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Treatment of Advanced Gastric Carcinoma with 5-Fluorouracil Adriamycin, and Mitomycin C (FAM)

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Summary. *Thirty-three evaluable patients with advanced gastric adenocarcinoma were treated with a combination of 5-fluorouracil, adriamycin, and mitomycin C (FAM). Two complete and five partial remissions (21% response rate) were observed. The overall median survival of all 33 patients was 5.9 months. Responding patients had significantly better survival than the non-responders ($P < 0.02$). Analysis of the results according to sex, pretreatment performance status, and the histologic differentiation of the tumor failed to demonstrate that any of these factors influenced therapeutic results. The low response rate to FAM found in this study might be related to the fact that in the majority of the patients (85%) the primary gastric tumor had not been resected. The side-effects of this regimen were moderate. Taking into account the low response rate and the moderate myelotoxicity observed, a more intensive use of these three drugs in combination is suggested.*

Introduction

Gastric carcinoma has been considered relatively resistant to chemotherapy. Cytostatic drugs known to have some effect in the treatment of the advanced stage of this disease include 5-fluorouracil (5-FU), mitomycin C, BCNU, methyl CCNU, and adriamycin. The objective response rate to these drugs, as reported in the literature, is 18%–36% and the median duration of the responses, 2.7–5 months [7]. The combination of 5-FU and chloroethylnitrosoureas was reported to have a better therapeutic effect [2, 8], but in a later study this combination gave no better results than 5-FU alone [9]. Recently, the combination of 5-FU, adriamycin, and mitomycin-C (FAM), introduced by Macdonald et al. [5, 6], has been shown to give better results than any other combination previously used. An objective response of 42% (26 of 62) was found in patients with metastatic gastric carcinoma. The median survival of responding patients was 12.5 months, as against 3.5 months in the non-responders. Bitran et al. [1] used a similar combination. Six of their 11 patients (55%) attained an objective response. Another study, reported by the Southwest Oncology Group [10], showed an objective response in 28 of 76 patients (37%) with advanced gastric carcinoma treated with FAM. Luporini et al. [4] recently reported a response rate of 50% (17 of 34) in previously untreated patients with advanced gastric cancer. In this report we present our results in the treatment of patients with advanced gastric carcinoma by the FAM combination.

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Materials and Methods

Forty-seven consecutive patients with a diagnosis, proven by biopsy, of metastatic or non-resectable gastric adenocarcinoma and who had not received prior chemotherapy were treated in our Center with the FAM combination between December 1978 and September 1981. Of the 47 patients, 33 were evaluable for response to the therapy. Two patients died 1 month after the initiation of the therapy without being evaluable. Seven patients had no measurable lesions and another five received inadequate therapy. The clinical characteristics of the 33 evaluable patients are listed in Table 1. Two-thirds, of the listed patients were male. The liver was the most common site of metastases, and in the majority of these cases (85%) the primary gastric tumor was not resectable. The combination was administered in cycles of 8 weeks, as previously described by Macdonald et al. [5, 6], and consisted of 5-FU 600 mg/m^2 IV on days 1, 8, 29, and 36, adriamycin 30 mg/m^2 on days 1 and 29, and mitomycin C 10 mg/m^2 on day 1. Blood counts were performed on days 1, 8, 29, and 36 of each cycle. A full dose was given when the wbc count was $\geq$ 3,500/mm^3 and thrombocytes $\geq$ 100,00/mm^3. One half of the dose of each of the three agents was given when the wbc count was 2,500–3,500/mm^3 and/or thrombocytes 75,000–100,000/mm^3. Treatment was withheld when the wbc was $<$ 2,500/mm^3 and/or the thrombocytes $<$ 75,000/mm^3.

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Table 1. Patients' characteristics and response to therapy

Patient no.	Age/sex	Performance[a] status	Sites of disease[b]	Response	Duration of response (months)	Survival (months)
1	59/M	70	Abdominal mass, liver	PR	22	23
2	66/M	70	Abdominal mass, ascites	PR	2.5	4.5
3	65/M	50	Abdominal mass, liver	PR	4	6.5
4	40/F	90	Liver	CR	8+	8+
5	32/M	90	Liver, supraclavicular nodes	PR	4	5.5+
6	57/M	80	Liver	CR	6.5+	6.5+
7	63/F	80	Liver	PR	2+	2+
8	51/F	50	Peritoneum, ascites	NR	–	3.5
9	61/M	90	Liver, peritoneum	NR	–	4.5
10	37/F	60	Pelvic mass, peritoneum, ascites	NR	–	2
11	53/M	80	Liver	NR	–	3
12	69/M	80	Abdominal mass	NR	–	2.5
13	58/M	50	Liver	NR	–	4.5
14	68/F	50	Abdominal mass, supraclavicular nodes	NR	–	2
15	54/M	80	Liver, peritoneum	NR	–	7
16	53/M	100	Peritoneum, supraclavicular nodes	NR	–	4
17	72/M	80	Liver	NR	–	9
18	58/F	90	Peritoneum, para-aortic nodes	NR	–	11
19	61/F	50	Liver, peritoneum	NR	–	7
20	41/M	70	Abdominal mass	NR	–	1.5
21	39/M	70	Abdominal mass	NR	–	4
22	67/F	80	Abdominal mass	NR	–	12+
23	76/M	80	Liver	NR	–	5.5
24	64/M	80	Liver	NR	–	2
25	75/M	70	Abdominal mass	NR	–	5
26	56/M	50	Liver, ascites	NR	–	5
27	73/F	50	Abdominal mass	NR	–	8
28	66/M	80	Abdominal mass, liver	NR	–	1.5
29	57/M	70	Liver, peritoneum	NR	–	6+
30	59/M	70	Liver	NR	–	3
31	50/M	70	Abdominal mass, pleural effusion and lung metastases	NR	–	2.5
32	82/F	80	Skin lesions	NR	–	8
33	68/F	70	Liver	NR	–	2

[a] Karnofsky scale
[b] Only five patients (nos. 3, 4, 20, 26, and 32) underwent resection of the primary gastric tumor

Therapeutic results were assessed 8 weeks after initiation of the therapy. Patients who died earlier were not excluded. A complete response (CR) was defined as the disappearance of all measurable lesions. A partial response (PR) was defined as a 50% or more reduction in the product of the two largest perpendicular diameters of all measurable lesions as determined by physical examination by radiographic studies and by liver scan, without evidence of progression in other sites. In the case of hepatomegaly, a 30% reduction in the sum of measurements below the xiphoid process and both costal margins at the midclavicular lines, and improvement or stability of pretreatment liver function tests were required. No response (NR) was defined as stable or progressive disease. Survival and duration of response were measured from initiation of the therapy.

Results

The number of courses of FAM given to the 33 evaluable patients ranged from one to nine (median two courses). The results of the treatment are shown in Table 1. There were two CR and five PR among 33 evaluable patients (21% response rate). The upper confidence limit for the response rate of 7 of 33 is 35% for a confidence level of 95%. The confidence interval is 0.07–0.35.

The duration of the response ranged 2+ to 22 months. All objective responses were achieved after the first course. The assessment of the objective response was as follows: Patients 2, 3, 4, 5, 6, and 7 had palpable lesions (liver, upper abdominal mass and supraclavicular nodes). The measurements of these lesions decreased according to the criteria previously described in this paper. In patient 2 there was also complete disappearance of the ascites. In patients 3, 4, and 6 tumor regression of liver metastases was also confirmed by improvement of the liver scan. In patient 1 the decrease in tumor size was evidenced by upper GI barium X-ray. All responding

patients with liver metastases had an improvement in the liver function tests.

FAM was continued in 10 of the 26 patients classified under NR after the first course, but none of these patients responded. The overall median survival of the 33 patients was 5.9 months, and that of NR patients was 4.8 months (Fig. 1). The median survival of responding patients has not yet been reached. However, responding patients had significantly better survival than the non-responders ($P < 0.02$). The durable remission in patient 1 is noteworthy. This patient had an unresectable tumor of the cardia, with infiltration to the lower third of the esophagus and metastatic spread over the liver. At operation only a biopsy was taken. Following nine courses of FAM given over 18 months there was a significant resolution of the gastric mass and improvement in the liver function tests. The patient underwent another operation and a small tumor was found at the gastro-esophageal junction, penetrating into the serosa without evidence of regional lymph node involvement or liver metastases. This time a subtotal gastrectomy and partial esophagectomy was performed, with removal of the whole tumor. Unfortunately, recurrent disease developed 4 months after the operation and the patient died with liver and brain metastases 23 months after the initiation of chemotherapy.

An attempt was made to determine whether the therapeutic results of FAM were correlated with sex, pretreatment performance status (Karnofsky scale), and histologic differentiation of the tumor. The response rate for 22 males was 23% and their median survival was 4.8 months. The corresponding values for 11 females (18% and 7.7 months) were not significantly different. Similarly, there were no significant differences between the response rate and median survival of 16 patients with pretreatment performance status of 80%–100% (25% and 7.2 months) and those of 17 patients with pretreatment performance of 50%–70% (18% and 4.4 months). Information concerning the degree of tumor differentiation was available in 29 cases. Fourteen patients had poorly differentiated adenocarcinoma. Three of them (21%) responded to FAM and the median survival in this histologic subgroup was 4.0 months. Of 15 patients with moderately or well-differentiated adenocarcinoma, 4 (27%) achieved an objective response and their median survival was 7.2 months. These differences were not statistically significant.

Of the five patients who underwent resection of the primary gastric tumor, two had an objective response, as against five of 28 patients in whom resection of the gastric tumor was not performed. The number of patients is too small to allow a statistical analysis concerning the possible relation between resection of the primary tumor and the response to FAM.

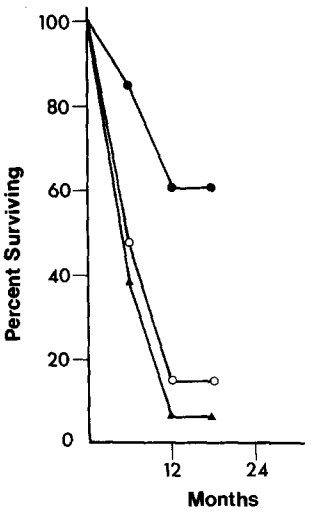

Fig. 1. Actuarial survival curves of responding, non-responding, and all patients (Z-test used). (●——●) Responders (7); (▲——▲) non responders (26); (○——○) all patients (33). $P < 0.02$

Table 2. Doses of drugs administered during the first three courses of FAM

Drug	Percentage of projected dose		
	1st course (33 patients)	2nd course (17 patients)	3rd course (8 patients)
5-FU	95	87	84
Adriamycin	97	94	84
Mitomycin C	100	97	94

FAM was generally well tolerated and there was no case of drug-related death. Most patients experienced mild nausea and/or vomiting on days 1 and 29. Leukopenia of $< 4{,}000/mm^3$ was observed in 18 of 31 patients evaluable for myelotoxicity (58%). Counts below 2,000 wbc/mm^3 were seen in 7 cases (23%). Thrombocytopenia $< 100{,}000/m^3$ was noted in only nine of 31 (29%), and in only 1 case (3%) was it below $50{,}000/mm^3$.

During the first course the doses of drugs had to be reduced due to myelotoxicity in four of 33 patients. During the second course, drug doses were reduced in four of 17 and during the third course in three of eight patients. The percentages of the projected drug doses administered during the first three courses are shown in Table 2, which shows that only minimal reductions in drug doses were required.

Discussion

The response rate to FAM in advanced gastric cancer found in the current study (21%) is lower than the one reported by others [1, 4, 6, 10]. The low response rate observed in our study does not seem to be related to protocol violations, as dose reductions were minimal. All the patients who failed to respond to the first course also failed to respond to subsequent courses. Therefore, prolonging the therapy is unlikely to result in a higher response rate.

The present series is similar to that of Macdonald et al. [6] in the age and sex distribution of the patients and the main sites of metastatic disease. A major difference between these two studies is that the percentage of patients who underwent resection of the primary gastric tumor was obviously lower in our series (15%) than in that of Macdonald et al. (45%). The latter investigators [6] and others [8] did not find a significant correlation between resection of the gastric tumor and the response to chemotherapy. On the other hand, Levi et al. [3] reported that the presence of an unresected gastric tumor adversely influenced the response to the combination of adriamycin, 5FU, and BCNU. It is possible that the low response rate to FAM found in our study is due to the high proportion of patients with unresected primary gastric tumors.

Like other studies [4, 6], the present study also does not indicate that the initial performance status and the degree of tumor differentiation are factors that influence the response to FAM. The relatively mild toxicity of the FAM regimen [4, 6] was confirmed in this study. Bitran et al. [1] used a more intensive form of FAM with an acceptable toxicity.

Previous studies have shown that survival was significantly prolonged in patients who responded to FAM [1, 4, 6]. Six of the 26 responding patients (23%) in the series of Macdonald et al. [6] survived for longer than 24 months. In our series too, response to FAM was associated with longer survival.

In view of the response rate of 21% (with upper confidence limit 35%) we do not feel justified in continuing to use the FAM regimen as described in this study. Taking into consideration the relatively mild toxicity of this regimen, we are currently testing a more intensive combination of these three drugs, in an attempt to improve the therapeutic results.

References

1. Bitran JD, Desser RK, Kozloff MF, Billings AR, Shapiro CM (1979) Treatment of metastatic pancreatic and gastric carcinoma with 5-fluorouracil, adriamycin and mitomycin C (FAM). Cancer Treat Rep 63: 2049
2. Kovach JS, Moertel CG, Schutt AJ, Hahn RG, Reitmeier RJ (1974) A controlled study of combined 1.3-bis(2-chloroethyl)-1-nitrosourea and 5-fluorouracil for advanced gastric and pancreatic cancer. Cancer 33: 563
3. Levi JA, Dalley DN, Aroney RS (1979) Improved combination chemotherapy in advanced gastric cancer. Br Med J 2: 1471
4. Luporini G, Fraschini P, Beretta G, Labianca R, Formenti S (1981) UICC Conference on Clinical Oncology, Abstract 12, 382
5. Macdonald JS, Wooley PV, Smythe T, Ueno W, Hoth D, Schein PS (1979) 5-Fluorouracil, adriamycin and mitomycin C (FAM) combination chemotherapy in the treatment of advanced gastric cancer. Cancer 44: 42
6. Macdonald JS, Schein PS, Wooley PV, Smythe T, Ueno W, Hoth D, Smith F, Boiron M, Gisselbrecht C, Brunet R, Lagarde C (1980) 5-Fluorouracil, doxorubicin, mitomycin C (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med 93: 533
7. Moertel CG (1975) Clinical management of advanced gastrointestinal cancer. Cancer 36: 675
8. Moertel CG, Mittelman JA, Bakemeier RF, Engstrom P, Hanley J (1976) Sequential and combination chemotherapy of advanced gastric cancer. Cancer 38: 678
9. Moertel CG, O'Connell MJ, Lavin PT (1979) Chemotherapy of gastric carcinoma. (Abstract) Proc AACR/ASCO 20: 288
10. Panettiere FJ, Heibrun L (1979) Experience with two treatment schedules in the combination chemotherapy of advanced gastric carcinoma. In: Mitomycin C: Current status and new developments. Academic Press, New York, p 145

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