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# GASTRIC CANCER. TREATMENT OF ADVANCED DISEASE AND NEW DRUGS

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## 1. ABSTRACT

Gastric cancer is most chemosensitive among gastrointestinal tumors. However, the role of chemotherapy in advanced disease and its advantage over best supportive care has been adequately addressed only in the last decade. First generation regimens, such as 5-Fluorouracil (5-FU), Doxorubicin, Mitomycin C (FAM) have been used until early 90's, when evidence from randomized studies came up in favour of second generation regimens, such as 5-FU, Doxorubicin, high-dose Methotrexate (FAMTX), which in turn was proven less active than a third generation regimen, such as epirubicin, cisplatin, continous infusion 5-FU (ECF) in a randomized study. Newer treatment options came up over last years. The Swiss Group for Clinical Cancer Research has carried out a randomized three-arm phase II study with ECF or docetaxel, cisplatin (TC), or docetaxel, cisplatin, 5-FU (TCF) in advanced gastric cancer. TCF has been selected as the combination to be further evaluated in a formal comparison with ECF. Oxaliplatin is being tested in advanced gastric cancer. Two recently published phase II studies of biweekly infusional 5-FU, folinic acid, and oxaliplatin have shown a considerable therapeutic activity. Irinotecan is another drug under investigation in advanced gastric cancer, both as single agent and in combination. A randomized phase II-III study of irinotecan plus cisplatin or irinotecan plus folinic acid/5-FU has recently been completed; the latter arm was proven worth undergoing a formal comparison with a standard CF regimen.Oral fluoropyrimidines represent a suitable therapeutic option in selected groups of patients.Marimastat is a matrix metalloproteinase inhibitor, whose main toxicity is musculoskeletal. A randomized phase III study of marimastat versus placebo as manteinance therapy in advanced gastric cancer has shown a significant survival advantage for the marimastat arm, both in the total patient population and in the subgroup of patients who had previously received chemotherapy. Since a clear gold standard for advanced gastric cancer does not yet exist, the inclusion of patients in well designed clinical trials is to be considered the best treatment option.

**Table 1.** Chemotherapy and best supportive care versus best supportive care alone in advanced gastric cancer

| Treatment | OS (months) | *P* value | Reference |
|---|---|---|---|
| FEMTX<br>BSC | 12<br>3 | <0.001 | 1 |
| FAMTX<br>BSC | 10<br>3 | <0.001 | 2 |
| ELF<br>BSC | 7.5+<br>4 | 0.05 | 3 |
| (E)LF<br>BSC | 8<br>5 | 0.12<br>(0.003 multivariate analysis) | 4 |

## 2. INTRODUCTION

The majority of patients with gastric cancer develop metastases during the course of their disease and become eligible for chemotherapy. Although gastric cancer can be regarded as the most chemosensitive among gastrointestinal tumors, the impact of chemotherapy on survival in advanced disease is limited. This issue has been addressed by four randomized trials which have evaluated the impact of chemotherapy on survival compared to best supportive care (1-4). In the control groups, median survival was 3 to 5 months, while in the chemotherapy arms it was 7.5 to 12 months. In three of the four studies, the improvement in median overall survival was statistically significant. In the 2 studies which evaluated also quality of life (3-4), an improvement was observed as well. Details on the above four trials are shown in table 1.

## 3. THERAPEUTIC ADVANCES

### 3.1. Evolution of the pharmacologic approach

First-generation chemotherapy regimens, such as 5-Fluorouracil (5-FU), Adriamycin, Mitomycin C (FAM) were proven to be less effective than second-generation regimens, such as 5-FU, Adriamycin, high-dose methotrexate (FAMTX). In fact, an EORTC study showed that FAMTX gave a better response rate than FAM (41% versus 9%), and a longer median survival (42 versus 29 weeks) (5). Subsequently, a randomized trial showed that the combination of etoposide, doxorubicin and cisplatin (EAP) was no more effective than FAMTX, and led to significantly greater toxicity (6). More recently, the epirubicin, cisplatin, continuous infusion 5-FU (ECF) regimen was proven to be more active than FAMTX in a randomized study, in which ECF led to a longer median overall survival than FAMTX (8.9 versus 5.8 months) (7). Another important third-generation regimen is PELF (cisplatin, epirubicin, leucovorin, 5-FU), which compared favourably both with FAM regimen (8), and, more recently, with FAMTX (9). In particular, in the latter trial, a statistically significant difference between the 2 arms in terms of objective responses and complete responses was observed. The survival rates after 12 months and 24 months were also higher among patients receiving PELF, but these differences were not statistically significant. Details on the main randomized trials of combination chemotherapies in advanced gastric cancer are shown in table 2. From the critical analysis of available data, it can currently be stated that a regimen like ECF can be considered as a reference regimen. However, some newer compounds, such as docetaxel, oxaliplatin, irinotecan are under extensive investigation.

### 3.2 Newer cytotoxic approaches

#### 3.2.1. Docetaxel

Docetaxel is a more recent therapeutic option in advanced gastric cancer. When used alone, docetaxel is able to induce responses in about 20% of patients (10); when combined with cisplatin the response rate may rise to 40-50%, and median overall survival to 9-10 months (11, 12).

The Swiss Group for Clinical Cancer Research (SAKK) has carried out a randomized three-arm phase II study with ECF or docetaxel, cisplatin (TC), or docetaxel, cisplatin, 5-Fluorouracil (TCF) in advanced gastric cancer. Despite an increased toxicity, docetaxel-based regimens looked more efficacious than ECF. In particular, TCF looked the most promising regimen in terms of response rate and time to progression, and it has been selected as the combination to be further evaluated in a formal comparison with ECF (13). Details on this study are provided in table 3. In parallel with SAKK study, a multinational phase III study (V325) of TCF versus cisplatin/5-FU (CF) was started. In this study, patients were randomized to receive either docetaxel 75 mg/m$^2$ plus cisplatin 75 mg/m$^2$ on day 1 every 3 weeks plus continuous infusion 5-FU 750 mg/m$^2$ on days 1-5 every 3 weeks or cisplatin 100 mg/m$^2$ on day 1 plus continuous infusion 5-FU 1000 mg/m$^2$ on days 1-5 every 4 weeks. TCF had been previously selected as the test arm based on the phase II randomized portion of V325. Interim analysis in the phase III, carried out on 232 patients, has shown a therapeutic advantage in terms of response rate (39% versus 23%; p=0.012) and time to progression (5,2 versus 3.7 months; hazard ratio 1.704) in favour of the TCF arm (14).

#### 3.2.2. Oxaliplatin

Oxaliplatin is another compound under investigation in advanced gastric cancer, mainly in combination with leucovorin and infusional 5-FU. Two clinical trials with fairly similar doses and schedules of the three drugs have been published, and a clinical activity has been consistently demonstrated. In particular, in the Louvet study (15), an overall response rate of 44.9% was observed in 49 assessable patients; median time to progression and overall survival were 6.2 months and 8.6 months, respectively. In the more recent Al-Batran study (16), one complete response and 15 partial remissions were observed in 37 assessable patients, for an overall response rate of 43%; median overall survival was 9.6 months, and the observed toxicities (mainly hematologic and gastrointestinal) were fairly manageable.

#### 3.2.3. Irinotecan

Irinotecan has shown efficacy in the treatment of metastatic gastric cancer, both when used alone and in combination, in either pretreated or unpretreated patients (17). Single-agent response rate averages 20%; when irinotecan is administered in combination with cisplatin or with leucovorin and 5-FU, the response rate increases to up to 50%, and median overall survival is about 10 months

**Table 2.** Combination chemotherapy for advanced gastric cancer

| Treatment | No. of pts | Intention-to-treat response rate (%) | Median survival | Reference |
|---|---|---|---|---|
| FAM vs FAMTX | 105<br>107 | 9<br>41<br>*P*=0.0001 | 29 wks<br>42 wks<br>*P*=0.004 | 5 |
| FAMTX vs EAP | 30<br>30 | 33<br>20 | 7.3 months<br>6.1 months | 6 |
| FAMTX vs ECF | 130<br>126 | 21<br>45<br>*P*=0.0002 | 5.7 months<br>8.9 months<br>*P*=0.0009 | 7 |
| PELF vs FAMTX | 94<br>93 | 39<br>22<br>*P*=0.009 | 7.7 *months*<br>6.9 *months* | 9 |

**Table 3.** TCF vs TC vs ECF as systemic treatment for advanced gastric carcinoma: A randomized phase II trial of the Swiss Group for Clinical Cancer Research (SAKK)

| | ECF | TC | TCF |
|---|---|---|---|
| Patient Number | 40 | 38 | 41 |
| Response Rate | 46% | 42% | 55% |
| Time to Progression | 5.0 months | 4.3 months | 7.3 months |
| Overall survival | 8.0 months | 11.0 months | 10.4 months |

ECF: epirubicin, cisplatin, continuous infusion 5-FU, TC: docetaxel , cisplatin, TCF docetaxel, cisplatin, 5-FU

(18, 19). Pozzo *et al.* (20) have recently published the results of a randomized phase II study of irinotecan in combination with 5-FU and folinic acid (FA) or with cisplatin in patients with advanced gastric cancer. The overall response rate in the 59 patients treated with irinotecan/5-FU/FA was 42.4%, with a complete response rate of 5.1%. In the irinotecan/cisplatin arm, 32.1% of 56 patients had an objective response, and 1.8% of patients had a complete response. The median time to progression was 6.5 months in the irinotecan/FA/FU arm, and 4.2 months in the irinotecan/cisplatin arm (P<0.0001). Median survival was 10.7 and 6.9 months, respectively (P=0.0018). Safety profiles were acceptable in the two arms. On the basis of these data, irinotecan/5-FU/FA was selected as the best combination to be tested in a phase III study versus a standard cisplatin-5-FU regimen.

### 3.2.4. Oral fluoropyrimidines

5-FU prodrugs have undergone evaluation in advanced gastric cancer over last years, due to their ease of administration and their pharmacokinetic consistency with a 5-FU continuous infusion. UFT, a combination of ftorafur and uracil, has induced a response rate of about 28% in 3 phase II trials (21-23). S-1, a combination of ftorafur, gimestat (dihydropyrimidine dehydrogenase inhibitor), and otastat potassium (gastrointestinal protector), has induced a 49% overall response rate in a phase II study (24). Capecitabine was used in a pilot phase II study in 32 patients with advanced gastric cancer and yielded an overall response rate of 19.4% and a median survival of 8.8 months (25).

Taken as a whole, these data confirm that oral fluoropyrimidines can be considered in the therapeutic armamentarium against advanced gastric cancer; they might replace 5-FU in combination regimens, or, even more appropriately, be used alone in elderly or poor performance status patients, in whom a more aggressive regimen could not be indicated.

### 3.3. Biologic agents – Marimastat

Marimastat is a broad spectrum, low molecular weight matrix metalloproteinase inhibitor, which has been shown to inhibit tumor growth in a xenograft model of human gastric cancer (26). A phase I study of marimastat in patients with advanced gastric cancer showed an increase in endoscopically observed fibrous stroma, and a decrease in hemorrhagic appearance, accompanied by symptomatic improvement, in about one third of patients (27). The main toxicity associated with marimastat was musculoskeletal pain and inflammation. A randomized placebo-controlled trial of marimastat as maintenance therapy in patients with advanced gastric cancer was subsequently carried out in order to establish whether the biological activity seen in the phase I study would translate into a survival advantage. Three hundred and sixty-nine patients with advanced gastric adenocarcinoma, who had received no more than a single regimen of 5-FU-based chemotherapy, were randomized to receive either marimastat (10 mg b.d.) or placebo. A slight difference in survival in the intention-to-treat population in favour of marimastat was observed (P=0.07). This survival benefit was maintained over a further two years of follow-up (P=0.024). The median survival was 138 days for placebo and 160 days for marimastat, with 2-year survival of 3% and 9%, respectively. A significant survival benefit was observed in the pre-defined subgroup of 123 patients who had previously received chemotherapy (P=0.045). After 2 additional years of follow-up, this benefit further increased (P=0.006), with 2-year survival of 5% and 18%, respectively (28).

## 4. CONCLUSION AND PERSPECTIVES

In spite of new pharmacologic approaches, remarkable modifications in the survival of patients with advanced gastric cancer have not been observed over the last years. Based upon the results of randomized trials, ECF can still be considered a reasonable standard regimen for

advanced gastric cancer. As for new biologic and target-based therapies, very few data exist in gastric cancer, with the important exception of marimastat, whose significant clinical results in advanced gastric cancer await confirmation. However, further studies testing the activity of biologic agents, both alone and in combination with cytotoxics, are ongoing. For the time being, in view of the lack of a clearly defined gold standard, the enrolment of patients in well-designed clinical studies is to be considered the wisest approach.

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