Int J Clin Exp Med 2017;10(1):467-478
www.ijcem.com /ISSN:1940-5901/IJCEM0025340

Original Article

Efficacy and safety of docetaxel, cisplatin and fluorouracil regimen compared with epirubicin, cisplatin and fluorouracil regimen for gastric carcinoma: a meta-analysis

Shuiyin Zhu[1*], Kaigang Xie[1*], Xiangcheng Qin[2], Xiaoping Teng[1], Hongcun Sha[1], Xiaoming Hong[1], Dongjie Wang[1]

[1]Department of General Surgery, Ningbo Yinzhou No. 2 Hospital, Ningbo 315100, China; [2]Department of Urology, Ningbo Yinzhou No. 2 Hospital, Ningbo 315100, China. [*]Equal contributors.

Received January 31, 2016; Accepted April 23, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Gastric cancer (GC) is currently the second leading cause of cancer deaths worldwide. By searching the PubMed, Embase and CNKI databases, we conducted a meta-analysis to determine the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma. Studies were pooled, and the relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated. Version 12.0 STATA software was used for statistical analysis. Nine relevant articles were included for this meta-analysis study. We observed that the partial response (PR) (RR=1.26, 95% CI 1.01 to 1.58) and the overall response rate (ORR) (RR=1.24, 95% CI 1.03 to 1.50) in gastric carcinoma patients treatment with DCF was significantly improved than that with ECF. There was no significant difference in the incidence of hemoglobin decline, neutropenia and thrombocytopenia, however, the incidence of leukocytopenia in GC patients treatment with DCF is significantly higher than that with ECF. And the incidence of peripheral neuritis in GC patients with DCF was significantly higher than that with ECF (RR=10.26, 95% CI: 3.94~26.76; P=0.506, I^2=0%). There was no significant difference in stomatitis, nausea-vomiting and diarrhea. In conclusion, this meta-analysis indicated that Docetaxel based treatment (DCF) showed better palliation and improvement of overall response rate (ORR) as compared with epirubicin based treatment (ECF). The chemotherapy-related toxicity of DCF regimen is acceptable to some extent. The current study, therefore, provides valuable information to help physicians make treatment decisions for their patients with GC.

Keywords: Gastric cancer, DCF regimen, ECF regimen, meta-analysis

Introduction

Gastric cancer (GC) is the fourth of the world rankings incidence of various types of cancer and is the second as a cause of cancer-related death [1]. It is also the second most frequent malignancy in China [2]. Radical gastrectomy is currently the only possible curative approach for gastric cancer, but recurrences are common, being detected in approximately 60% of patients [3]. More patients are diagnosed with late stage GC in China than in South Korea and Japan, with up to 60% of patients in stage III according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system [4, 5]. For these patients, systemic chemotherapy is the mainstay of treatment [6, 7].

Over the last decade, new chemotherapy regimens have been developed for the treatment of advanced gastric cancer, including epirubicin-cisplatin plus continuousinfusion fluorouracil (ECF) [8]. Compared with fluorouracil (FU)-doxorubicin-methotrexate in a phase III randomized trial, ECF yielded a superior overall response rate (ORR; 21% v 45%, respectively), superior median time to progression (TTP; 3.4 v 7.4 months, respectively), and better overall survival (OS; 5.7 v 8.9 months, respectively), leading the investigators to propose ECF as a standard therapy [9, 10]. More recently, agents belonging to the taxane, camptothecin, and platinum classes have been studied as systemic therapy for gastric cancer [11, 12]. In particular, docetaxel (60 to 100 mg/m^2) monotherapy

yielded response rates of 17% to 24% in phase II studies [13-15]. The chemotherapy regimen of docetaxel, cisplatin and 5-fluorouracil (DCF) has been used to treat the advanced stage or metastatic gastric carcinoma with encouraging survival outcomes [16, 17] and better quality of life [18, 19] in several studies. However, it was reported in some researches [20, 21] that more toxicity, such as hematotoxicity, happened in DCF than in other regimens. Therefore, evaluation of benefits against the chemotherapy-related toxicities was needed. Present meta-analysis was conducted to evaluate the efficacy and safety of DCF for gastric carcinoma, compared with those of ECF regimen.

Materials and methods

Search strategy

We are looking for relevant research to August 2015 with the following terms and their combinations through PubMed, EMBASE and China National Knowledge Infrastructure (CNKI) databases: "docetaxel", "epirubicin" and "gastric cancer". All scan summary, research, and references were reviewed. In addition, reference is also retrieved the manuscript is manually search for further relevant publications.

Selection criteria

Controlled clinical trials to assess the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma were included if they meet the following criteria: 1) eligibility is limited to randomized controlled trials (RCT) of GC; 2) study compared the efficacy and safety of DCF regimen for gastric carcinoma; 3) research report specific data related response rate (WHO Criteria) and decrease adverse events (AEs); 4) only ECF regimen randomized controlled trials may be included.

Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. The efficacy outcomes were: (1) complete response (CR); (2) partial response (PR); (3) overall response rate (ORR). The safety outcomes included: (1) Hemoglobin decline; (2) Leukocytopenia; (3) Neutropenia; (4) Thrombocytopenia; (5) Stomatitis; (6) Nausea-vomiting; (7) Diarrhea; (8) Peripheral neuritis.

Statistical analysis

All results summarized using STATA Software (version 12, StataCorp, College Station, TX). We calculated the risk ratio (RR) and 95% confidence intervals for dichotomous data. Preliminary analysis using a fixed effect model (Mantel-Haenszel method), if there are study heterogeneity (P<0.1), using a random effects model. By Begg's funnel plot and Egger's test to assess publication bias visually evaluated symmetry (P<0.05 was considered statistically significant).

Results

Characteristics of the studies

There were 171 papers relevant to the search words. Subsequently, 111 irrelevant articles were excluded. The remaining articles were systematically reviewed, and all 21 articles qualified for full-text reading. After full-text reading, 12 articles were deemed unsuitable and were therefore excluded, and 9 articles were identified to be included for qualitative analysis. Finally, 9 articles [22-30] including 9 studies were incorporated into the current meta-analysis (**Table 1**). The flow chart of selection of studies and reasons for exclusion is presented in **Figure 1**.

Quantitative synthesis

All 9 studies including 637 patients explored the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma.

Complete response (CR): This outcome was reported in eight trials, all comparing DCF to ECF. There were 551 cases of patients, 280 cases in DCF group, 271 cases in ECF group. The heterogeneity was not statistically significant (P=0.976, I^2=0%), the fixed effect model was used. The difference in the complete response was not significant (RR=1.44, 95% CI 0.70 to 2.98), as shown in **Figure 2A**.

Partial response (PR): This outcome was reported in eight trials, all comparing DCF to ECF.

Table 1. Characteristics of randomised controlled trials included in this meta-analysis

Authors/year of publication	Demographic data	Intervention & control	Efficacy	Safety
Sadighi/2006 [22]	86 patients with primary or recurrent gastric cancer (III-IV stage).	DCF: docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2. 21 days for a cycle ECF: epirubicin 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2. 21 days for a cycle	ORR	Fatigue, Nausea and vomiting, Diarrhoea, etc.
Roth/2007 [23]	121 patients with unresectable gastric cancer, metastatic or locally carcinoma.	DCF: docetaxel 85 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 300 mg/m^2. 21 days for a cycle ECF: epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 200 mg/m^2. 21 days for a cycle	CR, PR, ORR	Neutropenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.
Li/2008 [24]	104 patients with primary or recurrent gastric cancer (III-IV stage).	DCF: docetaxel 75 mg/m^2, cisplatin 20 mg/m^2 and 5-FU 500 mg/m^2. 21 days for a cycle ECF: epirubicin 35 mg/m^2, cisplatin 40 mg/m^2 and 5-FU 425 mg/m^2. 7 days for a cycle	CR, PR, ORR	Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.
Lu/2008 [25]	54 patients with primary gastric cancer.	DCF: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 500 mg/m^2. 21 days for a cycle ECF: epirubicin 60 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 500 mg/m^2. 21 days for a cycle	CR, PR, ORR	Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.
Gao/2010 [26]	64 patients with stage IIIB-IV gastric carcinoma.	DCF: docetaxel 60 mg/m^2, cisplatin 25 mg/m^2, 5-FU 1000 mg/m^2. 21 days for a cycle ECF: epirubicin 50 mg/m^2, cisplatin 25 mg/m^2, 5-FU 1000 mg/m^2. 21 days for a cycle	CR, PR, ORR	Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.
Liang/2010 [27]	58 patients in DCF arm and control arm with advanced gastric cancer.	DCF: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 300 mg/m^2. 21 days for a cycle ECF: epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, 5-FU 200 mg/m^2. 21 days for a cycle	CR, PR, ORR	Nausea/vomiting, Diarrhoea, etc.
Yang/2011 [28]	56 patients with stage III-IV gastric carcinoma.	DCF: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 2.4 g/m^2. 21 days for a cycle ECF: epirubicin 50 mg/m^2, cisplatin 25 mg/m^2, 5-FU 2.4 g/m^2. 21 days for a cycle	CR, PR, ORR	Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.
Liu/2013 [29]	62 patients with advanced gastric carcinoma.	DCF: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 300 mg/m^2. 21 days for a cycle ECF: epirubicin 60 mg/m^2, cisplatin 75 mg/m^2, 5-FU 300 mg/m^2. 21 days for a cycle	CR, PR, ORR	Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.
Teker/2014 [30]	86 patients with gastric carcinoma.	DCF: docetaxel 50-75 mg/m^2, cisplatin 50-75 mg/m^2 and 5-FU 500-750 mg/m^2. 21 days for a cycle ECF: epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, 5-FU 200 mg/m^2. 21 days for a cycle	CR, PR, ORR	Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.

DCF: docetaxel, cisplatin and fluorouracil; ECF: epirubicin, cisplatin and fluorouracil; CR: complete response; PR: partial response; ORR: overall response rate.

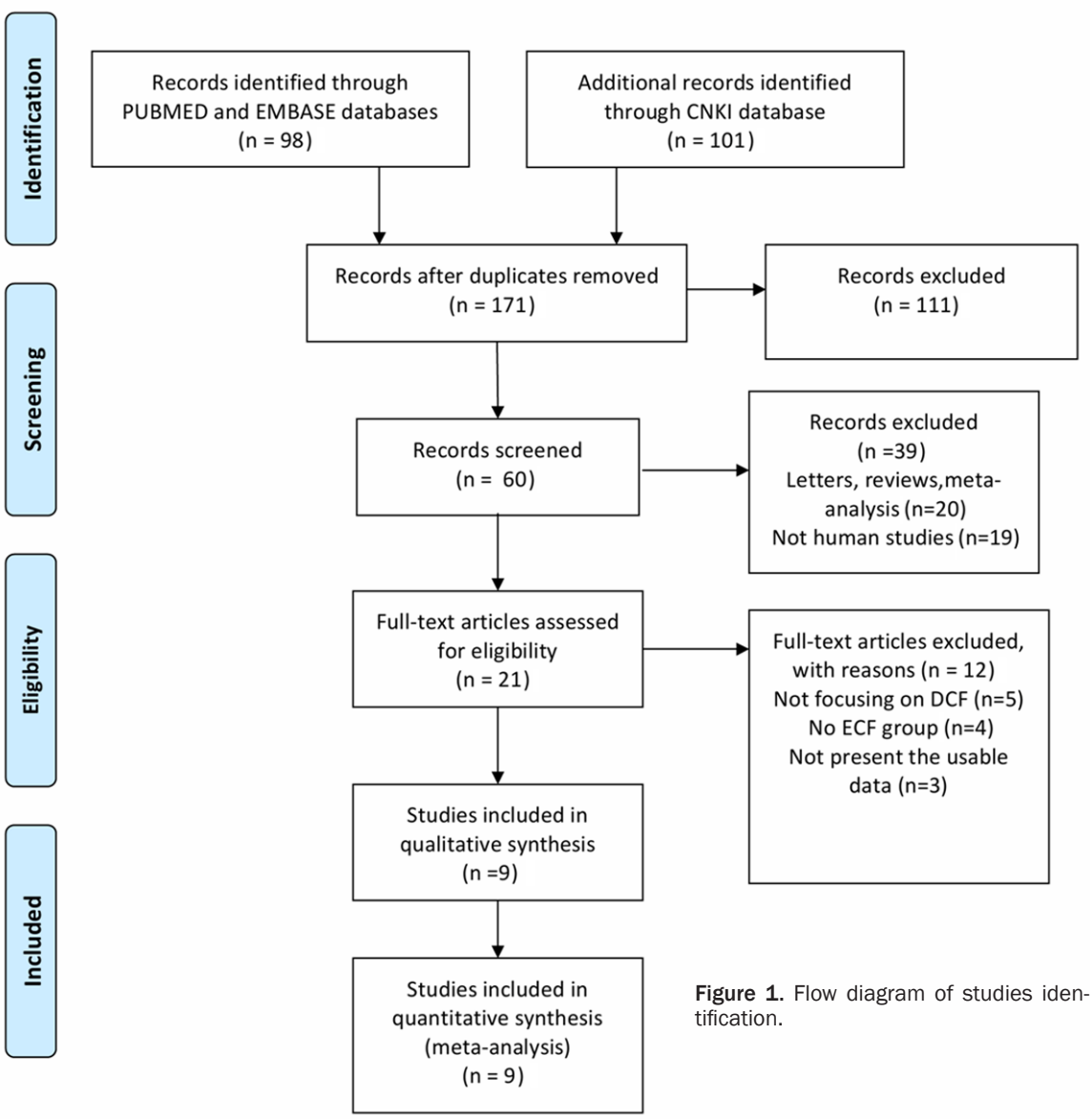

Figure 1. Flow diagram of studies identification.

There were 551 cases of patients, 280 cases in DCF group, 271 cases in ECF group, the heterogeneity was not statistically significant, the fixed effect model was used (P=0.883, I^2=0%). The difference in the partial response was significant (RR=1.26, 95% CI 1.01 to 1.58), as shown in **Figure 2B**.

Overall response rate (ORR): This outcome was reported in nine trials, all comparing DCF to ECF. There were 637 cases of patients, 324 cases in DCF group, 313 cases in ECF group, the heterogeneity was not statistically significant, the fixed effect model was used (P=0.779, I^2=0%). The difference in the overall response rate was significant (RR=1.24, 95% CI 1.03 to 1.50), as shown in **Figure 2C**.

Hemoglobin decline: This outcome was reported in four trials, all comparing DCF to ECF. A total of 227 patients were enrolled, 115 patients in the DCF group, 112 cases in the ECF group, there was no heterogeneity between the study (P=0.666, I^2=0%), the fixed effect model was used. There was no significant difference in the incidence of hemoglobin decline (RR=1.10, 95% CI: 0.91~1.35), as shown in **Figure 3A**.

Leukocytopenia: This outcome was reported in six trials, all comparing DCF to ECF. A total of 412 patients were enrolled, 209 patients in the DCF group, 203 cases in the ECF group, there was no heterogeneity between the study (P= 0.282, I^2=20.1%), the fixed effect model was

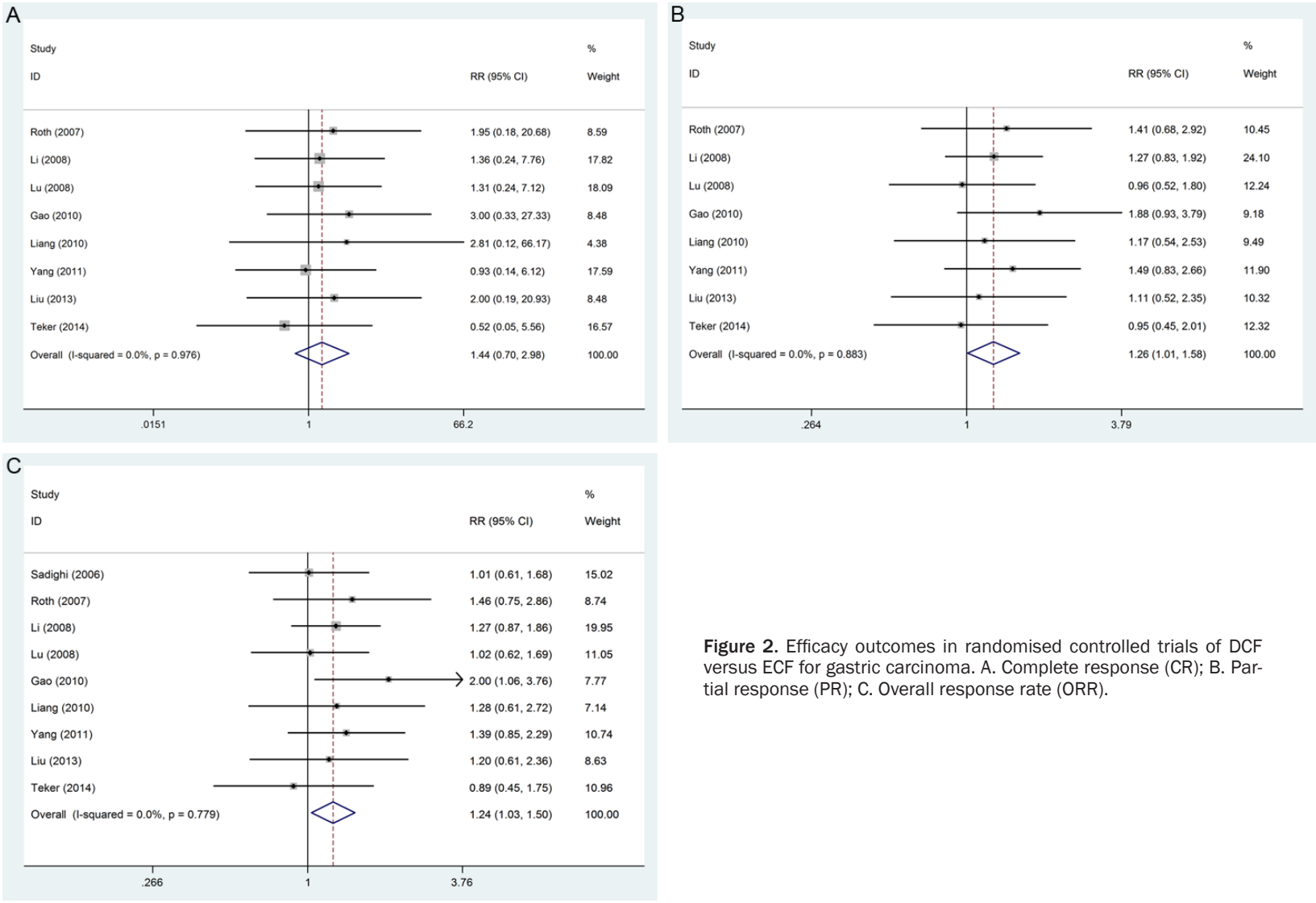

Figure 2. Efficacy outcomes in randomised controlled trials of DCF versus ECF for gastric carcinoma. A. Complete response (CR); B. Partial response (PR); C. Overall response rate (ORR).

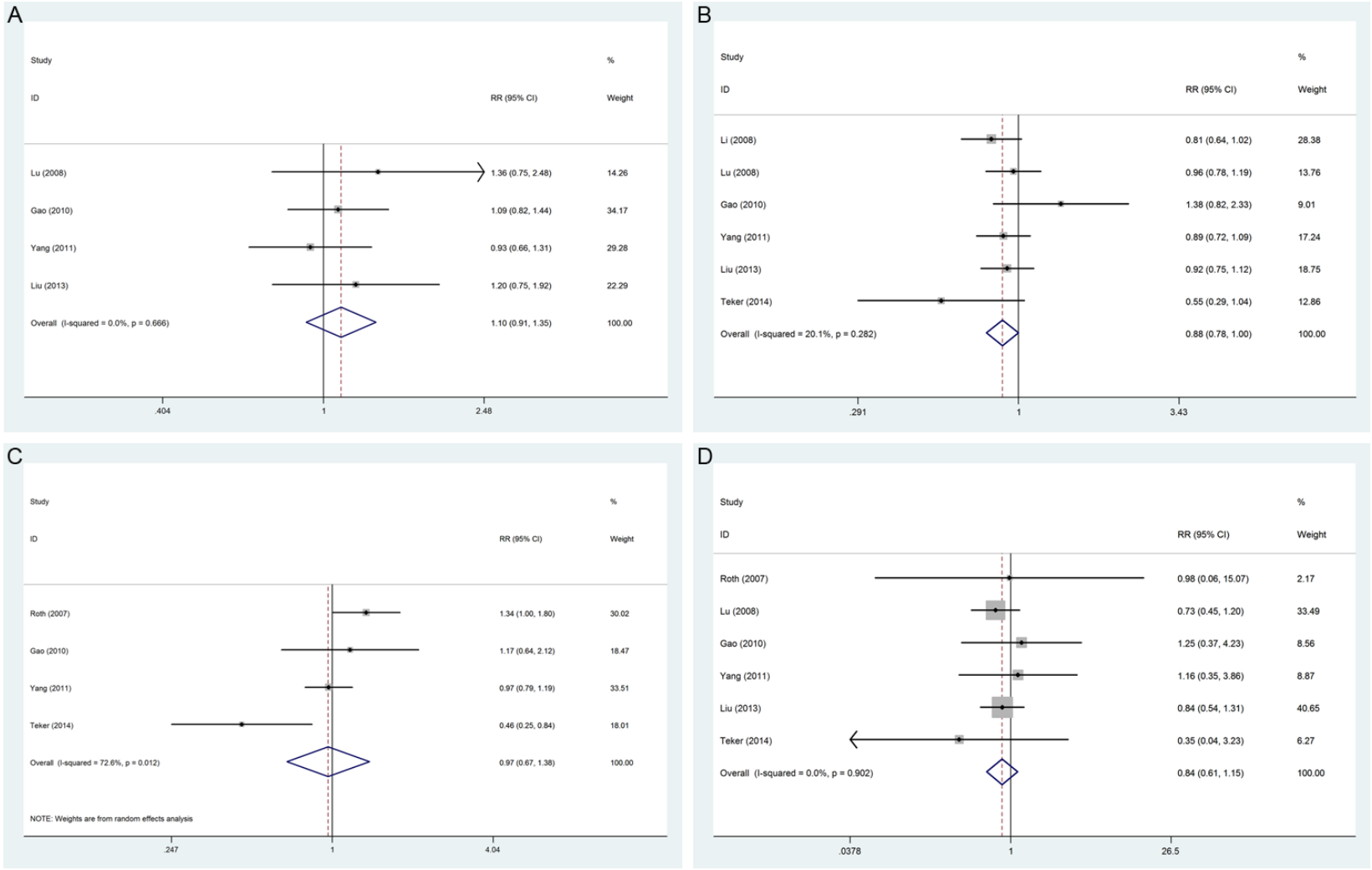

Figure 3. Hematologic toxicity of treatment in randomised controlled trials of DCF versus ECF for gastric carcinoma. A. Hemoglobin decline; B. Leukocytopenia; C. Neutropenia; D. Thrombocytopenia.

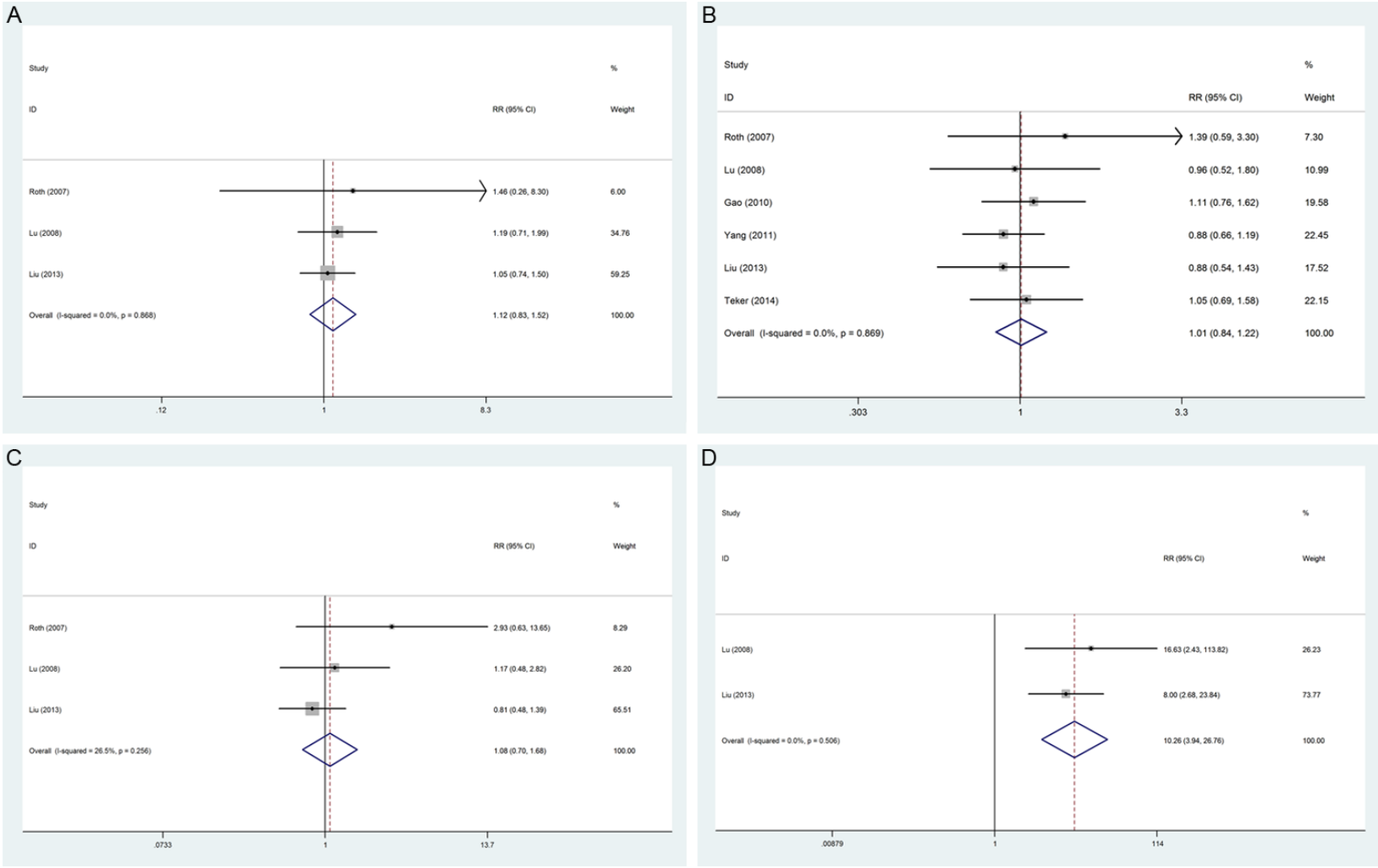

Figure 4. Nonhematologic toxicity of treatment in randomised controlled trials of DCF versus ECF for gastric carcinoma. A. Stomatitis; B. Nausea-vomiting; C. Diarrhea; D. Peripheral neuritis.

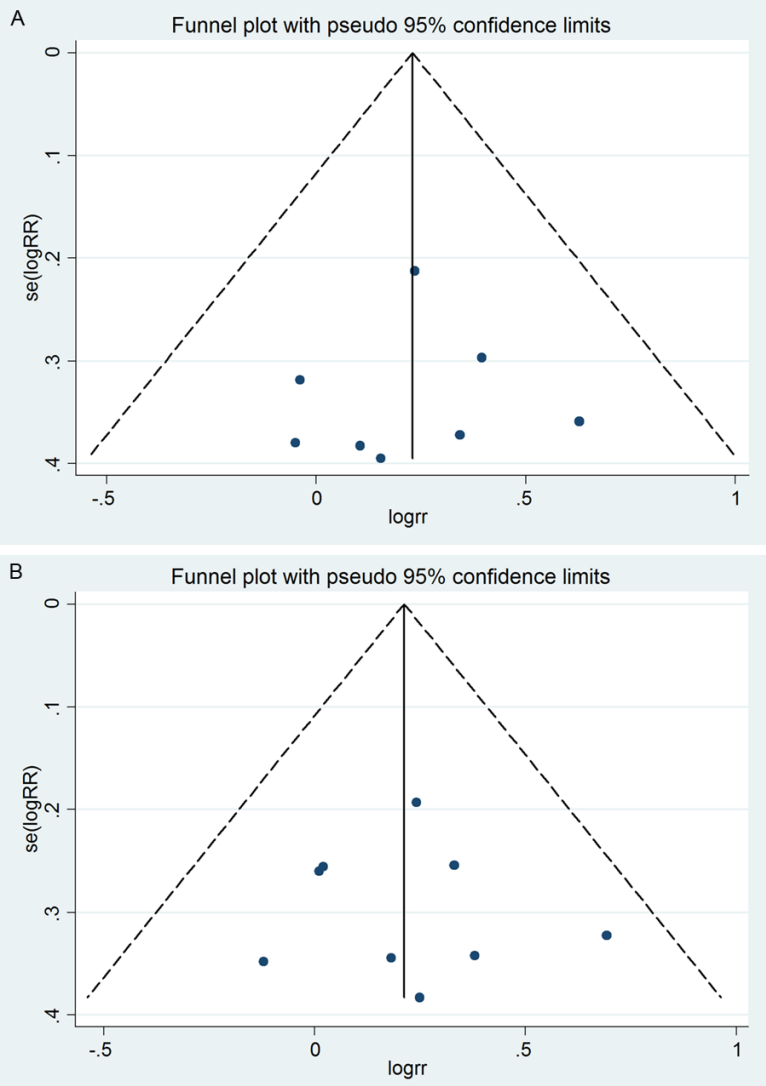

Figure 5. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Incidence of partial response (PR); B. Incidence of overall response rate (ORR).

used. There was significant difference in the incidence of leukocytopenia (RR=0.88, 95% CI: 0.78~1.00), as shown in **Figure 3B**.

Neutropenia: This outcome was reported in four trials, all comparing DCF to ECF. A total of 287 patients were enrolled, 143 patients in the DCF group, 144 cases in the ECF group, there was significant heterogeneity between the study (P=0.012, I^2=72.6%), the random effect model was used. However, there was no significant difference in the incidence of neutropenia (RR=0.97, 95% CI: 0.67~1.38), as shown in **Figure 3C**.

Thrombocytopenia: This outcome was reported in six trials, all comparing DCF to ECF. A total of 393 patients were enrolled, 197 patients in the DCF group, 196 cases in the ECF group, there was no heterogeneity between the study (P=0.902, I^2=0%), the fixed effect model was used. However, there was no significant difference in the incidence of thrombocytopenia (RR=0.84, 95% CI: 0.61~1.15), as shown in **Figure 3D**.

Stomatitis: This outcome was reported in three trials, all comparing DCF to ECF. A total of 188 patients were enrolled, 96 patients in the DCF group, 92 cases in the ECF group, there was no heterogeneity between the study (P=0.868, I^2=0%), the fixed effect model was used. However, there was no significant difference in the incidence of stomatitis (RR=1.12, 95% CI: 0.83~1.52), as shown in **Figure 4A**.

Nausea-vomiting: This outcome was reported in six trials, all comparing DCF to ECF. A total of 393 patients were enrolled, 197 patients in the DCF group, 196 cases in the ECF group, the heterogeneity was not statistically significant, the fixed effect model was used (P=0.869, I^2=0%). But there was no significant difference in the incidence of nausea-vomiting (RR=1.01, 95% CI: 0.84~1.22), see **Figure 4B**.

Diarrhoea: This outcome was reported in three trials, all comparing DCF to ECF. There were 188 cases of patients, 96 cases in DCF group, 92 cases in ECF group, the heterogeneity was not statistically significant, the fixed effect model was used (P=0.256, I^2=26.5%). But there was no significant difference in the incidence of diarrhoea (RR=1.08, 95% CI: 0.70~1.68), as shown in **Figure 4C**.

Peripheral neuritis: This outcome was reported in two trials, all comparing DCF to ECF. There were 107 cases of patients, 55 cases in DCF group, 52 cases in ECF group, the heterogene-

ity was not statistically significant, the fixed effect model was used (P=0.506, I^2=0%). But the difference in the incidence of peripheral neuritis was significant (RR=10.26, 95% CI: 3.94~26.76), as shown in **Figure 4D**.

Publication bias

Finally, the Egger's regression test showed no evidence of asymmetrical distribution in the funnel plot in the partial response (Begg's test P=0.711; Egger's test P=0.836) and overall response rate (Begg's test P=0.602; Egger's test P=0.826) (**Figure 5**).

Discussion

Gastric cancer is a significant health problem worldwide, with approximately 930,000 new cases diagnosed and 700,000 deaths attributed to the disease each year [31]. Surgical resection is the mainstay of curative treatment, but it can be performed in a small subgroup of patients: only 30-50% of patients undergoing surgical exploration can be operated with curative intent, with 5-year survival rates of about 60% and 34% for stage I and stage II disease, respectively [32]. Clinical trials of neoadjuvant and adjuvant therapy have been conducted to improve these results. New cytotoxic agents have been evaluated in large phase III trials in metastatic setting, showing interesting results [33, 34].

Advanced gastric cancer is considered to be that diagnosed as non-resectable disease, either because it is locally advanced (30% of the cases at diagnosis) or that presenting as metastatic disease (another 30%). Also included in this definition are cases of relapse after surgery (60% of the resected). Thus, overall, approximately 84% of patients with gastric cancer will have advanced disease and median survival of these patients without chemotherapy is only 3-4 months [35, 36]. "Classical" chemotherapy regimens, mainly CF (cisplatin plus infusional 5 FU) and ECF (cisplatin plus infusional 5 FU plus Epirubicin) obtain responses in 20-40% of the patients and improve quality of life. Nevertheless, duration of these responses is short with very few complete responses. Median time to tumor progression (TTP) with these regimens is only about 4-5 months and median survival does not exceed 7-10 months [37, 38]. The V-325 study demonstrated that adding docetaxel (D) to a frequently used regimen of cisplatin and 5-fluorouracil (CF) provided benefits with regard to overall survival, response rate, time-to-disease progression, clinical benefit, and health-related quality of life [39]. Although the DCF regimen provides these advantages, it is accompanied by an increase in toxicity compared with the doublet regimen. The toxicity profile of DCF is acceptable only with appropriately selected patients and comprehensive toxicity management strategies. The objective of the current meta-analysis was to explore the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma.

In this study, we conducted a meta-analysis to determine the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma. Nine relevant studies including 637 patients were included for this meta-analysis study. We observed that the partial response (PR) (RR=1.26, 95% CI 1.01 to 1.58) and the overall response rate (ORR) (RR=1.24, 95% CI 1.03 to 1.50) in gastric carcinoma patients treatment with DCF was significantly improved than that with ECF. There was no significant difference in the incidence of hemoglobin decline, neutropenia and thrombocytopenia, however, the incidence of leukocytopenia in GC patients treatment with DCF is significantly higher than that with ECF. And the incidence of peripheral neuritis in GC patients with DCF was significantly higher than that with ECF (RR=10.26, 95% CI: 3.94~26.76; P=0.506, I^2=0%). There was no significant difference in stomatitis, nausea-vomiting and diarrhea. The current study, therefore, provides valuable information to help physicians make treatment decisions for their patients with GC.

A number of limitations in this meta-analysis should be addressed. First, our analysis was limited by its use of summary data rather than data from the individual patients from each trial. Individual patient data are needed to better account for the control arm, to standardize the analysis to perform an intent-to-treat analysis, to perform a more complete analysis of the variation of treatment effects according to patient. Secondly, in this study, there is potential for publication bias, because we do not

take some unpublished papers and abstracts, and consider their data are not available to us. A third of a potential limitation is that language can also introduce a bias. Specifically, we select only the English and Chinese languages, the exclusion of other qualified researchers. Despite these limitations, this is the first example of a meta-analysis on the efficacy and safety of docetaxel, cisplatin and fluorouracil (DCF) regimen compared with epirubicin, cisplatin and fluorouracil (ECF) regimen for gastric carcinoma. Application of statistical methods to the results of several studies with our meta-analysis, and to achieve strong objectivity, all the research methods were strict inclusion and exclusion criteria, to demonstrate the effectiveness and significance of our conclusions.

In conclusion, this meta-analysis indicated that Docetaxel based treatment (DCF) showed better palliation and improvement of overall response rate (ORR) as compared with epirubicin based treatment (ECF). The chemotherapy-related toxicity of DCF regimen is acceptable to some extent. Further studies with larger data set and well-designed models are required to validate our findings.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Dongjie Wang, Department of General Surgery, Ningbo Yinzhou No. 2 Hospital, 1 Qianhe Road, Yinzhou, Ningbo 315100, China. Tel: +86-574-83039999; Fax: +86-574-83039999; E-mail: djwang_med@163.com

References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.

[2] Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999; 49: 33-64.

[3] Buzzoni R, Bajetta E, Di Bartolomeo M, Miceli R, Beretta E, Ferrario E, Mariani L. Pathological features as predictors of recurrence after radical resection of gastric cancer. Br J Surg 2006; 93: 205-209.

[4] Shan F, Li Z, Bu Z, Zhang L, Wu A, Wu X. [The analysis of gastric cancer staging AJCC]. Zhongguo Shiyong Waike Zazhi 2011; 8: 675-680.

[5] Shen D, Ni X, He C, Cao H, Shen Y. [Comparison of value for predicting prognosis between 6th and 7th editions of TNM staging system in gastric cancer patients]. Zhonghua Xiaohua Zazhi 2012; 9: 536-539.

[6] Field K, Michael M, Leong T. Locally advanced and metastatic gastric cancer: current management and new treatment developments. Drugs 2008; 68: 299-317.

[7] Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; CD004064.

[8] Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, Nicolson V, Nash A, Sacks N, Ford H, Carter R, Hill A. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994; 5: 609-616.

[9] Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15: 261-267.

[10] Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, Joffe JK, Mackean M, Mansi J, Leahy M, Hill A, Oates J, Rao S, Nicolson M, Hickish T. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: Results of a randomized trial. Br J Cancer 1999; 80: 269-272.

[11] Louvet C, André T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, François E, Jacob JH, Levoir D, Taamma A, Rougier P, Cvitkovic E, de Gramont A. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002; 20: 4543-4548.

[12] Schoffski P. New drugs for treatment of gastric cancer. Ann Oncol 2002; 13 Suppl 4: 13-22.

[13] Einzig AI, Neuberg D, Remick SC, Karp DD, O'Dwyer PJ, Stewart JA, Benson AB 3rd. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: The Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol 1996; 13: 87-93.

[14] Sulkes A, Smyth J, Sessa C, Dirix LY, Vermorken JB, Kaye S, Wanders J, Franklin H, LeBail N, Verweij J. Docetaxel (Taxotere) in advanced gastric cancer: Results of a phase II clinical trial-EORTC Early Clinical Trials Group. Br J Cancer 1994; 70: 380-383.

[15] Taguchi T. An early phase II clinical study of RP56976 (docetaxel) in patients with cancer of

the gastrointestinal tract. Gan To Kagaku Ryoho 1994; 21: 2431-2437.
[16] Lorenzen S, Hentrich M, Haberl C, Heinemann V, Schuster T, Seroneit T, Roethling N, Peschel C, Lordick F. Splitdose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol 2007; 18: 1673-1679.
[17] Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Marabotti C, Van Cutsem E; V-325 Study Group. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25: 3205-3209.
[18] Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Awad L, Van Cutsem E; V-325 Study Group. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25: 3210-3216.
[19] Sadighi S, Mohagheghi MA, Montazeri A, Sadighi Z. Quality of life in patients with advanced gastric cancer: a randomized trial comparing docetaxel, cisplatin, 5-FU (TCF) with epirubicin, cisplatin, 5-FU (ECF). BMC Cancer 2006; 6: 274-279.
[20] Li CP, Chen JS, Chen LT, Yen CJ, Lee KD, Su WP, Lin PC, Lu CH, Tsai HJ, Chao Y. A phase II study of weekly docetaxel and cisplatin plus oral tegafur/uracil and leucovorin as firstline chemotherapy in patients with locally advanced or metastatic gastric cancer. Br J Cancer 2010; 103: 1343-1348.
[21] Van Cutsem E. The treatment of advanced gastric cancer: new findings on the activity of the taxanes. Oncologist 2004; 9 Suppl 2: 9-15.
[22] Sadighi S, Mohagheghi MA, Montazeri A, Sadighi Z. Quality of life in patients with advanced gastric cancer: a randomized trial comparing docetaxel, cisplatin, 5-FU (TCF) with epirubicin, cisplatin, 5-FU (ECF). Bmc Cancer 2006; 6: 1-6.
[23] Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, Köberle D, Borner MM, Rufibach K, Maibach R, Wernli M, Leslie M, Glynne-Jones R, Widmer L, Seymour M, de Braud F; Swiss Group for Clinical Cancer Research. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007; 25: 3217-3223.
[24] Li W, Ji DL, Lin HM. [Effects of docetaxel, cisplatin fluorouracil and calcium folinate in treatment of patients with advanced stomach cancer]. Zhong Liu Fang Zhi Yan Jiu 2008; 35: 590-592.
[25] Lu WK, Cai J, Ma D, Yang W, Yu LJ, Zhang Z. [A comparison between ECF and DCF therapeutic regimen in the treatment of advanced gastric carcinoma]. Qi Lu Yi Xue Za Zhi 2008; 23: 384-388.
[26] Gao H, Ding X, Wei D, Xu T, Cheng P, Zhang T. [Docetaxel versus epirubicin combined with cisplatin, leucovorin and fluorouracil for advanced gastric carcinoma as first line therapy: a randomized trial]. Lin Chuang Zhong Liu Xue Za Zhi 2010; 15: 529-533.
[27] Liang B, Han N, Yang JM. [Clinical study of comparative efficacy of DCF regimen vs. ECF regimen in treating advanced gastric cancer]. Zhongguo Zhong Liu Lin Chuang Yu Kang Fu 2010; 17: 59-61.
[28] Yang Y, Xu Y, Li YF, DO Oncology. [Clinical study in the first-line chemotherapy for advanced gastric cancer by DCF program]. Zhongguo Zhong Liu Wai Ke Za Zhi 2011; 3: 294-301.
[29] Liu J. [A clinical study of DCF scheme and ECF scheme in the treatment of advanced gastric cancer]. Zhongguo Yi Shi Jin Xiu Za Zhi 2013; 36: 17-19.
[30] Teker F, Yilmaz B, Kemal Y, Kut E, Yucel I. Efficacy and safety of docetaxel or epirubicin, combined with cisplatin and fluorouracil (DCF and ECF), regimens as first line chemotherapy for advanced gastric cancer: a retrospective analysis from Turkey. Asian Pac J Cancer Prev 2014; 15: 6727-32.
[31] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across 5 continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24: 2137-2150.
[32] Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999; 49: 33-64.
[33] Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastriccancer. Cochrane Database Syst Rev 2010; CD004064.
[34] Wagner AD, Moehler M. Development of targeted therapies in advanced gastric cancer: promising exploratory steps in a new era. Curr Opin Oncol 2009; 21: 381-385.
[35] Rivera F, Vega ME. Chemotherapy of advanced gastric cancer. Cancer Treatment Reviews 2007; 33: 315-324.
[36] Morabito A, Carillio G, Longo R. Systemic treatment of gastric cancer. Crit Rev Oncol Hematol 2009; 70: 216-34.

[37] Ajani JA. Chemotherapy for advanced gastric or gastroesophageal cancer: defining the contributions of docetaxel. Expert Opin Pharmacother 2006; 7: 1627-1631.
[38] Nishiyama M, Wada S. Docetaxel: its role in current and future treatments for advanced gastric cancer. Gastric Cancer 2009; 12: 132-141.
[39] Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, Majlis A, Assadourian S, Van Cutsem E. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fl uorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005; 23: 5660-5667.