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Comparison of efficacy and tolerance between combination therapy and monotherapy as first-line chemotherapy in elderly patients with advanced gastric cancer: Study protocol for a randomized controlled trial

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ABSTRACT

Introduction: The combination of a fluoropyrimidine [5-fluorouracil (5-FU), capecitabine, or S-1] with a platinum analog (cisplatin or oxaliplatin) is the most widely accepted first-line chemotherapy regimen for metastatic or recurrent advanced gastric cancer (AGC), based on the results of clinical trials. However, there is little evidence to guide chemotherapy for elderly patients with AGC because of under-representation of this age group in clinical trials. Thus, the aim of this study is to determine the optimal chemotherapy regimen for elderly patients with AGC by comparing the efficacies and safeties of combination therapy versus monotherapy as first-line chemotherapy.

Methods: This study is a randomized, controlled, multicenter, phase III trial. A total of 246 elderly patients (≥70 years old) with metastatic or recurrent AGC who have not received previous palliative chemotherapy will be randomly allocated to a combination therapy group or a monotherapy group. Patients randomized to the combination therapy group will receive fluoropyrimidine plus platinum combination chemotherapy (capecitabine/cisplatin, S-1/cisplatin, capecitabine/oxaliplatin, or 5-FU/oxaliplatin), and those randomized to the monotherapy group will receive fluoropyrimidine monotherapy (capecitabine, S-1, or 5-FU). The primary outcome is the overall survival of patients in each treatment group. The secondary outcomes include progression-free survival, response rate, quality of life, and safety.

Discussion: We are conducting this pragmatic trial to determine whether elderly patients with AGC will obtain the same benefit from chemotherapy as younger patients. We expect that this study will help guide decision-making for the optimal treatment of elderly patients with AGC.

Abbreviations: AGC, advanced gastric cancer; 5-FU, 5-fluorouracil; OS, overall survival; RCT, randomized controlled trial; PFS, progression-free survival; RR, response rate; QoL, quality of life; KG-7, Korean Cancer Study Group geriatric tool; CGA, comprehensive geriatric assessment; ECOG, Eastern Cooperative Oncology Group; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; AST/ALT, aspartate aminotransferase/alanine aminotransferase; UNL, upper normal limit; CCr, creatinine clearance; HER-2, human epidermal growth factor receptor-2; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; CT, computed tomography; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core quality of life questionnaire; EORTC QLQ-STO22, European Organization for Research and Treatment of Cancer quality of life questionnaire-gastric; SAE, serious adverse event; CRF, case report form; ADL, activities of daily living; IADL, independent activities of daily living; KCSG, Korean Cancer Study Group; DSMB, data safety monitoring board; FAS, full analysis set; IIT, intent to treat; PPS, per-protocol set; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; SEER, Surveillance, Epidemiology, and End Results

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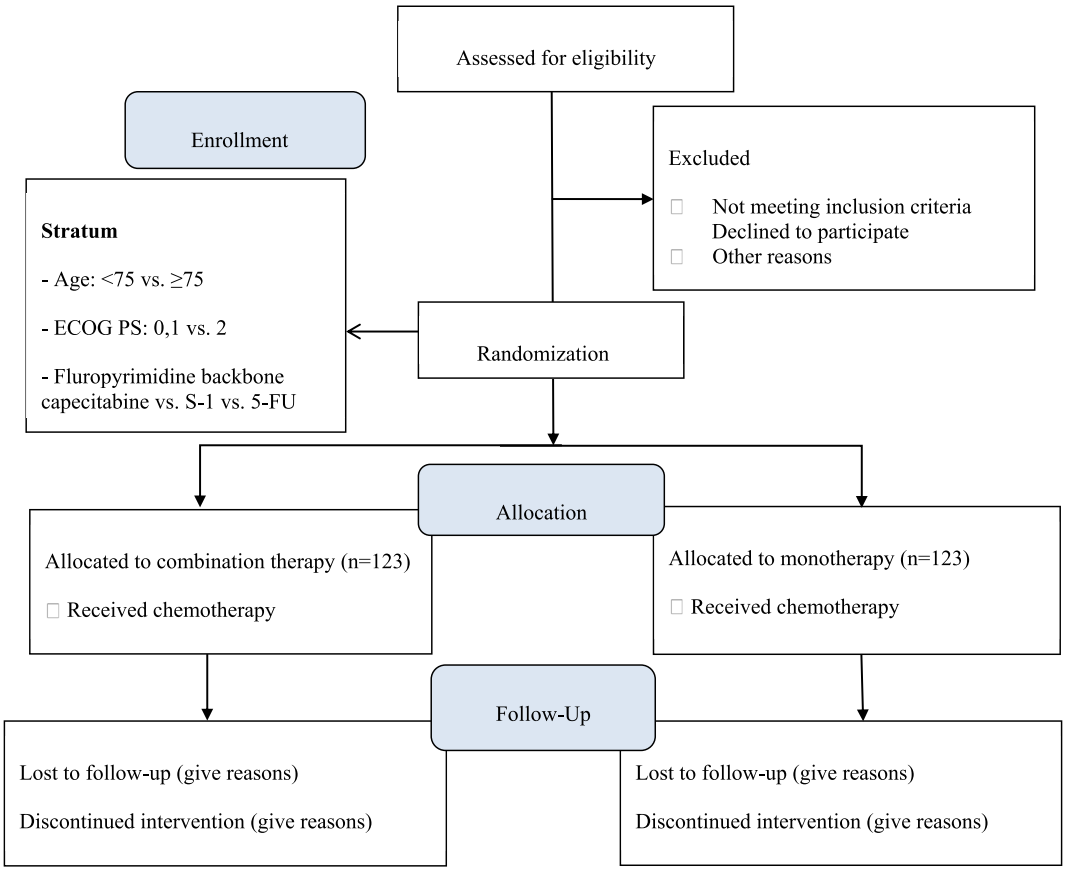

Fig. 1. Study design of phase III RCT of chemotherapy in elderly patients with AGC.

1. Introduction

Systemic chemotherapy has established quality of life and survival advantages compared to supportive care alone in advanced gastric cancer (AGC) [1–3]. 5-Fluorouracil (5-FU) has been the backbone of most regimens for AGC for several decades, and is used most commonly in combination with a platinum agent, with or without an anthracycline or a taxane [4–9]. Based on recent phase III clinical trials, the combination of a fluoropyrimidine (5-FU, S-1, or capecitabine) with a platinum analog (cisplatin or oxaliplatin) is the most widely accepted first-line chemotherapy regimen for metastatic or recurrent AGC [4–9]. However, elderly cancer patients often present with concomitant comorbidities and age-associated physiologic problems, such as impaired organ function and functional changes that make the selection of optimal treatment difficult. In real world clinical practice, either combination therapy with reduced doses or monotherapy are commonly used for elderly cancer patients with consideration of chemotherapy toxicity associated with combination therapy. Currently, there is little evidence to guide optimal treatment for elderly patients with AGC because of under-representation of this age group in clinical trials [10–12]. The SPIRITS trial demonstrated a statistically significant benefit in overall survival (OS) for patients receiving S-1/cisplatin combination therapy compared with S-1 monotherapy [9]. Trumper et al. suggested that elderly (≥70 years old) patients with AGC without significant comorbidities should be treated with the same regimens as younger patients, based on a retrospective analysis of three UK multicenter randomized trials [13]. However, the SPIRITS trial only involved patients less than 75 years old, and extrapolation of the results from retrospective analysis to elderly patients must be undertaken cautiously. Ideally, standard treatment of AGC in elderly patients should be based on the results of clinical trials focused on elderly patients. In a randomized multicenter phase II trial of capecitabine vs. S-1 as first-line treatment in elderly patients (≥65 years old) with metastatic or recurrent AGC, both capecitabine and S-1 monotherapies were active and tolerable as first-line treatment [14]. However, there have been no large-scale randomized controlled trials (RCTs) of chemotherapy for elderly patients with AGC, and such trials are needed to establish evidence to guide decisions about optimal treatment. Thus, we are conducting an RCT of combination therapy versus monotherapy as first-line chemotherapy in elderly patients with metastatic or recurrent AGC.

1.1. Research aims

The aim of this study is to evaluate and compare the efficacies and safeties between combination therapy and monotherapy as first-line chemotherapy in elderly patients (≥70 years old) with metastatic or recurrent AGC. The primary objective is to compare OS between patients receiving combination therapy and monotherapy. The secondary objectives are to compare progression-free survival (PFS), response rate (RR), safety, and quality of life (QoL) between the two treatment groups. In addition, we will conduct a geriatric assessment at baseline using the Korean Cancer Study Group Geriatric tool (KG-7) and/or comprehensive geriatric assessment (CGA) to determine which geriatric assessment variables are associated with an increased risk of chemotherapy toxicity.

2. Methods/design

2.1. General design

This is a randomized, open, multicenter, parallel-group trial to compare the efficacies and safeties between combination therapy (fluoropyrimidine plus platinum) and monotherapy (fluoropyrimidine) as first-line chemotherapy in elderly patients (≥70 years old) with