Original Article

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

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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, I2=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 continuous infusion 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/m²) monotherapy...
Efficacy and safety of DCF with ECF 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”. Allscan 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, I²=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

<table>
<thead>
<tr>
<th>Authors/year of publication</th>
<th>Demographic data</th>
<th>Intervention &amp; control</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
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<tbody>
<tr>
<td>Sadighi/2006 [22]</td>
<td>86 patients with primary or recurrent gastric cancer (III-IV stage).</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 60 mg/m² and 5-FU 750 mg/m². 21 days for a cycle ECF: epirubicin 60 mg/m², cisplatin 60 mg/m² and 5-FU 750 mg/m². 21 days for a cycle</td>
<td>ORR</td>
<td>Fatigue, Nausea and vomiting, Diarrhoea, etc.</td>
</tr>
<tr>
<td>Roth/2007 [23]</td>
<td>121 patients with unresectable gastric cancer, metastatic or locally carcinoma.</td>
<td>DCF: docetaxel 85 mg/m², cisplatin 75 mg/m² and 5-FU 300 mg/m². 21 days for a cycle ECF: epirubicin 60 mg/m², cisplatin 60 mg/m² and 5-FU 200 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Neutropenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.</td>
</tr>
<tr>
<td>Li/2008 [24]</td>
<td>104 patients with primary or recurrent gastric cancer (III-IV stage).</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 60 mg/m² and 5-FU 750 mg/m². 21 days for a cycle ECF: epirubicin 35 mg/m², cisplatin 40 mg/m² and 5-FU 425 mg/m². 7 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.</td>
</tr>
<tr>
<td>Lu/2008 [25]</td>
<td>54 patients with primary gastric cancer.</td>
<td>DCF: docetaxel 75 mg/m², cisplatin 75 mg/m² and 5-FU 500 mg/m². 21 days for a cycle ECF: epirubicin 60 mg/m², cisplatin 75 mg/m² and 5-FU 500 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.</td>
</tr>
<tr>
<td>Gao/2010 [26]</td>
<td>64 patients with stage IIIb-IV gastric carcinoma.</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 25 mg/m², 5-FU 1000 mg/m². 21 days for a cycle ECF: epirubicin 50 mg/m², cisplatin 25 mg/m², 5-FU 1000 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.</td>
</tr>
<tr>
<td>Liang/2010 [27]</td>
<td>58 patients in DCF arm and control arm with advanced gastric cancer.</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 60 mg/m² and 5-FU 300 mg/m². 21 days for a cycle ECF: epirubicin 50 mg/m², cisplatin 60 mg/m², 5-FU 200 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Nausea/vomiting, Diarrhoea, etc.</td>
</tr>
<tr>
<td>Yang/2011 [28]</td>
<td>56 patients with stage III-IV gastric carcinoma.</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 60 mg/m² and 5-FU 300 mg/m². 21 days for a cycle ECF: epirubicin 50 mg/m², cisplatin 25 mg/m², 5-FU 2.4 g/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.</td>
</tr>
<tr>
<td>Liu/2013 [29]</td>
<td>62 patients with advanced gastric carcinoma.</td>
<td>DCF: docetaxel 60 mg/m², cisplatin 75 mg/m² and 5-FU 300 mg/m². 21 days for a cycle ECF: epirubicin 60 mg/m², cisplatin 75 mg/m² and 5-FU 500 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Hemoglobin decline, Leukocytopenia, Thrombocytopenia, Nausea/vomiting, etc.</td>
</tr>
<tr>
<td>Teker/2014 [30]</td>
<td>86 patients with gastric carcinoma.</td>
<td>DCF: docetaxel 50-75 mg/m², cisplatin 50-75 mg/m² and 5-FU 500-750 mg/m². 21 days for a cycle ECF: epirubicin 50 mg/m², cisplatin 60 mg/m², 5-FU 200 mg/m². 21 days for a cycle</td>
<td>CR, PR, ORR</td>
<td>Leukocytopenia, Thrombocytopenia, Nausea/vomiting, Diarrhoea, etc.</td>
</tr>
</tbody>
</table>

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

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
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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.
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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. 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
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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.

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