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Perspectives in Cancer Research

Current Status of Chemotherapy for Gastric Cancer

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Abstract—*High response rates to combination chemotherapy reported by the end of the seventies led many oncologists to recommend standard treatment for gastric cancer. In randomized trials conducted by different groups, the response rate with fluorouracil (F), adriamycin (A), mitomycin C (M) ranged between 17 and 39% and was advocated for adjuvant treatment. However, further studies indicate that combination chemotherapy has no beneficial effect on survival compared with 5-FU alone. Several studies assessing the FAM regimen versus control in the adjuvant settting show, so far, no difference between the treatment arms.*

Other agents and combinations have recently been investigated. Cisplatin (P) is active in gastric cancer. In six studies using a combination with FA (FAP), the response rate ranged between 29 and 55% with a median survival of 4–12 months. Other combinations using P with F or etoposide and A have also been promising. Recently, the EORTC Gastrointestinal Group, using a combination of sequence of high dose methotrexate and F with A (FAMTX) reported 22 positive responses out of 66 eligible patients, including nine complete responders. These new treatments are currently being tested by different groups in a randomized trial. For the time being, apart from 5-FU alone, chemotherapy in advanced gastric cancer should not be administered on a routine basis outside clinical trials.

INTRODUCTION

HIGH response rates to combination chemotherapy reported by the end of the seventies have led many oncologists to recommend standard treatment for gastric cancer. Data from the literature prior to 1984 have been discussed extensively [1, 2]. More recent data from randomized trials, however, have questioned the value of the application of combination chemotherapy on a routine basis in advanced disease. Results from older and more recent phase II studies and from randomized trials in advanced disease and in an adjuvant setting will be discussed with implications for future studies.

PHASE II STUDIES

5-Fluorouracil (5-FU) has been the principal single agent used in the treatment of advanced disease for more than 20 years and its response rate in collected series appears to be around 20%. Other drugs with reported activity include adriamycin (A), mitomycin C (M) and the nitrosoureas methyl-CCNU (Me) and BCNU (B) [3]. Using combinations of these drugs, response rates ranging between 8 and 65% have been reported. In the majority of these trials the median survivals of responders have been compared with those of non-responders, a comparison that is only of limited value and has been severely criticized [4]. In some trials the survivals of all patients have been stated to range between 5 and 11 months. Many investigators have employed the combination of 5-FU (F), A and M (FAM), first published in 1977 [5] and updated in 1980, in combination with patients treated in France [6]. A summary of the studies employing combinations of F, A, M and a nitrosourea is shown in Table 1.

RANDOMIZED TRIALS

Results of multicenter phase III trials have invariably been inferior to those of single institution phase II studies. Randomized trials in advanced gastric cancer have compared different multidrug

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Table 1. *Phase II trials in advanced gastric cancer*

Regimen	No. responders/No. evaluable patients (%)	Median survival all patients (months)	Reference
FAM	26/62 (42)	5	[6]
FAM	6/11 (55)	6	[7]
FAB	18/35 (52)		[8]
FAM	23/52 (45)	7	[9]
FAMB	7/19 (38)	5	[9]
FAM	28/81 (35)		[10]
FAM	12/21 (57)	11	[11]
FAM	26/40 (65)		[12]
FAM	4/22 (18)	7	[13]
FAM	2/25 (8)	6	[14]
FAMMe	12/35 (34)		[15]
	164/403 (41)	6	

regimens or a multidrug regimen versus a single drug constituent. In three consecutive studies performed by the Gastrointestinal Tumor Study Group (GITSG), MeFA was found to produce the best results although the gain in median survival was only a few weeks [16–18]. The Southwest Oncology Group (SWOG) has conducted two trials with FAM in one of the arms. The response rates ranged between 22 and 30% and the median survivals were less than 6 months [19, 20]. The study conducted by the Eastern Cooperative Oncology Group (ECOG) produced a 39% response rate for FAM and it was concluded that FAM should be strongly advocated for adjuvant treatment [21]. In two large trials, however, combination chemotherapy did not yield superior results 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 rate, the survival in all three arms of the study was the same [22]. In the Italian study, FAM + BCNU (BAFMI) was compared with 5-FU. There were no significant differences in the reponse rates or the survivals [23]. The limited value of the most commonly employed combination chemotherapy protocols is further substantiated by the results of the study conducted by the Gastrointestinal (GI) Group of the European Organization for Research and Treatment of Cancer (EORTC). In this trial, MeFA was compared with FA. The response rates were <20% in both arms with overlapping survival curves [24]. The results of two other trials question the role of doxorubicin in the treatment of advanced gastric cancer. In one study, FAB was compared with FB with no significant differences in response rates or survivals [25] and in the other study, FAB was compared with A. In this latter trial, FAB produced a significantly higher response rate than A alone (40 vs. 13%) and a significantly longer survival for patients with measurable disease, although for all patients, including those with nonmeasurable disease, the difference in survival was not significant. The conclusion of the authors was that the activity of A is probably lower than suggested in the literature and that combination chemotherapy has no proven value over 5-FU alone, which still must be considered the most active single agent [26]. A summary of the results of randomized trials is presented in Table 2. When analyzing these sometimes conflicting data it must be remembered that there are often substantial differences between these studies regarding definitions of measurable disease and whether or not early deaths, protocol violations, losses to follow-up etc., are kept in the denominator of the response. It is apparent, however, that the median survival of patients with advanced gastric cancer does not exceed 6 months and that combination chemotherapy has no beneficial effect on survival, compared with 5-FU alone.

ADJUVANT STUDIES

Several multicenter adjuvant trials have been reported, the older ones employed mostly combinations of 5-FU plus a nitrosourea; the more recent ones evaluated the FAM regimen. The Veteran Administration Surgical Oncology Group (VASOG) reported on 5-FU + Me versus controls with no differences at 4 years [27]. The GITSG reported the only positive study until now, 5-FU + Me being significantly better than controls [28], but these results could not be reproduced by ECOG [29]. Assessing the FAM regimen versus controls the International Collaborative Cancer Group recently reported that after a median follow-up of 4 years of 300 evaluable patients, the relapse rate in the treatment arm was 49% versus 53% in the controls. Also there was no difference in the subsets of patients with positive or negative nodes [30]. Other phase III studies of FAM versus controls

*Table 2. Prospectively randomized trials in advanced gastric cancer**

Regimen	No. responders/No. patients with measurable disease	No. of patients treated	Median survival (months)	Reference
MeFA	7/15 (47)	38	3	
vs.				[16]
A	4/17 (24)	36	2	
MeFa	3/10 (30)	34	8	
vs.				[17]
FAM	3/12 (25)	43	7	
MeFA	4/16 (25)	76	7	
vs.				
FAM	3/18 (17)	78	6	
vs.				[18]
FA	1/19 (5)	78	6	
FAM	25/83 (30)	120	5	
vs.				[19]
FAM (sequential)	19/81 (23)	119	5	
FAM	6/27 (22)	27	5	[20]
FAM	18/46 (39)	46	7	
vs.				[21]
MeFA	11/39 (29)	39	6	
FAM	5/13 (38)	51	7	
vs.				[22]
5-FU	2/11 (18)	51	7	
BAFMi	9/41 (22)	43	6	
vs.				[23]
5-FU	6/41 (15)	42	7	
MeFA	5/28 (18)	85	8	
vs.				[24]
FA	3/29 (10)	88	5	
FAB	4/17 (24)	38	5	
vs.				[25]
FB	2/18 (11)	45	4	
FAB	30/75 (40)	94	8	
vs.				[26]
A	9/70 (13)	93	5	
Combination chemotherapy	158/587 (27)	1142	6	

*Some trials had more treatment arms than presented in this overview.

(under them a study conducted by EORTC) are still in progress. Considering the results published until now and the low level of activity of FAM in advanced disease observed in randomized trials, it appears unlikely that a positive result will emerge from these studies.

SECOND GENERATION PHASE II TRIALS

Cisplatin (P) is active in gastric cancer [31–33]. Therefore, P has been added to FA (FAP). In six studies the response rates ranged between 29 and 55% and the median survivals from 4 to 12 months [34–39]. A summary of these trials is shown in Table 3. In some of these studies a histologically documented complete response has been reported.

Although a randomized trial comparing FAP with FA + triazinate (FAT) or MeFA demonstrated no significant difference in survivals [40], FAP might be considered for further testing in randomized trials. On the other hand, because we have demonstrated that FA is not sufficiently active [24], cisplatin has also been investigated in combination with 5-FU, resulting in 14 responses out of 31 patients [41].

A further second generation regimen consists of the combination of etoposide (E), A and P (EAP).

Table 3. Phase II studies with FAP in advanced gastric cancer

No. responders/No. evaluable patients (%)	No. complete responders (%)	Median survival (months)	Reference
10/35 (29)	0		[34]
1/3 (33)	1	4	[35]
9/18 (50)	0	12	[36]
13/26 (50)	3	9	[37]
11/32 (34)	3	8	[38]
20/36 (55)	0	7	[39]
64/150 (43)	7 (5)	8	

A response rate of 72% in 44 patients has been reported including some histologically documented complete responses [42]. This protocol should certainly be investigated further in a randomized study.

Finally, the combination of sequential high-dose methotrexate (MTX) and 5-FU, combined with A (FAMTX), first published in 1982 with a response rate of 63% [43], has been updated in 1986, yielding a response in 59 of 100 patients including 12 complete responses and a median survival of 9 months. Three patients died from toxicity [44]. The EORTC GI Group has conducted a multicenter phase II study with this regimen and has reported 22 responders out of 66 eligible patients including nine complete responders, three of which were histologically documented. These results are the best reported by our group in advanced gastric cancer. There were also, however, four toxic deaths, three of them associated with major protocol violations [45]. Two other small series have been published in a letter indicating a high toxicity with this regimen [46, 47]. Therefore, we 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 fully comparable to the toxicity of FAM [48]. This trial has now been extended to a phase III study evaluating the response rate and the survival of FAMTX versus FAM. A summary of the data obtained so far with FAMTX in phase II studies is shown in Table 4.

In some trials sequential MTX/5-FU in lower doses and with other time intervals has been investigated, but these studies have all yielded low response rates. Doses of MTX in these trials ranged between 100 and 600 mg/m^2 and time intervals between 30 min and 24 h. The response rates ranged between 0 and 21% [49–52]. Moreover, in the phase II study conducted by the EORTC GI Group, two of 24 evaluable patients experienced life threatening toxicity [51], suggesting that a lower dose of MTX results in less activity of the sequential MTX/5-FU based chemotherapy, but not in an attenuation of the potential toxicity from MTX.

Table 4. Phase II studies with FAMTX in advanced gastric cancer

No. responders/No. evaluable patients (%)	No. complete responders (%)	Median survival (months)	Toxic deaths	Reference
59/100 (59)	12	9	3	[44]
22/66 (33)	9	6	4	[45]
0/20			4	[46]
2/12 (17)			1	[47]
83/198 (42)	21 (11)		12	

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