Adjuvant chemotherapy of gastric cancer: which regimens?

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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. Surgical resection with curative potential is the only treatment modality of scientific proven effectiveness. Many phase III trials of adjuvant therapy have been conducted, however, postoperative treatment modalities have not proven to be superior to post-surgical 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.

Introduction

Gastric cancer is one of the most common cancers worldwide, although its incidence has steadily declined during the last decades in Western countries in both sexes [1–3]. As with other tumours, prognosis is clearly related to stage: based on TNM staging, the depth of invasion, presence of lymph-node metastases and number of lymph-nodes involved predict the risk of relapse [4].

Surgery remains the mainstay therapy for gastric cancer, although at present there is no consensus about the optimal extent of lymph-node dissection [5–7]. However, among patients who undergo a curative resection, 38–67% will develop a clinically evident loco-regional recurrence [8].

The role of adjuvant therapy in gastric cancer has been studied extensively over 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 randomised clinical trials of adjuvant chemotherapy, because few studies have shown a significant positive impact on survival as compared to surgery alone, but their impact is weakened by their small sample size [9]. The more favourable results were reported in Asian studies compared to 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 [8]. The majority are negative trials, but often they are underpowered and none of them was designed to observe a 5-year survival advantage of a magnitude of 7–10% which is still clinically relevant [9].

Which regimens?

Data from meta-analyses

Since 1993 there have been several published meta-analyses that have attempted to better assess any potential benefit of adjuvant therapy that may have been missed in the individual trials [16, 20–22] (Table 1).

The first early meta-analysis analyzed 11 randomized trials with a total of 2096 patients and concluded that adjuvant chemotherapy did not improve survival (odds ratio: 0.88; 95% CI 0.78–1.08) [16]. However, this analysis was criticized for a lack of sufficient statistical power and the studies chosen for inclusion [17, 18] and updated in 1994, obtaining a significant odds ratio (0.82; 95% CI 0.68–0.97) [19].

Recent meta-analyses showed, however, a marginal, but significant benefit of post-operative therapy. The meta-analysis of Earle and Maroun was based on 13 trials with 1990 patients.
The authors reported an odds ratio for death in the treated patients of 0.80 (95% CI 0.66–0.97), corresponding to a relative risk of 0.94 with an absolute survival benefit of 4%. Subgroups analysis showed a trend towards a larger magnitude of the effect when analysis was restricted to trials in which at least two-thirds of patients had lymph-node positive disease. Furthermore a trend towards a lower relative risk was recorded for patients treated with anthracyclines [20].

In 2000, Mari et al. reported a meta-analysis of 20 studies undertaken between 1983 and 1999: data from the 3568 patients analyzed showed a hazard ratio of death of 0.82 (95% CI 0.75–0.89) which represented a 18% reduction in the relative risk of death, with an absolute survival effect of 2–4%. In a subgroup analysis, the authors did not detect any statistical difference between trials with or without the use of anthracycline-based therapy; furthermore monotherapy gave significantly better results than polichemotherapy. This result is based on two randomised trials with mitomycin as monotherapy [21]. However it must be pointed out that these data derive from subgroups analyses retrospectively done. Finally, the meta-analysis of Panzini et al. 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 odd ratio in treated patients being 0.72 (95% CI 0.62–0.84) [22]. Although the meta-analyses suggest a potential survival benefit of adjuvant chemotherapy in resected gastric cancer (overall absolute increase of 5 years 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 [8]. 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 randomised trial by using second- or third generation chemotherapy regimens that seem to be more active in metastatic or locally-advanced disease.

### Cisplatin-based regimens

Four adjuvant studies have evaluated the role of cisplatin-based regimens (Table 2). The ITMO (Italian Trials in Medical Oncology) Group study compared surgery alone against surgery plus EAP regimen (etoposide, adriamycin and cisplatin) followed by 5-fluorouracil 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 statistical significant difference in 5-year overall survival (52% in the treatment group vs 48% in the control group; \( P = 0.869 \)) and disease free survival (49% in the treatment group vs 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 statistical significant difference, in presence of widespread nodal involvement (N+>6), the OS of the patients receiving chemotherapy was significantly better compared to the survival of control arm (42% vs 20%) [23]. The GOIRC and GISCAD Intergroup study compared a D1/D2 surgery alone against surgery followed by four cycles of PELF (cisplatin, epirubicin, leucovorin and 5-fluorouracil) in 258 patients. The hazard ratio for PFS was 0.88 (95% CI 0.64–1.23); the hazard ratio for OS was 0.91 (95% CI 0.64–1.28) [24]. The GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell’Apparato Digerente) study compared surgery followed by the Machover regimen (5-fluorouracil and leucovorin) versus surgery followed by weekly PELF (cisplatin, epirubicin, leucovorin and 5-fluorouracil). This trial was a study that did not have surgery alone as the control arm. These two studies have not yet published. The French Association for Surgical Research randomized 205 patients between surgery (any type of gastrectomy with a D1/D2 lymphadenectomy) and surgery followed by chemotherapy with PF (cisplatin and 5-fluorouracil). This study was unable to demonstrate any statistically significant difference in survival of patients in the experimental arm: in fact the 5-year survival rate was 39% in the control group and in the experimental arm [25].

### Regimens without cisplatin

The GOIM (Gruppo Oncologico Italia Meridionale) Group conducted a trial to explore the efficacy and tolerability of the addition of epirubicin to ELF (etoposide, leucovorin and 5-fluorouracil) regimen in previously untreated advanced gastric cancer patients. The ELFE combination appeared to be

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**Table 1. Data from Meta-analyses**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Studies</th>
<th>No. of Pts</th>
<th>ODDSs ratio/HR for death</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans [16]</td>
<td>11</td>
<td>2096</td>
<td>0.88 (95% CI 0.78–1.08)</td>
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<tr>
<td>Earle [20]</td>
<td>13</td>
<td>1990</td>
<td>0.80 (95% CI 0.66–0.97)</td>
<td>Advantage for doxorubicin-treated pts</td>
</tr>
<tr>
<td>Mari [21]</td>
<td>21</td>
<td>3658</td>
<td>0.82 (95% CI 0.75–0.89)</td>
<td>No difference between trials with or without doxorubicin</td>
</tr>
<tr>
<td>Panzini [22]</td>
<td>17</td>
<td>3118</td>
<td>0.72 (95% CI 0.62–0.84)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. European Trials of Adjuvant Chemotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
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<tr>
<td>ITMO</td>
<td>S vs S + EAP 5FU/LV</td>
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<tr>
<td>GOIRC</td>
<td>S vs S + PELF</td>
</tr>
<tr>
<td>GISCAD</td>
<td>S + 5FU/LV vs S + PELFw</td>
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<tr>
<td>GOIM</td>
<td>S vs S + ELFE</td>
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<tr>
<td>FFCD</td>
<td>S vs S + PF</td>
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effective and well tolerated for the therapy of this set of patients [26]. 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 registered onto this trial. Because of randomization, patients’ characteristics were well balanced between the treatment groups. The inclusion criteria and the study design are reported in Figure 1. All patients had a total or subtotal gastrectomy with, at least, a N2 lymphadenectomy and, after stratification for nodal involvement (N− vs N+), were randomized to follow-up (116 patients) or six cycles of ELFE regimen (112 patients). All patients were assessable for toxicity. Hematologic toxicity, diarrhea and stomatitis were the major grade 3–4 toxic effects. From June 2005, all patients will have had a minimum of 4 year’s follow-up and the number of events required for the primary outcome analysis of overall survival will be available.

**Future strategies**

Over the last years, several new drugs have been successfully tested against gastric cancer. Among them, docetaxel, irinotecan and the third-generation derivative oxaliplatin provide more effective and better tolerated regimens for the treatment of advanced gastric cancer. Single agent docetaxel was shown to induce a response rate of 19–22% in advanced gastric cancer. In V-325 phase III study, the association of cisplatin and 5-fluorouracil was compared to docetaxel, cisplatin and 5-fluorouracil in 223 patients with metastatic gastric cancer. The interim analysis of the study showed a statistically significant advantage in terms of PFS (5.2 vs 3.7 months; \( P = 0.0008 \)) and OS (10.2 vs 8.5 months; \( P = 0.00064 \)) for docetaxel-arm [27]. In a phase II randomized study of SAKK (Swiss Group for Clinical Cancer Research) the combination of docetaxel, cisplatin and 5-fluorouracil showed a superior activity to docetaxel and cisplatin and to ECF (epirubicin, cisplatin and 5-fluorouracil) [28]. Irinotecan has been tested as single agent in gastric cancer in several studies and shown to be active in first-line therapy with a response rate of 18–23%; furthermore, several trials have demonstrated the activity of irinotecan-based combinations [29]. In the phase II randomized V-306 study the association of irinotecan, 5-fluorouracil and leucovorin showed an high response rate (42%) with a better PFS and OS compared to irinotecan and cisplatin combination [30]. Finally another important characteristic of these new drugs in the treatment of gastric cancer is their relatively lack of cross-resistance with other cytotoxic agents, confirmed by their activity in pre-treated patients [31]. Based on these data, the evaluation of regimens incorporating new drugs in the adjuvant treatment of gastric cancer patients appear very interesting. In an ITMO trial patients with resected gastric cancer are randomized to receive six cycles of mitomycin-C or three cycles of irinotecan, 5-fluorouracil and leucovorin followed by three cycles of docetaxel and cisplatin. Likely, in an Italian Intergroup study (Intergrupo Nazionale Adiuvante Gastrico) will be investigated if the association of irinotecan, 5-fluorouracil and leucovorin followed by docetaxel and cisplatin improve the efficacy when compared to a 5-fluorouracil and leucovorin regimen. A randomized trial of neoadjuvant vs adjuvant docetaxel, cisplatin and 5-fluorouracil has also been designed by SAKK to evaluate the role of docetaxel-based combinations in the perioperative treatment of gastric cancer.

**Conclusions**

Despite the large number of trials, the evidence supporting the usefulness of adjuvant chemotherapy in curatively resected gastric cancer is not yet definitive. Likely, 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. There are a number of questions to which will be mandatory to answer. One major question is if perioperative systemic therapy may have a role either neoadjuvant treatment by increasing resectability and thus the local control or postoperatively by eradicating micrometastatic disease. Furthermore, experimental studies suggest that changes in residual tumor cell kinetic occur early after removal of a primary tumor. In a meta-analysis of randomized trials conducted in Western countries, delayed adjuvant chemotherapy has failed to show an effect on survival. It appears, therefore that the most favourable time for administration of adjuvant chemotherapy may be around the time of operation. The optimal timing of administration of chemotherapy (preoperative or postoperative) has become of increased interest. The quality of surgery is another critical point to be explained as soon as possible. In fact, the efficacy of adjuvant chemotherapy must be tested in relationship with adequate surgery before it may be considered standard therapy. Finally the role of radiotherapy needs also to be determined. The US Intergroup phase III study evaluated the combination of radiotherapy plus 5-FU/LV in resected gastric cancer vs surgery alone. The study showed a significant overall survival benefit in the chemoradiation arm (median OS: 36 vs 27 months; \( P = 0.005 \)); moreover, there was a significant increased local control in chemoradiation arm (30 vs 19 months; \( P = 0.001 \)) [32]. The results of trial have lead to a standardisation of this regimen in the United States. However, it is remarkable that this decision is based on a study in which the surgery performed

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**Figure 1. GOIM 9602: Study design.**

![Figure 1. GOIM 9602: Study design.](image-url)
References


27. Ajani JA, Van Cutsem E, Moiseyenko V et al. Docetaxel (D), cisplatin (C) 5-fluorouracil (F) compared to cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naive patients with metastatic or locally recurrent, unresectable gastric carcinoma: (MGC): interim results of a randomised phase III trial (V325). Proceeding of 39th ASCO Meeting. Abs n. 249. Chicago May 31–June 3, 2003.


