Systemic Chemotherapy in Gastric Cancer: Where Do We Stand Today?

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ABSTRACT
Gastric cancer is one of the major causes of cancer-related mortality worldwide. Its prognosis is poor, and surgery offers the only realistic chance of cure. Nevertheless, most of the patients present with inoperable tumors, while the recurrence rate after potentially curable resections is high. In these patients, systemic chemotherapy has been used for palliation of symptoms and possibly for prolongation of survival.

5-fluorouracil (5-FU) is the most widely used agent in chemotherapy of gastric cancer alone or combined with other cytotoxic drugs. Until recently, combination chemotherapy produced modest results, with no significant impact on survival. Progress in research studying the mechanisms of action of various chemotherapeutic agents led to the design of more active chemotherapy regimens. Combinations of 5-FU and cisplatin and the use of modulators of 5-FU activity have produced high response rates, including complete responses in more than 10% of patients with advanced gastric cancer, and, in certain studies, a small but significant survival benefit over older regimens.

Adjuvant chemotherapy has not generally produced a significant survival benefit in patients undergoing curative resection. The use of newer, more effective regimens is currently being investigated and might prove useful in certain high-risk groups.

Neoadjuvant chemotherapy, chemoradiotherapy, and chronomodulated administration of 5-FU, along with the use of novel chemotherapeutic agents, represent exciting areas for clinical research which might further improve the role of systemic chemotherapy in gastric carcinoma. The Oncologist 1998;3:171-177

INTRODUCTION
Gastric cancer is the most frequent malignant neoplasm of the stomach, with adenocarcinoma accounting for more than 90% of all carcinomas. It is one of the leading causes of cancer-related deaths worldwide [1, 2]. The incidence of gastric adenocarcinoma has been steadily declining from 1930 through 1980 throughout the world, although patterns vary widely [1]. Interestingly, this is mostly due to a decline of distal tumors (body and antrum), which are the most frequent, while the incidence of proximal tumors (gastroesophageal junction and cardia) has been rising since 1976 [3], suggesting a different mechanism of pathogenesis between these tumors.

The prognosis of gastric carcinoma is poor, with a five-year survival of 15%-20% [2]. A slight but definite improvement has been observed during the last 30 years [4]. The major causes for this grim outlook are late diagnosis and ineffective treatment for advanced disease. Excluding Japan, only 10%-20% of patients present with disease confined to the stomach, and more than one-third have distant metastases at the time of diagnosis [2]. Even after a potentially curative resection, only 20%-30% of the patients survive beyond five years, as shown by large population-based studies [5, 6].

Surgery offers the only realistic chance of cure. Subtotal gastrectomy is used for tumors of the distal third of the stomach, whereas total gastrectomy is required for proximal tumors. Widespread use of endoscopy, more radical surgical techniques, and improvement in the perioperative care have resulted in an increase in the percentage of potentially curative resections and better survival rates after such procedures in Europe and USA [4, 7]. Survival rates are higher in Japan, where early disease represents the majority of the cases, as a result of extensive endoscopic surveillance. In addition, more aggressive surgical procedures are used. These differences created a debate regarding the surgical management of gastric cancer, namely the importance of...
extended lymphadenectomy. Studies from Japan have shown that lymphadenectomy beyond 3 cm of the tumor has improved survival [7-9]. Nevertheless, two prospective randomized studies outside Japan [10, 11] failed to reproduce these results. In spite of the undoubted improvement in the surgical management of gastric cancer, still more than 50% of patients undergoing curative resection will relapse and eventually die of their disease, with local and regional recurrence being the most frequent pattern of failure [12].

Radiotherapy has also been used in advanced disease as well as adjuvant treatment. Although palliation can be achieved in certain cases, results have generally been modest, and prospective randomized studies have failed to demonstrate a survival benefit for patients receiving radiotherapy following surgery [13].

In this review, we will concentrate on the role of chemotherapy in gastric cancer, and especially the recent advances in this field which have created some hope for the future in the treatment of this highly lethal disease.

CHEMOTHERAPY IN ADVANCED DISEASE

As already mentioned, the majority of the patients with gastric cancer at the time of diagnosis have locally advanced disease. Since surgery cannot be curative in these cases, chemotherapy has been used in an effort to produce symptomatic improvement and prolong survival.

Several single agents have been used producing responses of 15% or more in phase II studies (Table 1). 5-fluorouracil (5-FU) is the most widely used agent, producing responses in approximately 20% of the patients [19]. In addition, mitomycin-C (MMC), adriamycin, and BCNU have shown similar results [20]. More recent studies, however, using well-defined response criteria, have failed to produce such results, showing response rates of less than 10% for 5-FU and adriamycin [21]. Cisplatin has been used recently and has shown promising results in more than one study [20]. Its synergism with 5-FU in vitro [22] makes it a particularly attractive agent for combination chemotherapy.

Combinations of active agents have been used since the late 1970s, aiming to improve the results of single-agent chemotherapy (Table 2). 5-FU has almost been universally used as the basis in the designing of combination treatment. The FAM regimen (5-FU, adriamycin, and MMC) has been used in the early 1980s as the treatment of choice in advanced gastric cancer, with the initial reports showing response rates of approximately 30% [20]. FAM-like regimens (5 FU/BCNU, FAMe) (Table 2) produced similar results, and several randomized studies failed to detect, with rare exceptions, significant differences among them [31]. It is interesting to point out that in these early studies: A) complete responses were extremely rare; B) there was no significant prolongation of survival, and C) in most of these studies, responses were evaluated only in a minority of patients. In addition, combination chemotherapy failed to demonstrate any significant survival advantage over single-agent treatment in randomized studies [32], although response rates were generally higher [33, 34].

Advances in basic research resulted in better understanding of the mechanism of action of many chemotherapeutic

| Table 1. Single-agent chemotherapy in advanced gastric cancer |
|---|---|---|---|
| Drug | n Patients | RR (%) | Reference |
| 5-FU | 392 | 21 | [14] |
| MMC | 211 | 30 | [14] |
| Cisplatin | 222 | 22 | [15] |
| CCNU | 37 | 8 | [16] |
| MTX | 28 | 11 | [17] |
| Adriamycin | 68 | 25 | [16] |
| BCNU | 23 | 17 | [18] |

RR = response rate; 5-FU = 5-fluorouracil; MMC = Mitomycin C; MTX = Methotrexate.

| Table 2. Combination chemotherapy in advanced gastric cancer |
|---|---|---|---|
| Combination | n Patients | RR (%) | MS (mo) | Reference |
| **First-generation regimens** |
| FAM (5-FU, adriamycin, MMC) | 453 | 33 | 6.5 | [23] |
| 5-FU, BCNU | 80 | 26 | 5.5 | [23] |
| FAMe (5-FU, adriamycin, CCNU) | 76 | 25 | 7 | [24] |
| **Second-generation regimens** |
| FAP (5-FU, adriamycin, cisplatin) | 26 | 50 | 9 | [25] |
| FPEPIR (5-FU, cisplatin, epirubicin) | 22 | 27 | | [26] |
| FP (5-FU, cisplatin) | 21 | 24 | | [26] |
| FLEP (5-FU/lucocurcin, epirubicin, cisplatin) | 90 | 35 | 8 | [27] |
| EAP (etoposide, adriamycin, cisplatin) | 67 | 64 | 9 | [28] |
| FAMTX (5-FU, adriamycin, high-dose MTX) | 100 | 59 | | [29] |
| ECF (epirubicin, continuous 5-FU, cisplatin) | 235 | 61 | 8.4 | [30] |

RR = response rate; 5-FU = 5-Fluorouracil; MMC = Mitomycin C; MTX = Methotrexate; MS = median survival; mo = months.
agents, including 5-FU, the main drug used in advanced gastric cancer. In vitro studies have shown that methotrexate (MTX) can enhance the activity of 5-FU by blocking the pyrimidine salvage pathway, thus leading to increased intracellular phosphoribosyl pyrophosphates. This shifts 5-FU into the RNA pathway, increasing the destruction of cancer cells [35]. On the other hand, there is in vitro synergism between 5-FU and cisplatin [22] and the addition of cisplatin to 5-FU and epirubicin has prolonged survival and increased response rates in a recent randomized study [36]. Based on these data, several second-generation regimens were developed in the late 1980s. FAMTX (5-FU, adriamycin, high-dose MTX) showed response rates ranging from 33% to 50% in phase II studies [29, 37, 38]. Several combinations of 5-FU with cisplatin have also been studied, yielding response rates between 25% and 55% [25-27]. In addition, a combination not containing 5-FU, the EAP (etoposide, adriamycin, cisplatin) based on the in vitro synergism between etoposide and cisplatin [39], was also developed. This regimen showed impressive response rates [28] and resulted in rendering operable previously unresectable tumors [40]. This was, however, achieved at the expense of significant toxicity. The same group studied another less toxic combination of etoposide, leucovorin, and 5-FU (ELF) [41]. Leucovorin is known to enhance 5-FU activity by stabilizing the FdUMP (the toxic metabolite of 5-FU)-thymidylate synthase complex. Preliminary results of a phase III trial suggest that ELF is equally as effective as FAMTX [42].

Second-generation regimens have been tested in phase II studies with better methodology regarding evaluation of responses, and, for the first time, complete responses of more than 10% were reported. In addition, two prospective randomized trials (Table 3) proved the superiority of the newer regimens, namely FAMTX [38] and PELF [43] over FAM. The latter showed response rates of only 9% and 15%, respectively. Survival was also significantly prolonged in the first study. Nevertheless, median survival still did not reach one year. The two most effective regimens, FAMTX and EAP, were also directly compared in a prospective randomized study (Table 3). Patients with unresectable or recurrent locoregional or metastatic disease were included. FAMTX showed higher activity, although not statistically significant, with significantly lower toxicity [39]. Of all 20 patients with locoregional disease, five underwent laparotomy following response to chemotherapy. In three cases, all gross tumor was removed. Interestingly, both regimens showed lower response rates than those reported in phase II studies. The authors concluded that FAMTX should be the standard chemotherapy in advanced gastric cancer and should be studied as adjuvant treatment in operable gastric cancer.

Continuous infusion of 5-FU has recently been studied in gastrointestinal cancer based on in vitro studies showing enhanced tumor cell killing with longer exposure to the drug [44]. Clinical studies in patients with advanced colorectal cancer have shown that continuous infusion of 5-FU increased response rates with lower toxicity than bolus administration [45]. Recently, it has also been used in advanced gastric cancer. The ECF regimen combines continuous infusion of 5-FU with cisplatin and epirubicin every three weeks. In a phase II study, responses were achieved in 61% of the patients, with 11% complete responses [30]. Treatment was well tolerated, and significant symptomatic improvement was observed even without objective response in a significant number of cases. Liver and lymph node metastases showed the highest response rates, while peritoneal disease responded poorly to chemotherapy. As described in the previous study, downstaging of the tumors allowed curative resection of previously inoperable disease, in certain cases. Quality of life was formally assessed, showing no significant negative impact of chemotherapy on emotional functioning and good symptomatic control in the majority of the patients.

ECF was compared with FAMTX in a recent randomized trial (Table 3) which included 274 patients with esophagogastric adenocarcinoma. ECF was superior both in response rates and survival and was less toxic than FAMTX [46]. Again, responses and survival in the FAMTX arm were lower than those previously reported. Hospital-based cost analysis on a subset of patients showed an incremental cost of $975 per life-year gained for both regimens, suggesting that chemotherapy in advanced gastric cancer using ECF or FAMTX is highly cost effective.

### Table 3. Randomized studies in advanced gastric cancer using second-generation regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n Patients</th>
<th>RR (%)</th>
<th>MS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMTX versus FAM</td>
<td>213</td>
<td>41 versus 9*</td>
<td>42 w versus 29 w*</td>
<td>[38]</td>
</tr>
<tr>
<td>PELF versus FAM</td>
<td>147</td>
<td>43 versus 15*</td>
<td>35 w versus 25 w</td>
<td>[43]</td>
</tr>
<tr>
<td>FAMTX versus EAP</td>
<td>60</td>
<td>33 versus 20</td>
<td>7.3 mo versus 6.1 mo</td>
<td>[39]</td>
</tr>
<tr>
<td>ECF versus FAMTX</td>
<td>274</td>
<td>45 versus 21*</td>
<td>8.9 mo versus 5.7 mo*</td>
<td>[46]</td>
</tr>
</tbody>
</table>

RR = response rate; MS = median survival; w = weeks; mo = months.

* Difference is statistically significant.

**ADJUVANT CHEMOTHERAPY**

As already mentioned, most of the patients undergoing curative resection for gastric cancer will eventually relapse and die of their disease. Extent of the primary...
tumor and nodal stage are considered the most important risk factors for relapse [7]. Therefore, there is clearly a need for additional treatment which would eliminate micrometastases and improve the prognosis after surgery. Chemotherapy has long been used as adjuvant treatment, and many first-generation regimens have been studied in patients with tumors extending beyond the mucosa [47-49].

In general, results have not justified the use of adjuvant chemotherapy as shown by a recent meta-analysis of randomized trials [50]. Nevertheless, certain studies have shown that subgroups of patients might benefit, especially those with stage III disease or lymph node metastases [48, 49, 51]. It is of interest that the combination of MMC with 5-FU is the standard treatment after curative surgery in Japan [52].

Intraperitoneal chemotherapy can also be used to prevent recurrence in the peritoneal cavity, which represents the most frequent site of failure following surgery. Phase I studies have shown favorable kinetics following instillation of 5-FU and MMC in the peritoneal cavity [53]. The role of such treatment remains to be evaluated in large prospective studies. The more effective second-generation regimens have not yet been extensively studied in the adjuvant setting, but several large randomized trials are under way, and their results are expected with great interest in the next five years. ECF has been used postoperatively in a small series of 29 patients with gastric adenocarcinomas [54]. Treatment was well tolerated, and three-year survival for stage III disease was 65.6%. Clearly, these encouraging results need confirmation, but they indicate that the use of more effective chemotherapy could reverse the disappointment from the use of the older regimens, which might reflect the moderate efficacy of the first-generation chemotherapy. A trial evaluating the use of ECF as neoadjuvant treatment in operable gastric cancer is already under way in the UK (MAGIC Trial).

**Chemoradiotherapy**

Both in vitro and in vivo data indicate that 5-FU can enhance the anti-tumor effect of radiation and, in fact, it might be a radiation sensitizer [55]. 5-FU has been used in combination with external radiotherapy in small studies. An early report indicated that continuous infusion of 5-FU followed by 5,000 rads achieved remission in all evaluable patients with gastroesophageal cancer [56]. A later study conducted by the North Cancer Treatment Group showed that concurrent administration of 5-FU/leucovorin and 4,500-5,000 rads is feasible, although toxicity was considerable [57]. The number of patients with gastric cancer entering this study was too small for a definite conclusion. Large prospective trials are needed to establish a role for chemoradiotherapy in advanced gastric cancer or following radical surgery. At the moment, it seems that this modality is not as promising as it has already been for esophageal carcinoma [58].

**Novel Chemotherapeutic Agents**

Although second-generation regimens such as EAP, FAMTX, and ECF have shown considerable efficacy in advanced gastric cancer, further increase in response rates is necessary if significant survival benefits are to be obtained. Therefore, novel agents are worth studying to design more effective chemotherapeutic combinations.

Two new agents which have shown promising results in several types of malignant neoplasms, taxotere and gemcitabine [59-61], have already been tested in gastric cancer in clinical and preclinical studies. Taxotere has already been investigated in two phase II clinical trials. In the European trial, a 24% response rate was reported in a series of 33 patients with advanced gastric cancer [59]. It is interesting that patients who had their primary tumor removed responded better. In a Japanese study, 20% of patients who showed no response to previous chemotherapy had a partial response to 60 mg/m² of three- or four-weekly taxotere doses [60]. Gemcitabine has shown promising results in animal models where human gastric cancer xenografts were used [61], but its activity in patients remains to be proved in clinical studies. Its potential synergy with cisplatin and MMC makes this agent attractive to study in clinical trials.

A DNA topoisomerase-I inhibitor, irinotecan (CPT-11) has also been used alone [62] or in combination with cisplatin [63] in phase I-II clinical studies. Response rates of 23% and 41%, respectively, with acceptable toxicity were reported. In the first study, objective responses in 20% of pretreated patients (mostly with 5-FU) were observed. Although experience with this new agent is still limited, these encouraging results show that it warrants further investigation in larger clinical trials.

**Conclusions and Future Steps**

The use of second-generation regimens which combine 5-FU and cisplatin or employ agents that modulate the activity of 5-FU have improved response rates in inoperable gastric cancer, and, in certain cases, have resulted in a small increase in survival (Table 3). The use of continuous 5-FU infusion is promising and may lead to the development of even more effective treatment, which could eventually alter the belief that gastric cancer is not a chemosensitive neoplasm, created by the modest results of the 1970s. It is worth mentioning that two recent randomized trials showed a significant survival benefit for combination chemotherapy compared to best supportive care [64, 65]. The fact that high-dose chemotherapy with autologous bone marrow transplantation has already been used in Japan
for the treatment of recurrent or inoperable gastric cancer [66] further underlines the change of attitude regarding chemotherapy in this disease. Quality of life is an important issue which should always be taken into consideration, especially when the primary objective of treatment is palliation. Symptomatic improvement can be achieved even without objective response [30], while quality of life is not impaired by chemotherapy, as shown by the use of standardized questionnaires in some studies where the newer regimens were used [30, 46].

The progress in the treatment of advanced disease may be translated in improvement in the role of chemotherapy in the adjuvant setting. Neoadjuvant treatment is another area where effective chemotherapy could improve the outcome of surgery by downstaging the tumor, while the role of chemoradiotherapy needs to be further evaluated. At the moment, adjuvant and neoadjuvant chemotherapy cannot be considered as standard treatment in gastric cancer.

In spite of the promising results of new agents such as taxotere, gemcitabine, and CPT-11, 5-FU remains the best-studied agent in gastric cancer. There is now a considerable amount of information regarding different routes of administration of this agent. Oral administration of fluoropyrimidines represents an exciting area of research. One approach involves the drug UFT, a combination of florafur, which is a 5-FU prodrug, with uracil. Preclinical studies have shown favorable tumor-to-serum 5-FU ratios after oral administration of UFT [67]. In a phase II study, UFT administration to 438 patients with gastrointestinal and breast carcinomas resulted in a 19%-32% response rate [68]. Oral administration might theoretically replace continuous infusion of 5-FU, which would add considerably to the quality of life of these patients. This possibility has to be evaluated in future clinical studies. The detection of the enzymes responsible for the metabolism of 5-FU and other agents and the findings of basic research showing that their activity, in certain cases, is regulated by circadian rhythms [69] have opened new avenues for administering chemotherapy. In addition, proliferative activity of human tissues, including bone marrow, show significant diurnal variations [70]. Based on these data, chronomodulated administration of 5-FU, as well as of oxaliplatin, a new platinum complex, has been used in advanced colon cancer. In this way, most of the dose of the drug is administered at a time when the lowest toxicity and the highest efficacy are anticipated. Results of phase I and II studies in advanced colon cancer have shown that dose intensity can be safely increased, while responses can be achieved in patients who did not respond to conventional administration of 5-FU [71]. Chronomodulated chemotherapy with or without radiation has also been used in advanced pancreatic [72] and esophageal [73] cancer. In the latter, superiority in survival over radiation alone was demonstrated in a preliminary report. This approach has not been used in advanced gastric cancer so far, but since 5-FU is still the most widely used agent, chronomodulated administration alone or combined with oxaliplatin represents an exciting area of clinical research for this disease.

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