Int J Clin Exp Med 2016;9(7):13712-13722
www.ijcem.com /ISSN:1940-5901/IJCEM0025304

Original Article

Meta-analysis of irinotecan monotherapy versus irinotecan-based combined second-line therapy for the treatment of advanced gastric cancer

Jia Xu[1*], Zi-Zhen Zhang[1*], Tian-Long Lin[1], Hui Cao[1], Han-Kwang Yang[2,3,4]

[1]Department of General Surgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Department of Surgery, Seoul National University Hospital, Seoul, Korea; [3]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea; [4]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea. [*]Equal contributors.

Received January 31, 2016; Accepted May 1, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: For advanced gastric cancer patients who have recurrence and metastasis after having received first-line chemotherapy, effective and reasonable second-line chemotherapy can extend the survival time and improve the quality of life. Irinotecan has been confirmed to be an effective second-line chemotherapy drug for advanced gastric cancer. However, the specific regimen remains controversial. Through meta-analysis, this study compared the efficacy and safety of irinotecan monotherapy and irinotecan-based combined therapy. Relevant literature was retrieved from the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases. Data were arranged and classified according to the traditional format. The outcome measures were OS (overall survival), PFS (progressive free survival), ORR (overall response rate), DCR (disease control rate), and grade 3-4 adverse events. Compared to irinotecan monotherapy, irinotecan-based combined therapy could significantly increase PFS (HR 0.78, 95% CI 0.63-0.98; *P*=0.03) and DCR (OR=1.62; 95% CI 1.10-2.37; *P*=0.01). However, there was no significant difference in OS (HR 0.89, 95% CI 0.71-1.11; *P*=0.31) and ORR (OR=1.55; 95% CI 0.94-2.55; *P*=0.09). In addition, pooled data revealed no significant difference in safety profiles for both grade 3/4 hematologic and grade 3/4 non-hematological events between the two groups. Treatment of advanced gastric cancer using irinotecan (CPT-11)-based second-line thermotherapy could significantly prolong PFS and increase DCR of patients. In addition, compared to irinotecan monotherapy, this combined therapy did not significantly increase serious toxic side effects of chemotherapy. Therefore, we recommend irinotecan-based combined chemotherapy as the second-line thermotherapy regimen for advanced gastric cancer.

Keywords: Irinotecan, therapy, advanced gastric cancer

Introduction

Gastric cancer is the second-leading cause of cancer death worldwide (17.9 million disability-adjusted life-years in 2013). In East-Asian areas with a high incidence of gastric cancer, the estimated mortality rates are even higher [1, 2]. In addition, there are no typical clinical symptoms at the early stage of gastric cancer, and many patients already have distant metastasis at their first visit; therefore, the opportunity forsurgical treatment may have already passed. Even for patients who receive surgical treatment for gastric cancer, more than 50% haveadvanced gastric cancer, resulting in an unfavorable long-term prognosis [3]. Therefore, in addition to surgical therapy, it is necessary to select reasonable and effective systemic chemotherapy regimens for improving survival rates and the quality of life of patients with advanced gastric cancer.

Currently, the use of fluoropyrimidines and derived drugs based on combined chemotherapy regimens as the standard first-line chemotherapy regimen for the treatment of advanced gastric cancer has received an extensive consensus; these include the EOX [4] and DCF [5] regimens extensively used in Europe and America as well as the SP regimen [6] used as the standard in Asian areas. However, for patients with advanced gastric cancer, the overall response rate (ORR) of the above first-line chemotherapy regimens was found to be

only 37%-54%, and the free-progressive survival (FPS) was only 5.6-7.0 months. A certain number of patients still had disease progression, recurrence, and metastasis after received first-line chemotherapy.

For the aforementioned advanced gastric cancer patients with first-line therapy failure, the selection of second-line chemotherapy regimens could significantly extend the overall survival (OS) of patients [7-9]. As one of the major second-line chemotherapy drugs for advanced gastric cancer, irinotecan has shown certain efficacy in many phase III clinical studies [7, 8]. A meta-analysis study of the second-line chemotherapy versus the best supportive care (BSC) in advanced gastric cancer showed that the median OS of patients was 4.0-5.3 months in the irinotecan monotherapy group and 2.4-3.8 months in the BSC group; the survival time of the former group was significantly longer than that of the latter (HR 0.55, 95% CI 0.40-0.77, *P*=0.0004) [10]. However, based on a comprehensive consideration of the efficacy and safety of these drugs, the selection of irinotecan monotherapy or irinotecan-based combined chemotherapy remains controversial. Therefore, this present study aimed to use meta-analysis to compare the efficacy and safety of irinotecan monotherapy and irinotecan-based combined therapy.

Materials and methods

Literature collection

We retrieved literature publicly published in the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databasesprior to June 30th, 2015. The search terms were "gastric or gastroesophageal or gastroesophagus or esophagogastric or stomach", "cancer or neoplasm or carcinoma or malignant or malignancy", "irinotecan or CPT-11", "second-line or salvage", and "chemotherapy or chemotherapeutic or antineoplastic agent". The search scope was limited in titles, abstracts, or keyword lists. In addition, we searched the reference lists of relevant articles/reviews and used the "related articles" feature in PubMed to identify additional articles. Furthermore, we also searched abstracts and presentations included in the American Society of Clinical Oncology (ASCO) conferences from 2005 to 2015 to identify relevant but unpublished studies.

Inclusion and exclusion criteria of the literature screening

Two researchers independently evaluated the retrieved literature. The inclusion criteria included the following: 1) patients were pathologically diagnosed with advanced gastric cancer (surgical radical resection could not be performed or there was postoperative recurrence and metastasis) and patients did not receive radiotherapy or chemotherapy within 1 month before the study; 2) literature related to the comparison of efficacy (PFS, OS, ORR, or DCR) and toxic side effects on the treatment of advanced gastric cancer between irinotecan monotherapy and irinotecan based combined therapy; 3) the study design was a clinical retrospective study or phase II/III controlled study; and 4) the original literature had clear follow-up censored data, and the follow-up rate was >95%. Studies were excluded if they included only the response rates and did not report survival analysis or the number of cases was fewer than 30 cases. Study features from the above published articles were extracted and then summarized and analyzed using the same method and standard. When the same patient population was published in several studies, only the newest, largest, or most complete study was selected.

Quality evaluation

The quality of the RCT studies was evaluated by two independent researchers using the Cochrane Handbook for Systematic Reviews of Interventions [11]. The study quality of the non-randomized studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [12]. When there was a difference of opinions, the results were discussed by the two researchers, or athird independent researcher was consulted.

Data extraction

Two independent researchers used the traditional format to arrange and classify data, and consistent opinions were obtained for each item. Data collected from the included studies included the following: 1) general information such as the first author, publication year, number of enrolled patients, ethnicity, male ratio, and mean age; 2) study features such as the type of experimental design, treatment schedule, median PFS, median OS, HR of PFS or OS

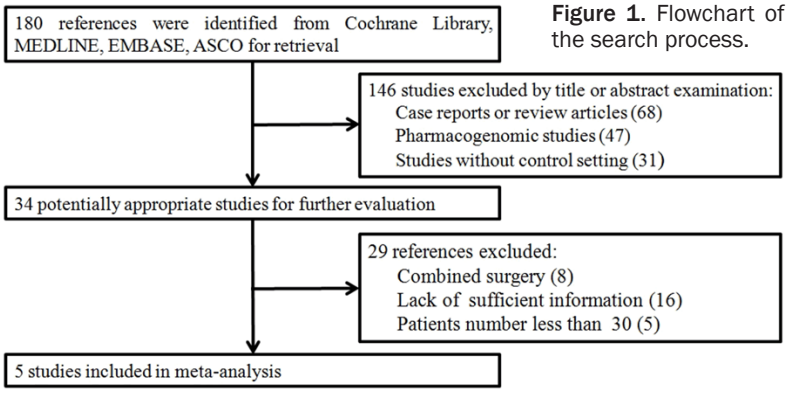


Figure 1. Flowchart of the search process.

and the corresponding 95% CI, ORR, and DCR; and 3) grade 3 or 4 adverse drug events.

Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software. The primary endpoints of this study were PFS and OS. The correlation between chemotherapy regimens and primary endpoints was presented using HR and the corresponding 95% CI. The secondary endpoints in this study were ORR, DCR, and adverse events (AEs). According to Response Evaluation Criteria in Solid Tumors, ORR included partial and complete response rates. DCR referred to the ratios of patients with partial response, complete response, and stable diseases. The odds ratio (OR) represented the correlation between the chemotherapy regimen and the ORR of the irinotecan-based combination chemotherapy arm over the irinotecan monotherapy arm. The AEs of the included studies were evaluated using the common toxicity criteria of the National Cancer Institute (version 2). A fixed effects model was conducted to pool the HR or OR. The heterogeneity test was performed based on the traditional *Q* test and the I^2 index using standard methods. Values of $P<0.05$ or $I^2>30\%$ in the *Q* test were considered indicative of the presence of heterogeneity. The source of heterogeneity was explored using sensitivity analysis, subgroup analysis, or the random-effects model. Publication bias was evaluated using a Funnel plot. Whenthe two-tailed *P* value wasless than 0.05, the result was considered statistically significant.

Results

Eligible studies

A total of 180 references were retrieved using our initial search algorithm (**Figure 1**). According to the inclusion criteria, 146 studies were excluded after careful reading of the abstracts. After the entire articles of the remaining 34 studies were carefully reviewed, 29 studies were excluded due to discrepancies in the methods, a lack of sufficient information, or a small number of total cases (**Table 1**). Finally, 5 studies with 532 cases of patients were included in this meta-analysis [13-17]. There were 240 cases (45.1%) in the irinotecan-based combined therapy group and 292 cases (54.9%) in the irinotecan monotherapy group. The total number of patients enrolled in the studies ranged between 46 and 163, and the mean age of the patients ranged from 19 to 82 years old. The clinical characteristics of the patients in the included studies are listed in **Table 1**.

Evaluation of study quality

Among the 5 studies included in this study, 3 studies were randomized controlled trial (RCT) studies and 2 studies were retrospective studies. The quality of the two retrospective studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [15, 17]. The results were quality scores with a total of 8 stars (3 stars for selection, 2 stars for comparability, and 3 stars for outcomes, respectively). The quality of the three RCT studies was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions [13, 14, 16]. All RCT studies reported sufficient generation of the allocation sequence, and two studies [13, 14] reported allocation concealment (concealed to the investigators). All included studies did not report blinding. All three RCT studies did not have patients lost to follow-up. In addition, all studies were level B. The risk of bias for the three RCT studies is listed in **Table 2**.

PFS and OS

HR and the corresponding 95% CI for PFS and OS were directly extracted from the three RCT studies. Univariate analysis was performed to calculate the HR and the corresponding 95% CI from the references for PFS. The Q-test (Chi-square=0.94, $P=0.63$, $I^2=0.0\%$) did not indicate the presence of heterogeneity. Therefore,

Table 1. Baseline characteristics of the included studies

Authors	Publication year	Ethnicity	Study design	Group	Patients	Chemotherapy regimen (Group)	PS 0-1 (%)	mAge, (years)	mPFS, (months)	mOS, (months)
Hiquchi K [13]	2014	Japan	RCT (Phrase III)	CPT-11+CDDP	64	Irinotecan 60 mg/m^2 + cisplatin 30 mg/m^2, day 1, q2w	100%	66	3.8	10.7
				CPT-11	66	Irinotecan 150 mg/m^2 day 1, q2w	100%	67	2.8	10.1
Nishikawa K [14]	2015	Japan	RCT (Phrase III)	CPT-11+CDDP	82	Irinotecan 60 mg/m^2 + cisplatin 30 mg/m^2, day 1, q2w	100%	67	4.6	13.9
				CPT-11	81	Irinotecan 150 mg/m^2 day 1, q2w	100%	68	4.1	12.7
Oba M [15]	2011	Japan	Retrospective	CPT-11+CDDP	42	Irinotecan 70 mg/m^2 day 1, 15 + cisplatin 80 mg/m^2, day 1, q4w	100%	58	2.7	8
				CPT-11	92	Irinotecan 150 mg/m^2 day 1, q4w	99%	61	2.6	9.8
Sym SJ [16]	2013	Korea	RCT (Phrase II)	CPT-11+5-Fu+LV	30	Irinotecan 150 mg/m^2 + LV 20 mg/m^2 + 5-FU 2000 mg/m^2>48 h, day 1, q2w	90%	61	3.0	6.7
				CPT-11	29	Irinotecan 150 mg/m^2 day 1, q2w	93%	60	2.2	5.8
Ueda A [17]	2013	Japan	Retrospective	CPT-11+MMC	22	Irinotecan 150 mg/m^2 + MMC 5 mg/m^2, day 1, q2w	91%	62	3.9	9.6
				CPT-11	24	Irinotecan 150 mg/m^2, day 1, q2w	100%	65	3.7	8.7

PS, performance status; mAge, median age; mPFS, median progression-free survival; mOS, median overall survival.

Table 2. Quality of RCTs used in the meta-analysis

Authors	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective reporting	Other bias
Hiquchi K	Yes	Yes	Unclear	Yes	Yes	Yes
Nishikawa K	Yes	Yes	Unclear	Yes	Yes	Yes
Sym SJ	Yes	Unclear	Unclear	Yes	Yes	Yes

Yes=low risk of bias; Unclear=moderate risk of bias; No=high risk of bias.

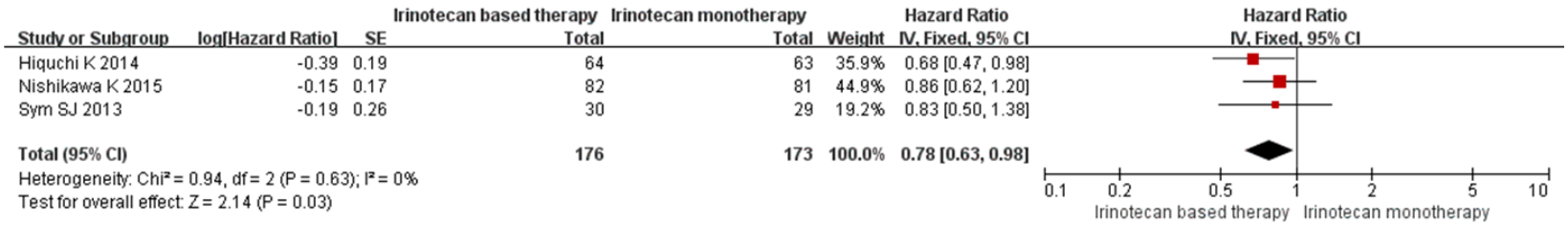


Figure 2. Standard forest plot of the hazard ratios (HR) for progressive free survival comparing irinotecan-based combined chemotherapy with irinotecan monotherapy. CI, confidence interval.

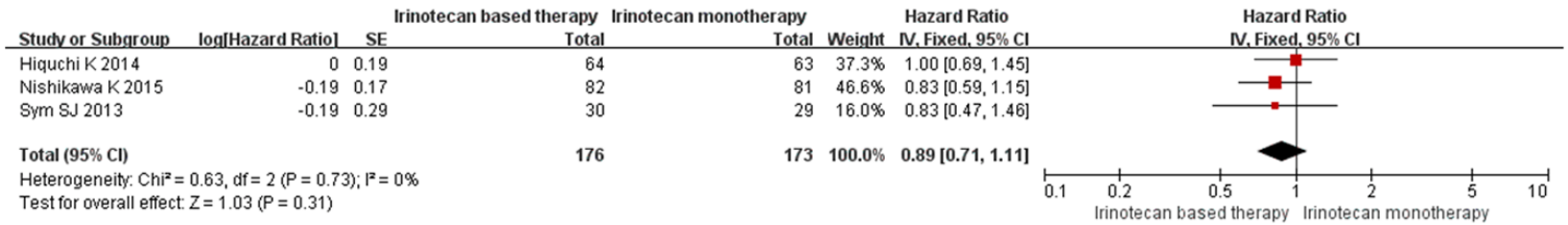


Figure 3. Standard forest plot of the hazard ratios (HR) for overall survival comparing irinotecan-based combined chemotherapy with irinotecan monotherapy. CI, confidence interval.

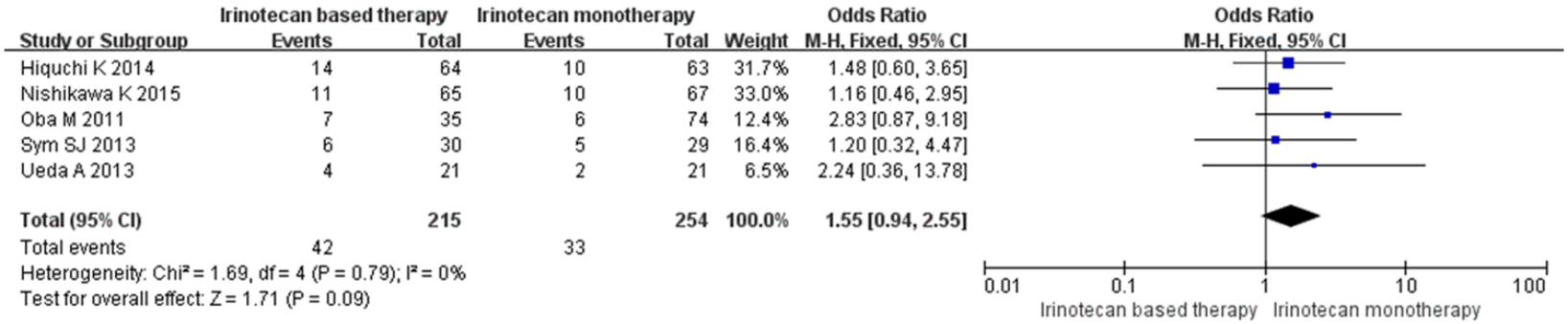


Figure 4. Standard forest plot of the odds ratios of the overall response rates comparing irinotecan-based combined chemotherapy with irinotecan monotherapy. CI, confidence interval.

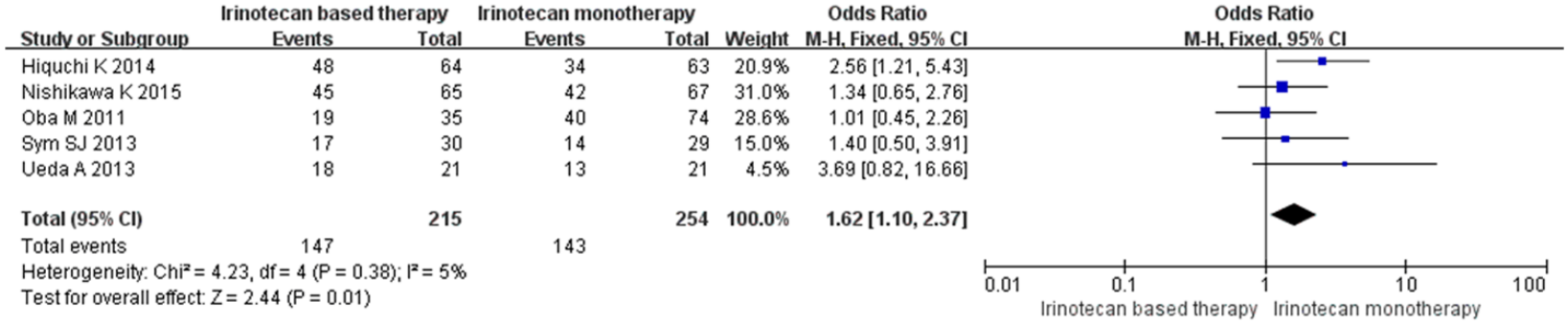


Figure 5. Standard forest plot of the odds ratios of the disease control rates coparing irinotecan-based combined chemotherapy with irinotecan monotherapy. CI, confidence interval.

Table 3. Outcome of the toxicity comparing irinotecan-based therapy versus irinotecan monotherapy as the second-line treatment in gastric cancer (grades 3 and 4)

Toxicity	Trials	Irinotecan-based therapy (%)	Irinotecan monotherapy (%)	Heterogeneity		OR (95% CI)	*P* value
				P value	I^2 (%)		
Hematological							
Leucopenia	4	28 (16)	28 (12)	0.15	44	1.24 [0.56, 2.76]	0.60
Neutropenia	4	81 (41)	66 (33)	0.75	0	1.41 [0.93, 2.11]	0.10
Febrile neutropenia	4	7 (4)	6 (3)	0.22	32	1.73 [0.38, 7.88]	0.48
Anemia	5	39 (16)	20 (7)	0.05	58	2.76 [0.93, 8.24]	0.07
Thrombocytopenia	5	4 (2)	4 (1)	0.78	0	1.22 [0.34, 4.33]	0.76
Non-hematological							
Fatigue	5	14 (6)	13 (4)	0.26	24	1.17 [0.55, 2.50]	0.68
Anorexia	5	24 (10)	26 (9)	0.21	31	1.17 [0.56, 2.43]	0.68
Nausea	4	10 (5)	10 (4)	0.42	0	1.22 [0.50, 2.96]	0.67
Diarrhea	5	7 (3)	12 (4)	0.32	14	0.76 [0.31, 1.88]	0.55

the meta-analysis used the fixed effects model. The final results indicated that AGC patients who received irinotecan-based combined therapy experienced a longer PFS than those who received irinotecan monotherapy (HR 0.78, 95% CI 0.63-0.98, *P*=0.03), as shown in **Figure 2**. The HR and corresponding 95% CI from the references for OS were calculated using univariate analysis. We also foundno heterogeneity using the Q-test (Chi-square=0.63, *P*=0.73, I^2=0.0%) with the fixed-effects model. As shown in **Figure 3**, pooled data from these 3 studies indicated that there was no significant difference in the OS benefit between irinotecan-based combined therapy and irinotecan monotherapy (HR 0.89, 95% CI 0.71-1.11, *P*=0.31). The results ofthe sensitivity analysis of PFS and OS suggested that our findings were statistically robust. The funnel plot showed no publication bias for either PFS or OS (Supplementary Figures 1, 2).

ORR and DCR

All five eligible studies reported raw data on tumor ORR, which included complete and partial tumor responses. Because no heterogeneity was found across studies (Chi-square=1.69; *P*=0.79; I^2=0.0%), the fixed-effects model could be used to perform the meta-analysis. Pooled data from these studies showed an overall ORR of 19.5% for the irinotecan-based combined regimens (42/215) and 13.0% for the irinotecan monotherapy (33/254); the difference between the two groups was not significant (OR=1.55; 95% CI 0.94-2.55; *P*=0.09) (**Figure 4**).

DCR data were extracted from all eligible studies, which included patients with complete/partial response and stable disease. The fixed effects model was used based on limited heterogeneity by the Q-test (Chi-square=4.23; *P*=0.38; I^2=5%). The final results indicated that the DCR of patients with irinotecan-based combined therapy was 68.4% (147/215), whereas that of patients with irinotecan monotherapy was 56.3% (143/254), indicating that combined therapycould improve the DCR for AGC patients compared with monotherapy (OR= 1.62; 95% CI 1.10-2.37; *P*=0.01) (**Figure 5**).

The results of the sensitivity analysis of ORR and DCR suggest that our findings were statistically robust. No publication bias the ORR or DCR was detected based on funnel plot analysis (Supplementary Figures 3, 4).

Toxicity

All five trials reported grade 3 or grade 4 toxicity results. The toxicity profile analyses for eligible trials are shown in **Table 3**. The most common grade 3/4 hematologictoxicities were neutropenia in both arms, andthe most frequent grade 3/4 non-hematological toxicities were anorexia for each arm. There was a significant heterogeneity (I^2>30%) in the pooled OR of leucopenia, febrile neutropenia, anemia and anorexia; thus, a randomized-effect model was applied. Pooled data revealed no significant difference in the safety profiles for both grade 3/4 hematologic and grade 3/4 non-hematological events. In addition, irinotecan monotherapy group had 2 cases of treatment-related deaths;

these patients died of septic shock [16] and respiratory failure due to pulmonary embolism [17]. There were no treatment-related deaths in the irinotecan-based combined therapy group.

Discussion

A large number of clinical trials have confirmed that first-line chemotherapy can significantly extend the survival time of patients with advanced gastric cancer. However, even the well-known S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS) trial showed that although S-1 plus cisplatin (CDDP) combined first-line chemotherapy could extend the median OS of advanced gastric cancer patients for more than 1 year (13.0 months), the median PFS was only 56 months and 74% of patients received subsequent second-line chemotherapy after the presence of drug resistance to the first-line therapy [18]. Therefore, for advanced gastric cancer, the selections of active and reasonable second-line chemotherapy based on the disease conditions of patients is an important measure to extend the survival time of patients and improve the quality of life of patients.

Irinotecan (CPT-11) is a derivative of camptothecin that binds reversibly to DNA topoisomerase-1 and induces cancer cell death by preventing religation of single-strand DNA breaks. Thuss-Patience et al. reported that compared to BSC, CPT-11 single-drug second-line therapy (250 mg/m^2 every 3 weeks, increased to 350 mg/m^2 depending on the toxicity) could significantly increase the OS (HR=0.48; 95% CI, 0.25-0.92; *P*=0.023) of advanced gastric cancer patients who were previously treated with only one regimen [7]. In addition, Goto et al. performed retrospective studies on patients with metastatic advanced gastric cancer who were treated with different second-line chemotherapy regimens and showed that irinotecan-containing regimens were the independent prognostic factoraffecting patients with metastatic advanced gastric cancer (HR: 0. 165; 95% CI: 0. 041-0. 665) [19]. These results suggest that CPT-11 is a key novel agent in the treatment of advancedgastric cancer in a second-line setting. However, currently, the specific treatment regimen using irinotecan in the second-line chemotherapy for advanced gastric cancer remains inconclusive. Some early non-controlled phase II clinical studies confirmed that in the irinotecan monotherapy regimen, the tumor reactive rate reached 12.5-20% and the median OS was 5 to 5.2 months [20-22]. In the irinotecan-based combined with 5-fluorouracil/leucovorin (5-FU/LV) therapy group, the tumor reactive rate reached 12.3-29% and the median OS was 6.2-7.6 months [23-25], whereas in the irinotecan-based combined with CDDP therapy group, the tumor reactive rate reached 25-31% and the median OS was 5-5.6 months [26, 27]. However, due to a lack of large-scale clinical case controlled studies, the selection of irinotecan monotherapy currently remains similar to that of the first-line chemotherapy regions. Thus, the selection of irinotecan-based combined chemotherapy continues to be controversial.

This study performed a meta-analysis on the prognostic indicators of the treatment of advanced gastric cancer between irinotecan monotherapy and irinotecan-based combined therapy. The results showed that irinotecan-based combined chemotherapy could significantly increase the disease control rate (OR= 1.62; 95% CI 1.10-2.37; *P*=0.01) of advanced gastric cancer patients, which was associated with a risk reduction of PFS by 22% (HR 0.78, 95% CI 0.63-0.98, *P*=0.03). Although the meta-analysis showed that there was no statistically significant difference between the OS of patients of the irinotecan-based combined therapy group and the monotherapy group, all RCTs studies included herein showed that the median OS values in the irinotecan-based combined chemotherapy group (6.7-13.9 months) were all longer than those in the irinotecan monotherapy group (5.8-12.7 months). In addition, In Japan and South Korea, when patients who received the second-line chemotherapy have disease progression, more than 70% patients would receive other third-line chemotherapy drugs. Therefore, different subsequent therapy regimens may also be confounding factors affecting the OS results of patients in these two groups [14, 28].

All patients included in this meta-analysis received fluoropyrimidines or platinum-based first-line chemotherapy, whereas in the second-line therapy, the irinotecan-combined chemotherapy drugs were mainly fluoropyrimidines or CDDP. The study results showed that in the second-line therapy, irinotecan combined with drugs used in the first-line chemotherapy could

still yield a relatively satisfactory disease control efficacy. In the study of Higuchi et al., approximately 56% patients received platinum-based first-line chemotherapy before being included in the study; however, the study results also showed that irinotecan combined with CDDP could significantly extend the PFS of patients compared to the irinotecan monotherapy (HR 0.68, 95% CI 0.47-0.98). Subsequent sub-group analysis also showed that for advanced gastric cancer patients who had received platinum-based therapy, the PFS of patients in the irinotecan combined with CDDP group was significantly extended compared to that in the irinotecan monotherapy group (HR 0.80; 95% CI 0.49-1.28). Based on the above results, we speculate that irinotecan-based combined second-line chemotherapy regimens have a synergistic effect and can improve the incidence of drug resistance caused by the first-line chemotherapy.

It is well known that palliative therapy should consider a balance of symptom control and toxicity and focus on improving the quality of life of patients. Therefore, in this study, we compared and analyzed the grade 3-4 toxic side effects of irinotecan-based combined chemotherapy and that of monotherapy. When the differences of the incidence of 9 items of common hematological and non-hematological complications after chemotherapy were compared, we found that bone marrow inhibition (reduction of neutrophils and anemia) was still the major toxic side effect of irinotecan-based second chemotherapy. Although the irinotecan-based combined arm had a tendency to have a greater incidence of adverse events than the irinotecan monotherapy, there was no significant difference between the two groups. In addition, treatment was generally well tolerated, and most of adverse events were manageable in both groups. It is worth noting that in this meta-analysis, there were only two chemotherapy-related deaths, which were patients in the irinotecan monotherapy group [16, 17]; in contrast, the irinotecan-based combined therapy group did not have any treatment-related deaths. The following two reasons may explain why the incidence of toxic side effects of chemotherapy was lower in this study: 1) adequate organ function and an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 were confirmed when the patients were enrolled in the study, and all patients had relatively strong tolerance to chemotherapy; and 2) the dose of the chemotherapy drug was properly reduced or the medication cycle was extended, and thus, a balance point between the efficacy and the toxic side effects of drugs was achieved. Therefore, during the selection of irinotecan-based combined second-line therapy, if the indication population is strictly selected and reasonable medication is applied, serious toxic side effects can be prevented.

After evaluation and analysis of the above results, we found that this present study still had a certain limitation. First, two of the eligible studies in our meta-analysis were not RCTs [15, 17]. This defect of the study quality had a certain effect on our analytic results; however, those studies did not influence the final results. Second, only five studies involving 532 AGC patients were included in this meta-analysis, and the relatively small sample size might not have had sufficient statistical power to detect a true association. Third, in this study, the chemotherapy drugs used in the irinotecan-based combined therapy were mainly 5-FU or CDDP, where as treatment using a combination of irinotecan with trastuzumab [29] and ramucirumab [30], which have been confirmed to be effective targeted drugs in the treatment of advanced gastric cancer, was not involved. Finally, because all of the studies included in this analysis were conducted in Asia, these conclusions need to be confirmed in additional high-quality RCTs and in Western studies.

Overall, our study shows that compared with irinotecan monotherapy, irinotecan-based combined chemotherapy is favorable for advanced gastric cancer patients after first-line chemotherapy failure, with an improved clinical benefit in term of PFS and DCR. In addition, there was no significant difference in the safety of these two chemotherapy regimens. Therefore, based on the results of this meta-analysis, we recommend irinotecan-based combined chemotherapy as the second-line thermotherapy regimen for advanced gastric cancer.

Acknowledgements

Projects of Science and Technology Commission of Shanghai Municipality (No. 15410723000).

Disclosure of conflict of interest

None.

Address correspondence to: Han-Kwang Yang, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehang-Ro, Jongno-Gu, Seoul 110-744, Korea. Tel: +82-2-2072-3797; Fax: +82-2-766-3975; E-mail: hkyangseoul@sina.com

References

[1] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, TeAo B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas J, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillman T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M.The Global Burden of Cancer 2013. JAMA Oncol 2015; 1: 505-527.

[2] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. Cancer J Clin 2012; 62: 10-29.

[3] Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29: 4387-4393.

[4] Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for esophagogastric cancer. N Engl J Med 2008; 358: 36-46.

[5] Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA; V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991-4997.

[6] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-221.

[7] Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer-a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011; 47: 2306-2314.

[8] Kang JH, Lee SI, Lim do H,Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012; 30: 1513-1518.

[9] Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA; COUGAR-02 Investigators. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15: 78-86.

[10] Kim HS, Kim HJ, Kim SY, Kim TY, Lee KW, Baek SK, Kim TY, Ryu MH, Nam BH, Zang DY. Second-line chemotherapy versus supportive cancer treatment in gastric cancer: a meta-analysis. Ann Oncol 2013; 24: 2850-2854.

[11] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. [updated September 2008]. The Cochrane Collaboration 2009.

[12] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in meta-analysis. http://wwwohrica/programs/clinical_epidemiology/oxfordasp Accessed 1 Nov 2013. 2003.

[13] Higuchi K, Tanabe S, Shimada K, Hosaka H, Sasaki E, Nakayama N, Takeda Y, Moriwaki T, Amagai K, Sekikawa T, Sakuyama T, Kanda T, Sasaki T, Azuma M, Takahashi F, Takeuchi M, Koizumi W; Tokyo Cooperative Oncology Group, Tokyo, Japan. Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for gastric cancer: A randomised phase III trial (TCOG GI-080/BIRIP trial). Eur J Cancer 2014; 50: 1437-1445.

[14] Nishikawa K, Fujitani K, Inagaki H, Akamaru Y, Tokunaga S, Takagi M, Tamura S, Sugimoto N, Shigematsu T, Yoshikawa T, Ishiguro T, Nakamura M, Morita S, Miyashita Y, Tsuburaya A, Sakamoto J, Tsujinaka T. Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with gastric cancer refractory to S-1 monotherapy: TRICS trial. Eur J Cancer 2015; 51: 808-816.

[15] Oba M, Chin K, Kawazoe Y, Takagi K, Ogura M, Shinozaki E, Suenaga M, Matsusaka S, Mizunuma N, Hatake K. Irinotecan monotherapy offers advantage over combination therapy with irinotecan plus cisplatin in second-line setting for treatment of gastric cancer following failure of fluoropyrimidine-based regimens. Oncol Lett 2011; 2: 241-245.

[16] Sym SJ, Hong J, Park J, Cho EK, Lee JH, Park YH, Lee WK, Chung M, Kim HS, Park SH, Shin DB. A randomized phase II study of biweekly irinotecanmonotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013; 71: 481-488.

[17] Ueda A, Hosokawa A, Ogawa K, Yoshita H, Mihara H, Ando T, Kajiura S, Fujinami H, Nishikawa J, Minemura M, Terada M, Kobayashi T, Horikawa N, Yabushita K, Note M, Sugiyama T. Non-randomized comparison between irinotecan plus mitomycin C and irinotecan alone in patients with gastric cancer refractory to fluoropyrimidine and platinum. Anticancer Res 2013; 33: 5107-5111.

[18] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-221.

[19] Goto A, Sukawa Y, Igarashi H, Onodera K, Aoki Y, Suzuki K, Yonezawa K, Yawata A, Kobayashi T, Kaneto H, Shimizu H, Wakasugi H, Matsunaga Y, Itoh M, Okuda H, Arimura Y, Shinomura Y. Irinotecan as the key chemotherapeutic agent in second-line treatment of metastatic gastric cancer after failure of first-line S-1 or S-1/CDDP therapy. Gan To Kagaku Ryoho 2011; 38: 1461-1466.

[20] Kanat O, Evrensel T, Manavoglu O, Demiray M, Kurt E, Gonullu G, Kiyici M, Arslan M. Single-agent irinotecan as secondline treatment for gastric cancer. Tumori 2003; 89: 405-407.

[21] Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, Yoshino M, Taguchi T, Ogawa N. Late phase II study of irinotecanhydrochloride (CPT-11) in gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho 1994; 21: 1033-1038.

[22] Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, Choi IJ, Ryu KW, Kim YW, Bae JM. Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol 2004; 34: 8-13.

[23] Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, Hill ME, Norman AR. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed oesophageal and gastric carcinoma. Ann Oncol 2004; 15: 64-69.

[24] Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Park YS, Im YH, Park K. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastriccancer. Br J Cancer 2005; 92: 1850-1854.

[25] Sym SJ, Ryu MH, Lee JL, Chang HM, Kim TW, Lee SS, Lee JS, Kang YK. Salvage chemotherapy with biweekly irinotecan, plus 5-fluorouracil and leucovorin in patients with gastric cancer previously treated with fluoropyrimidine, platinum, and taxane. Am J Clin Oncol 2008; 31: 151-156.

[26] Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, Charnsangavej C. Irinotecan/cisplatin in, treated gastric or gastroesophageal junction carcinoma. Oncology 2002; 16: 16-18.

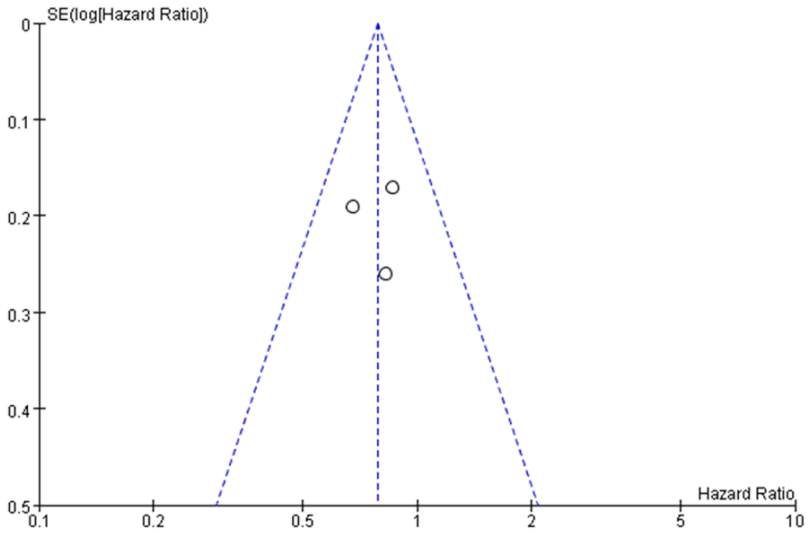
[27] Park SH, Choi EY, Bang SM, Cho EK, Lee JH, Shin DB, Ki Lee W, Chung M. Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes. Anticancer Drugs 2005; 16: 621-625.

[28] Liu L, Yu H, Huang L, Shao F, Bai J, Lou D, Chen F. Progression-free survival as a surrogate endpoint for overall survival in patients with third-line or later-line chemotherapy for gastric cancer. Onco Targets Ther 2015; 8: 921-928.

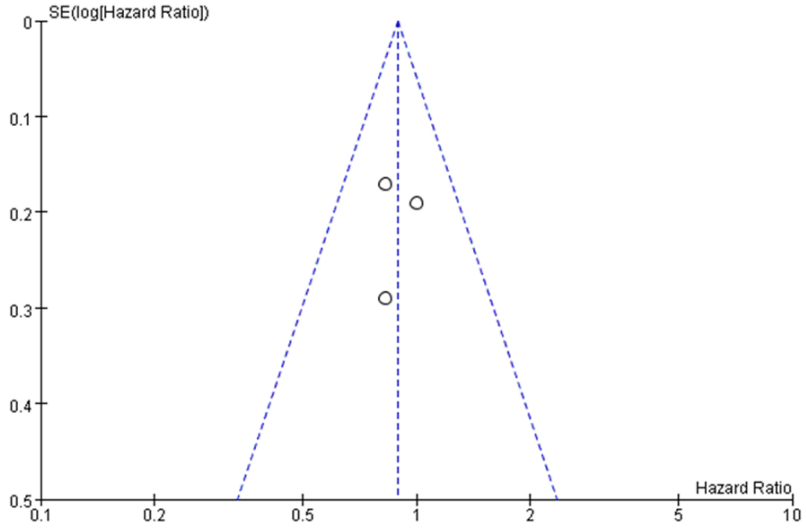
[29] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination

with chemotherapy versus chemotherapy alone for treatment of HER2-positive gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376: 687-697.

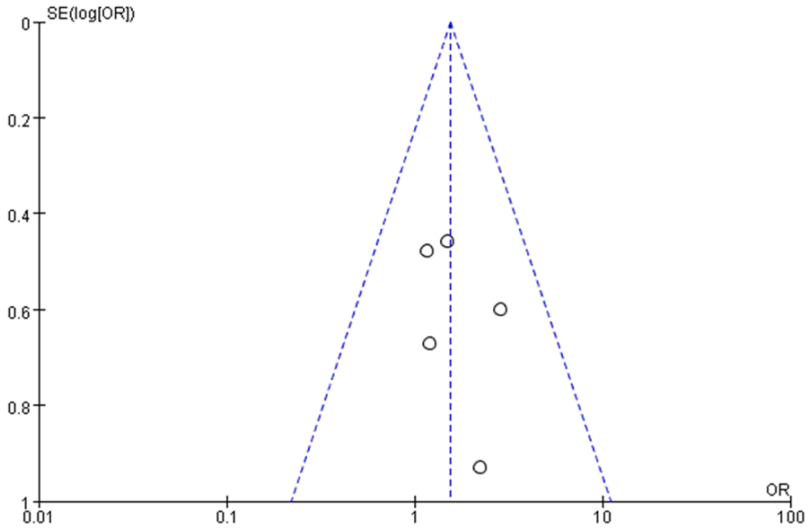
[30] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383: 31-39.



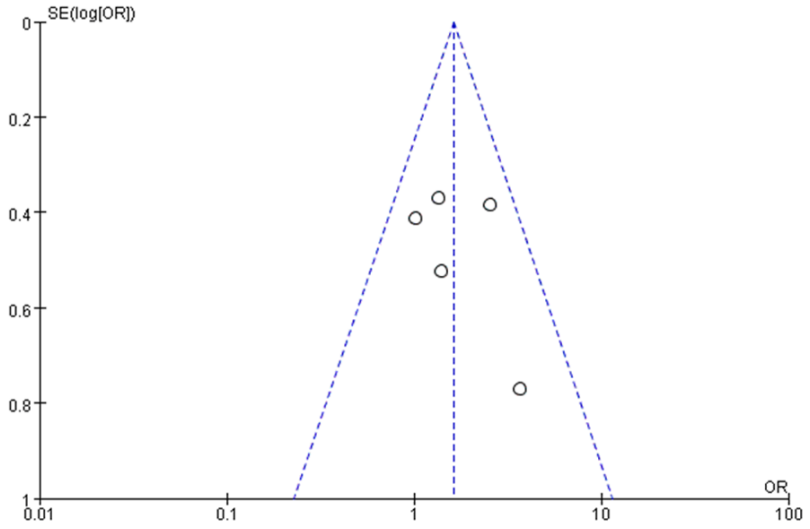
Supplementary Figure 1. Funnel plot for progressive free survival.



Supplementary Figure 2. Funnel plot for overall survival.



Supplementary Figure 3. Funnel plot for the overall response rate.



Supplementary Figure 4. Funnel plot for the disease control rate.