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5-Fluorouracil, adriamycin, and BCNU (FAB) combination chemotherapy for advanced gastric cancer

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Summary. *Thirty-two evaluable patients with advanced measurable gastric adenocarcinoma were treated with a combination of 5-fluorouracil, adriamycin, and BCNU (FAB). Two complete and fourteen partial responses were observed, with an overall response rate of 50%. The median duration of response was 10 months, and the median survival of all 32 patients, 7 months. Responding patients had significantly better survival than the nonresponders ($P < 0.001$).*

Analysis of the results according to pretreatment performance status, resectability of the primary tumor, and histologic differentiation of the malignancy demonstrates that only the first influenced the therapeutic results. The FAB regimen was well tolerated, allowing administration of nearly the whole of the projected drug dosages during the course of the therapy in all but three patients.

These results indicate that the FAB combination is an effective chemotherapeutic regimen in metastatic or locally advanced gastric carcinoma. Incorporation of this regimen into the design of combined-modality treatment would result in improved prognosis.

Introduction

Although there has been an unexplained decline in the incidence of carcinoma of the stomach in many countries during the last 50 years, it is still one of the leading causes of cancer death [28]. The majority of the patients have either a locally advanced or metastatic disease, and have a median survival after confirmed incurability of only 4.0 months [24]. Single-agent chemotherapy with such agents as 5-fluorouracil (5-FU), mitomyin C, and the nitrosoureas has produced objective responses in 13%–26% of patients [23]. These responses, however, have almost always been incomplete and very short, with no extension of patient survival. Regimens combining 5-FU and a nitrosourea (either BCNU or methyl-CCNU) have been reported to produce some increase in objective response rate with survival advantage for 5-FU and BCNU over BCNU alone [16], and 5-FU plus methyl-CCNU in comparison with methyl-CCNU alone [25]. No real advantage of these combinations over 5-FU alone has been demonstrated, however [16, 26].

As a result of the demonstration of the activity of adriamycin in advanced gastric cancer [9] this drug has been incorporated into many combination regimens.

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MacDonald et al. [20] showed an objective response rate of 42% with 5-FU, adriamycin, and mitomycin C. The median survival of responding patients was 12.5 months, as against 3.5 months for nonresponding patients. These results were later confirmed by other investigators [2, 4, 27] using the same combination. Similar results have also been reported with 5-FU, adriamycin, and BCNU or methyl-CCNU [11, 18, 19].

In this study, which was designed in 1979, we report our results with the combination of 5-FU, adriamycin, and BCNU (FAB) in the treatment of previously untreated patients with advanced gastric cancer.

Patients and methods

As of 31 August 1982, a total of 39 patients had been admitted to the study. All patients had histologically proven adenocarcinoma of the stomach and none had received prior chemotherapy or radiotherapy. Three patients died 20 days after the initiation of therapy. Four patients were lost to follow-up after the first course of treatment. The major characteristics of the 32 evaluable patients are given in Table 1.

Table 1. Pretreatment clinical characteristics

No. of patients evaluable	32
Age (years)	
Median	57
Range	31–79
Sex	
Male	19
Female	13
Performance status	
40–60	15
70–80	11
90–100	6
Status of primary tumor	
Resected	13
Not resected	19
Tumor histology	
Poorly differentiated	19
Moderately or well differentiated	13
Predominant measurable disease	
Abdominal mass	14
Liver	11
Lymph nodes	6
Bone	1

For admission to the study patients were required to have nonresectable, recurrent or metastatic malignant disease, and at least one measurable lesion to serve as an objective indicator of response to therapy. Palpable hepatomegaly was acceptable if the liver was proven to contain metastases and the liver edge extended at least 5 cm below the xiphoid process or costal margins on quiet respiration. Positive liver scans were used if there was a clearly defined perfusion defect greater than 5 cm in diameter. The predominant site of measurable disease was the abdomen in 14 patients (44%), liver in 11 (34%), lymph nodes in six (19%), and bone in one (3%). Histologically, gastric cancer was poorly differentiated in 19 (59%) patients, moderately or well differentiated in 13 (41%). All patients had recovered from the acute effects of surgery, and had no evidence of infection, active heart disease, leukopenia ($< 4{,}000$ cells/mm^3) or thrombocytopenia ($< 100{,}000$ cells/mm^3).

The performance status of each patient was assessed according to Karnofsky's criteria [15]. Total disability (Karnofsky performance status of 20–10) was considered a contraindication to therapy.

The FAB regimen was given in 4-week courses (Table 2). 5-Fluorouracil was administered in a dose of 300 mg/m^2 IV for 5 consecutive days (days 1–5). Adriamycin 40 mg/m^2 and BCNU 100 mg/m^2 were administered IV on day 1. Drug dosages were modified according to the degree of myelosuppression (Table 3). Reduced doses of adriamycin were given if the patient had any elevation of serum bilirubin.

Therapeutic responses were assessed according to WHO recommendations [21]. Briefly, complete response required absence of all known disease. Partial response required a reduction of 50% or more in the size of the lesions that had been measured to determine the effect of therapy, with no increase in any other lesion or appearance of new lesions. Significant deterioration in weight (greater than 5% body weight) or performance status (20% on the Karnofsky scale) precluded classification under complete or partial response. The tumor response had to have been determined by two observations not less than 4 weeks apart. Disease stabilization was declared if a 50% response or a 25% progression could not be established, again without deterioration in the patient's weight and performance status. Progression required a 25% or more increase in the size of one or more measurable lesions, the appearance of new areas of malignant disease, a decrease in weight by greater than 5% body weight, or a decrease in performance status by more than 20%.

Survival curves were calculated and plotted by the method of Kaplan and Meier [13] and were compared using the log rank test [5].

Table 2. FAB regimen for gastric cancer

5-Fluorouracil	300 mg/m^2 IV days 1–5 inclusive
Adriamycin	40 mg/m^2 IV day 1
BCNU	100 mg/m^2 IV day 1

Course frequency every 28 days

Table 3. Dose reduction schedule for myelosuppression

WBC/mm^3	PLT/mm^3	Drug dose (%)
$\geq 4{,}000$	$\geq 100{,}000$	100
3,999–2,500	99,999–75,000	50
$< 2{,}500$	$< 75{,}000$	0

Results

Two complete and 14 partial responses were observed, with an overall response rate of 50% (41% on a conservative estimate). An additional 19% of the patients were classified as having stationary disease, while in 31% of the patients the disease continued to progress. The median duration of response was 10 months. The median survival from the start of therapy for all 32 patients treated with FAB was 7 months. As shown in Fig. 1, the median duration of survival in responding patients was 12 months, with 30% of patients still living at 20 months. The median survival in patients who failed to respond (4 months) was virtually identical with that reported for untreated patients [24]. The difference in survival time between the responding and nonresponding patients was statistically highly significant ($P < 0.001$).

Pretreatment patient characteristics potentially influencing response were analyzed. Patients with initial performance status ranging from 70 to 100 showed a higher proportion of remission (65%) than those with a performance status of ≤ 60 (33%). Nonresectable primary tumor did not significantly reduce the likelihood of responding to chemotherapy. It is noteworthy that in one patient significant shrinkage of a large nonresectable primary tumor was observed after 4 months of therapy. This finding prompted an exploratory laparotomy, and a radical subtotal gastrectomy was performed. The patient subsequently refused further chemotherapy as an adjuvant to surgery, and is now free of disease 10 months after initiation of FAB treatment. Of 19 patients with poorly differentiated, and

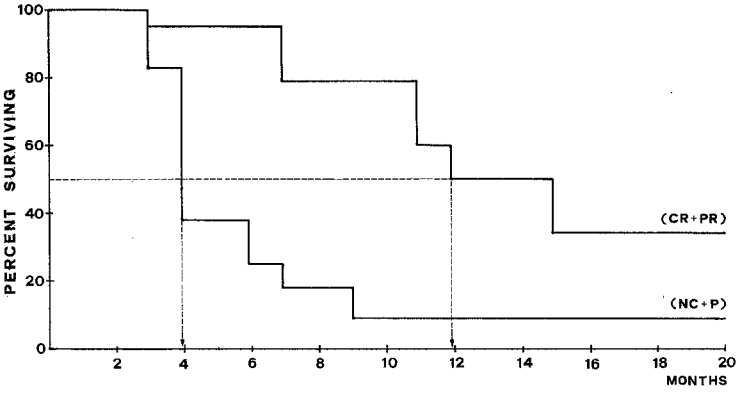

Fig. 1. Gastric carcinoma treated with FAB combination: survival curve shows CR + PR vs NC + P; $\chi^2 = 16.49$; $P < 0.001$

Table 4. Toxicity

	No. of patients (%)
Nausea/vomiting	25 (78)
Alopecia	23 (72)
Stomatitis	5 (16)
Diarrhea	3 (9)
WBC nadir[a]	
$< 4{,}000 \geq 2{,}500$	7 (22)
$< 2{,}500 \geq 1{,}500$	1 (3)
$< 1{,}500$	1 (3)
Platelet nadir[a]	
$< 100{,}000 \geq 50{,}000$	3 (9)
$< 50{,}000 \geq 30{,}000$	0 (0)
$< 30{,}000$	1 (3)
Fever	3 (9)
ECG changes	3 (9)

[a] Cells/mm^3

13 with moderately or well differentiated adenocarcinoma, 10 (52.5%) and 6 (46%), respectively, responded to FAB.

Thus, this regimen may be useful irrespective of histologic differentiation of the tumor.

Toxicity is reported in Table 4. The FAB regimen was generally well tolerated and there was no case of drug-related death. Most patients experienced mild nausea and/or vomiting on day 1. Reversible alopecia occurred in 72% of the cases. Mucous toxicity was infrequent and mild. Aside from ECG changes in a few patients, no other adriamycin-associated cardiac toxicity was encountered; however, only in two patients were doses of 550 mg/m^2 of adriamycin administered.

Of the 32 patients, 9 (28%) experienced hematologic toxicity. Severe leukopenia (leukocyte count $< 1{,}500$/mm^3) and severe thrombocytopenia (platelet count $< 30{,}000$/mm^3) occurred in only 1 patient. This patient had a pneumonic episode which was cleared with antibiotic therapy. All but 3 patients received almost the whole of the projected drug dosages during the treatment.

Discussion

Because of the ineffectiveness of single-drug therapy, over the past 8 years there have been several attempts to develop effective combination chemotherapy regimens in advanced gastric adenocarcinoma. Drug combinations including 5-FU and chloroethyl nitrosoureas (either BCNU or methyl-CCNU) or mitomycin C have been reported to produce response rates of 21%–48% with no evidence of a significant contribution to patient survival, although in earlier studies there had been evidence that the combination of 5-FU and either BCNU or methyl-CCNU could improve the duration of survival over that achieved with single-agent treatment [1, 7, 16, 25, 26]. Incorporation of adriamycin into these two-drug combinations resulted in a significant survival advantage for treated patients. The Gastrointestinal Tumor Study group, in a randomized multi-institutional clinical trial in advanced gastric carcinoma, found that the combination of 5-FU and adriamycin with either methyl-CCNU or mitomycin C offered a survival advantage compared with the use of the combination of 5-FU and methyl-CCNU with or without ICRF 159 [11]. The median survivals of 8 and 7 months, respectively, for the first two combinations were significantly superior to those associated with the last group. Similar results were obtained in a number of nonrandomized studies using a combination of 5-FU, adriamycin, and mitomycin C [2, 4, 12, 20, 27]. In these studies, response rates ranging from 21% to 55% were associated with a median survival of 5.5 to 7+ months.

The 50% response rate and 7-month duration of survival observed in our patients show significant activity of the FAB regimen in advanced gastric cancer, and compare well with the results of all the above-mentioned studies. Recently, Levi et al. have reported similar results with a slightly different regimen. In an initial study [19] of 35 patients they achieved a 52% response rate, with a median survival for responders of 12 months and 30% alive at 20 months. In a further study [18] the duration of survival was 6.3 months in 32 patients with advanced measurable gastric cancer.

It appears therefore that regimens containing 5-FU + adriamycin, and mitomycin C or a nitrosourea may contribute more to the length of survival than similar combinations lacking adriamycin. Although it has been suggested that similar results can be obtained with 5-FU + adriamycin alone [8], we must await the results of several ongoing prospective studies to find whether there is any advantage in adding mitomycin C or a nitrosourea to the combination of 5-FU + adriamycin.

Like other studies [19, 25], the present study indicates that the initial performance status is a factor influencing the response to chemotherapy. The initial performance status was also a leading determinant of survival in an analysis of 322 patients with advanced gastric cancer treated by the Gastrointestinal Tumor Study Group [17]. In contrast to other studies [22], an unresected primary tumor and a poorly differentiated malignancy did not seem to adversely affect subsequent response to therapy. Clearly further studies are needed to clarify this issue.

Chemotherapy toxicity was in general moderate. Although an occasional patient experienced severe myelosuppression, cumulative hematologic toxicity was not encountered, and dose adjustments were rarely made during therapy. This is an important point to emphasize for patients whose tumor must be treated for an unspecified time, and may allow increases in drug doses to further improve the results.

At present, in spite of the high rate of activity evidenced by several regimens, it seems that the results of chemotherapy in metastatic or locally advanced gastric cancer have reached a plateau, with a median survival ranging at best from 7 to 8 months [2, 4, 8, 10–12, 16, 18, 20, 27] even if a combination of the four most active single agents is used [3, 6, 14]. Obviously further improvement is needed: incorporation of these effective chemotherapy regimens in combined-modality treatment (surgery, radiotherapy, and chemotherapy) and the design of new combination chemotherapies may hopefully bring such improvement.

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