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Mitomycin C, Methyl-CCNU and 5-Fluorouracil in the Treatment of Metastatic Colorectal Carcinoma

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Summary. *The combination of mitomycin C, methyl-CCNU and 5-fluorouracil produced no objective tumor regressions in 25 evaluable patients with metastatic colorectal carcinoma. Patients who achieved stable disease survived significantly longer than patients who had progressive disease. This difference appeared to be more probably related to pre-treatment characteristics of the patients than caused by treatment. Serial CEA determinations revealed a parallel relationship with tumor behavior in 17 of 19 patients.*

Introduction

When used as single agents, mitomycin C, methyl-CCNU, and 5-fluorouracil produce 15%–20% response rates in advanced colorectal cancer [10]. The present study was designed to test the effectiveness and toxicity of a combination of these drugs in the treatment of metastatic colorectal cancer. The doses and scheduling of the drugs were based on the reports of Grillo-Lopez et al. [7] and of MacDonald et al. [9].

Studying the relationship between serial serum carcinoembryonic antigen (CEA) determinations and tumor response to chemotherapy was another objective of this study.

Materials and Methods

Biopsy-proven, measurable metastatic colorectal carcinoma was required for entry into this study. Patients who had received prior chemotherapy, who were ECOG performance status 4, or who were older than 70 years were excluded. Prior radiation therapy did not exclude patients providing there were measurable lesions outside of the irradiated field and patients had recovered from the effects of radiation. Additional eligibility requirements included: BUN less than 25 mg/dl, serum creatinine less than 1.5 mg/dl, bilirubin less than 1.5 mg/dl, leukocyte count greater than 4,000/mm^3, and platelet count greater than 150,000/mm^3.

The treatment schedule was: mitomycin C, 5 mg/m^2 IV and methyl-CCNU, 50 mg/m^2 PO on day 1, repeated every 6 weeks; and 5-fluorouracil 500 mg/m^2 IV on days 8, 15, 22, and 29 of a 42-day cycle. CBC and platelet counts were obtained weekly. Dose modifications were based on nadir counts with a 25% reduction for a leukocyte nadir below 2,000/mm^3 or platelet nadir below 75,000/mm^3 and on day-of-treatment counts with a 50% reduction for leukocyte count between 3,000 and 4,000/mm^3 or platelet count between 75,000 and 100,000/mm^3.

Complete remission (CR) was defined as the complete disappearance of all pre-existing, measurable lesions with no new lesions appearing. Partial remission (PR) was defined as a 50% reduction of the sum of the products of the largest diameter and its perpendicular for each measurable lesion. Stable disease was defined as less than 50% reduction or less than 25% increase in the measurable lesions, lasting for at least 12 weeks. Progression was defined as a greater than 25% increase in the sum of the products of the diameters of the measurable lesions or the appearance of a new lesion. Excluding patients with obvious tumor progression as defined above, a patient must have received two courses of treatment (12 weeks) to be considered fully evaluable.

Results

Thirty patients entered this trial. Twenty-five patients were evaluable for tumor response and 26 were evaluable for toxicity. The five patients who were unevaluable for tumor response included: a patient who did not have measurable disease, a patient who had no tumor measurements recorded after starting therapy, a patient who did not return after receiving the first dose of mitomycin C and methyl-CCNU, a patient who expired 3 days after receiving the first dose of mitomycin C and methyl-CCNU from causes not apparently related to tumor or treatment, and

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one patient who expired from septicemia during the first course of treatment.

No complete or partial responses were observed. Stable disease as defined above was observed in 12 patients, and disease progression occurred in 13 patients. Median survival from start of mitomycin C, methyl-CCNU, and 5-fluorouracil was 12 months for patients classified as having stable disease and 6 months for patients with progressive disease. According to Student's *t*-test, the survival differences are significant at the $P = 0.01$ level. The clinical characteristics of these two groups of patients are compared in Table 1. There are no important differences in the median ages or in the incidence of liver metastases. Worse performance status, a shorter interval from time of initial diagnosis to the time of diagnosis of metastases, and a lower median serum albumin level are observed in the patients with progressive disease.

Twenty-six patients who received 1–12 courses of treatment are evaluable for toxicity. The median number of treatment courses was three. Types and frequencies of the various toxicities are listed in Table 2. The median leukocyte count nadir was 3,700/mm^3. The lowest leukocyte count was 400/mm^3. This occurred during the frist treatment cycle, and the patient expired from septicemia. The median platelet count nadir was 97,000/mm^3 and the lowest platelet count was 31,000/mm^3. There were no episodes of hemorrhage secondary to thrombocytopenia.

Dose modifications were based on nadir counts and day-of-treatment counts as described previously. Seventeen of 26 patients required dose reductions because of hematologic toxicity.

Serum CEA determinations were done at the start of chemotherapy in 28 patients. In our laboratory, CEA values less than 2.5 ng/mg are considered normal. The initial CEA determination was less than 2.5 ng/ml in three patients, greater than 2.5 but less than 10 ng/ml in seven patients, greater than 10 but less than 100 ng/ml in four patients, and greater than 100 ng/ml in 14 patients.

Repeat CEA determinations were done during or at the completion of treatment in 19 patients. In this group of patients the mean number of CEA determinations per patient was 2.9, with a range of 2–5.

There was a parallel relationship between serial CEA levels and clinical assessment of tumor response in 17 of 19 patients. In 15 patients repeat CEA determinations were done shortly before or at the time of tumor progression, and in 13 of these patients the value increased. The rise in CEA was found 6–50 weeks after the initial CEA determination, with a mean of 18 weeks. The smallest increases in CEA were 26% (730–920 ng/ml) and 25% (700–879 ng/ml). In 11 patients repeat CEA levels at the time of tumor progression ranged from 300% to 1,000% higher than the initial CEA, with a median increase in CEA of 440%. In three patients who had initial CEA levels less than 3 ng/ml, a 4- to 8-fold increase occurred at the time of tumor progression. The CEA decreased from 360 to 280 ng/ml in one patient, and during the same time interval her abdominal CT scan revealed an approximately 25% decrease in an intra-abdominal mass. CEA determinations remained stable in three patients while their tumors

Table 1. Comparison of pre-treatment characteristics of patients with progressive disease versus patients with stable disease

	Progressive disease ($N = 13$)	Stable disease ($N = 12$)
Median age	60 years	58 years
Performance status (2–3)	6 patients	1 patient
Liver metastases	10 patients	9 patients
Median disease-free interval	7 months	14 months
Median serum albumin	3.9 gm/dl	4.4 gm/dl

Table 2. Grade of toxicity: ECOG criteria[a]

Type of Toxicity	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)	(Total toxicity)
Leukopenia[b] WB/mm^3	≥ 4,500 (6)	3,000–4,499 (17)	2,000–2,999 (2)	1,000–1,999 (0)	< 1,000 (1)	(20)
Thrombocytopenia[b] platelets/mm^3	≥ 130,000 (8)	90,000–129,999 (7)	50,000–89,999 (8)	25,000–49,999 (3)	< 25,000 (0)	(18)
Nausea and vomiting	(4)	(18)	(4)	(0)	–	(22)
Mucositis	(25)	(0)	(1)	(0)	–	(1)

[a] All patients had nadir counts
[b] Numbers in parentheses represent number of patients

remained clinically stable. One patient had tumor progression without change in serum CEA level. Another patient had tumor progression with a decrease in serum CEA level which occurred during the 4 weeks before the patient expired.

Mean and median pre-treatment serum albumin levels were both 3.9 gm/dl in 13 patients whose tumor responses were classified as progression, while they were 4.4 gm/dl in 12 patients whose tumor responses were classified as stable. According to Student's *t*-test, the difference in albumin levels is statistically significant at the $P = 0.05$ level.

Thirteen patients had pre-treatment serum albumin levels ≤ 3.9 gm/dl. Their median survival time was 6 months. Twelve patients had pre-treatment albumin levels ≥ 4.0 gm/dl. Their median survival duration was 12 months. The differences in survival are statistically significant at the $P = 0.02$ level.

Discussion

This regimen of mitomycin C, methyl-CCNU, and 5-fluorouracil resulted in mild to moderate hematologic toxicity without producing objective tumor regressions. Although survival was longer in patients who achieved stable disease, this was probably attributable to inherent differences in the patient populations rather than to activity of the drugs. Comparison of pre-treatment characteristics of patients whose tumor response was classified as stable disease with patients whose response was classified as tumor progression (Table 1) shows better performance status, longer disease-free intervals, and higher serum albumin levels in patients with stable disease. This suggests that the longer survival was attributable to better general condition, more indolent tumors, and better nutritional status rather than to the effects of treatment.

Following initial reports of improved response rates in metastatic colorectal carcinoma with methyl-CCNU plus 5-fluorouracil regimens [2, 5, 9, 11], subsequent trials have shown no advantage from combining these drugs [4, 8]. Greco et al. [6] have observed two partial responses in 19 patients when mitomycin C was combined with methyl-CCNU, vincristine, and 5-FU. The doses employed in their study were larger than in ours. Similarly Berenzweig et al. [3] combined four active drugs and observed one partial response and significant toxicity in 21 patients with metastatic colorectal carcinoma.

These results [3, 4, 8] along with our own data suggest that reduction of the doses and combination of active drugs which are currently available does not produce significant benefit in metastatic colorectal carcinoma.

Shani et al. [12] have defined a significant change in serum CEA as a 50% difference when the initial CEA is between 5 and 10 ng/ml and as a 25% difference when the initial CEA is greater than 10 ng/ml. Using these criteria to evaluate the relationship between serial CEA determinations and response of advanced colorectal cancer to chemotherapy, they observed increasing CEA levels in 10 of 17 patients who had progressive disease. Applying similar criteria to patients with colorectal carcinoma who were being treated with chemotherapy, Al-Sarraf et al. [1] found rising CEA levels in 14 of 21 patients with tumor progression. There is similar correlation in our trial, where 13 of 15 patients with progressing tumor had a rise in CEA level which was significant according to the criteria of both of these reports [1, 12]. The median increase in CEA in our patients was 4.4 times the initial CEA level. Interestingly, in three patients who had initial CEA levels less than 3 ng/ml there was a 4- to 8-fold increase in CEA when tumor progression was noted. These results suggest that following serial CEA levels in patients with colorectal carcinoma who are receiving chemotherapy provides additional documentation of tumor progression. Since no significant tumor regressions were observed in our patients, no data concerning CEA changes during tumor regression were obtained.

When patients classified as having stable disease were compared with patients classified as having progressing disease, statistically significant differences in survival and in mean pre-treatment serum albumin levels were observed. In addition, when survival durations in patients with initial serum albumin ≤ 3.9 gm/dl and in patients with serum albumin ≥ 4.0 gm/dl were compared the survival differences were statistically significant regardless of tumor response. These observations indicate that the pre-treatment serum albumin level may be an important prognostic indicator in patients with metastatic colorectal carcinoma, and they emphasize the requirement for careful examination of pre-treatment characteristics and careful pre-treatment stratification in randomized trials.

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