An Update on Biochemotherapy of Advanced Gastric and Gastroesophageal Adenocarcinoma

Peyman Haghighat, MD, MS, and Tanios Bekaii-Saab, MD, Columbus, Ohio

Key Words
Gastric, gastroesophageal, adenocarcinoma, chemotherapy, targeted therapy

Abstract
Gastric and gastroesophageal adenocarcinoma (GGA) are significant worldwide health problems. With most patients presenting with advanced disease, palliative chemotherapy plays a significant role in treatment. Results from recent phase III studies of cytotoxic agents in combination therapy, such as docetaxel, oxaliplatin, irinotecan, capecitabine, and S-1, have been encouraging and provide patients with additional therapeutic options. Although these forthcoming regimens have allowed for more flexible patient-tailored therapy, survival continues to be suboptimal. Although still in its infancy, targeted biotherapies, including inhibitors of the vascular endothelial and epidermal growth factor receptors, seems to be promising and its incorporation into the next generation of clinical trials will hopefully improve outcomes and help advance future treatments. This article reviews current active chemotherapeutic regimens and explores the role of novel targeted therapies in advanced GGA.

Cytotoxic Therapy
First- and Second-Generation Chemotherapy Regimens
Initial studies with 5-fluorouracil (5-FU) versus best supportive care established the role of chemotherapy as a measure that improves survival and quality of life in patients with GGA. First-generation chemotherapy regimens, including 5-FU, doxorubicin, and mitomycin (FAM), showed promising activity in early randomized trials. Second-generation chemotherapy regimens included 5-FU, doxorubicin, and methotrexate (FAMTX), which showed improved overall response rates (ORR; 41% vs. 9%) and median overall survival (mOS; 10.5 vs. 7.3 months) when compared with FAM alone in a randomized trial of 213 patients.

A more recent randomized phase III trial of 399 patients with advanced adenocarcinoma of the stomach compared 3 regimens: FAMTX, cisplatin plus 5-FU (CP), and etoposide and leucovorin plus 5-FU (ELF). No significant ORR or survival difference was seen among groups (Table 1). Another randomized phase III study of 295 previously untreated patients with advanced gastric cancer comparing CF, FAM, and 5-FU also showed...
no survival benefit among the arms. The CF regimen did, however, show a significantly higher ORR (51% for CF; 25% for FAM; 26% for 5-FU) and a longer time to progression (TTP; 5.5 months for CF; 3 for FAM; 2.3 for 5-FU) than the other 2 regimens. Other phase III clinical trials comparing combination chemotherapy with single-agent 5-FU have not shown survival benefits for combination chemotherapy regimens; however, consistent increased response rates have established a role for combination chemotherapy in the advanced setting.\(^{9,10}\)

Based on promising phase II data, epirubicin and cisplatin with 5-FU (ECF) was compared with FAMTX in a large randomized phase III trial.\(^{11,12}\) In 274 previously untreated patients with GGA receiving ECF or FAMTX, improved ORR (46% vs. 21%; \(P = .0002\)) and mOS (8.7 vs. 6.1 months; \(P = .0009\)) were observed favoring the ECF arm. With the exception of emesis and alopecia, ECF also showed a better overall toxicity profile with only 1 toxic death observed. At 2 years, 14% (vs. 5%) of patients in the ECF group were still alive.\(^{13}\) These findings were supported in the Cochran meta-analysis showing best survival results with regimens containing anthracyclines, cisplatin, and 5-FU.\(^{14}\) No phase III trials have compared ECF with CF; therefore, historically, both regimens have been considered a reference in advanced GGA.

### Newer Agents

#### Docetaxel

Several phase II trials have found docetaxel to be active in gastric cancer.\(^{15}\) Results of the phase II randomized Swiss Group for Clinical Cancer Research group study comparing docetaxel and cisplatin (DC); docetaxel, cisplatin, and 5-FU (DCF); and ECF in 119 chemo-naïve patients showed an ORR of 18.5%, 36.6%, and 25.0%, respectively.\(^{16}\) In the phase II V-325 study comparing DC with DCF in 158 chemo-naïve patients with advanced GGA, DCF showed a higher ORR compared with DC (43% vs. 26%), with manageable toxicities.\(^{17}\) This was followed by a multinational phase III randomized study of 445 patients receiving CF or DCF. The primary end point of this study, TTP, was significantly longer with DCF.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments</th>
<th>Total No. of Patients</th>
<th>GEJ (%)</th>
<th>ORR (%)</th>
<th>mOS (months)</th>
<th>mOS (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webb et al.(^{12})</td>
<td>ECF</td>
<td>274</td>
<td>22</td>
<td>45*</td>
<td>8.9</td>
<td>.00009</td>
</tr>
<tr>
<td></td>
<td>FAMTX</td>
<td></td>
<td></td>
<td>21</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Vanhoefer et al.(^{7})</td>
<td>FAMTX</td>
<td>399</td>
<td>NA</td>
<td>12</td>
<td>6.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td></td>
<td></td>
<td>20</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ELF</td>
<td></td>
<td></td>
<td>9</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Kang et al.(^{25}) (ML07132)</td>
<td>XP</td>
<td>316</td>
<td>NA</td>
<td>41*</td>
<td>10.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td></td>
<td></td>
<td>29</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>Cunningham et al.(^{26})</td>
<td>ECF</td>
<td>1002</td>
<td>25</td>
<td>40.7</td>
<td>9.9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>EOCF</td>
<td></td>
<td></td>
<td>42.4</td>
<td>9.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>EOX</td>
<td></td>
<td></td>
<td>46.4</td>
<td>9.9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>EOF</td>
<td></td>
<td></td>
<td>47.9</td>
<td>11.2</td>
<td>.02(^{1})</td>
</tr>
<tr>
<td>Van Cutsem et al.(^{19}) (V325)</td>
<td>DCF</td>
<td>445</td>
<td>44</td>
<td>37*</td>
<td>9.2</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td></td>
<td></td>
<td>25</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Dank et al.(^{22}) (V-306)</td>
<td>IF</td>
<td>337</td>
<td>19</td>
<td>31.8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td></td>
<td></td>
<td>25.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Boku et al.(^{23})</td>
<td>5-FU</td>
<td>704</td>
<td>NA</td>
<td>28*</td>
<td>11.4</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>S-1</td>
<td></td>
<td></td>
<td>38*</td>
<td>12.3</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td></td>
<td></td>
<td>9</td>
<td>10.8</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1 Selected Phase III Combination Chemotherapy Trials**

Abbreviations: 5-FU, 5-fluorouracil; CF, cisplatin, 5-FU; DCF, docetaxel, cisplatin, 5-FU; ECF, epirubicin, cisplatin, 5-FU; ECX, epirubicin, cisplatin, capecitabine; ELF, etoposide, leucovorin, 5-FU; EOF, epirubicin, oxaliplatin, 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; FAMTX, 5-FU, adriamycin, methotrexate; GEJ, gastroesophageal junction; IC, irinotecan, cisplatin; IF, irinotecan, 5-FU; mOS, median overall survival; NA, not applicable; NS, not significant; ORR, overall response rate; XP, capecitabine, cisplatin.

*Significant.

\(^{1}\)EOX vs. ECF.
Biochemotherapy of Advanced Gastric and GGA

compared with CF (5.6 vs. 3.7 months, \(P < .001\)). The mOS was also significantly longer with DCF (9.2 vs. 8.6 months; \(P = .02\)). Grade 3 to 4 treatment-related adverse events, including neutropenia (82% vs. 57%), febrile neutropenia (29% vs. 12%), diarrhea (19% vs. 8%), and lethargy (19% vs. 14%), were more frequent with DCF than CF.\(^\text{28}\) Toxic deaths were noted to be similar between the groups (8 in DCF, 12 in CF).

Based on these results, the FDA approved docetaxel in combination with CF for first-line treatment of patients with advanced GGA. However, appropriate patient selection and consideration of dose and schedule of this regimen is warranted.

**Irinotecan**

Irinotecan, a camptothecin derivative, has also shown promising activity in gastric cancer. Phase II trials of various combination regimens involving irinotecan in gastric cancer have yielded response rates ranging from 12.5% to 66.7%.\(^\text{19-22}\) In a randomized phase II trial (FFCD 9803), 146 untreated patients with GGA were administered 5-FU/leucovorin (5-FU/LV; arm A), 5-FU/LV plus cisplatin (arm B), or 5-FU/LV plus irinotecan (IF; arm C). ORRs were 13%, 27%, and 40% and mOSs were 6.8, 9.5, and 11.3 months, respectively.\(^\text{21}\) In the phase III V-306 study, 337 patients were randomized to receive IF or CF. A trend toward superiority for TTP, the primary outcome of the study, was noted for IF (5 vs. 4.2 months). No difference in mOS was noted. Overall, IF was better tolerated than CF, with diarrhea more common in the IF arm (21.6% vs. 7.2%), whereas neutropenia (52% vs. 25%) and febrile neutropenia (10.2% vs. 4.8%) were more common in the CF arm.\(^\text{22}\) Therefore, irinotecan in combination with 5-FU is an added option in the treatment of advanced GGA.

**Capecitabine and Oxaliplatin**

Capecitabine is an oral fluoropyrimidine rationally synthesized for efficient gastrointestinal tract absorption and conversion to 5-FU through a 3-step enzymatic process.\(^\text{23}\) To date, 2 phase III noninferiority trials have evaluated the role of capecitabine in GGA. In the ML07132 trial, 316 untreated patients with GGA received capecitabine plus cisplatin (XP) or CF arm. XP showed statistically significant superiority to CF with ORR (41% vs. 29%; \(P = .03\)) and progression-free survival (PFS; 5.6 vs. 5.0 months; \(P = .003\)), but only showed a trend with mOS (10.5 vs. 9.3 months; \(P = .27\)). Toxicities were similar between the groups, except for increased hand-foot syndrome observed in the XP arm (22% vs. 4%).\(^\text{24}\) In another phase III trial (REAL-2), 1002 patients were randomized to receive 1 of 4 epirubicin-based regimens, ECF; epirubicin, cisplatin, and capecitabine (ECX); epirubicin, oxaliplatin, and 5-FU (EOF); or epirubicin, oxaliplatin, and capecitabine (EOX). The primary end point was noninferiority in overall survival for triplet therapies containing oxaliplatin compared with cisplatin, and for those containing capecitabine compared with 5-FU. The mOS in the ECF, ECX, EOF, and EOX groups were found to be 9.9, 9.9, 9.3, and 11.2 months, respectively. Toxicities for capecitabine and 5-FU were similar; oxaliplatin showed higher incidences of grade 3/4 diarrhea and neuropathy versus cisplatin.\(^\text{25,26}\) Although ORR, PFS, and mOS did not differ significantly among the 4 regimens, mOS was found to be longer with EOX than with ECF (\(P = .02\)) in a secondary analysis. It was concluded that oxaliplatin is at least as effective as cisplatin and capecitabine is at least as effective as infusional 5-FU in overall survival.

**S-1**

S-1 is an oral fluoropyrimidine combining tegafur, a prodrug of 5-FU, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate, which theoretically can deliver prolonged levels of 5-FU with relatively less gastrointestinal toxicity.\(^\text{27}\) In a randomized phase III trial (SPIRITS), 305 Japanese chemo-naïve patients with advanced GGA were assigned to S-1 plus cisplatin versus S-1 alone. Overall survival, which was the primary end point of the study, was found to be significantly longer in the S-1 plus cisplatin arm versus S-1 alone (13.0 vs. 11.0 months; \(P = .04\)).\(^\text{28}\)

In a 3-arm phase III study of 704 patients investigating superiority of irinotecan plus cisplatin (IC) and noninferiority of S-1 to 5-FU, mOS was 12.3 (IC), 11.4 (S-1), and 10.8 months (5-FU). S-1 was found to be noninferior to 5-FU (\(P < .001\)).\(^\text{29}\) Based on these studies, S-1 plus cisplatin has become the standard of care for GGA in Japan. Studies performed in the West so far have shown interesting activity, with ORRs ranging between 26% and 55%; however, the optimal dose for S-1 has not been well defined.\(^\text{30-32}\) The First-Line Advanced Gastric Cancer Study (FLAGS), a large international phase III study comparing the effectiveness of S-1 plus cisplatin to CF, has recently completed accrual with preliminary results expected in 2009.
Targeted Therapies

Further progress is required in the treatment of GGA, and the next generation of clinical trials involving patients with advanced disease is incorporating targeted agents, such as inhibitors of the vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), into optimized cytotoxic platforms (Table 2).

VEGF inhibitors

Inhibition of tumor angiogenesis has emerged as a new therapeutic strategy in the treatment of several solid malignancies. In gastric cancer, VEGF expression is a negative prognostic factor that correlates with disease stage and presence of distant metastases.\(^33,34\) In a multicenter phase II study of untreated patients with metastatic gastric cancer, 47 were enrolled to receive bevacizumab, a humanized monoclonal antibody (mAb) targeting VEGF, in addition to IC. The median TTP was 8.3 months, an improvement of 75% over historical controls, and an ORR of 46.8% was observed. Notably, 12 (25.5%) patients developed grade 3/4 venous thromboembolisms and 3 (6%) developed gastric perforation or near-perforation.\(^35\)

A 2-arm, randomized, double-blind, multicenter phase III study is currently underway evaluating capecitabine/cisplatin plus bevacizumab or capecitabine/cisplatin plus placebo (AVAGAST, www.cancer.gov). Other anti-VEGF inhibitors are being explored in GGA, including sunitinib, a multitargeted tyrosine kinase inhibitor (TKI) that showed single-agent activity in second-line therapy for advanced GGA, with an ORR of 5% in 42 treated patients.\(^36\)

EGFR inhibitors

EGFR is a transmembrane glycoprotein that has been implicated in several cancers, including gastric cancer.\(^37\) Combination regimens with cetuximab, a chimeric mAb directed against the EGFR binding site, have shown good activity in advanced GGA, with ORRs ranging from 44.1% to 69.2%.\(^36,37\) The FOLCETUX study, a phase II trial in 38 untreated patients with advanced GGA, evaluated cetuximab in combination with FOLFIRI (5-FU, CPT-11, leucovorin). The ORR was 44.1% and median TTP was 8 months.\(^38\) A phase II multicenter Korean study evaluated cetuximab with modified FOLFOX6 in 40 previously untreated patients with recurrent or metastatic gastric cancer. The ORR in 38 evaluable patients was 50%, with a TTP of 4.8 months.\(^39\) Additionally, the role of cetuximab in combination with ECF, IC, or FOLFOX is being investigated in a phase II randomized study (CALGB 80403) in patients with metastatic esophageal or gastroesophageal junction cancer.

The role of other agents targeting EGFR in GGA is also being explored. Gefitinib, an oral TKI, has shown only modest activity in gastric cancer.\(^40,41\) In the SWOG0127 phase II trial, erlotinib, another oral TKI inhibiting EGFR, showed an ORR of 9% in 68 previously untreated patients with advanced GGA, with all responses seen in patients with gastroesophageal junction cancers and no response seen in the 25 patients analyzed with gastric cancer.\(^42\)

Conclusions

The role of biochemotherapy continues to evolve in advanced GGA. Results from recent phase III studies of

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>GEJ (%)</th>
<th>Previously Treated</th>
<th>TTP (Months)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al.(^35)</td>
<td>IC + bevacizumab</td>
<td>47</td>
<td>49</td>
<td>No</td>
<td>8.3</td>
<td>65</td>
</tr>
<tr>
<td>Bang et al.(^36)</td>
<td>Sunitinib</td>
<td>42</td>
<td>NA</td>
<td>Yes</td>
<td>4.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Pinto et al.(^38)</td>
<td>FOLFIRI + cetuximab</td>
<td>38</td>
<td>10.5</td>
<td>No</td>
<td>8</td>
<td>44.1</td>
</tr>
<tr>
<td>Han et al.(^39)</td>
<td>FOLFOX6 + cetuximab</td>
<td>40</td>
<td>NA</td>
<td>No</td>
<td>4.8</td>
<td>50</td>
</tr>
<tr>
<td>Doi et al.(^41)</td>
<td>Gefitinib</td>
<td>75</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>1.3</td>
</tr>
<tr>
<td>Dragovich et al.(^42)</td>
<td>Erlotinib</td>
<td>68*</td>
<td>63</td>
<td>No</td>
<td>NA</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: FOLFIRI, irinotecan, 5-FU, leucovorin; FOLFOX, oxaliplatin, 5-FU, leucovorin; GEJ, gastroesophageal junction; IC, irinotecan, cisplatin; NA, not available/applicable; ORR, overall response rate; TTP, time to progression.

*This includes 25 patients with gastric cancer with an ORR of 0%.
cytotoxic agents in combination therapy, such as docetaxel, oxaliplatin, irinotecan, capecitabine, and S-1, have provided patients with new therapeutic options. Although the addition of new regimens have allowed for more flexible patient-tailored therapy, survival continues to be suboptimal with an mOS of 9 to 11 months. Further exploration and integration of targeted agents into forthcoming regimens, along with correlative translational research, are essential for improving outcome and advancing future treatments. Furthermore, given the differences between adenocarcinoma of the gastroesophageal junction and gastric cancer in terms of origin, prognosis, and response to certain targeted therapies (such as EGFR inhibitors), future studies should focus on separating the 2 more clearly.

References


