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Review paper

Perspectives in chemotherapy of advanced gastric cancer

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A review of recent phase II and III studies in advanced gastric carcinoma is presented. Several combination regimens have been developed with high activity in locally advanced and metastatic disease. Among them are etoposide plus adriamycin plus cisplatin (EAP), etoposide plus 5-fluorouracil plus leucovorin (ELF), continuous infusion 5-fluorouracil plus cisplatin and high dose methotrexate plus 5-fluorouracil plus adriamycin (FAMTX). In locally advanced disease a resectability rate of ±50% has been reported with these protocols. So far only FAMTX has demonstrated superiority compared with 5-fluorouracil, adriamycin and mitomycin (FAM), which regimen has been considered 'standard' treatment for many years. Randomized studies in which the other regimens are being more definitely assessed are underway.

Key words: Chemotherapy, gastric cancer.

Introduction

5-Fluorouracil (5-FU) has been the principal single agent used in the treatment of advanced gastric cancer for more than 20 years and its response rate in collected series appears to be around 20%. During the last decade combination chemotherapy, especially FAM (5-fluorouracil, adriamycin and mitomycin), has been administered to many patients with advanced disease because of the high response rates reported by the end of the 1970s. Data from randomized trials comparing FAM versus 5-FU alone, however, have questioned the value of the application of this particular combination regimen on a routine basis in advanced disease.

Data from the literature until 1987 have been discussed in another review.[1] This review focuses on more recent phase II studies and randomized trials with implications for current treatment and future research.

Phase II studies

Studies with combinations of 5-FU, adriamycin (A) and mitomycin C(M) and/or the nitrosoureas methyl-CCNU (Me) and BCNU (B) have been extensively discussed.[1] Other drugs with apparent activity are the antimetabolites methotrexate (MTX) and triazinate (T) and cisplatin (P). The addition of the antifol triazinate in a dose of 200 mg/m^2 to FAM (FAM-T) resulted in a low response rate of 13% (four of 31 evaluable patients).[2] Phase II studies with P added to A and 5-FU (FAP) yielded response rates ranging between 29 and 59% and a median survival ranging from 4 to 12 months; these data have been discussed.[1] Cisplatin has also been assessed in combination with 5-FU, continuous infusion for 5 days, resulting in 22 (41%) responses of 53 patients[3] in one study and in 23 (53%) of 44 in another.[4] For locally advanced disease impressive results were reported with this schedule. Of 25 patients, 20 could be curatively resected after 1–4 cycles and 15 of them were disease-free after a median follow-up of 8 months.[4] Extremely impressive results were reported with epirubicin and cisplatin added to 5-FU in a continuous infusion for 3 weeks. Of 27 patients there were two complete (laparotomy documented) and 14 partial responses and in the oral communication it was stated that three complete and 24 partial responses of 33 patients were achieved (response rate 82%!).[5] A summary of these data is outlined in Table 1.

A further 'second generation' regimen consists of the combination of etoposide (E), A and P (EAP). The peculiarity of this protocol is that it is the only combination regimen in advanced gastric cancer that does not utilize 5-FU. A response rate of 64% in 67 patients with locally advanced or metastatic disease has been reported including eight

Table 1. Phase II studies with *P* plus continuous infusion of 5-FU in advanced gastric cancer

No. responders/ No. evaluable patients (%)	No. complete responders (%)	Median survival (months)	Reference
22/53 (41)	2	10	3
23/44 (52)	4	10, 18+[a]	4
16/27 (59)	2	NS	5[b]
61/124 (49)	8(6)	10	

[a] 10 months for patients with distant metastases, 18+ for patients with locally advanced disease.
[b] Epirubicin added to 5-FU and cisplatin; in oral presentation response rate of 82% reported.

pathologically documented complete responses. The median survival of all patients was 9 months.[6] In a later report, a total of 145 patients was described including 49 with locally advanced disease. The response was 57% with 15% complete response and a median survival of 10 months.[7] The same authors reported that of 33 patients with locally advanced disease, 23 (70%) achieved complete or partial response. Twenty of these patients underwent second-look laparotomy, five had a pathologically complete response, 10 had no evidence of disease after resection of the residual primary and in three patients the residual tumor could be resected but the resection margins were not tumor-free. In two patients the tumor was still non-resectable. The relapse rate in 20 patients who had no evidence of disease after chemotherapy ± surgery ± consolidation chemotherapy was 60% (12/20) after a median follow-up of 20 months and their overall median survival was 24 months. Nine of 12 relapsing patients had locoregional recurrence as first site of relapse. For all patients entered in the trial, the median survival was 18 months.[8] In a later paper two more patients were included in this series without essentially changing these results. After 30+ months of observation five patients were still disease-free.[7] Several other studies have sought to confirm these impressive results. In the trial reported from Argentina, 18 of 25 patients responded, the median survival of the responders was 27.5 weeks and of all patients 24.5+ weeks. There were 10 episodes of nadir sepsis in 83 cycles and two patients died of toxicity.[9] In a study reported from Japan, there were 13 responders of 29 evaluable patients and two toxic deaths.[10] An updated analysis of this study reported 15 responses of 35 patients and a median survival of all patients of 136 days.[11] In another German study only eight partial responses of 45 patients were reported; in two patients the primary could be resected after six cycles and the median survival of all patients was 9 months. The toxicity in this study was high.[12] Other investigators employed a slightly modified regimen and replaced A by epirubicin. They reported nine (33%) responses of 27 patients; one of these responses was complete and one patient was surgically converted to a complete response. The median actuarial survival in this study was 11 months.[13] Finally, investigators from Dana Farber Institute treated 28 patients and reported 43% response with 14% toxic deaths. Of 11 patients with locally advanced, unresectable disease, four were rendered surgically disease-free following EAP. Median survival in this study was 24 weeks.[14] A summary of studies employing combinations of cisplatin, etoposide and adriamycin or epirubicin is depicted in Table 2.

In order to enhance the activity of 5-FU, a high dose of leucovorin (L), which increases the intracellular concentration of reduced folates, has been added to 5-FU. Employing different schedules,

Table 2. Phase II studies with EAP in advanced gastric cancer

No. responders/ No. evaluable patients (%)	No. complete responders	Median survival (months)	Toxic deaths	Reference
83/145 (57)	22	10	3	7
18/25 (72)	3	6+	2	9
15/35 (43)		4.5	2	11
8/45 (18)		9		12
9/27 (33)	1	11		13[a]
12/28 (43)	3	6	4	14
145/305 (48)	29 (10%)	9	11 (4%)	

[a] Epirubicin substituted for adriamycin.

one study reported 13 responses of 27 patients, one reported 3 of 28 (but in this last study 48% of the patients were pretreated) and one reported 3 of 36 employing continuous infusion 5-FU and 9 of 39 with bolus 5-FU.[15–17] Etoposide has been added to leucovorin and 5-FU (ELF) yielding a 53% response rate in 51 patients older than 65 years or with cardiac risks, including 12% complete responses. This protocol according to the authors was very well tolerated, even in these elderly patients. The median survival was 11 months.[18] Results of 5-FU/leucovorin based regimens are summarized in Table 3.

Finally the combination of sequential high dose methotrexate (MTX) and 5-FU, combined with A (FAMTX), published for the first time in 1982,[19] has been studied by the EORTC G1 Group and results of this trial[20] and of other phase II studies with this regimen have been discussed.[1] Adriamycin has also been deleted from FAMTX. Four cycles of MTX-5-FU in the same dose as in FAMTX were administered to 20 patients with locally advanced surgically incurable cancer of the cardia or fundus. In 17 of these 20 patients the staging was based on both CT and laparotomy. In 14 patients a second-look was performed, and in eight the tumor had become resectable. The median survival of all patients was 14 months and of the resected patients 22 months.[21] On the other hand, results of studies employing intermediate doses of 100–600 mg/m^2 of MTX combined with 5-FU and with different time intervals were all negative.[1]

The International Collaborative Cancer Group (ICCG) assessed the FEMTX regimen in which adriamycin 30 mg/m^2 was replaced by epirubicin in doses of 50, 60 or 70 mg/m^2. There were no apparent differences in toxicity or activity between the three dose levels of epirubicin and overall the response rate was 37% which is comparable to the response rate to FAMTX.[22]

Randomized trials

In three large trials combination chemotherapy did not yield superior survival or response and survival compared to 5-FU alone. The North Central Cancer Treatment Group (NCCTG) compared FAM with FA and with 5-FU alone. Although the number of patients with measurable disease in this study was too small for a meaningful evaluation of differences in the response rates, the survival in all three arms of the study was the same.[23] In an Italian study FAM + BCNU (BAFMI) was compared with 5-FU. There were no significant differences in the response rate or the survival.[24] In another Italian study FAM was compared with 5-FU. In this study, that encompassed 127 patients, the response rate for FAM was 20% and for 5-FU 14%, with a median survival of 6 months in both arms.[25] A very low response rate to standard bolus 5-FU was also reported by the ICCG. There were only two (5%) partial responses of 40 patients randomized to 5-FU versus four (10%) partial responses of 40 patients randomized to epirubicin, with superimposable survival of 6 months in both arms.[26]

The GITSG published the results of a randomized trial of 5-FU plus doxorubicin with either P or Me or triazinate (T). Of a total of 249 patients, 94 had measurable disease and of these there were only 17 partial responses; FAP (20%); FAT (19%); MeFA (15%). The median survival was 31.1 weeks for FAP, 30.3 weeks for FAT and 23.5 weeks for MeFA. The median survival for FAP and FAT was statistically superior to MeFa.[27] Although the authors felt that the low response rate in their study might be explained by the Group's stringent response criteria, these data suggest that FAP or FAT produce at best a minor improvement in therapy and that further testing of FAP in randomized studies does not appear warranted. These data are corroborated by the preliminary

Table 3. Phase II studies with leucovorin/5-FU in advanced gastric cancer

No. responders/ No. evaluable patients (%)	No. complete responders (%)	Median survival (months)	Schedule of 5-FU	Reference
13/27 (48)	1	5.5	d 1–5 bolus	14
3/28 (11)		5	Weekly	15
3/36 (8)		4.7	d 1–4 CI	16
9/39 (23)	3	5.3	d 1–5 bolus	16
27/51 (52)	6	11	d 1–3 bolus	17[a]
55/181 (30)	10 (6)	5		

[a] Etoposide added to leucovorin/FU (ELF).

Table 4. Results of neoadjuvant chemotherapy for locally advanced gastric cancer

Total no. of patients	Regimen	No. with response	No. with second look	Resectable (%)	Reference
25	FU/cisplatin		21	20 (80)	4
35	EAP	24	21	19 (54)	7
11	EAP			4 (36)	14
17	FMTX		14	8 (47)	21
19	FAMTX		7	3 (16)	31
107				54 (50)	

results of a study from Spain comparing FAP with FAM with no significant differences in response rate, 3/13 vs 2/13.[28]

In another Spanish trial EEP has been compared with FEM (substituting epirubicin in EAP and FAM for adriamycin). So far, in 61 patients evaluable for response, no significant differences in response have emerged, but EEP was significantly more toxic.[29]

In 1985 the EORTC GI Group initiated a randomized trial, the first aim of which was to compare the toxicity of FAMTX with that of FAM. An interim analysis of this study showed that the toxicity of FAMTX was moderate and acceptable and comparable to the toxicity of FAM.[30] Therefore the trial was extended to a phase III study evaluating the response rate and the survival of FAMTX vs FAM. The study was closed with a total of 213 patients randomized. The study yielded a 41% response rate to FAMTX versus 9% to FAM ($p < 0.0001$), while the survival was 42 weeks in FAMTX versus 29 weeks in FAM (logrank test: $p = 0.004$). There were no major differences in the toxicity, although mucositis was more pronounced in FAMTX and there was a cumulative thrombocytopenia in FAM.[31]

Discussion

New 'second generation' combination chemotherapy regimens have been developed in phase II testing which appear to have a higher complete response rate and a longer survival than protocols such as FAM that were widely utilized in the 1980s. It has been stated that new protocols should have at least a response rate of 35% and a median survival of 7 months in phase II trials, before being submitted to phase III testing.[32] Of the second generation protocols FAP has undergone phase III testing with essentially negative results. The activity of continuous infusion of 5-FU plus cisplatin, of EAP and of ELF protocols should definitely be assessed in phase III trials. Results of multicenter phase III trials mostly lag far behind the 'promising' data initially reported in phase II studies. A randomized study comparing EAP with FAMTX is underway in Memorial Sloan Kettering Cancer Institute and preliminary data in a total of 39 patients show a 31% response to FAMTX and a 24% response to EAP with less toxicity with FAMTX.[33] The EORTC Gastrointestinal Group has initiated a phase III study comparing FAMTX with ELF and with 5-FU continuous infusion plus cisplatin.

Several of the newer regimens also yielded impressive results in locally advanced disease, leading to resectability in a significant percentage of patients (Table 4). This approach should be further investigated in larger multicenter series and the criteria for non-resectability (laparotomy or clinical staging?) should be clearly defined.

Until now, the FAMTX protocol is the only regimen which has shown a definite superiority in a randomized study in terms of response, toxicity and survival. For the time being, FAMTX, which will now be assessed in the adjuvant setting, must be considered the reference treatment in advanced gastric cancer.

Further studies should reveal whether the FAMTX protocol can be modified in order to achieve superior results.

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