Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis


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Background: Many patients with refractory or relapsed gastric cancer after first-line chemotherapy have received salvage chemotherapy in routine clinical practice. However, there was no evidence to support this treatment until recent phase III trials demonstrated substantial prolongation of overall survival. Therefore, we conducted a meta-analysis of these trials and investigated whether second-line chemotherapy was more effective than best supportive care.

Patients and methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2013), MEDLINE (1950 to March week 4, 2013) and EMBASE (1980–2013, week 13). In addition, we searched all abstracts and virtual meeting presentations from the American Society of Clinical Oncology (ASCO) conferences held between 2004 and 2013.

Results: The search process yielded 578 studies, two of which were randomized phase III trials that compared chemotherapy with supportive care. From the abstracts and virtual meeting presentations of ASCO held between 2004 and 2013, 127 articles were identified that evaluated second-line chemotherapy; only one relevant abstract was included in the meta-analysis. A total of 410 patients were eligible for analysis, of whom 150 received docetaxel chemotherapy, and 81 received irinotecan chemotherapy. A significant reduction in the risk of death [HR = 0.64, 95% confidence interval (CI) 0.52–0.79, P < 0.0001] was observed with salvage chemotherapy. When the analysis was restricted to irinotecan or docetaxel, there was still significant reduction in the risk of death with each chemotherapeutic agent. The HR was 0.55 (95% CI 0.40–0.77, P = 0.0004) for irinotecan and 0.71 (95% CI 0.56–0.90, P = 0.004) for docetaxel.

Conclusion: This meta-analysis demonstrated evidence to support second-line chemotherapy in advanced gastric cancer.

Key words: advanced gastric cancer, second-line chemotherapy, best supportive care, meta-analysis

introduction

Gastric cancer is the fourth most frequent malignant disease and the second most common cause of cancer-related death in the world [1]; it is also the second most frequent malignancy in Korea [2]. Although patients with early gastric cancer can be cured by surgical resection with perioperative or adjuvant chemotherapy, a large majority of patients experience a relapse after initial surgery or are diagnosed with unresectable, locally advanced or metastatic disease. Systemic chemotherapy with combination of fluoropyrimidine and platinum is now regarded as the standard treatment of these patients [3]. However, the efficacy of first-line treatment is modest, and most patients are nonresponders or eventually experience disease progression.

Even though patients with refractory gastric cancer have received salvage chemotherapy in routine clinical practice, especially in Asia, there was no evidence to support salvage chemotherapy until recent phase III trials demonstrated substantial prolongation of overall survival. Results of three randomized, controlled trials (RCT) were published as articles [4, 5] or abstract [6] and showed overall survival benefit from treatments with irinotecan or docetaxel compared with best supportive care (BSC) alone in patients for whom one or two prior treatments failed. We conducted a meta-analysis of these trials and investigated whether second-line chemotherapy was more effective than BSC.

methods

search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2013), MEDLINE (1950 to March week 4, 2013) and EMBASE (1980–2013, week 13) for articles that included the following search terms in their titles, abstracts, or keyword lists: ‘gastric or gastroesophageal or...
gastroesophageus or esophago gastric or stomach’, ‘cancer or neoplasm or carcinoma or malignant or malignancy’, ‘second-line or salvage or supportive care’, ‘chemotherapy or chemotherapeutic or antineoplastic agent’, and ‘randomized or randomized, controlled trial or randomised’. In addition, we searched the reference lists of relevant articles/reviews and used the ‘related articles’ feature in PubMed to identify additional articles. We searched all abstracts and virtual meeting presentations from the American Society of Clinical Oncology (ASCO) conferences held between 2004 and 2013 and sought expert opinion to identify relevant but unpublished studies.

We assessed all potentially eligible studies identified by the above search strategy. Clinical trials that met the following criteria were included in the meta-analysis: (i) trials comparing second-line or salvage treatment chemotherapy with BSC and (ii) prospective phase III randomized trials. Two review authors extracted data from each included study using an agreed-upon form and assessed the risk of bias. We resolved discrepancies through discussion.

**Statistical analysis**

The primary outcome measure of this meta-analysis was overall survival, defined as the time from the date of random assignment to date of death as a result of any cause. Survival analysis was conducted using the intention-to-treat population. A fixed effect model was used to calculate the pooled hazard ratio (HR) estimate. HRs for death were combined using an inverse formula: $SE = 95\% \text{ CI} / 1.96$. The traditional intervals (95% CIs) were used to determine the standard error (SE) using the t-test statistic. Significant heterogeneity was considered to be present for $P < 0.05$ in the Q test or for $I^2 > 30\%$. The $Z$-test for overall effect and its two-sided $P$-value were also assessed. RevMan v5.2 software was used to report outcomes.

**Results**

The search process yielded 578 studies, two of which were randomized phase III trials that compared chemotherapy with supportive care. From the abstracts and virtual meeting presentations of ASCO held between 2004 and 2013, 127 abstracts were identified that evaluated second-line chemotherapy; only one relevant abstract was included in the meta-analysis. Figure 1 shows the search process.

Finally, three randomized phase III trials that compared irinotecan or docetaxel with BSC were selected. A total of 410 patients were eligible for analysis, of whom 150 received docetaxel chemotherapy, and 81 received irinotecan chemotherapy. The characteristics of studies are described in Table 1.

The trials by Thuss-Patience et al. and Cook et al. were conducted in Europe, and the trial by Kang et al. took place in Asia. Enrolled patients were diagnosed with esophagogastric cancer. Most had an ECOG performance status of 0 or 1 and were treated in Asia. Enrolled patients were randomized to receive either irinotecan or supportive care.

Overall survival was compared for 238 patients who were assigned to irinotecan or supportive care. A significant reduction in the risk of death ($HR = 0.64, 95\% \text{ CI} 0.52–0.79, P = 0.0001$) was observed with salvage chemotherapy, as shown in Figure 2. Heterogeneity was not detected.

When the analysis was restricted to irinotecan or docetaxel, there was still a significant reduction in the risk of death associated with each chemotherapeutic agent, as shown in Figure 3 and 4. The HR was 0.55 ($95\% \text{ CI} 0.40–0.77, P = 0.0004$) for irinotecan and 0.71 ($95\% \text{ CI} 0.56–0.90, P = 0.004$) for docetaxel. There were no significant differences in treatment effect according to the chemotherapeutic agent.

Meta-analysis of the two trials in Europe also demonstrated that second-line chemotherapy reduced the risk of death by 37% compared with BSC ($HR = 0.63, 95\% \text{ CI} 0.47–0.84$; Figure 5).

**Table 1. Main characteristics of the studies included in the meta-analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Treatments</th>
<th>Objective response rate (%)</th>
<th>Disease control rate (%)</th>
<th>Median overall survival (months)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience et al. (2011)</td>
<td>21</td>
<td>&quot;Irinotecan 250 mg/m², every 3 weeks&quot;</td>
<td>0</td>
<td>53</td>
<td>4.0</td>
<td>0.48 (0.25–0.92)</td>
</tr>
<tr>
<td>Kang et al. (2012)</td>
<td>133</td>
<td>Docetaxel 60 mg/m², every 3 weeks</td>
<td>11</td>
<td>38</td>
<td>5.3</td>
<td>0.657 (0.485–0.891)</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>Best supportive care</td>
<td></td>
<td></td>
<td>2.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Cook et al. (2013)</td>
<td>84</td>
<td>Docetaxel 75 mg/m², every 3 weeks</td>
<td>7</td>
<td>46</td>
<td>5.2</td>
<td>0.67 (0.49–0.92)</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>Best supportive care</td>
<td></td>
<td></td>
<td>3.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Dose of irinotecan could be escalated to 350 mg/m² in subsequent cycles according to the protocol*
Many patients with advanced gastric cancer are refractory to first-line chemotherapy or experience disease progression after a short response to treatment. Despite lack of evidence for salvage chemotherapy in advanced gastric cancer it is common practice to offer further chemotherapy after first-line failure. Recently, three trials have demonstrated the prolongation of survival with second-line chemotherapy over BSC. The Korean trial by Kang et al. [5] is the largest complete randomized trial involving 202 patients. The trial by Thuss-Patience et al. in Europe was prematurely closed after only 40 patients enrolled due to enrollment difficulties and the trial by Cook et al. enrolled 168 European patients in a trial presented as an abstract [4, 6].

This meta-analysis demonstrated that there exists a clear clinical benefit from the use of second-line chemotherapy in patients with advanced gastric cancer with 36% reduction in the risk of death. These results were observed consistently regardless of the administered drugs, and the magnitude of the clinical benefit was similar between European and Asian populations in terms of survival (HR = 0.63 and 0.657, respectively).

The results of randomized clinical trials including a BSC arm can be affected seriously by the lack of standardization of BSC delivery. Considering the descriptions of BSC in articles, the authors were aware of the risk of bias and tried to provide consistent and preplanned BSC intervention. Kang et al. [5] attempted to describe the administration of BSC intervention in detail and to provide explicit guidance. Thuss-Patience et al. had patients in the BSC arm examined and evaluated at the same frequency and by the same methods as in the irinotecan arm [4]. Therefore, it is unlikely that the lack of standardization of BSC may be a source of bias.

If the patients in the BSC arm received chemotherapy during the study period or after progression, it could be an important factor reducing the power of the findings of these trials. In trials by Thuss-Patience et al. and Kang et al., only four patients (4.5%) among 88 patients enrolled in BSC arm received chemotherapy.

### Table 2. Brief characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Thuss-Patience et al.</th>
<th>Kang et al.</th>
<th>Cook et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan No. (%) BSC No. (%)</td>
<td>SLC No. (%) BSC No. (%)</td>
<td>Docetaxel ASC %</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21 (19)</td>
<td>133 (69)</td>
<td>84 (84)</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (55)</td>
<td>56 (56)</td>
<td>65 (66)</td>
</tr>
<tr>
<td>Range</td>
<td>43–73 (35–72)</td>
<td>31–83 (32–74)</td>
<td>25–84 (35–84)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 18 (86)</td>
<td>93 (70)</td>
<td>82 (80)</td>
</tr>
<tr>
<td></td>
<td>Female 3 (14)</td>
<td>40 (30)</td>
<td>18 (20)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 17 (81)</td>
<td>72 (54)</td>
<td>28 (28)</td>
</tr>
<tr>
<td></td>
<td>1 14 (74)</td>
<td>36 (32)</td>
<td>55 (55)</td>
</tr>
<tr>
<td></td>
<td>2 5 (26)</td>
<td>–</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Response to prior chemotherapy</td>
<td>CR/PR 7 (33)</td>
<td>54 (41)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>SD/PD 14 (67)</td>
<td>79 (59)</td>
<td>–</td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td>1 6 (29)</td>
<td>42 (32)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>≥2 15 (71)</td>
<td>91 (68)</td>
<td>–</td>
</tr>
<tr>
<td>Interval from last chemotherapy, months</td>
<td>&lt;3 18 (86)</td>
<td>101 (76)</td>
<td>75 (69)</td>
</tr>
<tr>
<td></td>
<td>≥3 3 (14)</td>
<td>32 (24)</td>
<td>25 (31)</td>
</tr>
</tbody>
</table>

ASC, active symptom control; BSC, best supportive care; CR, complete response; ECOG, eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease; SLC, salvage chemotherapy.

### Figure 2. Standard forest plot of the hazard ratio (HR) for death comparing second-line chemotherapy with best supportive care.

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If the patients in the BSC arm received chemotherapy during the study period or after progression, it could be an important factor reducing the power of the findings of these trials. In trials by Thuss-Patience et al. and Kang et al., only four patients (4.5%) among 88 patients enrolled in BSC arm received chemotherapy.
chemotherapy. Therefore, chemotherapy in the BSC arm may not affect the findings of the trials evaluated in this meta-analysis.

The efficacy of second-line chemotherapy was comparable among trials. The objective response rate (ORR) was about 10% and the disease control rate was above 40%. Different chemotherapy regimens such as docetaxel or irinotecan and administration schedule did not have any influence on the outcome.

Several recent trials support these results. Ueda et al. [7] conducted a phase III study comparing second-line chemotherapy regimens in 223 patients with advanced gastric cancer. Patients received either weekly paclitaxel (80 mg/m², days 1, 8, 15, every 4 weeks) or irinotecan (150 mg/m², every 2 weeks). There were no differences between treatment groups in terms of ORR, median overall survival, and toxic effect. Roy et al. [8] conducted a phase II study to evaluate the efficacy and safety of single-agent PEP02 with irinotecan or docetaxel in the second-line treatment of advanced gastric or gastroesophageal junction adenocarcinoma. Patients received either PEP02 (120 mg/m², every 3 weeks), docetaxel (75 mg/m², every 3 weeks), or irinotecan (300 mg/m², every 3 weeks). The ORR, the primary end point, was similar between treatment groups.

Although the benefit of second-line chemotherapy is evident, the disease control rate is just above 40%. In other words, almost half of patients do not benefit from second-line chemotherapy and suffer from chemotherapy toxic effect. Therefore, it is important to predict whether patients can benefit from second-line chemotherapy. Considering the results of univariate analysis for survival in two trials [4, 5], a good performance status and long chemotherapy-free interval (≥3 months) could be important positive prognostic indicators that could help physicians to make a decision regarding treatment. Several retrospective studies conducted to identify optimal prognostic factors have also suggested prognostic factors such as performance status, hemoglobin level, and time to progression of first-line chemotherapy [9–12].

Several limitations of this meta-analysis should be noted. Clinical and pathological factors were not analyzed thoroughly to identify prognostic factors, since the details about these factors were not available. The impact of second-line chemotherapy on quality of life was not analyzed due to lack of data. The trial by Cook et al. [6] addressed in the abstract that similar global health-related quality of life was observed in each arm. The other two trials did not report any assessment of quality of life.

In conclusion, this meta-analysis demonstrated evidence to support the efficacy of second-line chemotherapy in the treatment of advanced gastric cancer. Several agents are available, and physicians can choose a regimen depending on toxic effect profiles and previous chemotherapy agents. Clinical prognostic factors derived from previous trials may guide physicians in deciding on the best treatment plan to improve outcomes.
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disclosure
The authors have declared no conflicts of interest.

references

Results of the baseline positron emission tomography can customize therapy of localized esophageal adenocarcinoma patients who achieve a clinical complete response after chemoradiation

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