Neo-adjuvant and adjuvant chemotherapy of gastric cancer

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Gastric cancer is still a major health problem and a leading cause of cancer mortality despite a worldwide decline in incidence. Surgery is the primary curative treatment of locoregional gastric cancer. In Western countries, however, at the time of resection, most patients are expected to have regional lymph node involvement with poor prognostic implications. To improve these results, different trials have been carried out in the adjuvant or neo-adjuvant setting. Many phase III trials of adjuvant therapy have been conducted; however, postoperative treatment modalities have not proven to be superior to postsurgical observation alone. Therefore, at present the routine use of adjuvant therapy should be regarded as an investigational approach. Improved clinical trial designs with standardized surgical techniques and the incorporation of newer active drugs are needed. On the contrary, neo-adjuvant chemotherapy has shown promising results as suggested by the final results of UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial.

Key words: gastric cancer, prognosis, adjuvant and neo-adjuvant setting

Introduction

Despite its declining incidence in Western countries, gastric cancer remains the second most common cause of cancer death worldwide with more than 600,000 deaths per year [1–3]. Surgery is the only potentially curative treatment of localized gastric cancer and radical gastrectomy with extended lymphadenectomy is now recognized as a reasonably safe procedure in experienced centers [4, 5]. The survival benefit of extended lymphadenectomy, however, is yet to be proven in a large-scale randomized trial [6–9], and the prognosis for patients with locally advanced gastric cancer remains poor even after potentially curative resection with a high risk of locoregional or distant recurrence (Table 1) [11].

Globally, almost 60% of patients who undergo an R0 resection will relapse and die due to their disease; consequently, the overall 5-year survival rate of patients with resectable gastric cancer ranges from 10% to 30%. The high risk of relapse after surgery has led to search strategies to prevent relapse and to improve survival for gastric cancer patients, as preoperative or neo-adjuvant approaches or postoperative or adjuvant therapy strategies.

Neo-adjuvant chemotherapy

Primary chemotherapy, potentially useful for patients with advanced T and N stages, may result in downstaging of the tumors and consequently improving the curative resection rate. Furthermore, a theoretical benefit of neo-adjuvant chemotherapy concerns micrometastases that are undetectable at the start of treatment. Patients with locally advanced cancer are more or less likely to harbor distant micrometastases which could remain untreated for several weeks when the surgery-first strategy is selected. Finally, a further potential advantage of preoperative therapy includes improved tolerance since chemotherapy carried out immediately after gastric surgery is often marred by surgery-related gastrointestinal symptoms. A number of clinical trials have shown that preoperative chemotherapy is feasible and able to increase the rate of R0 resection. In particular, several small phase II trials with different cisplatin-based neo-adjuvant chemotherapy regimens have reported response rate between 40% and 60% and R0 resection rates up to 80%. In the small Dutch randomized trial, however, 59 patients were randomly assigned to receive the FAMTX regimen before surgery or to surgery alone. Complete or partial response was registered in 32% of the FAMTX group and there was no difference in terms of resectability. With a median follow-up of 83 months, the overall survival (OS) since randomization was 18 months in the FAMTX-treated patients versus 30 months in the surgery-alone group (P = 0.17). This trial did not show a beneficial effect of preoperative FAMTX [12].

The most important large phase III study is the UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial that was also the first well-powered phase III neo-adjuvant chemotherapy study to assess the efficacy of perioperative chemotherapy. Five hundred
and three patients with potentially resectable gastric cancer were randomly assigned to both preoperative and postoperative ECF chemotherapy versus surgery alone. ECF regimen consisted of epirubicin (50 mg/m²) and cisplatin (60 mg/m²) administered on day 1 and protracted venous infusion of 5-fluorouracil (5-FU; 200 mg/m²/day) on days 1–21, administered every 3 weeks for three cycles before and after surgery. The results of this trial demonstrated a statistically significant improvement of the study arm in progression-free survival (PFS) [hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.53–0.81; \( P < 0.001 \)] and OS compared with surgery alone (HR 0.75; 95% CI 0.60–0.93; \( P = 0.009 \); 5-year survival rate, 36% versus 23%). The resected tumors were significantly smaller and less advanced in the perioperative chemotherapy group [13].

**adjuvant chemotherapy**

The role of adjuvant therapy in gastric cancer has been studied extensively during the past three decades in an attempt to improve the prognosis of patients with gastric cancer who have undergone curative surgery. To date, no definitive conclusions have been drawn from randomized clinical trials of adjuvant chemotherapy because few studies have shown a significant positive impact on survival as compared with surgery alone, but their impact is weakened by their small sample size [14]. The more favorable results were reported in Asian studies compared with Western trials, but differences in tumor location, prevalence of early stages, extent of preoperative staging evaluation and a more extensive lymphadenectomy may also account for some of these results [14]. The majority are negative trials, but often they are underpowered and none of them were designed to observe a 5-year survival advantage of a magnitude of 7%–10% which is still clinically relevant [14]. The negative results of most previous clinical studies do not necessarily mean that adjuvant chemotherapy does not work. In fact, an important question is the old type of regimens employed as adjuvant treatment. For many years several randomized studies have investigated the possible role of postoperative therapy, by using the following chemotherapeutic agents: 5-FU, 5-FU in association with doxorubicin and mitomycin C (FAM regimen), mitomycin C and 5-FU, meCCNU plus 5-FU [4, 5, 15, 16]. In particular, the more widely used regimens were the first-generation 5-FU-based regimens, such as FAM or FAM-like regimens designed before introducing cisplatin in the treatment of metastatic disease. Despite the interesting response rate observed in the early studies which justified the premature adoption of FAM as the standard therapy for advanced gastric cancer, however, randomized trials did not show any advantage of using these ‘first-generation’ drug combinations over 5-FU alone [17, 18].

**Table 1. Patterns of relapse after gastric surgery**

<table>
<thead>
<tr>
<th>Study</th>
<th>Site of relapse</th>
<th>Local (%)</th>
<th>Peritoneal (%)</th>
<th>Distant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al. (2002)</td>
<td>40</td>
<td>54</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Mc Donald et al. [10]</td>
<td>29</td>
<td>72</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Gunderson et al. (2002)</td>
<td>38–93</td>
<td>30–43</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Results of meta-analyses**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Odds ratio/hazard ratio for death</th>
<th>Reduction of mortality (%)</th>
<th>Absolute survival effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans (1993)</td>
<td>11</td>
<td>2096</td>
<td>0.82 (95% CI 0.78–1.08), ( P = \text{NS} )</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Earle (1999)</td>
<td>13</td>
<td>1990</td>
<td>0.80 (95% CI 0.66–0.97), ( P = 0.012 )</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Mari (2000)</td>
<td>20</td>
<td>3658</td>
<td>0.82 (95% CI 0.75–0.89), ( P &lt; 0.001 )</td>
<td>18</td>
<td>2–4</td>
</tr>
<tr>
<td>Panzini (2002)</td>
<td>17</td>
<td>3118</td>
<td>0.72 (95% CI 0.62–0.84), ( P = \text{NR} )</td>
<td>28</td>
<td>NR</td>
</tr>
<tr>
<td>Janunger (2002)</td>
<td>21</td>
<td>3962</td>
<td>0.84 (95% CI 0.74–0.96), ( P = \text{NR} )</td>
<td>16</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI, confidence interval; NR, not relevant; NS, not significant.
data derive from subgroup analyses retrospectively done. The meta-analysis of Panzini et al. [25] analyzed data from 2913 patients enrolled in 17 randomized trials that had been published over the period 1981–1999 with the exclusion of studies with incompletely resected patients. A statistically significant reduction in the risk of death was confirmed, with an OR in treated patients being 0.72 (95% CI 0.62–0.84) [25]. Additionally, a significant survival benefit for patients who received adjuvant chemotherapy, compared with controls, was identified in a recent meta-analysis that included 21 randomized studies (OR 0.84; 95% CI 0.74–0.96) [26]. When Western and Asian studies were analyzed separately, no survival benefit was found for the treated patients in the Western groups (OR 0.96; 95% CI 0.83–1.12). Although the meta-analyses suggest a potential survival benefit of adjuvant chemotherapy in resected gastric cancer (overall absolute increase of 3-year survival of about 4%), the relevance of these data in the current clinical practice is restrained by a number of limitations such as lack of individual data recollection, publication bias, differences in patient populations and entry criteria of the trials. To date, adjuvant chemotherapy for gastric cancer should be considered still investigational: the potential reduction in risk of death should be confirmed in a well-designed large prospective randomized trial by using chemotherapy regimens that seem to be more active in metastatic or locally advanced disease.

trials following meta-analyses

Five adjuvant studies have evaluated the role of cisplatin-based regimens. The Italian Trials in Medical Oncology Group study compared surgery alone against surgery plus EAP regimen (etoposide, adriamycin and cisplatin) followed by 5-FU and leucovorin according to the Machover schedule in 274 patients. All patients underwent a subtotal or total gastrectomy with D2 dissection. The study failed to show any statistically significant difference in 5-year OS (52% in the treatment group versus 48% in the control group; \( P = 0.869 \)) and disease-free survival (DFS) (49% in the treatment group versus 44% in the control group; \( P = 0.421 \) ) but only a limited relative risk reduction for patients receiving chemotherapy (17% in DFS and 7% in OS). Although this study was unable to show any statistically significant difference, in presence of widespread nodal involvement (N+ >6), the OS of the patients receiving chemotherapy was significantly better compared with the survival of control arm (42% versus 20%) [27]. The Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) and Gruppo Italiano per lo Studio dei Carciniomi dell’Apparato Digerente (GISCAD) Intergroup study compared a D1/D2 surgery alone against surgery followed by four cycles of PELF (cisplatin, epirubicin, leucovorin and 5-FU) in 258 patients. The HR for PFS was 0.88 (95% CI 0.64–1.23) the HR for OS was 0.91 (95% CI 0.64–1.28) [28]. The GISCAD study compared surgery followed by the Machover regimen (5-FU and leucovorin) versus surgery followed by weekly PELF (cisplatin, epirubicin, leucovorin and 5-FU). This trial was a study that did not have surgery alone as the control arm. These two studies have not yet been published. The French Association for Surgical Research randomly assigned 205 patients between surgery (any type of gastrectomy with a D1/D2 lymphadenectomy) and surgery followed by chemotherapy with PF (cisplatin and 5-FU). This study was unable to demonstrate any statistically significant difference in survival of patients in the experimental arm: in fact, the 3-year survival rate was 39% in the control group and in the experimental arm [29].

The 7 years results of Federation Francophone de la Cancérologie Digestive (FFCD) randomized phase III trial showed a relative risk reduction of 26% for OS with a an absolute difference of 9.5% [29].

In a planned combined analysis of two trials of European Organization for Research and Treatment of Cancer and International collaborative cancer group (ICCG) enrolling 397 patients randomly assigned between surgery alone or surgery followed by Fluorouracil, doxorubicin, methotrexate (FAMTX) or Fluorouracil, epirubicin, methotrexate (FEMTX), no significant differences were found between the treatment and control arms for either DFS (HR 0.98, \( P = 0.87 \)) or OS (HR 0.98, \( P = 0.86 \)). The 5-year OS was 43% in the treatment arm and 44% in the control arm and the 5-year DFS was 41% and 42%, respectively [30]. The Gruppo Oncologico Italia Meridionale (GOIM) Group conducted a trial to explore the efficacy and tolerability of the addition of epirubicin to ELF (etoposide, leucovorin and 5-FU) regimen in previously untreated advanced gastric cancer patients. The epirubicin, leucovorin, 5-fluorouracil and etoposide (ELFE) combination appeared to be effective and well tolerated for the therapy of this set of patients [31]. Based on this background, the GOIM Group evaluated the role of this non-cisplatin regimen as adjuvant treatment. A total of 228 patients curatively resected were enrolled onto this trial. All patients had a total or subtotal gastrectomy with, at least, a D1 lymphadenectomy and, after stratification for nodal involvement (N− versus N+), were randomly assigned to follow-up (116 patients) or six cycles of ELFE regimen (112 patients). With a median follow-up of 60 months, the 5-year OS was 48% in the treatment arm and 43.5% in the control arm (HR 0.91; 95% CI 0.69–1.21; \( P = 0.610 \)); the 5-year DFS was 44% in the treatment arm and 39% in the control arm (HR 0.88; 95% CI 0.66–1.17; \( P = 0.305 \)). In node-positive patients the 5-year OS was 41% in the treatment arm and 34% in the control arm (HR 0.84; 95% CI 0.69–1.01; \( P = 0.068 \)), while the 5-year DFS was 39% in the treatment arm and 31% in the control arm (HR 0.88; 95% CI 0.78–0.91; \( P = 0.051 \)). Therefore, these results do not support the adjuvant treatment with ELFE regimen in radically resected gastric cancer patients [32]. In a recent randomized phase III trial with 1059 patients of ACTS-GC comparing S-1 monotherapy versus surgery alone for stage II/III after curative D2 gastrectomy, OS at 3 years for all randomly assigned patients was 80.5% (95% CI 76.6% to 84.4%) for S-1 and 70.1% (65.5% to 74.6%) for controls. HR of death for S-1 was 0.68 (0.52–0.87; \( P = 0.0024 \)). This regimen was proposed as the standard treatment of stage II/III gastric cancer patients after curative D2 dissection.

conclusions and perspectives

Despite the large number of trials, the evidence supporting the usefulness of adjuvant chemotherapy in curatively resected
gastric cancer is not yet definitive and, at present, no standard adjuvant chemotherapeutic regimen has been established. The advent of new regimens inducing higher response rates indicates that gastric cancer is a chemosensitive tumor; therefore, from a theoretical point of view, regimens with higher activity, may have more efficacy as adjuvant therapy. In an Italian Intergroup study (Intergroupo Nazionale Adjuvante Gastrico) it will be investigated if the association of irinotecan, 5-FU and leucovorin followed by docetaxel and cisplatin improve the efficacy when compared with a 5-FU and leucovorin regimen. The role of radiotherapy needs also to be determined. The USA Intergroup phase III study evaluated the combination of radiotherapy plus 5-FU/leucovorin (LV) in resected gastric cancer versus surgery alone. The study showed a significant OS benefit in the chemoradiation arm (median OS: 36 versus 27 months; \( P = 0.005 \)); moreover, there was a significant increased local control in chemoradiation arm (30 versus 19 months; \( P = 0.001 \)) [10]. The results of the trial have lead to a standardization of this regimen in the USA. It is, however, remarkable that this decision is based on a study in which the surgery carried out was often not up to the desired standards. For example, D2 lymph node dissection was recommended for all patients, but only 10% received this treatment. For this reason, radiotherapy may have been making for incomplete surgery and it seems difficult to recommend it for patients who underwent adequate surgery. Because of the modest benefit associated with adjuvant chemotherapy, the investigation of efficacy of new drugs as adjuvant treatment is warranted. Instead, based on the results of the MAGIC trial, a preoperative chemotherapy should be offered to patients who have a stage II–III. Finally, new biologic agents (anti-epidermal growth factor receptor (EGFR), antiangiogenesis) might also contribute to improvement of results in the future as well as tailored therapy based on the molecular profile of both the cancer and the patient.

references