SEQUENTIAL CHEMOIMMUNOTHERAPY OF COLORECTAL CANCER

Evaluation of Methotrexate, Baker's Antifol and Levamisole

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Fifty-two untreated patients with colorectal cancer were randomized to receive 5-fluorouracil (5-FU) alternating either with methotrexate (MTX) or Baker's Antifol (BAF) with or without the immunostimulant, levamisole (Program I). Fifty-five patients who had received prior treatment were randomized to receive methyl-CCNU (Me) with MTX or BAF (Program II). Fifteen of these patients had failed to respond to initial therapy with 5-FU plus MTX or BAF and subsequently received Me plus the alternate antifol. Overall response rate for each of programs I and II was 10%. The responses were 1/11 with 5-FU-MTX plus levamisole, 2/12 with 5-FU-MTX, 1/8 with 5-FU-BAF plus levamisole, 0/8 with 5-FU-BAF, 2/20 with Me-MTX and 2/21 with Me-BAF. The median survival times (MST) for patients receiving Programs I and II were 10 and 5 months, respectively. The MST for all patients receiving MTX was significantly longer than that of patients receiving BAF. Survival was not influenced by levamisole administration. Both chemotherapy programs were well tolerated. The sequential administration of 4 active agents failed to improve the results of treatment of colorectal cancer.

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THE CHEMOTHERAPY OF gastrointestinal cancer has made few significant advances since the introduction of 5-Fluorouracil (5-FU) 2 decades ago. This antimetabolite has produced objective tumor regression in 20% of patients.[1,2,6,24] When given in combination with a nitrosourea or mitomycin C, the response rate increases up to 30% to 40%, but the duration of tumor response is short and the effect on survival is minimal.[3,5,7,8,15,17,18,20] Consequently, investigation of newer chemotherapeutic agents and treatment modalities is justified. Methotrexate (MTX) and Baker's Antifol (BAF) have shown activity against a variety of solid tumors. Each produces objective tumor regression in about 15% of patients with colorectal cancer.[14,16,21] BAF has the advantage of not requiring an active transport system for intracellular incorporation and has shown antitumor activity in patients with prior exposure to MTX.[21] However, comparative studies of their clinical efficacy have not yet been conducted.

Based on the favorable results achieved with sequential chemotherapy in animal models,[4-13,23] this clinical study was designed to evaluate this approach in patients with advanced colorectal cancer. 5-FU was administered sequentially with either MTX or BAF, thus allowing for a comparison of the antitumor activity of MTX with BAF. To evaluate if cross-resistance exists between these antifols, after failing on initial treatment, patients were offered the other antifol administered in combination with methyl-CCNU (Me). Also, encouraged from the initial results of nonspecific immunotherapy with levamisole in the treatment of malignant melanoma,[10] lung[25] and breast[11,22] cancers, we studied in a randomized fashion the influence of levamisole on the antitumor effect of above chemotherapy. The results of treatment with these regimens are presented here.

PATIENTS AND METHODS

This study was conducted in a consecutive series of patients with proven metastatic colo-

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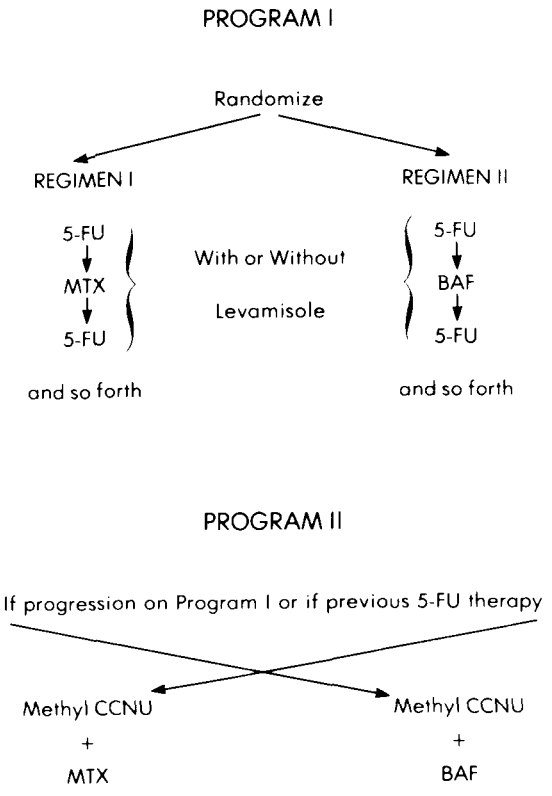

FIG. 1. Represents the study design. Patients with colorectal cancer with no prior treatment were randomized to receive 5-FU alternating with MTX or BAF. They were also independently randomized to receive or not to receive levamisole (Program I). Patients with prior treatment were randomized to receive Me in combination with MTX or BAF (Program II). Patients who failed on Program I were assigned to receive Me plus the alternate antifol (patients who failed on MTX were assigned to BAF and vice versa).

rectal cancer referred to the Department of Developmental Therapeutics of The University of Texas M. D. Anderson Hospital and Tumor Institute between September 1975 and June 1977. Fifty-two untreated patients were treated on Program I which included randomization of patients to receive 5-FU alternating with MTX or BAF. They were also independently randomized to receive or not to receive levamisole (Fig. 1). 5-FU was administered at the dose of 500 mg/m^2/day intravenously (iv) for 5 days (days 1–5) repeated every 6 to 7 weeks depending upon the patient's recovery from toxicities. Each dose of 5-FU was dissolved in 200 ml of 5% dextrose solution given iv over 1 hour. MTX was given at the dose of 15 mg/m^2/day iv or intramuscularly (im) daily for 3 days beginning 3 to 4 weeks after a course of 5-FU. Patients randomized to receive BAF were given a dose of 250 mg/m^2/day iv for 3 days instead of MTX. Each dose of BAF was mixed in 100 ml of 5% dextrose solution given over 1 hour. Three weeks after administration of either antifolate, the cycle beginning with 5-FU chemotherapy was repeated. Patients randomized to receive levamisole were given a dose of 150 mg/m^2/day orally on days 7, 8, 14, 15, 21 and 22 of treatment with each chemotherapeutic agent.

Forty patients who had received prior treatment with 5-FU were randomized to receive Me in combination with MTX or BAF. An additional 15 patients who failed on primary therapy with Program I were assigned to receive Me plus the alternate antifol (patients who had received MTX initially were assigned to BAF and vice versa). The dose of Me was 150 mg/m^2/day orally after 4 hours of fasting on day 1 and was repeated every 6 to 7 weeks depending upon the patient's recovery from toxicities. BAF and MTX were administered at the doses mentioned earlier starting concomitantly with Me and repeated 3 or 4 weeks later depending on recovery from toxicities.

The initial doses of MTX and BAF were reduced in patients with impairment of renal and hepatic functions because of pharmacologic consideration. In patients with abnormal renal function (serum creatinine level of greater than 2.0 mg/100 ml and/or creatinine clearance of less than 50 ml/minute), the initial dose of MTX was reduced to 10 mg/m^2/day. In patients with abnormal liver function, the initial dose of BAF was reduced to 150 mg/m^2/day. The subsequent doses of all agents were adjusted to maintain a tolerated degree of hematologic (absolute neutrophil count of 750 to 1000/mm^3 and platelet count of 75,000 to 100,000/mm^3) and nonhematologic toxicities.

The antitumor responses to treatment were assessed in patients with measurable disease according to the following criteria: complete remission, complete disappearance of all evidence of disease; partial remission, significant tumor shrinkage $\geq$50% of the sum of the products of the 2 largest diameters of all measurable lesions. Disease stabilization, responses less than partial remission or no change in tumor, for a minimum of 8 weeks (patients with no measurable disease, such as those with ascites, diffuse intra-abdominal carcinomatosis and pelvic masses who achieved objective improvement, were included in this category) and dis-

TABLE 1. Patient Characteristics

	5-FU + MTX		5-FU + BAF		Cross-over		Prior 5-FU	
	LEV	No LEV	LEV	No LEV	ME-MTX	ME-BAF	ME-MTX	ME-BAF
No. patients entered	16	14	11	11	8	7	18	22
No. early deaths	1	0	1	0	0	0	0	0
No. evaluable patients	15	14	10	11	8	7	18	22
Sex: Male	9	7	6	6	6	0	8	13
Female	6	7	4	5	2	7	10	9
Age (years):								
Median	54	55	55	59	49	47	51	53
Range	15–71	40–70	46–70	42–75	28–64	32–61	28–67	19–67

ease progression, appearance of new lesions and any enlargement of preexisting lesions.

Prior to treatment, all patients had complete evaluation with history and physical examination, complete blood count (CBC), urinalysis, serum creatinine, alkaline phosphatase, bilirubin, serum glutamic oxaloacetic transaminase, plasma carcinoembryonic antigen (CEA), chest x-ray and liver scan. Ongoing analysis included twice weekly CBC, blood chemistry determinations and tumor measurements at 3 week intervals and appropriate radiologic and isotopic examinations at 2 to 3 month intervals. All side effects associated with administration of the treatments were recorded and analyzed. Prior to initiation of the treatment, a signed consent was obtained from each patient according to institutional policies.

The survival calculations were made from the day of initiation of chemotherapy by the method of Kaplan and Meier for censored and uncensored data.[12] A two-tailed generalized Wilcoxon test[9] was used to evaluate the statistical significance of the difference between the survival curves.

RESULTS

Ninety-two consecutive adult patients with metastatic colorectal cancer were entered to the study; their characteristics are summarized in Table 1. There were two early deaths.

The antitumor response could be evaluated in 39 patients on Program I. Eleven patients were not evaluable for treatment response because of difficulty in adequately measuring the areas of tumor involvement. Their responses to treatment were evaluated only in terms of stabilization of disease or tumor progression. Four of 39 (10%) evaluable patients treated on Program I responded (Table 2). The response was slightly better for patients treated with 5-FU-MTX than 5-FU-BAF chemotherapy (3/23 vs 1/16; $p = 0.8$). Disease stabilization occurred in 23 of 39 (60%) patients with measurable disease and in 11 of 17 (69%) patients whose lesions could not be measured. The administration of levamisole did not influence the response rate to 5-FU-MTX and 5-FU-BAF chemotherapy. The median time to response was 1.5 months. The median duration of tumor regression was 3 months (range 1 to 10+ months); it was longer in patients treated with MTX than BAF (4.5 vs 2.5 months) and with chemotherapy alone than with chemoimmunotherapy (6 vs 2.5 months).

Forty-one of the 55 patients on Program II were evaluable for response. The remaining 14 patients did not have measurable disease and their response was evaluated only in terms of stabilization of disease or tumor progression. There was no remarkable difference in response rate between the patients treated with Me-MTX and those with Me-BAF (2/20 vs 2/21). The response of patients who were entered to the program directly was better than those who crossed over after failing on Program I (4/27 vs 0/14; $p = 0.3$). None of

TABLE 2. Responses in Patients with Measurable Lesions and No Prior Treatment in Relation to the Antifolate and Levamisole Administration

	5-FU + MTX		5-FU + BAF		5-FU + MTX or BAF	
Responses	LEV	No LEV	LEV	No LEV	LEV	No LEV
Complete	—	1	—	—	—	1
Partial	1	1	1	—	2	1
Stabilization	6	9	4	4	10	13
Progression	4	1	3	4	7	5
TOTAL	11	12	8	8	19	20

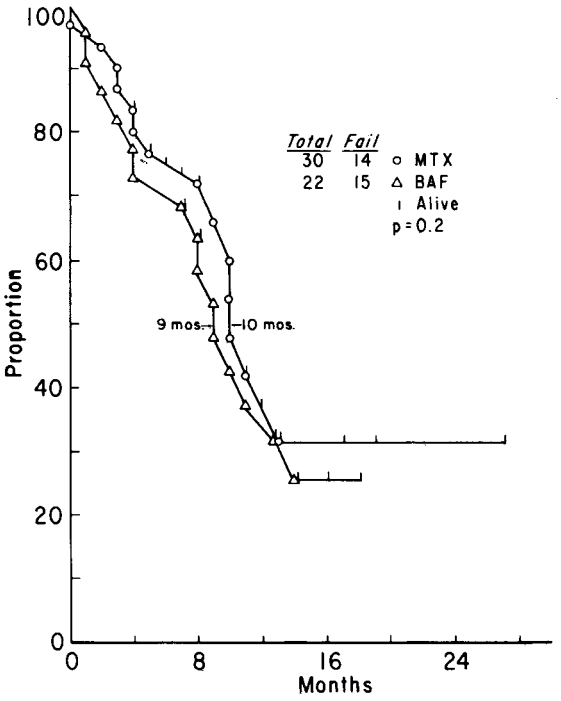

FIG. 2. Chemoimmunotherapy of advanced colorectal cancer with 5FU-MTX or BAF ± Levamisole: Survival from onset of treatment related to the Antifol administered.

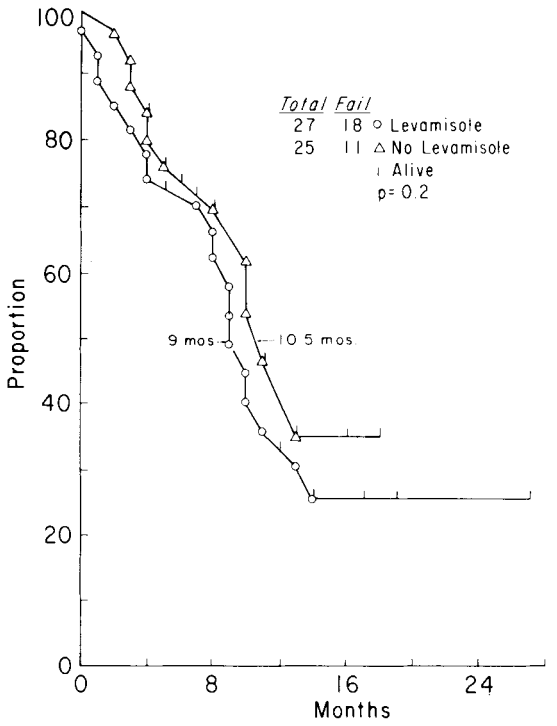

FIG. 3. Chemoimmunotherapy of advanced colorectal cancer with 5FU-MTX or BAF ± Levamisole: Effect of Levamisole on survival.

the 7 patients who failed to 5-FU-MTX sequential treatment responded to Me-BAF chemotherapy while 1 of 7 patients who failed on 5-FU-BAF responded to Me-MTX combination chemotherapy. When the patients treated with both Programs I and II were combined, 5 out of 43 (12%) patients treated with 5-FU-MTX or Me-MTX responded compared with 3 out of 36 (8%) of patients treated with 5-FU-BAF or Me-BAF. The median time to response on Program II was 1.5 months. The median duration of tumor regression was 4 months (range 2 to 6 months); it was longer with Me-MTX than Me-BAF (4 vs 2.5 months).

The survival rates for patients treated on these programs are shown in Figs. 2–5. Because the survival rates for patients with disease stabilization were similar to those for patients who achieved tumor regression, the survival results for these patients were combined and represented as responses in the figures. The median survival duration of patients treated with Program I was 10 months. Survival of responding patients was longer than for patients who failed to respond to treatment (median, 13 vs 4 months; $p = 0.001$). Among patients treated on Program I, survival duration was not influenced by the sequential administration of 5-FU with either antifol (median, 10 vs. 9 months; $p = 0.2$) (Fig. 2), or by the administration of levamisole (median, 9 vs. 10.5 months; $p = 0.2$) (Fig. 3). The survival duration of patients treated with Program II (excluding cross-over patients) was 5 months. The survival of responding patients was longer than that of patients who failed to respond to treatment (median, 8 vs. 4 months; $p = 0.001$), and that of Me-MTX treated patients was significantly longer than that of patients treated with Me-BAF (median, 6 vs. 4 months; $p = 0.01$) (Fig. 4). Considering all patients receiving Programs I and II, the survival of patients treated with MTX was significantly longer than that of patients treated with BAF (median, 9.3 vs. 6 months; $p = 0.01$) (Fig. 5).

The toxicities of the chemotherapy regimens are summarized in Tables 4 and 5. The degree of leukopenia and thrombocytopenia was moderate, although it was more severe and cumulative in patients treated with the methyl CCNU-containing regimens. Hematologic toxicities were relatively milder with BAF-containing arms of both programs. The nonhematologic toxicities consisted mainly of

nausea and vomiting which were most common with 5-FU and Me courses while skin rash, although infrequent, was more common during treatments with BAF. Mucositis was equally common with 5-FU and the antifolates. Other toxicities were less common. Toxicities associated with the administration of levamisole were seen in 7 patients. These toxicities included febrile reaction in 2, anxiety and nervousness in 2, personality change in 2, blurring of vision in 1, bitter taste in mouth in 1 and malaise in 1 patient. In 3 patients, the toxicities were such that necessitated permanent discontinuation of levamisole. Table 6 summarizes the dose modifications introduced during the treatment. The doses of each of the chemotherapeutic agents were escalated or de-escalated in about 20% of the courses.

DISCUSSION

Over the past 20 years, several antimetabolites have been investigated for antineoplastic activity against advanced gastrointestinal carcinoma. BAF is a new addition to this family of chemotherapeutic agents and is active in colorectal cancer.[16,21] It has been shown to be active in patients with prior exposure to MTX.[21] In Program I, the efficacy of MTX was compared to that of BAF when given sequentially with 5-FU. While in Program II, the same comparison was done when these antimetabolites were combined with Me. Immunotherapy with levamisole was used in combination with the sequential antimetabolite administration in view of the encouraging results obtained in patients with neoplasms of other organs.[10,11,22,25]

The overall rate of response to Programs I and II was very modest. Tumor regression ≥50% was obtained in 10% of patients with each of the treatment programs. Although these results are less favorable when compared with those of other studies reported in the literature[3,8,15,18] in which responses ranging from 19% to 45% have been attributed to a variety of drug combinations that include 5-FU and Me, a comparison with those results shows that the absence of patient selection and strict criteria for evaluation of response may account for the low response rate in our study. In fact, the survival duration for patients treated with our first treatment program appears improved compared with the median survival times, ranging from 6 to

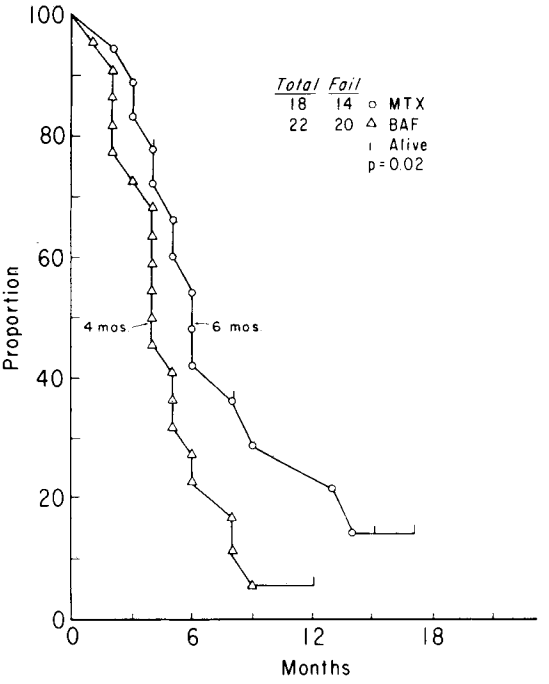

FIG. 4. Chemotherapy of advanced colorectal cancer with Me-MTX or BAF: Survival from onset of treatment related to the Antifol administered.

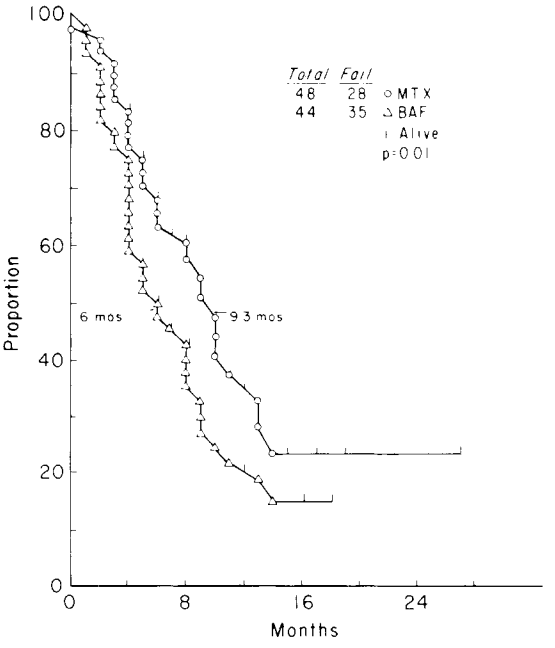

FIG. 5. Chemoimmunotherapy of advanced colorectal cancer with 5-FU-MTX or BAF ± Levamisole and Me-MTX or BAF: Survival from onset of treatment related to the Antifol administered.

TABLE 3. Responses in Previously Treated Patients with Measurable Lesions

Responses	Cross-over		Prior 5-FU only		Overall	
	ME-MTX	ME-BAF	ME-MTX	ME-BAF	ME-MTX	ME-BAF
Complete	—	—	—	—	—	—
Partial	—	—	2	2	2	2
Stabilization	2	3	5	2	7	5
Progression	5	4	6	10	11	14
TOTAL	7	7	13	14	20	21

8 months obtained by the other treatment programs. The median survival duration of 10 months for all patients on Program I reflects the improvement of the survival of patients who had tumor response or disease stabilization, which was significantly better than that of patients who had disease progression (13 vs. 4 months; $p = 0.001$). The same difference was seen in patients treated on Program II (8 vs. 4 months; $p = 0.001$). In the group of patients treated on Program I, the administration of levamisole immunotherapy did not appear to influence the response rate, response duration and survival obtained with chemotherapy alone. In both treatment programs, there was slightly better responses to those regimens containing MTX compared with those containing BAF. In the small number of patients who failed to 5-FU-MTX chemotherapy and crossed over to receive Me-BAF, no responses were seen, contrary to the expectations which were based on the theoretical advantage of BAF over MTX. Also, the median duration of survival of patients treated with Me-MTX was significantly longer than that of patients treated with Me-BAF. A similar difference between MTX and BAF was seen when the survival of all patients on Programs I and II are considered. There was no disproportionate distribution of prognostic factors such as performance status, extent of malignant disease or impairment of liver function to account for the better response rate and survival obtained with MTX-containing regimens. However, more frequent escalation of MTX dose to the maximum tolerable toxicity when such escalations were done to a lesser degree with BAF, in order to avoid severe hematologic and mucocutaneous toxicities seen with this drug particularly in pa-

TABLE 4. Hematologic Toxicity

	5-FU*	MTX	BAF	ME-MTX	ME-BAF
No. of courses given	134	62	44	71	50
% Patients with myelosuppression†	53	24	10	56	38
Lowest leukocytes $\times 10^3$					
Median	3.7	4.2	5.2	3.1	3.3
Range	0.6–10.5	0.5–9.7	1.9–10.1	0.4–10	0.65–8.9
Day	18	12	8	17	13
% Courses ≤ 1000	4	2	0	3	8
% Courses ≤ 500	0	2	0	2	0
Lowest neutrophils $\times 10^3$					
Median	1.8	2.5	2.6	1.6	2.1
Range	0–8.4	0.4–6.0	0.4–7.0	0–7.5	0.35–7.6
Day	18	14	8	18	13
% Courses ≤ 1000	30	17	6	24	14
% Courses ≤ 500	23	11	3	8	6
Lowest platelets $\times 10^3$					
Median	220	256	244	129	169
Range	24–521	100–680	95–600	9–553	12–451
Day	15	10	10	16	21
% Courses $\leq 100{,}000$	5	2	3	15	4
% Courses $\leq 50{,}000$	2	0	0	8	2

* 5-FU was administered sequentially with MTX or BAF.

† Absolute neutropenia $\leq 1000/mm^3$ and thrombocytopenia $\leq 100{,}000/mm^3$.

TABLE 5. Nonhematologic Toxicities Related to Treatment Courses

	5-FU*	MTX	BAF	ME-MTX	ME-BAF
% Courses with toxicity	37	23	27	38	45
% Nausea, vomiting or diarrhea	22	9	11	23	28
% Mucositis	13	13	14	12	17
% Infection	9	2	0	5	10
% Skin rash	4	4	11	0	17
% Bleeding	0	0	0	5	2
% Drowsiness/Ataxia	2	0	0	0	2
% Alopecia	2	0	0	1	0

* 5-FU was administered sequentially with MTX or BAF.

tients with liver disease, could have been a major factor.

The sequential administration of 5-FU with MTX or BAF to patients with metastatic colorectal cancer resulted in modest improvement in the duration of survival but failed to improve the response rate to above that with 5-FU alone. Whether a higher response rate could have been obtained if 5-FU was given sequentially with a cycle nonspecific drug instead of BAF or MTX remains highly speculative. The response rate with such a combination in an earlier trial[19] was not any better. The addition of levamisole to the antimetabolites did not appear to improve the response rate or the survival of the patients. MTX was significantly more effective than BAF in prolonging the duration of survival without significantly increasing the response rate when given in combination with Me to patients with prior exposure to 5-FU.

TABLE 6. Percent Dose Modifications by Courses

Changes	5-FU	MTX	BAF	ME
No change	65	56	61	68
Decreased	15	23	20	18
Increased	20	20	19	14

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