Evolving Chemotherapy for Advanced Gastric Cancer

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Key Words. Gastric cancer • Taxane • Paclitaxel • Docetaxel • Oxaliplatin • Irinotecan • S-1 • Capecitabine

Learning Objectives

After completing this course, the reader will be able to:

1. Identify the current standard of care and new chemotherapy options for patients with advanced gastric cancer.
2. Discuss recently reported results of phase II and phase III randomized trials of chemotherapy for the treatment of advanced gastric cancer.
3. Outline the clinical implications of recent clinical trial findings and future treatment strategies.
4. Describe regimens that have quality-of-life benefits for patients with advanced gastric cancer and how patients should be selected and managed appropriately.

Abstract

Gastric cancer is the fourth most commonly diagnosed cancer and is the second leading cause of cancer death worldwide. More than 50% of patients undergo surgery, but even after a curative resection, 60% of patients relapse locally or with distant metastases. Despite the fact that many advances have occurred in the management of gastric cancer, it continues to carry a poor prognosis, amplifying the importance of palliative chemotherapy. When compared with best supportive care alone, combination chemotherapy yields a significant advantage in the management of advanced gastric cancer. However, no single regimen has emerged or been accepted as clearly superior over another. Numerous phase II studies have demonstrated promising results with newer agents including irinotecan, docetaxel, capecitabine, S-1, and oxaliplatin. Recently reported phase III results with these agents now demonstrate positive developments in the treatment options for patients with advanced gastric cancer. The Oncologist 2005;10(suppl 3):49–58

Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and is the second leading cause of cancer death worldwide [1]. The highest incidences of gastric carcinoma are seen in Japan, Korea, China, South America, and Eastern European nations, with the lowest typically observed in the U.S. and Canada [2]. Although the overall incidence of gastric cancer has declined over the past several decades, the site of origin within the stomach has changed: distally located cancers are less frequent and proximal cancers of the gastric cardia are more prevalent [3]. Patients with gastric cancer typically present with advanced disease. For patients presenting with earlier stages of disease, more than 50% undergo surgery, but even after a curative resection, 60% of these patients eventually relapse locally or with distant metastases. Numerous advances have occurred in the management of gastric cancer, including improvements in diagnosis, histologic classifica-
tion, molecular biology, and treatment (e.g., adjuvant chemoradiation following surgical resection); however, gastric cancer continues to carry a poor prognosis. The role of palliative chemotherapy is, therefore, of utmost importance [1, 4].

**Combination Chemotherapy as A Cornerstone Treatment of Advanced Gastric Cancer**

Single agents with activity in advanced gastric cancer include 5-fluorouracil (5-FU), cisplatin (Platinol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com), the anthracyclines doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com) and epirubicin (Ellence®, Pfizer Pharmaceuticals, New York, http://www.pfizer.com), mitomycin C (Mutamycin®; Bristol-Myers Squibb), and etoposide (Etopophos®, VePesid®; Bristol-Myers Squibb), with pooled response rates in the range of 10%–20% [5, 6]. Various combinations of these agents have been sought to improve upon these response rates. Former commonly used regimens that have become unpopular in the past 5–6 years include 5-FU, doxorubicin, and mitomycin (FAM); 5-FU, doxorubicin, and high-dose methotrexate (FAMTX); epirubicin, cisplatin, and 5-FU (ECF); and etoposide, leucovorin (LV), and 5-FU (ELF) [5]. Three phase III trials comparing several of these combination chemotherapy regimens with best supportive care (BSC) in patients with advanced gastric cancer yielded significantly superior overall survival times (8–12 months) for these combinations compared with BSC (3–5 months) alone (Table 1) [7–9], but all these trials contained only a small number of patients. Quality-of-life improvements were also observed with combination chemotherapy in one of these trials [9]. As a next step, investigators compared various combination regimens to elucidate the optimal regimen. Results of phase III randomized trials comparing cytotoxic combinations showed no single regimen as clearly superior over another (Table 2) [10–14].

**Newer Cytotoxic Agents to Treat Advanced Gastric Cancer: Phase II Trial Findings**

Even though the combination of 5-FU and cisplatin is considered a mainstay in the treatment of gastric cancer (and accepted by nearly all regulatory agencies as a reference regi-

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**Table 1.** Summary of selected phase III trials of chemotherapy versus best supportive care (BSC) for advanced gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murad et al. [7]</td>
<td>FAMTX vs. BSC</td>
<td>30</td>
<td>50</td>
<td>9 vs. 3 (p = .001)</td>
</tr>
<tr>
<td>Pyrhonen et al. [8]</td>
<td>FEMTX vs. BSC</td>
<td>41</td>
<td>29</td>
<td>12.3 vs. 3.1 (p = .0006)</td>
</tr>
<tr>
<td>Glimelius et al. [9]</td>
<td>ELF vs. BSC</td>
<td>61</td>
<td>NR</td>
<td>8 vs. 5 (NS)</td>
</tr>
</tbody>
</table>

*Treatment vs. best supportive care.

Abbreviations: ELF, etoposide, leucovorin, and 5-fluorouracil; FAMTX, 5-fluorouracil, doxorubicin, and methotrexate; FEMTX, 5-fluorouracil, epirubicin and methotrexate; NR, not reported.

**Table 2.** Summary of selected phase III trials comparing combination chemotherapy in advanced gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Response rate (%)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanhoefer et al. [10]</td>
<td>FAMTX</td>
<td>133</td>
<td>12</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>ELF</td>
<td>132</td>
<td>9</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>FUP</td>
<td>134</td>
<td>20</td>
<td>7.2</td>
</tr>
<tr>
<td>Ohtsu et al. [11] (JCOG9205)</td>
<td>5-FU</td>
<td>105</td>
<td>11.4</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>105</td>
<td>34.3</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>UFTM</td>
<td>70</td>
<td>8.6</td>
<td>6</td>
</tr>
<tr>
<td>Icli et al. [12]</td>
<td>ECF</td>
<td>67</td>
<td>15.3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>EEC</td>
<td>64</td>
<td>20.3</td>
<td>6</td>
</tr>
<tr>
<td>Webb et al. [13]</td>
<td>ECF</td>
<td>111</td>
<td>45</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>FAMTX</td>
<td>108</td>
<td>21</td>
<td>5.7</td>
</tr>
<tr>
<td>Ross et al. [14]</td>
<td>ECF</td>
<td>289</td>
<td>42.4</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>285</td>
<td>44.1</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Abbreviations: CF, cisplatin and 5-fluorouracil; ECF, epirubicin, cisplatin, and 5-fluorouracil; EEC, epirubicin, etoposide, and cisplatin; ELF, etoposide, leucovorin, and 5-fluorouracil; FAMTX, 5-fluorouracil, doxorubicin, and methotrexate; 5-FU, 5-fluorouracil; FUP, infusional fluorouracil plus cisplatin; JCOG, Japan Clinical Oncology Group; MCF, mitomycin, cisplatin, and 5-fluorouracil; UFTM, uracil, 5-fluorouracil, tegafur, and mitomycin.
imien against which all other regimens must be compared), there is clearly a need to improve upon the response rate and survival time that this combination has produced. Results of phase II trials have identified other cytotoxic agents that may offer superior efficacy and less toxicity for patients with advanced gastric cancer. These include docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com), paclitaxel (Taxol®; Bristol-Myers Squibb), capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com), S-1 (Taiho Pharma USA Inc., Princeton, NJ, http://www.taiho.co.jp/english/rnd.html), irinotecan (Camptosar®; Pfizer Pharmaceuticals), and the third-generation platinum derivative oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us).

Docetaxel and Paclitaxel

Docetaxel and paclitaxel have demonstrated encouraging activity in the treatment of patients with advanced gastric cancer. Small phase II trials of single-agent paclitaxel and docetaxel in both the first- and second-line treatment settings have produced response rates in the range of 11%–24% [15–20]. The single-agent activity observed in these trials demonstrated a lack of complete crossresistance and nonoverlapping toxicities with other agents active in gastric cancer. Researchers further investigated the role of the taxanes when combined with standard 5-FU plus cisplatin–based regimens. Paclitaxel-containing combinations have yielded response rates of 22%–51% and median survival times of 6–14 months [21–25]. Regardless of the agents with which paclitaxel was combined, the administration time of paclitaxel, or the population treated, therapy was well tolerated. Myelosuppression was the most frequently occurring adverse event.

Based on the encouraging results seen with single-agent docetaxel, several phase II studies evaluated both doublet and triplet docetaxel-based regimens in advanced gastric cancer (Table 3) [26–31]. One trial specifically enrolled patients in the second-line treatment setting, thus the lower response rate and survival time [31]. Response rates in the first-line treatment setting were in the range of 33%–55%, with median survival times of approximately 9–10 months. The Swiss Group for Clinical Cancer Research (SAKK) conducted a three-arm, multicenter phase II trial to compare the European standard combination, ECF, with a docetaxel-based regimen—either docetaxel–cisplatin (DC) or docetaxel–cisplatin–5-FU (DCF) [32]. Preliminary results from the 119 evaluable patients indicate that DCF was superior in terms response rate. These findings indicate that docetaxel-based chemotherapy yields favorable response rates and appears to be a reasonable treatment approach for patients with newly diagnosed or recurrent advanced gastric cancer. Even though the DCF regimen was more active than the ECF regimen, it did result in a considerably higher rate of complicated neutropenia, suggesting the need for proper patient selection and patient management (including consideration of primary G-CSF prophylaxis). The DCF regimen is being studied by SAKK in a phase III trial.

Table 3. Summary of selected phase II trials of docetaxel in advanced gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment setting</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins et al. [26]</td>
<td>First-line</td>
<td>Docetaxel + irinotecan 5-FU + docetaxel</td>
<td>42</td>
<td>37.5</td>
<td>9</td>
</tr>
<tr>
<td>Ajani et al. [27]</td>
<td>First-line</td>
<td>Docetaxel + cisplatin 5-FU + docetaxel</td>
<td>76</td>
<td>26</td>
<td>10.5</td>
</tr>
<tr>
<td>Thuss-Patience et al. [28]</td>
<td>First-line</td>
<td>Docetaxel + 5-FU continuous i.v. Epirubicin + cisplatin + 5-FU</td>
<td>43</td>
<td>40</td>
<td>9.5</td>
</tr>
<tr>
<td>Kettner et al. [29]</td>
<td>First- and second-line</td>
<td>Docetaxel + cisplatin (MC)</td>
<td>46</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Ridwelski et al. [30]</td>
<td>First- and second-line</td>
<td>Docetaxel + cisplatin (SC)</td>
<td>39</td>
<td>37.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Park et al. [31]</td>
<td>Second-line</td>
<td>Docetaxel + cisplatin</td>
<td>41</td>
<td>17.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Roth et al. [32]</td>
<td>SAKK</td>
<td>Docetaxel + cisplatin + 5-FU</td>
<td>41</td>
<td>55*</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + cisplatin</td>
<td>38</td>
<td>42*</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epirubicin + cisplatin + 5-FU</td>
<td>40</td>
<td>46*</td>
<td>8</td>
</tr>
</tbody>
</table>

*These are investigator-designated responses. The independent review resulted in considerably lower response rates, particularly for ECF and DC.

Abbreviations: 5-FU, 5-fluorouracil; MC, multicenter; SAKK, Swiss Group for Clinical Cancer Research; SC, single center.
**Oxaliplatin**

Oxaliplatin has proven to be active in various tumor types and is a key component in 5-FU–LV-based chemotherapy regimens for the treatment of metastatic colorectal cancer. Because 5-FU is considered a cornerstone of therapy for gastric cancer, combining it with oxaliplatin is logical, and there is considerable evidence of preclinical synergy between the two agents. Three phase II studies have evaluated oxaliplatin in combination with various 5-FU–LV regimens and are listed in Table 4 [33–35]. Two studies used bimonthly infusional 5-FU–LV–oxaliplatin (FOLFOX-4 and FOLFOX-6), while the third used a weekly administration schedule (FUFOX). Regardless of the regimen used, the 5-FU–LV–oxaliplatin combination yielded response rates in the range of 38%–54% and median overall survival times of approximately 10 months (range, 8–11). Moreover, complete and partial response rates and times to disease progression were similar among the trials. The safety profile of the oxaliplatin–5-FU regimen is very desirable, resulting in lower rates of grade 3–4 toxicities.

As anticipated, the most commonly occurring grade 3–4 toxicities with these combinations were hematologic, which were more frequent with the bimonthly infusional regimens than with the weekly regimen. Oxaliplatin therapy is associated with peripheral neuropathy (PN), and grade 3–4 PN was more prominent with bimonthly infusions than with weekly administration.

The first interim analysis of an ongoing, multicenter, randomized phase II trial comparing 5-FU–LV–oxaliplatin (FLO) with 5-FU–LV–cisplatin (FLP) as first-line therapy for patients with advanced gastric cancer was recently reported [36]. The primary end point was the 6-month progression-free survival rate. Patients randomized to FLO received 5-FU (2,600 mg/m²) as a 24-hour infusion with LV (200 mg/m²) and oxaliplatin (85 mg/m²) on day 1. Patients in the FLP arm received 5-FU (2,000 mg/m²) as a 24-hour infusion with the same dose of LV and cisplatin (50 mg/m²) on day 1. Both regimens were repeated every 2 weeks. To date, the overall response rates for patients receiving FLO and FLP are 39% and 24%, respectively, indicating a trend toward superiority for the oxaliplatin-based therapy. Grade 3 or higher toxicities are low in both treatment arms, thus no dose adjustments have been made. Accrual will continue to a target of 180 patients. The oxaliplatin–5-FU–LV combination, regardless of the administration method used, is efficacious and tolerable in patients with advanced gastric carcinoma and may be considered a viable treatment alternative.

### Table 4. Summary of selected phase II trials of oxaliplatin in advanced gastric cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Louvet et al. [33] FOLFOX-6 repeated every 2 weeks</th>
<th>DeVita et al. [34] FOLFOX-4 repeated every 2 weeks</th>
<th>Lordick et al. [35] FUFOX repeated weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Oxaliplatin, 100 mg/m² i.v. day 1; leucovorin, 400 mg/m² i.v. over 2 hours; 5-FU, 400 mg/m² i.v. bolus; 5-FU, 3,000 mg/m² continuous i.v. over 46 hours</td>
<td>Oxaliplatin, 85 mg/m² i.v. day 1; leucovorin, 200 mg/m² i.v. over 2 hours; 5-FU, 400 mg/m² i.v. bolus; 5-FU, 600 mg/m² continuous i.v. over 22 hours</td>
<td>Oxaliplatin, 50 mg/m² i.v.; 5-FU, 2,000 mg/m² i.v. over 24 hours; leucovorin, 500 mg/m² i.v.</td>
</tr>
<tr>
<td>No. of patients</td>
<td>53</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>45</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>CR/PR</td>
<td>2/20</td>
<td>4/19</td>
<td>2/0</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>8.6</td>
<td>11.2</td>
<td>11.4</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>6.2</td>
<td>7.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Adverse events (% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>21</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; 5-FU, 5-fluorouracil; ORR, overall response rate; OS, overall survival; PR, partial response; TTP, time to disease progression.
S-1
S-1, a fourth-generation oral fluoropyrimidine containing the 5-FU prodrug, tegafur, along with 5-chloro-2,4-dihydroxypyridine (CDHP) and oxonic acid, was developed to further enhance the oral efficacy of tegafur. Several phase II studies [37–39] have established the efficacy of single agent S-1 in patients with advanced gastric cancer using doses ranging from 35 mg/m² per day to 80 mg/m² per day. Response rates in those trials were in the range of 26%–49%, with one patient achieving a complete response [37]. Grade 3 and 4 toxicities were primarily hematologic and included a decrease in hemoglobin and hematocrit, leukopenia, and granulocytopenia. Diarrhea was the most frequent nonhematologic toxicity.

Encouraging results from several studies evaluating S-1 combination therapies have recently emerged. A phase I trial combined a fixed dose of S-1 (80 mg/m² per day) with an escalating dose of irinotecan, producing an overall response rate of 58.3% [40]. In another phase I trial, Ueda and colleagues [41] combined the same dose of S-1 with two dose levels of weekly paclitaxel, 50 mg/m² and 60 mg/m². The combination appeared to be effective and well tolerated at the 50-mg/m² dose level of paclitaxel. The combination of S-1 and cisplatin, a logical combination in the management of advanced gastric cancer, has also yielded promising results. A Japanese phase I/II study [42] used escalating doses of cisplatin (60 mg/m², 70 mg/m², and 80 mg/m² on day 8) with a fixed (80 mg/m² per day) dose of S-1 administered for 21 consecutive days followed by a 2-week rest period. The maximum-tolerated dose of cisplatin in the phase I portion was 70 mg/m²; therefore, 60 mg/m² was recommended for the phase II portion of the study. The combination produced a 74% response rate in 19 evaluable patients; the median survival time was 383 days [42]. Based on these results, we initiated a phase I pharmacokinetic trial of S-1 combined with cisplatin in 16 patients with advanced gastric cancer [43]. Cisplatin was administered on day 1, and S-1 was administered orally twice daily on days 1–21 of each 28-day cycle. A median of four cycles of therapy was received. The median time to disease progression was 5.7 months, and the overall response rate was 37.5% (in 12 evaluable patients). The tolerable combination in western patients was determined to be S-1 at a dose of 50 mg/m² per day plus cisplatin at a dose of 75 mg/m². Interestingly, the tolerable dose of S-1 was substantially higher in Japanese patients. This discrepancy is thought to be a result of more efficient cytochrome P450 CYP2A6 enzyme in western patients, resulting in a faster rate of metabolism of tegafur and a higher area under the concentration–time curve (AUC) of 5-FU than in Asian patients. Clearly, S-1 has significant activity both as a single agent and in various combinations in the management of patients with advanced gastric cancer. Additional trials are currently under way that will further elucidate its role.

Capecitabine
Capecitabine is an oral fluoropyrimidine derivative used as a single agent for the treatment of metastatic colorectal cancer and is currently under investigation in various combination regimens for advanced gastric cancer. Early studies evaluated single-agent capecitabine in advanced gastric cancer, showing clinical activity [44, 45]. In a phase II trial reported by Koizumi and colleagues [45], patients with advanced disease received a minimum of two cycles of capecitabine (828 mg/m²) orally twice daily for 3 weeks followed by a week of rest. The overall response rate in 31 evaluable patients was 19.4%, with a median survival time of 8.1 months. The median duration of response and time to disease progression were 4.1 months and 2.8 months, respectively. Grade 3 or higher drug-related toxicities were relatively infrequent.

Phase II studies of capecitabine combination regimens have also been conducted. One phase II study evaluated the combination of capecitabine and docetaxel in chemotherapy-naïve patients with advanced gastric cancer [46]. Distinct mechanisms of action and nonoverlapping toxicity profiles formed the rationale for this combination. Forty-two patients were enrolled and received capecitabine (1,250 mg/m² orally twice daily) on days 1–14 plus docetaxel (75 mg/m²) on day 1 of a 21-day cycle. Of 38 evaluable patients, the overall response rate was 60%, median progression-free survival time was 5.2 months, and overall survival time was 10.5 months. The capecitabine–docetaxel doublet was associated with more grade 3–4 toxicities, primarily hand-foot syndrome (50%) and neutropenia (15%), than single-agent capecitabine. Further investigations of lower treatment doses to offset these toxicities are warranted.

Park and colleagues [47] conducted a phase II trial of oxaliplatin–capecitabine (XELOX) in patients with nonresectable advanced gastric cancer. Patients received a maximum of eight cycles of oxaliplatin (130 mg/m²) on day 1 with capecitabine (1,000 mg/m² orally twice daily) on days 1–14 of a 21-day cycle. Of 20 evaluable patients, one achieved a complete response and 11 achieved partial responses, for an overall response rate of 60%. The median progression-free and overall survival times had not yet been reached. The combination was well tolerated, with mild toxicities reported. A multi-institutional phase II study of this combination is in development.

Irinotecan
Recent data have emerged on the use of irinotecan in advanced gastric cancer, both as a single agent and in
various combination regimens. Active irinotecan-based combinations include cisplatin–irinotecan, 5-FU–LV–irinotecan, and irinotecan–oxaliplatin (Table 5) [48–52]. These combinations have produced acceptable response rates and overall survival times but have also been associated with significant grade 3–4 neutropenia and diarrhea. Diarrhea is the major dose-limiting toxicity of irinotecan therapy and occurred in approximately 20% of patients (range, 6%–27%). Overall, results of these trials indicate that these irinotecan combinations are clinically active, warranting further investigation in phase III randomized trials.

NEWER CYTOTOXIC AGENTS TO TREAT ADVANCED GaSTRIC CANCER: PHASE III TRIAL FINDINGS

Encouraging evidence from phase II trial findings of newer cytotoxic combinations prompted the initiation of phase III trials to test these regimens. Findings from these trials demonstrate several active combinations.

REAL-2

The ongoing REAL-2 trial is using a 2×2 design to evaluate several modifications of the ECF regimen, including the substitution of capecitabine for 5-FU and oxaliplatin for cisplatin (EOF, EOX, ECX) [53]. Stratification factors include extent of disease, performance status, and center. An interim analysis of the first 80 randomized patients showed a low incidence of grade 3–4 toxicities. As such, a protocol-planned dose escalation of capecitabine to 1,250 mg/m² orally daily was implemented. Response and toxicity data are available for 198 of the 204 randomized patients (Table 6). The response rates for all four treatment arms are comparable, with a trend toward superior efficacy with the EOX regimen. The has already met its target accrual of over 1,000 patients, and survival results are anticipated in 12–18 months.

V-325

The V-325 trial, the largest international phase III trial in advanced gastric cancer presented to date, randomized 457 chemotherapy-naïve patients to receive docetaxel–cisplatin–5-FU (DCF) chemotherapy or the standard reference regimen of cisplatin–5-FU (CF) [54]. The total weekly doses of cisplatin and 5-FU were identical in both treatment groups (docetaxel, 75 mg/m² on day 1; cisplatin, 75 mg/m² on day 1; and 5-FU, 750 mg/m² per day as a continuous i.v. infusion on days 1–5 every 3 weeks, or cisplatin, 100 mg/m² on day 1, and 5-FU, 1,000 mg/m² per day as a continuous i.v. infusion on days 1–5 every 4 weeks), thereby allowing for a pure evaluation of the substitution of docetaxel. Time to disease progression was the primary end point, while overall survival, duration of response, safety, and quality of life were secondary end points. The median age was 55 years, and 97% of patients had metastatic disease.

Final results of the V-325 study were recently presented (Table 7). The primary end point, time to progression, was met with all measured outcome parameters, demonstrating that DCF chemotherapy is significantly superior to the reference regimen of CF. The risk for disease progression was
32.1% lower with this regimen (hazard ratio [HR], 1.473; 95% confidence interval [CI], 1.189–1.825). Similarly, overall survival was statistically significantly superior with DCF than with CF, with a 22.7% lower risk for death (HR, 1.293; 95% CI, 1.041–1.606). As expected, grade 3–4 adverse events occurred more frequently in the DCF group than in the CF group (81% versus 75%), with diarrhea and stomatitis as the most common events (20% versus 8% and 21% versus 27%, respectively). These adverse events were manageable. Grade 3–4 neutropenia was also more frequent in the DCF arm than in the CF arm (82% versus 57%). Of note, however, quality of life, including global health status, was maintained for a longer period of time with the DCF regimen. These results suggest that, compared with CF alone, docetaxel added to CF improves response rate, time to progression, overall survival, quality of life, and clinical benefit for patients with advanced gastric cancer. The higher rate of complicated neutropenia remains a concern, but with proper patient selection, primary growth factor prophylaxis, and aggressive patient management, it is not problematic. Whether CF should always be combined with docetaxel as frontline therapy for untreated patients with advanced gastric cancer remains an open question, but docetaxel should become part of the frontline therapy of advanced gastric cancer.

**ECF Versus Docetaxel–Carboplatin–5-FU**

Recently reported results of a phase III trial comparing docetaxel–carboplatin–5-FU (DCbF) with ECF confirmed the value of docetaxel in advanced gastric cancer [55]. Sixty-four patients were randomized to receive either DCbF (docetaxel, 75 mg/m² on day 1; carboplatin, AUC 6, on day 2; and 5-FU, 1,200 mg/m² per day for 3 days every 21 days) or ECF. All patients received G-CSF with each treatment cycle. The DCbF regimen was associated with a higher response rate (67% vs. 47%), longer median survival time (12.4 months vs. 8.7 months; \( p = .0005 \)), and greater 2-year survival rate (20% vs. 14%; \( p = .03 \)) than ECF. The number of patients in that trial is too small for a definitive conclusion.

**Table 6. REAL-2 trial: results and toxicity data of the second interim analysis [53]**

<table>
<thead>
<tr>
<th>Treatment every 21 days x 8 cycles</th>
<th>No. of patients</th>
<th>RR (%)</th>
<th>Grade 3–4 hematologic toxicity (%)</th>
<th>Grade 3–4 nonhematologic toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF: epirubicin, 50 mg/m² i.v. day 1; cisplatin, 60 mg/m² i.v. day 1; 5-FU, 200 mg/m² per day continuous i.v.</td>
<td>49</td>
<td>31</td>
<td>N, 34%; FN, 8%</td>
<td>S, 0; D, 2; PPE, 4</td>
</tr>
<tr>
<td>EOX*: epirubicin, 50 mg/m² i.v. day 1; oxaliplatin, 130 mg/m² iv. day 1; capecitabine, 1,000–1,250 mg/m² orally daily</td>
<td>49</td>
<td>48</td>
<td>N, 46/25a; FN, 0/19a</td>
<td>S, 0/0a; D, 6/6a; PPE, 6/6a</td>
</tr>
<tr>
<td>ECX*: epirubicin, 50 mg/m² i.v. day 1; cisplatin, 60 mg/m² i.v. day 1; capecitabine, 1,000–1,250 mg/m² orally daily</td>
<td>46</td>
<td>35</td>
<td>N, 36/40a; FN, 10/0a</td>
<td>S, 0/0a; D, 0/0a; PPE, 4/16a</td>
</tr>
<tr>
<td>EOF: epirubicin, 50 mg/m² i.v. day 1; Oxaliplatin, 130 mg/m² i.v. day 1; 5-FU, 200 mg/m² per day continuous i.v.</td>
<td>54</td>
<td>39</td>
<td>N, 24; FN, 14</td>
<td>S, 10; D, 10; PPE, 2</td>
</tr>
</tbody>
</table>

*Results of capecitabine dose of 1,000/1,250 mg/m².

Abbreviations: C, cisplatin; D, diarrhea; 5-FU, 5-fluorouracil; FN, febrile neutropenia; N, neutropenia; PPE, palmar-plantar erythema; RR, response rate; S, stomatitis.

**Table 7. Summary of final results of V-325 trial [54]**

<table>
<thead>
<tr>
<th></th>
<th>DCF (n = 227)</th>
<th>CF (n = 230)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>37</td>
<td>25</td>
<td>.0106</td>
</tr>
<tr>
<td>Time to progression (months)</td>
<td>5.6</td>
<td>3.7</td>
<td>.0004</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td>9.2</td>
<td>8.6</td>
<td>.0201</td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>18</td>
<td>9</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CF, cisplatin and 5-fluorouracil; DCF, docetaxel, cisplatin, and 5-fluorouracil; NR, not reported.

**V306**

The activity and better safety of 5-FU–LV–irinotecan has been proven in a randomized phase II trial, thus it became the experimental arm of the phase III trial to be compared with the reference regimen of CF, hence the rationale for its evaluation in the phase III setting [49]. Results of the V306 trial, an open-label multicenter study in the first-line treatment of advanced gastric cancer, were recently reported [56]. The primary end point was time to disease progression, with secondary end points of overall survival, time to treatment failure, and safety. Patients were
randomized to receive either irinotecan (80 mg/m²) as a 30-minute infusion, followed by LV (500 mg/m²) over 2 hours, followed by 5-FU (2,000 mg/m²) as a continuous i.v. infusion over 22 hours (IF; repeated weekly for 6 weeks) or cisplatin (100 mg/m²) over 1–3 hours, followed by 5-FU (1,000 mg/m² per day) as a continuous i.v. infusion for 5 days (CF; repeated every 4 weeks). Of 337 patients randomized, 333 were treated and evaluable for response and toxicity. The irinotecan-based regimen demonstrated a trend toward a longer time to disease progression and greater overall survival; however, these differences were not significant (HR, 1.23 and 1.08, respectively). Significantly more patients in the CF group withdrew from the study as a result of adverse events compared with patients in the IF group (21.5% vs. 10%; p = .004). Grade 3–4 diarrhea was the most troublesome adverse event experienced by patients in the irinotecan group (21.6% vs. 7.2%), whereas nausea (4.8% vs. 9%), neutropenia (25% vs. 52%), stomatitis (2.4% vs. 16.9%), and febrile neutropenia (4.8% vs. 10.2%) were all more commonly seen in patients receiving CF. Based on the results of the V306 trial, IF may be considered a reasonable alternative to a platinum-based regimen as first-line treatment of patients with advanced gastric cancer, but it provides no efficacy advantage.

**Conclusions**

Gastric cancer is the second leading cause of cancer death worldwide and continues to carry a poor prognosis, making it a therapeutic challenge for oncologists. Although combination chemotherapy may be superior to BSC, the optimal combination regimen has remained elusive, possibly until now. Promising results have been demonstrated with docetaxel in a randomized phase III trial. Irinotecan with infusional 5-FU appears to be equal to cisplatin and 5-FU in efficacy and more desirable in terms of toxic effects. The results of phase III trials investigating oxaliplatin, capecitabine, and S-1 are pending. The V-325 trial showed an incremental benefit of adding docetaxel to the reference CF regimen as first-line therapy for patients with advanced or locally recurrent gastric cancer. With these findings, docetaxel has emerged as a new therapeutic option and should be incorporated into frontline regimens. Because DCF is an intensive combination, some consideration must be given to the use of docetaxel with less intensive regimens (such as with oral fluoropyrimidines or a cisplatin analogue, such as oxaliplatin). However, no other phase III trial has demonstrated the value of the addition of a single agent (such as docetaxel) in improving valuable endpoints (time to progression, overall survival time, response rate, quality of life, and clinical benefit). Alternatively, several non-cisplatin-based regimens appear promising as alternative first-line treatment options. These regimens, which have not been sufficiently explored, include the oxaliplatin–capecitabine EOX regimen being studied in the REAL-2 trial and the irinotecan-based IF regimen, which demonstrated a superior safety profile in the V306 trial. In conclusion, new combination chemotherapy regimens are available to treat patients with advanced gastric cancer. Other avenues, such as sequential administration, two-drug combination regimens, and combinations with targeted agents, still need to be explored in an effort to further expand the effectiveness of current cytotoxic regimens. There is a great need for well-designed prospective clinical trials in gastric cancer. By performing numerous phase III trials, one can be certain that current standards will change and our patients will benefit immensely. In parallel with the conduct of multitude of clinical trials, we also need to study patient genetics and the molecular biology of cancer.

**Disclosure of Potential Conflicts of Interest**

Dr. Ajani has received research grants from sanofi-aventis and Taiho Pharma, USA. He is on the speaker circuit for sanofi-aventis.

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