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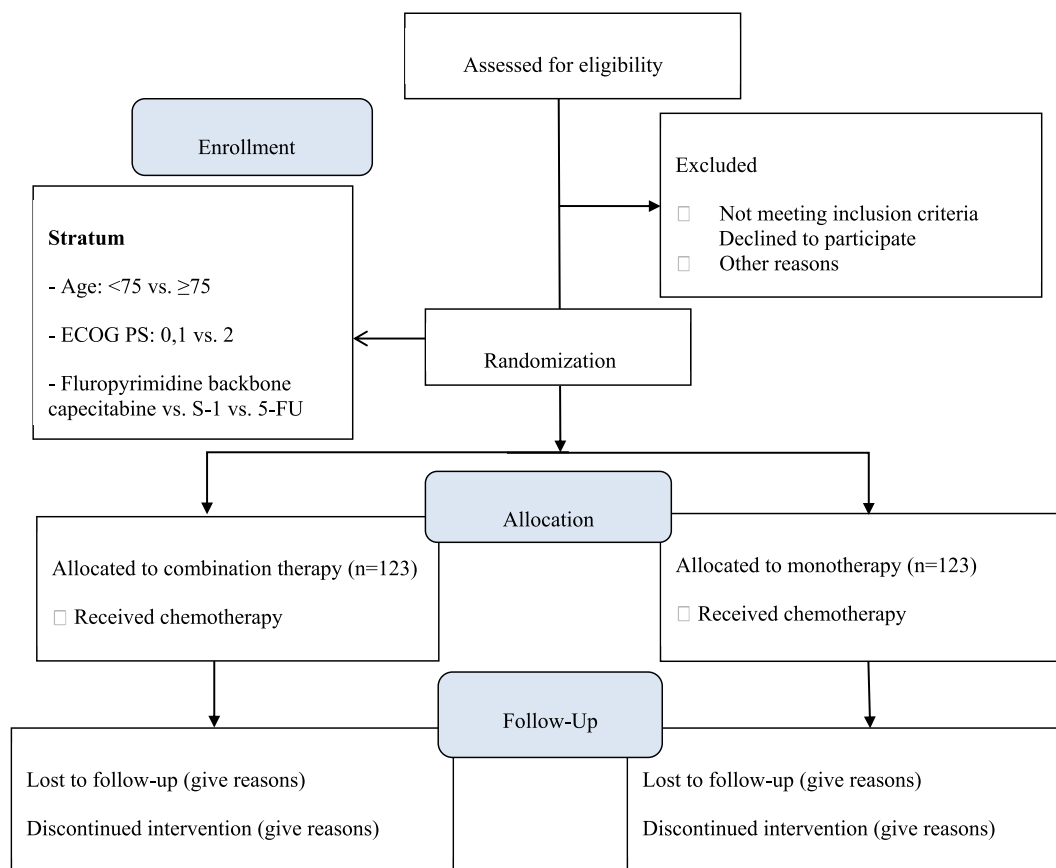
Fig. 1. Study design of phase III RCT of chemotherapy in elderly patients with AGC.

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 co-morbidities 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 co-morbidities 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

metastatic or recurrent AGC. Following the initial screening and obtaining of consent, eligible patients will be allocated to either the combination therapy or monotherapy group in a 1:1 ratio using a computer-generated permutated-block randomization sequence with the following stratification factors: (1) age ($<$ 75 years vs. $\geq$ 75 years), (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0–1 vs. 2), and (3) type of fluoropyrimidine agents (capecitabine vs. S-1 vs. 5-FU). Participants will be enrolled via a 24-hour web system (http://eresearch.ncc.re.kr). Neither participants nor investigators will be blinded to the allocated treatment. A total of 246 patients will be recruited over a 36-month period and a follow-up of the enrolled patients will last until end of the study where the last patient completes 12-month of follow-up, resulting in a total study period of 48 months (Fig. 1). The study will be conducted at 25 Korean hospitals consisting of academic hospitals and a national cancer center.

2.2. Study population

Elderly patients ($\geq$ 70 years old) with metastatic or recurrent AGC will be recruited for this study. The following criteria must be met for inclusion in the study: (1) confirmative diagnosis of gastric or gastro-esophageal junction adenocarcinoma and adenocarcinoma equivalents (for example, undifferentiated carcinoma or poorly differentiated carcinoma); (2) metastatic or recurrent AGC with no history of previous palliative chemotherapy; (3) aged 70 years or older; (4) ECOG PS of grade 0–2; (5) the existence of at least one lesion that is measurable, or is non-measurable but assessable, according to the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1); (6) sufficient bone marrow/liver/renal function as determined using the following laboratory findings obtained within 7 days of the start of chemotherapy: hemoglobin $\geq$ 9.0 g/dL, white blood cells $\geq$ 3000/μL, neutrophils $\geq$ 1500/μL, platelets $\geq$ 100 $\times$ 10^3/μL, total bilirubin $\leq$ 1.5 $\times$ upper normal limit (UNL), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$ 3.0 $\times$ UNL (if liver metastasis exists, AST/ALT should be $\leq$ 5.0 $\times$ UNL for inclusion), serum creatinine $\leq$ 1.5 $\times$ UNL (if serum creatinine exceeds 1.5 mg/dL, creatinine clearance (CCr) must be above 50 mL/min); and (7) remaining life expectancy of at least 3 months. Exclusion criteria are: (1) histologic types other than adenocarcinoma or adenocarcinoma equivalents; (2) human epidermal growth factor receptor-2 (HER-2) positive AGC; (3) clinically identified gastric outlet obstruction, bleeding, or perforation of the digestive tract that has not been resolved; (4) recent radiotherapy within 2 weeks of random assignment to a treatment group; (5) recent major surgery within 4 weeks of random assignment to a treatment group; (6) recent diagnosis (within 5 years) of another active primary cancer other than appropriately treated cervical carcinoma *in situ* and basal or squamous cell carcinoma of the skin; (7) central nervous system metastasis with uncontrollable symptoms; (8) significant heart disease, liver disease, or active infection that is medically uncontrollable; (9) male patients who have no intention of using contraceptives during the study period; (10) mental or neurological conditions, or dementia that hinders the understanding and submission of informed consent.

2.3. Study treatment and outcome assessments

Group A consists of four different combination regimens of a fluoropyrimidine plus a platinum agent as follows: (1) capecitabine/cisplatin: cisplatin is administered intravenously at a dose of 80% (50 mg/m^2) of 60 mg/m^2 over 15 min on day 1, and capecitabine is orally administered at a dose of 80% (1000 mg/m^2) of 1250 mg/m^2 twice a day from day 1 to day 14 in a 21-day cycle; (2) S-1/cisplatin: cisplatin is administered intravenously at a dose of 80% (50 mg/m^2) of 60 mg/m^2 over 15 min on day 1, and S-1 is orally administered at a dose of 80% (30 mg/m^2) of 40 mg/m^2 twice a day from day 1 to day 14 in a 21-day cycle; (3) capecitabine/oxaliplatin: oxaliplatin is administered intravenously at a dose of 80% (100 mg/m^2) of 130 mg/m^2 over

2 h on day 1, and capecitabine is orally administered at a dose of 80% (800 mg/m^2) of 1000 mg/m^2 twice a day from day 1 to day 14 in a 21-day cycle; (4) 5-FU/oxaliplatin: oxaliplatin is administered intravenously at a dose of 80% (80 mg/m^2) of 100 mg/m^2 over 2 h on day 1, leucovorin is administered intravenously at a dose of 80% (80 mg/m^2) of 100 mg/m^2 over 2 h on day 1, and 5-FU is administered intravenously at a dose of 80% (1900 mg/m^2) of 2400 mg/m^2 over 46 h in a 14-day cycle.

Group B consists of three regimens of a fluoropyrimidine only as follows: (1) capecitabine: capecitabine is orally administered at a dose of 1250 mg/m^2 twice a day from day 1 to day 14 in a 21-day cycle (capecitabine at a dose of 1000 mg/m^2 twice a day is administered when CCr is $<$ 60 mL/min); (2) S-1: S-1 is orally administered at a dose of 40 mg/m^2 twice a day from day 1 to day 14 in a 21-day cycle (S-1 at a dose of 30 mg/m^2 twice a day is administered when CCr $<$ 60 mL/min); (3) 5-FU: leucovorin is administered intravenously at a dose of 100 mg/m^2 over 2 h on day 1, and 5-FU is administered intravenously at a dose of 2400 mg/m^2 over 46 h in a 14-day cycle.

The selection of a fluoropyrimidine backbone (capecitabine vs. S-1 vs. 5-FU) is determined by the attending physician before randomization. In group A, after the first cycle of chemotherapy, the dose of chemotherapeutic agents can be escalated to 100%; this is at the discretion of the physician if National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) non-ematological or hematological toxicity of grade 2 or higher has not occurred with the first administration of the reduced dose (80%), and the patient agrees to dose escalation.

No more than 21 days before study treatment, patients undergo a screening assessment of the following: (1) medical history, physical examination (including ECOG PS), comorbidity, and concomitant medications; (2) vital signs, body weight, and height; (3) hematologic tests; (4) biochemical tests including CCr; (5) chest radiograph and 12-channel electrocardiogram; (6) pregnancy test; (7) imaging tests for tumor response assessments, including abdominal and pelvic computed tomography (CT) scan, chest CT scan (if intrathoracic metastasis, supraclavicular, or axillary lymph node metastasis is suspected), bone scan, or other image studies (if necessary); (8) QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ STO22 Korean version) [15,16]; and (9) geriatric assessment by KG-7 (all patients) and/or CGA (optional). During the study treatment, all patients will be reviewed and assessed before the commencement of each cycle of chemotherapy as follows: (1) physical examination and ECOG PS; (2) hematologic and biochemical tests; (3) vital signs, body weight and height; (4) adverse events and concomitant medication; and (5) S-1 or capecitabine medication compliance. At the end of the study treatment, patients will be assessed as follows: (1) physical examination and ECOG PS; (2) hematologic and biochemical tests; (3) imaging tests for tumor response assessment according to the RECIST (version 1.1); (4) adverse events and concomitant medications; (5) S-1 or capecitabine medication compliance; and (6) QoL questionnaires.

Drug administration will be continued until disease progression, intolerable adverse events, or patients' withdrawal of consent. Decisions on dose reduction and/or delay during chemotherapy will be made in response to chemotherapy-related non-hematological and hematological toxicities. Tumor response assessment will be performed according to the RECIST (version 1.1), with the first four assessments every 6 weeks ($\pm$ 2 weeks) and subsequent assessments every 8 weeks ($\pm$ 2 weeks) until disease progression is confirmed. For patients whose treatment has been discontinued for reasons other than disease progression, tumor response assessment will be performed using imaging tests every 8 weeks ($\pm$ 2 weeks) until the confirmation of disease progression or the start of second-line cancer treatment. QoL will be assessed using the questionnaires (EORTC QLQ-C30 and EORTC QLQ STO 22 Korean version). It will be assessed prior to study treatment (no more than 21 days before study treatment) and thereafter every 6 weeks ($\pm$ 2 weeks) for the first two assessments followed by

Assessment items		Screening		Administration (the cycle continues until the occurrence of disease progression or intolerable adverse events)									End of treatment	Follow-up
Study period (week)		-3	-1	1	2	3	4	5	6	7	8	9		
Study period (day)		-21	-7	1	8	15	22	29	36	43	50	57		
Informed consent		●												
Allocation			●											
Intervention	Chemotherapy of a 14-day cycle			●		●		●		●		●		
	Chemotherapy of a 21-day cycle			●			●			●				
P/E, Hematologic test/ biochemical test	Chemotherapy of a 14-day cycle		●	●		●		●		●		●	●	
	Chemotherapy of a 21-day cycle		●	●			●			●			●	
Tumor response assessment		●							●				●	
Geriatric assessment KG-7, CGA			●											
QoL assessment			●						●				●	
Adverse events assessment	Chemotherapy of a 14-day cycle					●		●		●		●	●	
	Chemotherapy of a 21-day cycle						●			●			●	
Survival follow-up														●

Fig. 2. Flow diagram of study procedures and outcome assessments.

subsequent assessments every 12 weeks (± 2 weeks). Safety analysis will be based on the occurrence of adverse events and the results of blood tests, and all adverse events will be graded according to the NCI CTCAE 4.03. All adverse events that occur during the drug administration period (i.e., up to 28 days following the last administration) must be recorded on the patient's chart as well as in the case report form (CRF), regardless of their severity or causal relationship with study drugs. We will also conduct a geriatric assessment using the KG-7 screening tool (all patients) and/or CGA (optional; because of the time and resource requirements) before initiation of study treatment. Geriatric assessment variables (activities of daily living (ADL), independent activities of daily living (IADL), nutrition, comorbidities, cognitive function, and psychosocial status) will be evaluated to determine which variables are associated with an increased risk of chemotherapy toxicity.

After the end of the study treatment, the patient will be followed-up every 3 months to assess OS. During this follow-up period, data on cancer treatment after the end of study treatment and survival status will be collected. Flow diagram of study procedures is shown in Fig. 2.

2.4. Study coordination, data management, and monitoring

The Korean Cancer Study Group (KCSG) data center is responsible for data management, statistics, and monitoring of this clinical trial. Study data will be collected, managed, and securely maintained by using the eVelos system, which is a web-based clinical trial management system (http://eresearch.ncc.re.kr) supported by the KCSG data center.

In this study, an independent data safety monitoring board (DSMB) is established to oversee the study procedures and ongoing data collation. No member of the DSMB has direct involvement in the conduct of the study, nor do they have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial.

2.5. Statistical considerations

Efficacy analysis is primarily based on the full analysis set (FAS; all eligible patients who were randomly assigned) that most clearly shows the intention to treat (IIT) principle, but the analysis will also be performed on the per-protocol set (PPS; treated patients eligible and assessable for response without major protocol violations), with both results reported. The primary endpoint of this study is superiority in median OS from combination therapy compared with monotherapy, which is defined as the time from randomization of patients to the date of death from any cause. The Kaplan-Meier method will be used to estimate the survival distribution, and the stratified log-rank test to compare the survival curves between the two treatment groups. The point estimate of hazard ratios (HRs) and their 95% confidence intervals (CIs) will be calculated using the Cox regression model. Secondary endpoints including PFS, RR (according to RECIST criteria), safety, and QoL will be analyzed to supplement the results of the primary analysis. PFS will be calculated from the date of randomization to the first date of documented progressive disease or the date of death from any cause. Data from patients who were alive and from those who were free of progression were censored at the date of the last follow-up visit for overall and progression-free survival, respectively. Comparison of discrete variables between the two treatment groups will be performed using a chi-squared test or Fisher's exact test when appropriate, and further evaluated using logistic regression analysis. For continuous variables, a Student's t-test or Mann–Whitney U test for nonparametric data will be used. All tests will be two-sided and a P-value of less than

0.05 will be considered statistically significant.

The sample size of this study was calculated on the basis of previously reported several phase III studies which included a fluoropyrimidine (5-FU, S-1, or capecitabine) plus a platinum analog (cisplatin or oxaliplatin) as first-line treatment of patients with metastatic or recurrent AGC [4–8]. The median OS was 7.9–11.2 months in the group receiving the combination of a fluoropyrimidine and a platinum analog. Mostly younger patients were enrolled in these studies (median age: 55–64 years), and the proportion of patients ≥ 65 years old were 24% and 31.5% in two studies (4,7). Regarding fluoropyrimidine monotherapy, in a randomized phase II study of capecitabine vs S-1 as first-line treatment in elderly patients (≥65 years old) with metastatic or recurrent unresectable gastric cancer, the median OS was 9.5 months with capecitabine monotherapy and 8.2 months with S-1 monotherapy [14]. We expect that more elderly patients will be included in our phase III study according to inclusion criteria (≥70 years old).

Based on the above considerations, we assumed to observe a primary outcome of median OS of 10 months for patients treated with combination therapy versus 7 months for patients treated with monotherapy. With the following assumptions, a total of 194 events would be required to achieve at least 80% power, for which 222 patients are needed; (i) enrollment period: 36 months, (ii) follow-up period: 12 months, (iii) one-sided type I error rate (α): 0.05. Providing for potential dropout rate of 10%, an enrollment of 246 patients was finally set for this study, with 123 patients in each group.

We plan to perform an interim analysis twice. The first will be conducted on the first 50 consecutively enrolled patients for safety analysis. The second will be conducted when about 50% of the total required events (97 cases) occur, for the superiority test. The stopping boundary will be calculated using the O'Brien-Fleming error spending function, and the HR will then be calculated. Based on the O'Brien-Fleming error spending function, the one-sided nominal significance level that will demonstrate superiority is 0.0089 in this interim analysis. The one-sided nominal significance level for the final analysis is 0.0465. The DSMB will review the results of each of the interim analyses, and make recommendations concerning the continuation, modification, or termination of the trial.

3. Discussion

There have been no published large-scale randomized controlled studies evaluating the optimal chemotherapy for elderly patients with AGC so far, and thus, currently there is no widely accepted standard chemotherapy regimen. Recently, a result from a phase IIII trial, which had compared the efficacy between capecitabine (X) and capecitabine plus oxaliplatin (XELOX) in elderly patients (≥70 years old) with AGC, was reported [17]. However, the study was early terminated due to the poor patient accrual (N = 50) and thus an unplanned interim analysis was conducted. Although the study result suggested the superiority of XELOX compared with X [(median OS 11.1 months versus 6.3 months)], the statistical difference between the two arms was not proven (HR 0.58, 95% CI 0.30–1.12, P = 0.108) and the result is still inconclusive. Therefore, we believe that well-conducted large-scale randomized controlled studies are still needed to determine optimal chemotherapy regimen in these patients.

In real world clinical practice, elderly cancer patients are less likely to be offered chemotherapy and tend to receive less intensive treatment because of concerns regarding their ability to tolerate the therapy [18]. In addition, other than chronologic age, oncologists are left with little guidance when it comes to identifying risk factors predictive of chemotherapy toxicity in elderly patients. The commonly used oncology performance status measure (Karnofsky performance status [KPS]) did not identify elderly patients at increased risk of chemotherapy toxicity [19].

We are conducting this pragmatic trial to determine whether the elderly cancer patients who are eligible to participate in this study will

obtain the same benefit from chemotherapy as younger patients. We also expect to identify elderly patients with AGC at greatest risk of toxicity by determining which geriatric assessment variables are associated with an increased risk of chemotherapy toxicity.

The number of elderly cancer patients is on the rise, and according to recent Surveillance, Epidemiology, and End Results (SEER) data from the United States, 60.8% of gastric cancers are diagnosed in patients older than 65 years: the median age at diagnosis of gastric cancer was 69 years and the median age of gastric cancer-related death was 72 years [20]. To our knowledge, this is the first large-scale RCT of chemotherapy focused on elderly patients with metastatic or recurrent AGC. We expect that this study will help guide decision-making for the optimal treatment of elderly patients with AGC, and also improve the care of these patients in real world clinical practice.

3.1. Trial status

Recruitment started in February 2014. Since the patient enrollment was slower than we expected, patients are still being recruited at the time of submission.

Ethical approval

The study protocol, patient information sheet, and informed consent form must be approved by the Institutional Review Board (IRB) at each participating center prior to the start of study. The study protocol was approved by the central KCSG IRB on November 13, 2013 and was registered at Clinicaltrials.gov (NCT02114359 on April 9, 2014).

Consent

The process of consent will be in accordance with the Declaration of Helsinki. All eligible participants will be fully informed that they are being asked to participate in an RCT. The procedures involved in the study and the chances of being assigned randomly to one of the two treatment groups will be fully explained both verbally and via an information sheet approved by the hospital's IRB. The participants will be given an informed consent document, which includes an information sheet and a consent form. The document includes all components required by the Korean Good Clinical Practice (KGCP) and additional components stipulated by domestic regulations in Korea. The document should be written in a language comprehensible to the participant and indicate who will provide information to the participant. A signed consent form will be obtained from each participant. Each participant must be provided with a copy of the signed consent form, and the investigator will keep the original document. Participants will be aware of their right to withdraw from the study at any time with no impact on usual clinical care received.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ISC conceived and designed the study and co-wrote the study protocol. KWL, JHP, and JWK assisted with study design. JHP co-wrote the study protocol. KWL, MHR, DYZ, KHK, MJK, HSH, and SAK reviewed the protocol and lead patient recruitment strategies. BHN provided expert statistical consultation. KWL drafted the manuscript. All authors read and approved the final manuscript.

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