Chemotherapy for locally advanced and metastatic gastric cancer: state of the art and future perspectives

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Abstract. – Despite a decline in the incidence in Western countries, gastric cancer is still the second most common cause of cancer-related death worldwide. Many advances have been made in diagnosis and treatment of gastric cancer in the last decades but the prognosis for gastric cancer patients remains disappointing, especially in more advanced stages. The poor outcome associated with surgical resection with curative intent has generated intensive investigation of combined modality treatment approaches including systemic chemotherapy and radiotherapy to prevent recurrences and improve survival. In this setting the use of perioperative chemotherapy or postoperative chemoradiotherapy has demonstrated to give survival benefits. In advanced disease, major improvements of the last years are represented by the introduction of oral fluoropyrimidines and drugs such as docetaxel or irinotecan and the demonstration of efficacy of the anti-HER2 agent trastuzumab.

Key Words: Gastric cancer, Adjuvant chemotherapy, Cisplatin, 5-FU, Trastuzumab, Docetaxel, Irinotecan.

Introduction

Despite its incidence in Europe and North America has declined over the last three decades, gastric cancer is still one of the most common cause of cancer-related deaths worldwide, representing a challenging problem for oncologists, with an estimated 755,000 new cases diagnosed annually around the world! Surgery remains the mainstay of any curative treatment for gastric cancer, however patients with locally advanced disease show high rates of loco-regional or distant recurrence even after potentially curative resections. In the past few years, important advances have been made in the adjuvant setting where survival benefits have been demonstrated with the use postoperative chemoradiotherapy and perioperative chemotherapy. In advanced disease, patients prognosis remains very poor and the primary goal of systemic chemotherapy is palliation. In this setting, major improvements are represented by the introduction in clinical practice of oral fluoropyrimidines, as capecitabine and S-1, and the use of new chemotherapy agents, such as docetaxel and irinotecan. Even more recent is the demonstration that trastuzumab added to chemotherapy can improve overall survival of HER2 positive gastric cancer patients.

Adjuvant Treatment

The role of adjuvant chemotherapy in gastric cancer has been extensively studied in the past three decades, often with disappointing results. Meta-analyses of clinical trials in this setting have shown only a small benefit deriving from adjuvant chemotherapy on overall survival, with risk of death reduction by 12-18%. However, no clear conclusions could be drawn from these meta-analyses that showed methodological limits, included small clinical trials and analyzed older chemotherapy regimens, used before the introduction of cisplatin in the treatment of gastric cancer. More recently, four clinical trials have evaluated the role of cisplatin-based chemotherapy regimens in the adjuvant treatment of gastric cancer. In a study by GOIRC (Gruppo Oncologico Italiano di Ricerca) 258 patients with adenocarcinoma of the stomach, were randomized to receive surgery alone or surgery followed by four cycles of PELF (cisplatin, epirubicin, leucovorin and 5-FU). In this study adjuvant chemotherapy did not improve disease-free survival (HR of recurrence= 0.92, 95% CI= 0.66-1.27) or overall
survival (HR of death= 0.90, 95% CI= 0.64-1.26)8. A French Federation Francophone de Cancerologie Digestive (FFCD) study on adjuvant chemotherapy, randomized 260 gastric cancer patients to postoperative chemotherapy, with 5-FU and cisplatin, or surgery alone. Also this study failed to demonstrate a benefit in terms of survival for adjuvant chemotherapy7. Similar results were obtained from an ITMO group study comparing surgery alone with adjuvant EAP (etoposide, adryamicin, cisplatin) chemotherapy9 and from a GISCAD study comparing postoperative chemotherapy with 5-FU versus weekly PELF regimen9.

The efficacy of adjuvant chemoradiotherapy after gastric cancer resection was evaluated in a large phase III trial, the US Intergroup 0116, which randomized 556 patients who underwent surgery for gastric or esophageal gastric cancer junction to postoperative chemotherapy or observation10. In this study the use of adjuvant chemoradiotherapy compared to surgery alone resulted in a statistically significant improvement in median overall survival (35 versus 26 months, HR= 1.31, 95% CI= 1.08-1.61) and disease-free survival (30 versus 19 months, HR= 1.52, 95% CI= 1.25-1.85). The treatment was particularly effective in improving local control, lowering the incidence of local relapse (from 29% to 19%). However, quality of surgical treatment in the study was poor, with only 10% of patients receiving D2 lymph node resection and more than half (54%) who underwent D0 resection. These observations suggest the possibility that chemoradiotherapy could be a reasonable option for patients with resected gastric cancer in case of inadequate surgery.

**Table I.** Perioperative chemotherapy trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Chemotherapy regimen</th>
<th>Hazard Ratio for disease-free survival</th>
<th>Hazard Ratio for overall survival</th>
<th>5 years overall survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGIC</td>
<td>504</td>
<td>ECF</td>
<td>0.66 (0.53-0.81)</td>
<td>0.75 (0.60-0.93)</td>
<td>36 vs 23</td>
</tr>
<tr>
<td>FFCD 9703</td>
<td>224</td>
<td>5FU, CDDP</td>
<td>0.63 (0.46-0.86)</td>
<td>0.69 (0.50-0.95)</td>
<td>38 vs 24</td>
</tr>
</tbody>
</table>
FU and cisplatin should be considered for stage II-IV M0 gastric cancer patients.

**Advanced Gastric Cancer Treatment**

Despite a remarkably improvement in the diagnosis and treatment of gastric cancer, approximately two thirds of patients presents unresectable advanced disease at the time of diagnosis, with a median survival of less than 9 months. Advanced or recurrent gastric cancer is still incurable, but the role of chemotherapy in this group of patients remains crucial for symptoms palliation and improved survival. During the past two decades, various randomized trials have been carried out for metastatic gastric cancer. Some of these trials demonstrated that a 5-fluorouracil (5-FU)-based regimen provided superior survival in patients with advanced gastric cancer when compared with the best supportive care. Moreover, randomized trials comparing monotherapy with combination regimens consistently showed increased response rates in favour of combination regimens, whereas similar survival rates were usually found. When compared with best supportive care, a consistent survival benefit of combination chemotherapy has been demonstrated in advanced gastric cancer.

One of the first multidrug regimen used in advanced gastric cancer was the combination of 5-FU, doxorubicin and mitomycin (FAM), which achieved a response rate of more than 40%. In addition, it was also well tolerated, producing only moderate bone marrow suppression. However, a randomized three-arm trial performed by the NCCTG including 305 patients with advanced gastric and pancreatic cancer, comparing the FAM regimen with 5-FU as single agent and 5-FU plus doxorubicin, was not able to show a significant survival difference among patients treated with these regimens, although higher response rates were observed in patients receiving combination chemotherapy compared with 5-FU alone. Subsequently, a further randomized trial performed by EORTC comparing FAM regimen with FAMTX (5-FU, Adriamycin and methotrexate): FAMTX showed significantly superior response rate and improved overall survival and became the reference regimen in this setting.

In the past several years, several randomized studies compared FAMTX vs various combination schedules, in order to identify the optimal regimen in advanced gastric cancer (Table II).

The results of these trials showed that, although in many studies response rates for platinum containing regimens were significantly better than for regimens without platinum, usually this did not translate in an improved median survival. However the Webb trial comparing FAMTX and ECF (epirubicin, cisplatin, 5-FU) suggested that ECF may be considered superior over FAMTX in terms of both response rate (45% vs 21%) and median survival (8.9 vs 5.7 months). These impressive results were con-

<table>
<thead>
<tr>
<th>Author (years)</th>
<th>N° pts</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>Median survival</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelsen et al (1992)</td>
<td>30</td>
<td>FAMTX</td>
<td>33</td>
<td>30 weeks</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>EAP</td>
<td>20</td>
<td>29 weeks</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>37 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocconi et al (1994)</td>
<td>52</td>
<td>FAM</td>
<td>15</td>
<td>5.6 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>PELF</td>
<td>43</td>
<td>8.1 months</td>
<td>NS</td>
</tr>
<tr>
<td>Webb et al (1997)</td>
<td>130</td>
<td>FAMTX</td>
<td>21</td>
<td>5.8 months</td>
<td>0.0009</td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>ECF</td>
<td>45</td>
<td>8.9 months</td>
<td>NS</td>
</tr>
<tr>
<td>Vanhoefer et al (2000)</td>
<td>134</td>
<td>FUP</td>
<td>20</td>
<td>7.2 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>ELF</td>
<td>9</td>
<td>7.2 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>133</td>
<td>FAMTX</td>
<td>12</td>
<td>6.7 months</td>
<td></td>
</tr>
<tr>
<td>Ross et al (2002)</td>
<td>289</td>
<td>ECF</td>
<td>42</td>
<td>9.4 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>285</td>
<td>MCF</td>
<td>44</td>
<td>8.7 months</td>
<td>NS</td>
</tr>
<tr>
<td>Cocconi et al (2003)</td>
<td>200</td>
<td>PELF</td>
<td>98</td>
<td>7.7 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>FAMTX</td>
<td></td>
<td>6.9 months</td>
<td></td>
</tr>
</tbody>
</table>

FAMTX: 5-FU, doxorubicin, methotrexate; FAM: 5-FU, doxorubicin, mitomycin C; ELF: etoposide, leucovorin, 5-FU; EAP: etoposide, doxorubicin, cisplatin; PELF: cisplatin, epirubicin, leucovorin, 5-FU; ECF: epirubicin, cisplatin, 5-FU; FUP: infusional 5-FU, cisplatin; MCF: mitomycin C, cisplatin, 5-FU; NS: not significant.
confirmed by other subsequent studies, and the Authors regarded the ECF regimen as the standard of care and the reference treatment for oesophago-gastric cancer patients with good performance status. Recently developed new agents, such as capecitabine, docetaxel, paclitaxel, irinotecan, S-1, and oxaliplatin may have potentials that will break through this status. Newer-generation regimens with these agents are now being investigated in randomized trials throughout the world. Promising results were achieved with a regimen of docetaxel, cisplatin and 5-FU (DCF). In fact, the phase III trial V325, comparing CF (cisplatin and 5-FU) VS DCF regimen, showed that DCF was superior in term of time to progression, response rate and overall survival. Based on results from this study, FDA (Food and Drugs Administration) approved DCF for the treatment of patients with advanced gastric cancer. New drugs combination were also tested in a large, randomized, phase III study, the REAL-2 trial. The results of this study demonstrated the non inferiority of EOX (epirubicin, oxaliplatin, capecitabine)

<table>
<thead>
<tr>
<th>Protocol IDs</th>
<th>Title</th>
<th>Design</th>
<th>Status</th>
<th>Trial description</th>
</tr>
</thead>
</table>
| AVF4200g     | A study of bevacizumab in combination with capecitabine and cisplatin as first-line therapy in patients with advanced gastric cancer | Phase III, Randomized | Closed | Arm 1: capecitabine/cisplatin plus bevacizumab  
Arm 2: capecitabine/cisplatin plus placebo |
| BO18255      | ToGA study – A study of herceptin (trastuzumab) in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer | Phase III, Randomized | Closed | Arm 1: herceptin in combination with a fluoropyrimidine and cisplatin  
Arm 2: chemotherapy alone |
| 104578       | Lapatinib in combination with weekly paclitaxel in patients with ErbB2 amplified advanced gastric cancer | Phase III, Randomized | Active | Arm 1: lapatinib plus paclitaxel  
Arm 2: only paclitaxel |
| EGF110656    | LOGiC – Lapatinib optimization study in ErbB2 (HER2) positive gastric cancer: A phase III global, blinded study designed to evaluate clinical endpoints and safety of chemotherapy plus lapatinib | Phase III, Randomized | Active | Arm 1: capecitabine/oxaliplatin plus lapatinib  
Arm 2: capecitabine/oxaliplatin alone |
| CCR3024      | REAL 3 Version 1.3: Trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer | Phase III, Randomized | Active | Arm 1: EOX  
Arm 2: EOX + panitumumab |
| ML22367      | A study of avastin (bevacizumab) in combination with xeloda (capecitabine) and cisplatin as first-line therapy for advanced gastric cancer | Phase III, Randomized | Active | Arm 1: capecitabine/cisplatin plus bevacizumab  
Arm 2: capecitabine/cisplatin alone |
| EMR 200048-052 | Erbitux in combination with xeloda and cisplatin in advanced esophago-gastric cancer | Phase III, Randomized | Active | Arm 1: capecitabine plus cetuximab  
Arm 2: capecitabine alone |
| CRAD001R 2301 | Safety and efficacy of RAD001 (everolimus) monotherapy plus best supportive care in patients with advanced gastric cancer (AGC) | Phase III | Active | This study is designed to assess the safety and efficacy of RAD001 monotherapy in patients with advanced gastric cancer which has progressed after one or two lines of prior chemotherapy |
regimen vs ECF, with a remarkable safety advantage. Recent data also emerged on the use of irinotecan in advanced gastric cancer, in particular in combination with 5-FU and leucovorin (FOLFIIRI), with acceptable response rates and overall survival time. The use of biological agents may represent a further step towards the improvement of advanced gastric cancer treatment. At the present time, the role of biological agents, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER)-2-targeted monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and angiogenesis inhibitors is the subject of ongoing clinical trials. During the recent ASCO meeting, a randomized phase III trial aiming to determine the efficacy of trastuzumab in combination with chemotherapy (5-fluorouracil or capecitabine and cisplatin) versus chemotherapy alone in patients with HER-2 positive gastric cancer was presented. The results showed that trastuzumab plus chemotherapy is superior to chemotherapy alone, with a median overall survival significantly improved in the experimental arm (13.5 vs 11.1 months, respectively).

In the tables we reported several ongoing clinical trials regarding treatment for advanced gastric cancer (Table III).

In conclusion, substantial progress has been made in the treatment of advanced gastric cancer, but the rates of cure are still poor compared to other tumor sites. Future applications of newer cytotoxic drugs, targeted therapies and integration of molecular determinants of tumor behaviour, prognosis and response to therapy may help to improve on current standard treatments and facilitate the delivery of more tailored therapeutic interventions.

References


