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Clinical Trial Results

A Phase III Study to Compare the Efficacy and Safety of Paclitaxel Versus Irinotecan in Patients with Metastatic or Recurrent Gastric Cancer Who Failed in First-line Therapy (KCSG ST10-01)

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01224652
- **Sponsor(s):** Investigator-initiated trial
- **Principal Investigator:** Jae Yong Cho
- **IRB Approved:** Yes

Lessons Learned

- Irinotecan could not be proven noninferior to paclitaxel as a second-line treatment for patients with metastatic or recurrent gastric cancer.
- The failure to demonstrate noninferiority may have been a result of insufficient patient enrollment.
- Both agents were tolerable but showed different toxicity profiles.

Abstract

Background. This phase III study compared the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer (MRGC) who had experienced disease progression following first-line chemotherapy.

Methods. Patients were randomized to receive either paclitaxel (70 mg/m^2; days 1, 8, 15, every 4 weeks) or irinotecan (150 mg/m^2 every other week). The primary endpoint was progression-free survival (PFS).

Results. This study was stopped early due to low accrual rate. A total of 112 patients were enrolled; 54 were allocated to paclitaxel and 58 to irinotecan. Median PFS for the paclitaxel and irinotecan groups was 3.5 and 2.1 months, respectively (hazard ratio [HR], 1.27; 95% confidence interval [CI], 0.86–1.88; p = .234). Noninferiority of irinotecan to paclitaxel was not proved because the upper boundary of the 95% CI (1.88) exceeded the predefined upper margin of noninferiority (1.32). Median overall survival (OS) was 8.6 months in the paclitaxel group and 7.0 months in the irinotecan group (HR, 1.39; 95% CI, 0.91–2.11; p = .126). Among toxicities greater than or equal to grade 3, neutropenia (11.5%) was the most common,

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followed by peripheral neuropathy (7.7%) in the paclitaxel group, and neutropenia (34.5%) followed by nausea, vomiting, and anemia (8.6%, respectively) in the irinotecan group.

Conclusion. Although paclitaxel showed numerically longer PFS and OS compared with irinotecan, this was statistically insignificant. Both irinotecan and paclitaxel are valid second-line treatment options in MRGC. ***The Oncologist*** 2019;24:18–e24

Discussion

Second-line chemotherapy for metastatic or recurrent gastric cancer (MRGC) has been shown to improve survival in previous clinical trials. Although taxane or irinotecan are commonly used as second-line chemotherapy for MRGC, few previous studies have directly compared the efficacy between taxane and irinotecan. In our study, therefore, we compared the efficacy and safety of irinotecan and paclitaxel as second-line therapy in MRGC. PFS and OS were not statistically different (Figs. 1 and 2). However, noninferiority of irinotecan compared with paclitaxel could not be confirmed because of low patient enrollment. Toxicity profiles of irinotecan and paclitaxel were different.

Like our study, a previous Japanese phase III trial (WJOG 4007) compared the efficacy of paclitaxel versus irinotecan. The WJOG 4007 study was conducted to verify the hypothesis that irinotecan has superior OS to paclitaxel, and the authors concluded that both irinotecan and paclitaxel are reasonable second-line treatment options for MRGC because no significant difference in OS was observed. However, strictly speaking, the noninferiority of one agent to the other was also not proved in the WJOG 4007, considering the study design. When results of WJOG 4007 and our studies are compared, an interesting finding is observed simultaneously; paclitaxel showed numerically longer PFS (3.6 vs. 2.3 months [WJOG 4007; p = .33]; 3.5 vs. 2.1 months [our study; p = .234]) and OS (9.5 vs. 8.4 months [WJOG 4007; p = .38]; 8.6 vs. 7.0 months [our study; p = .126]) compared with irinotecan. As the difference in survival outcomes was not statistically significant in both WJOG 4007 and our studies, the observation of possible superiority of paclitaxel over irinotecan can only be considered hypothesis-generating.

Patient enrollment was less than expected and is the most important limitation in interpreting study results. During the study period, results of WJOG 4007 were reported, and this drove investigators to be less interested in our study and thus to enroll patients less often.

In conclusion, noninferiority of irinotecan compared with paclitaxel could not be proven. The hazard ratio of PFS crossed the boundary needed to prove noninferiority. Although paclitaxel showed numerically longer PFS and OS compared with irinotecan, this was statistically insignificant. Therefore, both irinotecan and paclitaxel are thought to be valid second-line treatment options in MRGC. Considering different toxicity profiles and treatment schedule, the choice of chemotherapeutic agents must be based on medical condition and compliance of patients.

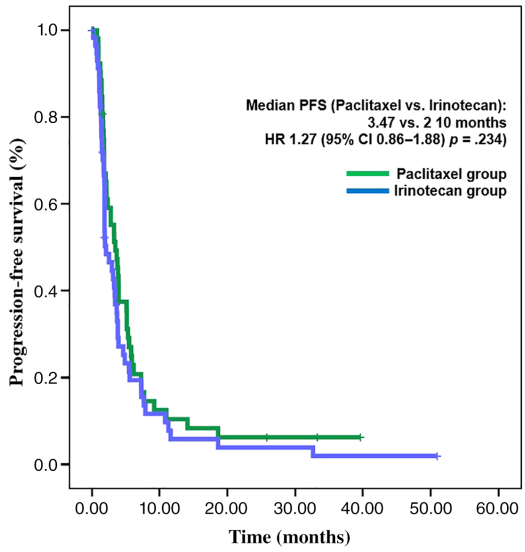

Figure 1. Progression-free survival.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

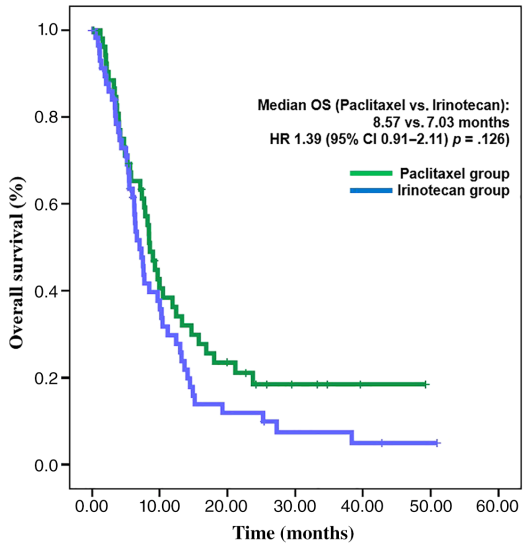

Figure 2. Overall survival.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Trial Information	
Disease	Gastric cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study - 1	Phase III
Type of Study - 2	Randomized
Primary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Overall response rate
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	
For sample size calculation, median PFS of the paclitaxel group was assumed to be 3.5 months based on literature review [1–3]. The efficacy of irinotecan was hypothesized to be noninferior to that of paclitaxel, which means median PFS of irinotecan would be at least longer than 2.65 months. Accordingly we decided noninferiority would be claimed if the upper boundary of the 95% CI of the hazard ratio did not exceed 1.32. Using a one-sided test with 2.5% alpha and 20% beta errors, planned accrual and follow-up periods of 24 and 12 months, and an expected dropout rate of 10%, 260 patients per group were needed. That is, a total of 520 patients were planned. The primary endpoint was PFS defined as time from the randomization to disease progression or death from any cause, whichever came earlier. Secondary endpoints were OS, overall response rate (ORR), and safety profiles. OS was defined as time from the randomization to death from any cause. PFS and OS were analyzed using the Kaplan-Meier method in intention-to-treat population. The HR of irinotecan compared with paclitaxel in PFS and OS analyses was calculated using the Cox proportional hazards regression model. ORR was the proportion of patients with complete response (CR) plus partial response (PR) among patients with one or more measurable lesions in baseline computed tomography. Patients with nontarget lesion only were excluded from the ORR analysis.	
Investigator's Analysis	Active but results overtaken by other developments

Drug Information for Phase III Control	
Drug 1	
Generic/Working Name	Paclitaxel
Trade Name	Taxol
Company Name	Boryung Pharmacetutical
Drug Type	Small molecule
Drug Class	Microtubule-targeting agent
Dose	70 mg/m^2
Route	IV
Schedule of Administration	Paclitaxel (Taxol; 70 mg/m^2) mixed with 100–250 mL of normal saline was administered intravenously over 1 hour on days 1, 8, and 15, every 4 weeks. The 4-week schedule was considered one cycle. Premedication for paclitaxel using corticosteroid and antihistamine was conducted following each institution's policy.

Drug Information for Phase III Experimental	
Drug 1	
Generic/Working Name	Irinotecan
Trade Name	Campto
Company Name	CJ HealthCare Corp.
Drug Type	Small molecule
Drug Class	Topoisomerase I
Dose	150 mg/m^2
Route	IV
Schedule of Administration	Irinotecan (Campto; 150 mg/m^2) mixed with 100–250 mL of 5% dextrose water was administered intravenously over 1 hour on days 1 and 15, every 4 weeks. The 4-week

	schedule was considered one cycle. In patients developing irinotecan-induced cholinergic symptoms (abdominal pain and diarrhea), atropine was used as premedication.

Patient Characteristics for Phase III Control	
Number of Patients, Male	38
Number of Patients, Female	16
Stage	All patients had metastatic or recurrent disease.
Age	Median (range): 58.5 (38–82)
Number of Prior Systemic Therapies	Median (range): 1 (1)
Performance Status: ECOG	0 — 0 1 — 52 2 — 2 3 — 0 Unknown — 0
Other	Additional information is shown in Table 1. During the period from February 2011 through January 2015, a total of 116 patients were screened, and 112 patients were enrolled at 16 sites in Korea. During the enrollment period, patient accrual rate was low, and we decided to stop this study early even though the target number of patients was 520.
Cancer Types or Histologic Subtypes	Well differentiated 4 Moderately differentiated 10 Poorly differentiated 38 Undifferentiated 1 Cannot be assessed 1

Patient Characteristics for Phase III Experimental	
Number of Patients, Male	40
Number of Patients, Female	18
Stage	All patients had metastatic or recurrent disease.
Age	Median (range): 59 (38–77)
Number of Prior Systemic Therapies	Median (range): 1 (1)
Performance Status: ECOG	0 — 0 1 — 56 2 — 2 3 — 0 Unknown — 0
Other	Additional information is shown in Table 1.
Cancer Types or Histologic Subtypes	Well differentiated 34 Moderately differentiated 16 Poorly differentiated 5 Undifferentiated 2 Cannot be assessed 1

Primary Assessment Method for Phase III Control	
Title	**Paclitaxel arm**
Number of Patients Screened	54
Number of Patients Enrolled	54
Number of Patients Evaluable for Toxicity	52
Number of Patients Evaluated for Efficacy	54
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (2.6%)
Response Assessment PR	*n* = 5 (13.2%)
Response Assessment SD	*n* = 16 (42.1%)

Response Assessment PD	*n* = 14 (36.8%)
Response Assessment OTHER	*n* = 2 (5.3%)
(Median) Duration Assessments PFS	3.5 months, CI: 2.2–4.7
(Median) Duration Assessments OS	8.6 months, CI: 7.1–10.0
Outcome Notes	

Between February 2011 and January 2015, a total of 116 patients were screened, and 112 patients were enrolled at 16 sites in Korea. Among 112 patients, 54 were allocated to paclitaxel and 58 to irinotecan. There were three patients who did not meet the eligibility criteria; the three patients were randomized to paclitaxel and received the study treatment. Although the enrollment of these three patients was a major protocol violation, these patients were included in the intention-to-treat analysis per study protocol. Thus, the full analysis set consisted of 54 patients in the paclitaxel group and 58 in the irinotecan group (*n* = 112). Of these patients, two in the paclitaxel group and one in the irinotecan group did not receive the allocated treatment because of consent withdrawal before the first dose. Therefore, the safety analysis set included 52 patients in the paclitaxel group and 57 in the irinotecan group. Response evaluation was conducted on patients with at least one measurable lesion; 38 of 54 in the paclitaxel group and 44 of 58 in the irinotecan group.

Primary Assessment Method for Phase III Experimental

Title	Irinotecan arm
Number of Patients Screened	58
Number of Patients Enrolled	58
Number of Patients Evaluable for Toxicity	57
Number of Patients Evaluated for Efficacy	58
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (2.3%)
Response Assessment PR	*n* = 5 (11.4%)
Response Assessment SD	*n* = 15 (34.1%)
Response Assessment PD	*n* = 16 (36.4%)
Response Assessment OTHER	*n* = 7 (15.9%)
(Median) Duration Assessments PFS	2.1 months, CI: 1.4–2.8
(Median) Duration Assessments OS	7.0 months, CI: 5.6–8.4

Adverse Events

Adverse events are shown in Table 2.

Serious Adverse Events (Paclitaxel)

Name	Grade	Attribution
Anorexia (1 patient)	3	Possible
Diarrhea (1 patient)	3	Possible
Fatigue (1 patient)	2	Possible
Fever (1 patient)	2	Possible
Gastric Hemorrhage (2 patients)	3	Possible
Gastric Hemorrhage (1 patient)	2	Possible
Hypotension (1 patient)	3	Possible
Oral mucositis (1 patient)	3	Probable
Vomiting (1 patient)	3	Possible
Vomiting (1 patient)	2	Possible

In the paclitaxel group, a total of 11 serious adverse events were reported in 7 patients. Gastric hemorrhage (tumor bleeding) developed in two patients; one patient developed two events of gastric hemorrhage (grade 2 [one event] and grade 3 [one event], respectively). Vomiting developed in two patients (grade 2 [one event] and grade 3 [one event], respectively).

Serious Adverse Events (Irinotecan)		
Name	**Grade**	**Attribution**
Abdominal pain (1 patient)	3	Possible
Anorexia (1 patient)	2	Probable
Anorexia (3 patients)	3	Possible
Fatigue (1 patient)	3	Possible
Febrile neutropenia (1 patient)	3	Definite
Fever (2 patients)	2	Possible
Gastric hemorrhage (1 patient)	4	Possible
Nausea (1 patient)	3	Probable
Neutrophil count decreased (1 patient)	4	Definite
Sepsis (1 patient)	4	Possible
Sepsis (1 patient)	5	Possible
Vomiting (1 patient)	3	Possible

In the irinotecan group, a total of 15 serious adverse events were reported in 13 patients. Anorexia, fever, and sepsis were reported in four, two, and two patients, respectively. One patient with sepsis died from it.

Assessment, Analysis, and Discussion	
Completion	Study terminated before completion
Terminated Reason	Did not fully accrue
Investigator's Assessment	Active but results overtaken by other developments

Gastric cancer (GC) is a major cause of cancer-related death, with more than 720,000 deaths worldwide [4]. In Korea, where GC is one of the most common types of cancer, GC is estimated to be the fourth and fifth most common cause of death in male and female cancer patients, respectively [5]. In general, fluoropyrimidine-based doublet chemotherapy, or triplet chemotherapy for highly selected patients, is widely used as palliative first-line therapy in patients with metastatic or recurrent GC (MRGC) [6,7]. If the tumor shows human epidermal growth factor 2 amplification, addition of trastuzumab to fluoropyrimidine plus platinum is now the standard first-line treatment [8]. After failure of first-line chemotherapy, second-line therapy with docetaxel or irinotecan showed improved overall survival (OS) compared with best supportive care in previous phase III trials [9–11].

Paclitaxel, a microtubule stabilizing agent that inhibits depolymerization during cell division, has been tested as a second-line chemotherapy for MRGC in previous single-arm studies [12]. Overall response rate (ORR) was 16%–24%, with median OS of 5–8 months [1–3,13–15]. Irinotecan inhibits topoisomerase I from unwinding DNA strands during DNA replication and has also been examined as a second-line therapy in previous single-arm studies, which showed 12%–20% of ORR and about 5 months of OS [16,17]. These efficacy data seemed to be comparable between irinotecan and paclitaxel in the second-line setting for MRGC, and both agents have been widely used in clinics in Korea. As there were no data from randomized clinical trials that directly compared the efficacy and safety of paclitaxel and irinotecan as second-line therapy in MRGC, we designed and conducted this phase III trial.

In this phase III trial, patients with histologically confirmed metastatic or recurrent gastric adenocarcinoma were eligible if they were older than 18 years and had disease progression to the palliative first-line chemotherapy. If patients experienced recurrence during or within 6 months after the completion of adjuvant chemotherapy following curative surgery, they were allowed to be enrolled to this trial. Other eligibility criteria were Eastern Cooperative Oncology Group performance status of 0–2; evaluable tumor lesions with or without measurable target lesions based on RECIST, version 1.1; adequate organ functions including bone marrow, kidney, and liver; and more than 16 weeks of expected survival. Patients were excluded if they had received more than one line of prior chemotherapy or had been exposed to taxane or irinotecan prior to this trial.

This was an investigator-initiated, multicenter, randomized, phase III trial conducted at 16 centers in Korea. The study protocol was approved by the institutional review board of each participating institution and the Korean Cancer Study Group (KCSG; trial number, KCSG ST10-01). This trial was registered with ClinicalTrials.gov (NCT01224652). The randomization was performed centrally at the KCSG data center using the method of permuted block randomization. Patients were randomly assigned in a ratio of 1:1 to either paclitaxel or irinotecan.

Paclitaxel (Taxol; 70 mg/m^2) was administered intravenously on days 1, 8, and 15, every 4 weeks. Irinotecan (Campto; 150 mg/m^2) was administered intravenously on days 1 and 15, every 4 weeks. For both agents, the 4-week schedule was considered one cycle. Predefined dose reduction or delay were conducted to manage treatment-related

toxicity. If neutropenia or thrombocytopenia of greater than or equal to grade 3 or clinically significant nonhematologic toxicities developed, dose reduction of paclitaxel (60 mg/m^2) and irinotecan (120 mg/m^2) was performed. If clinically significant hematologic or nonhematologic toxicities developed again despite dose reduction, no more dose reduction was conducted and the study treatment was permanently withdrawn. If the administration of study treatment was delayed more than 4 weeks due to delayed recovery from toxicities, the study treatment was also permanently withdrawn. The study treatment was continued until disease progression, death, development of unacceptable toxicity, or a patient's refusal of further therapy.

Tumor response evaluation using computed tomography was performed every 8 weeks (windows, ±7 days) based on RECIST (version 1.1). Hematologic laboratory test (complete blood count with differentiation) was repeated every week during the first cycle and then checked before the administration of study drugs (day 1, 8, and 15 for paclitaxel; day 1 and 15 for irinotecan). Chemistry was performed on the first day of each cycle. Adverse event was assessed at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Between February 2011 and January 2015, a total of 116 patients were screened, and 112 patients were enrolled at 16 sites in Korea. During the enrollment period, the accrual rate was low, and the result of a randomized phase III trial (WJOG4007), which had a similar design to our study, was reported in 2013 [18]. Therefore, we decided to stop this study early even though the target number of patients was 520. Among 112 patients, 54 were allocated to paclitaxel and 58 to irinotecan. Thus, full analysis set consisted of 54 in the paclitaxel group and 58 in the irinotecan group (n = 112). Of these patients, two in the paclitaxel group and one in the irinotecan group did not receive the allocated treatment because of consent withdrawal before the first dose. Therefore, safety analysis set included 52 in the paclitaxel group and 57 in the irinotecan group (Fig. 3; CONSORT diagram).

Table 1 summarized baseline characteristics across two treatment groups. The median time interval from the start of the first-line chemotherapy to the date of randomization for the study treatment in all 112 patients was 7.1 months (range, 1.0–37.7). Overall, each variable was well balanced between two groups. All patients had received fluoropyrimidine-based first-line chemotherapy prior to the enrollment into this study. Although there seemed to be a little imbalance in first-line chemotherapy regimens between the two groups, this was not statistically significant. In both groups, oxaliplatin-based doublet chemotherapy was the most common treatment used as the first-line therapy.

The data cutoff date was December 4, 2015. Median treatment duration in paclitaxel and irinotecan groups were 10.5 (range, 0–90.3) and 6.2 (range, 0–138.3) weeks, respectively. Mean dose intensities (± standard deviation) were 46.2 (±10.8) mg/m^2/week in the paclitaxel group and 60.9 (±15.3) mg/m^2/week in the irinotecan group, respectively.

Adverse events were observed in 96.3% of all the study population. Severe adverse events (grade ≥3) occurred in 32.7% of patients in the paclitaxel group and 45.6% in the irinotecan group (p = .177). Table 2 summarized adverse events according to the grade in each group. In the paclitaxel group, the most common adverse event was peripheral neuropathy (51.9%), followed by anemia (40.4%) and fatigue (40.4%). Neutropenia and anorexia were also frequent. Among adverse events greater than grade 3, neutropenia was the most common (11.5%). Peripheral neuropathy of greater than or equal to grade 3 was observed in 7.7% of the patients. In the irinotecan group, the most common adverse event was neutropenia (48.3%), followed by nausea (46.6%) and anorexia (44.8%). Diarrhea, anemia, and fatigue were also frequent. The most common severe adverse event (greater than or equal to grade 3) was neutropenia (34.5%). Peripheral neuropathy was more common in the paclitaxel group compared with the irinotecan group, whereas diarrhea was more prevalent in the irinotecan group. The irinotecan group also showed more frequent grade 3 or 4 neutropenia compared with the paclitaxel group.

Irinotecan did not show statistically different progression-free survival (PFS) compared with paclitaxel. Median PFS was 2.1 months in the irinotecan group and 3.5 months in the paclitaxel group, respectively (hazard ratio [HR], 1.27; 95% confidence interval [CI], 0.86–1.88; p = .234; Fig. 1). Noninferiority of irinotecan could not be confirmed because the CI exceeded the limit of predefined noninferiority margin of 1.32. Median OS was 7.0 months in the irinotecan group and 8.6 months in the paclitaxel group. The difference was not statistically significant (HR, 1.39; 95% CI, 0.91–2.11; p = .126; Fig. 2). Of 54 patients in the paclitaxel group, 30 (56%) received poststudy treatment, and irinotecan-containing regimens were most commonly used (83%; 25/30). Of 58 patients in the irinotecan group, 36 (62%) received poststudy chemotherapy, and these patients received taxane-based regimens most commonly (81%; 29/36). Thus, a total of 66 patients (59%) received at least one line of treatment after end of the study treatment. Response evaluation was conducted on patients with at least one measurable lesion (38 of 54 in the paclitaxel group and 44 of 58 in the irinotecan group). Response rate was also similar between two treatment groups. ORRs of paclitaxel group and irinotecan group were 15.8% and 13.6%, respectively (p = .355; Table 3).

The role of second-line chemotherapy for MRGC has been shown in recent phase III trials. Irinotecan was found to be effective as a second-line chemotherapy in German AIO trial despite low accrual [10]. A large phase III trial from Korea established the role of second-line chemotherapy, where irinotecan or docetaxel was chosen according to physician's discretion. In this trial, second-line chemotherapy showed superior OS compared with best supportive care alone (5.3 vs. 3.8 months [median]; HR, 0.657; p = .007) [9]. In the COUGAR-02 trial, second-line docetaxel showed improved OS compared with active symptom control group (5.2 vs. 3.6 months [median]; p = .01), although docetaxel was associated with more toxicity [11].

In our study (KCSG ST10-01), we compared the efficacy and safety of irinotecan and paclitaxel as second-line therapy in MRGC. However, noninferiority of irinotecan

compared with paclitaxel could not be confirmed in our study. The most crucial reason for this is low patient enrollment, which was translated into lower power to test the hypothesis. Like our study, a previous Japanese phase III trial (WJOG 4007) compared the efficacy of paclitaxel versus irinotecan as a second-line chemotherapy in MRGC [18]. The WJOG 4007 study was conducted to verify the hypothesis that irinotecan has superior OS to paclitaxel, and the authors concluded that both irinotecan and paclitaxel are reasonable second-line treatment options for MRGC because no statistically significant difference in OS was observed between paclitaxel and irinotecan. However, strictly speaking, the noninferiority of one agent to the other was not proved in the WJOG 4007, considering the study design. When results of KCSG ST10-01 and WJOG 4007 studies are compared, an interesting finding is observed simultaneously in both studies: Paclitaxel showed numerically longer PFS (3.6 vs. 2.3 months in WJOG 4007 [p = .33]; 3.5 vs. 2.1 months in our study [p = .234]) and OS (9.5 vs. 8.4 months in WJOG 4007 [p = .38]; 8.6 vs. 7.0 months in our study [p = .126]) compared with irinotecan, although statistically insignificant. In our study, paclitaxel showed comparable PFS and OS to those reported in recent phase III studies (2.9–3.6 months of PFS and 6.9–9.5 months of OS) [18–20]. As the difference in survival outcomes was not statistically significant in both WJOG 4007 and our studies, the observation of possible superiority of paclitaxel over irinotecan is just hypothesis-generating. All toxicity profiles of irinotecan and paclitaxel were different. Among toxicities of greater than or equal to grade 3, neutropenia (11.5%) was the most common, followed by peripheral neuropathy (7.7%) in the paclitaxel group, and neutropenia (34.5%) followed by nausea, vomiting, and anemia (8.6%, respectively) in the irinotecan group. These toxicity profiles were consistent with previous reports and manageable [9,10,14,17,18]. Taken together, we authors agree that both irinotecan and paclitaxel are reasonable second-line treatment options in MRGC.

During our study period, ramucirumab, a monoclonal antibody inhibiting vascular endothelial growth factor receptor 2, was approved for second-line treatment as monotherapy or in combination with paclitaxel based on two pivotal phase III trials [19,21]. In the REGARD trial, ramucirumab monotherapy showed longer OS compared with placebo (5.2 vs. 3.8 months [median]; HR, 0.776; p = .047). Median PFS was also improved with ramucirumab (2.1 vs. 1.3 months [median]; HR, 0.483; p < .0001) [21]. Likewise, in the RAINBOW trial, the combination of ramucirumab and paclitaxel showed superior PFS (4.4 vs. 2.9 months [median]; HR, 0.635; p < .0001) and OS (9.6 vs. 7.4 months [median]; HR, 0.807; p = .017) compared with paclitaxel alone [19]. However, in the preplanned subgroup analysis in the both studies, the OS in Asian patients were not statistically different between each treatment group [19,21], although the subgroup analysis in the RAINBOW trial showed the superiority of PFS in the ramucirumab plus paclitaxel group compared with paclitaxel plus placebo group even in Asian patients [19]. Furthermore, ramucirumab-related adverse events such as gastrointestinal perforation or proteinuria should not be ignored, although the incidence was not frequent. Thus, cytotoxic chemotherapy such as paclitaxel or irinotecan is still a viable option to treat patients with MRGC in the second-line setting.

Clinical trials comparing ramucirumab plus irinotecan versus irinotecan or comparing ramucirumab plus irinotecan versus ramucirumab plus paclitaxel are not expected to be conducted in the future, considering the similar efficacy of paclitaxel and irinotecan and proven superior efficacy of ramucirumab plus paclitaxel to paclitaxel alone. Instead, comparison between ramucirumab with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil) and ramucirumab with paclitaxel is now ongoing (NCT03081143). This study would be another indirect indicator to see if irinotecan has a different efficacy over paclitaxel when combined with ramucirumab.

Far fewer patients enrolled than expected, limiting our interpretation of study results. During the study period, the outcome of WJOG 4007 was reported, and this drove investigators to be less interested in this study and thus to enroll patients much less. Furthermore, confirmative landmark trials established the evident role of ramucirumab as a second-line treatment in MRGC [19,21]. In Korea, many kinds of clinical trials are conducted for MRGC. This often results in enrollment competition between various trials that have similar eligibility criteria. It is estimated that many investigators allocated patients to other clinical trials because neither paclitaxel nor irinotecan were novel investigational drugs.

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Disclosures

The authors indicated no financial relationships.

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Figures and Tables

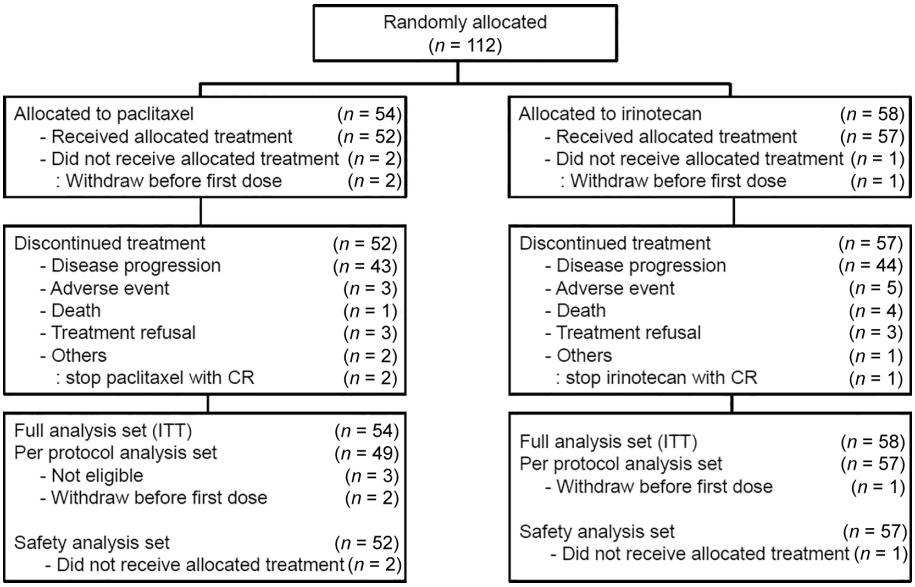

Figure 3. Consolidated Standards of Reporting Trials diagram. Abbreviations: CR, complete response; ITT, intention-to-treat.

Table 1. Baseline characteristics

Characteristic	Paclitaxel group		Irinotecan group		*p* value
	n = 54	%	*n* = 58	%	
Age, years					.775[a]
Median (range)	58.5	(38–82)	59	(38–77)	
Sex					.872
Male	38	70.4	40	69.0	
Female	16	29.6	18	31.0	
ECOG PS[b]					>0.999[c]
1	52	96.3	56	96.6	
2	2	3.7	2	3.4	
Prior gastrectomy					.641
Yes	35	64.8	40	69.0	
No	19	35.2	18	31.0	
First-line of chemotherapy					.402[c]
Doublet chemotherapy					
Oxaliplatin plus fluoropyrimidine	31	57.4	34	58.6	
Cisplatin plus fluoropyrimidine	10	18.5	16	27.6	
Fluoropyrimidine monotherapy	6	11.1	5	8.6	
Trastuzumab plus capecitabine/cisplatin	2	3.7	2	3.4	
Others	5	9.3	1	1.7	
Primary tumor site					.324[c]
Stomach	51	94.4	51	87.9	
Gastroesophageal junction	3	5.6	7	12.1	
Measurable lesion					.512
Yes	38	70.4	44	75.9	
No	16	29.6	14	24.1	
Peritoneal metastasis					.834
Yes	29	53.7	30	51.7	
No	25	46.3	28	48.3	
No. of organs involved by metastasis					.402
One	20	37.0	26	44.8	
Two or more	34	63.0	32	55.2	
Time interval between two lines of treatment[d]					>0.999
< median (7.1 months)	27	50.0	29	50.0	
≥ median (7.1 months)	27	50.0	29	50.0	

Unless otherwise noted, each *p* value was calculated by chi-square test.
[a]*t* test.
[b]No patients had a grade 0 of ECOG PS.
[c]Fisher's exact test.
[d]Time interval between two lines of treatment was defined as duration from the start of the first-line chemotherapy to the date of randomization in this trial.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Adverse events

	Paclitaxel group (*n* = 52)								Irinotecan (*n* = 57)							
	All grade		Grade 1–2		Grade 3		Grade 4		All grade		Grade 1–2		Grade 3		Grade 4	
Adverse event[a]	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Anemia	21	40.4	19	36.5	2	3.8	0	0.0	22	37.9	17	29.8	4	6.9	1	1.7
Neutropenia	19	36.5	13	25.0	5	9.6	1	1.9	28	48.3	8	14.0	12	20.7	8	13.8
Thrombocytopenia	5	9.6	4	7.7	1	1.9	0	0.0	7	12.1	7	12.3	0	0.0	0	0.0
Febrile neutropenia	3	5.8	0	0.0	3	5.8	0	0.0	1	1.7	0	0.0	1	1.7	0	0.0
Anorexia	18	34.6	17	32.7	1	1.9	0	0.0	26	44.8	22	38.6	4	6.9	0	0.0
Nausea	9	17.3	7	13.5	2	3.8	0	0.0	27	46.6	22	38.6	5	8.6	0	0.0
Vomiting	7	13.5	6	11.5	1	1.9	0	0.0	13	22.4	8	14.0	5	8.6	0	0.0
Diarrhea	8	15.4	7	13.5	1	1.9	0	0.0	23	39.7	23	40.4	0	0.0	0	0.0
Constipation	8	15.4	8	15.4	0	0.0	0	0.0	6	10.3	6	10.5	0	0.0	0	0.0
Fatigue	21	40.4	21	40.4	0	0.0	0	0.0	22	37.9	19	33.3	3	5.2	0	0.0
Myalgia	6	11.5	6	11.5	0	0.0	0	0.0	3	5.2	3	5.3	0	0.0	0	0.0
Peripheral neuropathy	27	51.9	23	44.2	4	7.7	0	0.0	9	15.5	8	14.0	1	1.7	0	0.0

[a]Only adverse events observed more than 10% in any groups were listed with the proportion (%) of patients.

Table 3. Response rate

	Paclitaxel group		Irinotecan group		
Response	*n* = 38	%	*n* = 44	%	*p* value[a]
Complete response	1	2.6	1	2.3	
Partial response	5	13.2	5	11.4	
Stable disease	16	42.1	15	34.1	
Progressive disease	14	36.8	16	36.4	
Not assessable	2	5.3	7	15.9	
ORR	6	15.8	6	13.6	.783
DCR	22	57.9	21	47.7	.358

[a]Each *p* value was calculated by chi-square test.
Abbreviations: DCR, disease control rate; ORR, overall response rate.