Grants-in-Aid for Cancer Research (17S-3, 17S-5), from the Ministry of Health, Labor and Welfare, Japan. Grants for Cancer Research, from the Korean Gastric Cancer Association, Korea.

End-Points

The primary end-point is overall survival. The secondary end-points are progression-free survival and adverse events associated with gastrectomy or chemotherapy.

Eligibility Criteria

Tumors are staged according to the Japanese Classification of Gastric Carcinoma (11).

Inclusion Criteria

Patients are included in the trial if they meet all of the following criteria: (i) histologically proven primary gastric adenocarcinoma, (ii) presence of only one of the following patterns of metastasis, which is confirmed by both computed tomography (CT) scan and staging laparoscopy (or open laparotomy): (a) hepatic metastasis (H1) (2–4 lesions, maximum diameter <5 cm), (b) peritoneal dissemination (P1) without massive ascites or intestinal obstruction or (c) extensive para-aortic lymph node metastasis (No. 16a1 and/or b2), (iii) clinical T1-3, (iv) no evidence of para-aortic and/or retropancreatic lymph node metastasis (i.e. N0–2) in the cases of hepatic or peritoneal metastasis, (v) no evidence of other distant metastasis than H1, P1 or LN 16a1/b2, (vi) no apparent pleural effusion, (vii) length of esophageal invasion 3 cm or less with no need of thoracotomy for resection, (viii) not stump carcinoma, (ix) aged 20–75 year old, (x) performance status (PS) of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) scale, (xi) sufficient oral intake without active bleeding from the gastric tumor, (xii) no prior treatment of chemotherapy or radiation therapy against any other malignancies, and no prior treatment for gastric cancer except EMR (endoscopic mucosal resection), (xiii) adequate organ functions defined as indicated below: (a) WBC $\geq 3000/mm^3$, WBC $\leq 12\ 000/mm^3$, (b) Hb ≥ 8.0 g/dl without any transfusion 2 weeks before enrollment, (c) Plt $\geq 100\ 000/mm^3$, (d) AST ≤ 100 IU/l, (e) ALT ≤ 100 IU/l, (f) T.Bil ≤ 2.0 mg/dl, (g) Cr ≤ 1.2 mg/dl, (h) Ccr ≥ 60 ml/min/body and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active double cancer (synchronous double cancer and metachronous double cancer within five disease-free years), excluding carcinoma *in situ* (lesions equal to intraepithelial or intramucosal cancer), (ii) pregnant or breast-feeding women, (iii) severe mental disorder, (iv) systemic administration of corticosteroids, (v) medication of furucytocin, fenytoin or warfarin, (vi) active bacterial infection or mycosis, affecting systemic condition, (vii) unstable angina or myocardial infarction within 6 months of the trial, (viii) unstable hypertension, (ix) diabetes mellitus, uncontrolled or controlled with insulin, (x) severe respiratory disease requiring continuous oxygen therapy.

Randomization

After confirmation of the above criteria, registration is made by telephone call or fax to the JCOG Data Center in Japan, and by web system to Seoul National University Hospital (SNUH) Data Center in Korea. Patients are randomized in each country by a minimization method of balancing the arms according to institution, nodal status (N0–1/N2–3) and non-curable factor (hepatic/peritoneal/para-aortic metastasis).

Treatment Methods

Gastrectomy Plus Chemotherapy

Either a total, distal or proximal gastrectomy with D1 lymph node dissection is performed depending on the tumor location with the metastatic lesions untouched. Neither complete D2 lymphadenectomy nor combined resection of adjacent organs except for gallbladder, mesocolon and diaphragm is acceptable. Within 8 weeks after surgery, the patient is placed on a chemotherapy regimen, S-1 + CDDP. Oral S-1 is administered at a dose of 80 mg/m^2/day for 3 consecutive weeks followed by a 2-week rest. Cisplatin is delivered on Day 8 at a dose of 60 mg/m^2. This regimen is repeated every 5 weeks until disease progression.

Chemotherapy Alone

Patients receive the same chemotherapy as described above without any operation until disease progression.

Follow-up

Patients are assessed every months to detect any adverse events with verbal interview, physical examination and blood tests, including a complete blood cell count and measurements of liver and renal function, until progressive disease. Abdominal CT scan and measurements of CEA and CA19-9 are carried out every 3 months.

Study Design and Statistical Methods

This trial is designed to evaluate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in terms of overall survival. The hypothesis to be tested is that 2-year overall survival on gastrectomy followed by chemotherapy is greater than that (20–25%) obtained by chemotherapy alone by 10%. If a 10% improvement in a 2-year overall survival rate is demonstrated, gastrectomy followed by chemotherapy will be the preferred treatment. The planned sample size is 330, 165 cases per arm, with 2 years follow-up after 4 years of accrual. This will provide an 80% power with a one-sided alpha of 5%.

Interim Analysis, Monitoring and Audit

Two interim analyses are planned, with adjustments for repeated comparisons taken into account by the Lan and DeMets method. We use the O'Brien–Fleming-type alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report and will consider stopping the trial early, in agreement with SNUH Data Center. Central monitoring is performed by the respective Data Center in each country to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the respective Data Center independently every 6 months. The monitoring summary is exchanged between the two countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged.

PARTICIPATING INSTITUTIONS

Japan: Iwate Medical University, Sendai National Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Komagome Hospital, Tokyo Medical and Dental University, Cancer Institute Hospital, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Gifu Municipal Hospital, Shizuoka Prefectural General Hospital, Aichi Cancer Center, Fujita Health University, Kyoto 2nd Red Cross Hospital, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, National Osaka Medical Center, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Itami City Hospital, Wakayama Medical University, Hiroshima City Hospital, National Shikoku Cancer Center, Oita University.

Korea: Ajou University Hospital, Chonnam University Hwasun Hospital, Dong-A University Hospital, Hanyang University Hospital, Kangnam St Mary's Hospital, Korea Cancer Center Hospital, Korea University Guro Hospital, Kosin University Hospital, Kyungpook University Hospital, National Cancer Center, Samsung Medical Center, Seoul National University Hospital, Seoul National University Bundang Hospital, Yonsei University Severance Hospital, Yonsei University Youngdong Hospital.

Conflict of interest statement

Mitsuru Sasako states that he has received honoraria from Taiho Pharmaceutical Company for giving educational lectures in 2007.

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