A Controlled Evaluation of Recent Approaches to Biochemical Modulation or Enhancement of 5-Fluorouracil Therapy in Colorectal Carcinoma

By Thomas R. Buroker, Charles G. Moertel, Thomas R. Fleming, Lloyd K. Everson, Stephen A. Cullinan, James E. Krook, James A. Mailliard, Robert F. Marschke, David J. Klaassen, John A. Laurie, and Merrit D. Moon

Three hundred thirty-five previously untreated patients with advanced colorectal carcinoma were randomly assigned to treatment with 5-fluorouracil (5-FU) alone, 5-FU plus N-(phosphonacetyl)-L-aspartic acid (PALA), 5-FU plus high-dose thymidine, 5-FU plus levamisole, or 5-FU plus methyl CCNU, vincristine, and streptozotocin (MOF-Strept). Dosages were designed to produce definite toxicity in the majority of patients, although the nature of dose-limiting reactions varied considerably among regimens. 5-FU alone and 5-FU plus levamisole produced mucocutaneous reactions, diarrhea, and leukopenia; 5-FU plus PALA produced primarily mucocutaneous reactions and diarrhea; 5-FU plus thymidine produced leukopenia with occasional neurotoxicity and hypotension; and MOF-Strept produced substantial nausea and vomiting with both thrombocytopenia and leukopenia. Objective response rates among patients with measurable disease varied from 12% (5-FU plus PALA) to 34% (MOF-Strept), but none of the regimens were significantly superior to 5-FU alone. Both interval to progression and survival were comparable among the five regimens with no reasonable chance that any combination regimen could produce as much as a 50% improvement when compared with 5-FU alone. Whereas we observed definite modulation of 5-FU dose–toxicity relationships, particularly with the thymidine and PALA combinations, this did not result in a detectable improvement in therapeutic effect. None of the combination regimens, administered in the dosages and schedules we used, can be recommended as standard therapy of advanced colorectal carcinoma.

J Clin Oncol 3:1624–1631. © 1985 by American Society of Clinical Oncology.

ADVANCED colorectal carcinoma is one of the most common oncologic challenges encountered in the Western world. Nevertheless, there is little evidence of effective therapy for such patients other than symptomatic and supportive care. 5-Fluorouracil (5-FU) is considered by many as the standard of chemotherapy, but in larger experiences with this agent, response rates have only been in the 15% to 20% range. These responses are usually partial, sometimes questionable, and generally very transient. To date there has been no convincing evidence that any chemotherapy of colorectal cancer contributes to either the duration or the quality of life.

Although a large number of alternative drugs have been studied in colorectal cancer, none has exceeded the meager effectiveness of 5-FU. A hope frequently pursued in clinical research has been that the activity of 5-FU can be enhanced either by adding the activity of other cytotoxic drugs or, more recently, by favorably modulating the effects of 5-FU itself. Although enhanced activity by such methods has occasionally been suggested in pilot studies or in phase 2 trials, these claims have seldom been substantiated by the essential definitive study—a randomized comparison with 5-FU used alone. The purpose of the study reported here is to evaluate, by such a randomized and controlled comparison, a number of recent approaches that have either been

From the Iowa Oncology Research Association CCOP, Des Moines; Mayo Clinic, Rochester, Minn; University of Washington, Seattle; The Fargo Clinic CCOP, Fargo, ND; Illinois Oncology Research Association CCOP, Peoria; Duluth Clinic CCOP, Duluth, Minn; Creighton University, Omaha; Central Plains Clinic, Sioux Falls, SD; Saskatchewan Cancer Center, Saskatoon, Saskatchewan, Canada; Grand Forks Clinic, Grand Forks, ND; and the Quain and Ramstad Clinic, Bismarck, ND.

Submitted April 26, 1985; accepted Aug 5, 1985.

Supported by Public Health Service Grants No. CA 25224 and CA 37404 from the National Cancer Institute, National Institutes of Health, DHHS.

Address reprint requests to Thomas R. Buroker, MD, Iowa Methodist Medical Plaza, 1212 Pleasant, Des Moines, IA 50309.

0732-183X/85/0312-0008$3.00/0

shown in animal models to enhance 5-FU activity or have been claimed to produce favorable results on the basis of early human trials. We chose for our evaluation the combinations of 5-FU with thymidine; with N-(phosphonacetyl)-L-aspartic acid (PALA); with levamisole; and with methyl CCNU, vincristine, and streptozotocin (MOF-Strept).

Thymidine given at high doses in animal model systems has been shown to increase both therapeutic activity and toxicity of 5-FU and to improve the therapeutic index of this agent.[1] These effects presumably occur through the action of thymidine in blocking oxidative metabolism of 5-FU and increasing 5-FU incorporation into RNA. Rustum demonstrated in colon 26 tumor and in a transplanted colon tumor in rats that thymidine plus 5-FU produced a significant prolongation of survival time when compared with 5-FU alone.[2] Studies by Woodcock et al,[3] by Kirkwood and Frei,[4] and by Vogel et al[5] demonstrated that in humans, pretreatment with thymidine increased the biologic activity of 5-FU up to eight-fold as measured by hematologic toxicity. In the study of Woodcock et al, the single colorectal cancer patient treated who was not a prior 5-FU failure had a response of 8 months duration. They also observed one additional response among patients who had failed 5-FU. In the study of Vogel et al, two of five previously untreated colorectal cancer patients responded for 4+ and 7 months.

PALA is a potent inhibitor of aspartate transcarbamylase and has a broad spectrum of activity in animal model tumor screens.[6] In human trials the dose-limiting toxicities were mucocutaneous reactions with minimal hematologic effects. Overall therapeutic results were discouraging, specifically in colorectal cancer: a Mayo Clinic study demonstrated only one response among 30 patients,[7] a study of the Baltimore Cancer Research Program showed no responses among 21 patients,[8] and a New York Memorial study demonstrated only two minor responses among 19 evaluated patients.[9] Continued interest in PALA, however, was stimulated by animal model evidence that this agent inhibits pyrimidine synthesis and thereby enhances 5-FU activity by increasing its conversion to fluorouridine monophosphate (FUMP).[6] Synergistic activity with the PALA–5-FU combination was demonstrated in murine tumor systems.[6] Pilot and phase 2 trials of this combination in humans showed the dose-limiting toxicity to be mucocutaneous effects.[10,11] In the phase 2 trial of Bedikian et al, a relatively discouraging 14% response rate was recorded among 50 patients, but an additional 54% were stated to have achieved "disease stabilization."[11]

Levamisole is an agent that has been used extensively to treat parasitic infections in man and domestic animals. It has also been shown to have immunomodulatory effects. Two randomized, controlled studies have raised the possibility that it may have some role in the treatment of colorectal carcinoma. The first was a small surgical adjuvant study reported by Verhaegen et al in which levamisole-treated patients had a significantly improved survival when compared with untreated controls.[12] The second study, conducted at the University of Wisconsin (Madison), showed that advanced-disease patients treated with combined 5-FU and levamisole lived significantly longer than patients treated with 5-FU alone.[13] If this result could be confirmed it would be the first time that any regimen has demonstrated such significant survival improvement for advanced colorectal cancer in randomized trials.

In 1981, a New York Memorial study reported a 32% objective response rate among 77 patients treated with MOF-Strept.[14] In a randomized trial, this group showed that this combination produced superior response rates and survival when compared with their own variant of the 5-FU, methyl CCNU, vincristine combination.[15] In contrast, however, the Gastrointestinal Tumor Study Group reported only a 4% response rate among 41 patients treated with MOF-Strept and they discouraged further use of this combination.[16] Again it would seem appropriate that the activity and toxicity of the MOF-Strept combination be placed in perspective by a randomized comparison with 5-FU alone.

With this background we initiated a randomized controlled comparison of 5-FU alone with 5-FU plus high-dose thymidine, 5-FU plus PALA, 5-FU plus levamisole, and MOF-Strept. We elected to use survival as our primary endpoint in patients with both measurable and nonmeasurable disease and also to evaluate objective response rates among those patients with measurable disease.

METHODS

Patient Selection

All patients were required to have histologic or cytologic confirmation of unresectable or metastatic colorectal cancer. An exception to the requirement for histologic confirmation of metastasis was made in the patient with a previous histologically confirmed primary colorectal carcinoma and who presented with multiple pulmonary metastasis that had shown progression on two chest x-rays taken at least 1 month apart. Patients could be entered with either measurable or nonmeasurable disease. Measurable disease was defined as a tumor mass that could be clearly measured in two dimensions on either physical examination or chest x-ray. Malignant hepatomegaly was used as a measurable lesion if a clearly defined liver edge extended at least 5 cm below the xyphoid process or costal margins on quiet respiration. A radioactive liver scan could be used to document a measurable lesion if there was a clearly defined perfusion defect measuring at least 5 cm in greatest diameter. It was also required that the patient be ambulatory and maintaining a reasonable state of nutrition. Contraindications to selection included a WBC count $< 4{,}000/mm^2$ or a platelet count $< 130{,}000/mm^2$, a serum creatinine > 1.5 mg/dL, complete disability (Eastern Cooperative Oncology Group [ECOG] performance score 4), recent major surgery (exploration and biopsy only, < 14 days; resection or bypass surgery, < 21 days), an uncontrolled infectious process, frequent vomiting or severe anorexia, any previous chemotherapy, and intensive radiation to the axial skeleton within the preceding 4 weeks.

Tissue from each patient was submitted to a pathology review committee to ensure eligibility and proper histopathologic classification.

Randomization Procedures

After determining eligibility and obtaining written informed consent, patients were stratified according to performance score and the presence and location of measurable disease. Patients were then randomized to treatment with 5-FU alone, 5-FU plus PALA, 5-FU plus thymidine, 5-FU plus levamisole, or MOF-Strept.

Treatment Methodology

5-FU alone. 5-FU was administered in undiluted form by rapid intravenous (IV) injection at a dose of 500 mg/m^2 daily for 5 consecutive days. Courses were repeated every 5 weeks.

5-FU plus thymidine. Thymidine was administered by a single IV infusion over 90 minutes at a total dose of 45 g. Two hours following initiation of the thymidine infusion, 5-FU was administered by rapid IV injection in a single dose of 300 mg/m^2. The single doses of thymidine and 5-FU were repeated at 4-week intervals.

5-FU plus PALA. 5-FU was administered by rapid IV injection at a dosage of 300 mg/m^2 for 5 consecutive days. PALA was administered by rapid IV injection at a dose of 625 mg/m^2/d for 5 consecutive days. On day 1, 5-FU was administered 4 hours after PALA. On days 2 through 5, 5-FU was administered after PALA, but no delay was required. Courses of therapy were repeated every 5 weeks.

5-FU plus levamisole. 5-FU was administered in undiluted form by rapid IV injection at a dose of 500 mg/m^2/d for 5 consecutive days. These courses were repeated every 5 weeks. Levamisole was administered orally at a dose of 50 mg every 8 hours on days 14, 15, and 16, and days 21, 22, and 23 of each 5-FU cycle. This corresponded to the regimen used by Davis et al.[13]

MOF-Strept. 5-FU was administered in undiluted form by rapid IV injection at a dose of 300 mg/m^2/d on days 1 through 5 and 36 through 40. Methyl CCNU was administered orally at a dosage of 30 mg/m^2/d on days 2 through 6. Vincristine was administered by rapid IV injection at a dose of 1 mg/m^2 on days 1 and 36. Streptozotocin was administered by rapid IV injection at a dose of 500 mg/m^2 on day 1 and every 7 days thereafter. This cycle of treatment was repeated every 10 weeks. This corresponded to the method used by the New York Memorial group.[15,16]

For all regimens, WBC count and platelet counts were obtained weekly. For the 5-FU plus thymidine regimen, patients were evaluated every 4 weeks, while for all other regimens, this evaluation occurred every 5 weeks. The evaluation consisted of a history and physical examination, measurement of indicator lesions, hematology and chemistry panel (including serum creatinine), urinalysis, and a chest x-ray. If the chest x-ray was negative pretreatment, this was repeated only with every other evaluation. If severe toxicity had been obtained with a previous treatment course, drug dosages were appropriately reduced with subsequent therapy. Treatment was continued until disease progression was documented.

Evaluation of Results

The primary endpoint of our overall study was patient survival. It was planned to enter a minimum of 300 eligible and evaluable patients. For the comparison of any one of our drug combinations with 5-FU, this would permit our test for treatment effect to have .90 probability of detecting a true doubling in survival time (eg, from 6 to 12 months), while having only a .05 probability of obtaining a false-positive result when there were no true differences in survival.

A secondary objective was to assess objective response rates among those patients who had measurable disease. Standard criteria for declaring objective response were used, ie, a 50% or greater reduction in the product of longest perpendicular diameters of bidimensionally measurable lesions or a 30% or greater decrease in the sum of liver measurements below the xyphoid process at costal margin. It was required that this result be observed at least 4 weeks after the onset of therapy, but there was no requirement for duration of response.

Statistical Methods

Each combination regimen was compared to treatment with 5-FU alone with respect to duration of survival following randomization, time to disease progression, objective regression rates among measurable patients, and toxic reactions. Survival curves were constructed using the Kaplan-Meier method.[17] The log rank statistic[18] was used to assess consistency of the data with equality of survival curves, while the Cox partial likelihood score statistic[19] was used to assess consistency of the data with the hypothesis that any one of the combinations would yield at least a 50% improvement in survival over 5-FU alone. More generally, the Cox proportional hazards model[19] was used to inspect the association of treatment with survival when adjusting

for covariates. P values were two-sided. Interim analyses of the survival data were performed using the O'Brien–Fleming group sequential boundary as a guideline.[20] Early termination did not occur. Thus, essentially no adjustment of the P values given below is required.

RESULTS

A total of 347 patients were randomized on this study. The entries of two patients were cancelled after randomization, and ten patients were found to be ineligible. The primary reason for ineligibility (seven patients) was failure to confirm metastatic disease according to protocol criteria. Four patients were lost to analysis due to ineligibility or cancellation on the 5-FU alone arm, four patients on 5-FU plus PALA, two patients on 5-FU plus thymidine, two patients on MOF-Strept, and none on 5-FU plus levamisole. A total of 335 eligible patients were properly started on therapy and are included in the analysis below. These represent 97% of all patients randomized. At the time of this writing the study is very mature with 318 patients (95%) having shown progressive disease and 278 patients (83%) having been followed to the time of death.

The pretreatment characteristics of our patients are displayed according to the treatment arm in Table 1. It is noteworthy that most of these patients were in excellent general condition. Seventy-six percent had an ECOG performance score of 0 or 1. Fifty-five percent had measurable disease, primarily in liver or lung. There are imbalances between treatment arms in sex ratio, grade of anaplasia, and patients admitted to study with progressive pulmonary lesions but no histologic proof of metastasis.

Toxicity

The toxic reactions experienced according to treatment arm and severity are documented in Table 2. MOF-Strept was characterized by substantially more frequent and more severe nausea and vomiting, and this was the only regimen characterized by a substantive incidence of thrombocytopenia. 5-FU plus PALA had substantially more frequent mucocutaneous reactions and somewhat more frequent diarrhea, but less hematologic toxicity than 5-FU alone or any of the other regimens. On the other hand, 5-FU plus thymidine had a reduced incidence of mucocutaneous reactions and of diarrhea with comparable hematologic toxicity when compared with 5-FU alone. The most unique toxicity of this regimen was a substantially increased incidence of neurologic effects. These reactions were primarily headache (seven patients), lethargy (four patients), dizziness with ataxia (four patients),

Table 1. Patient Characteristics

Characteristics	5-FU Alone	5-FU Plus PALA	5-FU Plus Thymidine	5-FU Plus Levamisole	MOF-Strept
Total patients	69	65	67	66	68
Female/Male	26/43	37/28	27/40	31/35	42/26
Median age (yr)	62	62	65	66	64
Performance score*					
0–1	52	49	50	51	53
2–3	17	16	17	15	15
Measurable disease	37	34	35	40	38
Measurable metastatic site					
Liver	18	16	17	21	18
Lungs	12	14	16	16	14
Other	7	4	2	3	6
Site of primary					
Colon	58	50	57	47	52
Rectum	11	15	10	19	16
Confirmation of metastasis					
Histologic	69	63	59	60	65
Progression on chest x-ray	0	2	8	6	3
Grade of anaplasia					
Low	1	9	7	11	6
Medium	50	47	44	43	51
High	18	9	11	12	11

*ECOG score: 0, fully active to 4, totally disabled.

Table 2. Toxicity

	5-FU Alone (%) (n = 69)		5-FU Plus PALA (%) (n = 65)		5-FU Plus Thymidine (%) (n = 67)		5-FU Plus Levamisole (%) (n = 66)		MOF-Strept (%) (n = 68)	
Nonhematologic										
Nausea	54		54		64		50		98	
Severe		4		8		12		3		32
Vomiting	19		29		43		27		82	
Severe		4		6		12		3		29
Stomatitis	43		65		28		39		22	
Severe		12		28		4		6		3
Diarrhea	32		40		25		38		28	
Severe		7		14		9		5		3
Dermatitis	16		37		3		9		3	
Alopecia	19		29		13		30		25	
Hematologic (first course only)*										
Leukopenia										
< 4,000/μL	67		33		60		88		82	
< 2,000/μL	20		3		20		28		19	
Thrombocytopenia										
< 130,000/μL	22		7		16		17		65	
< 50,000/μL	0		0		0		0		11	

*Based on 94% of patients who had adequate counts to determine nadirs.

and occasional confusion (two patients). One patient died in irreversible coma. There were also nine patients who experienced transient hypotension following drug administration. The addition of levamisole to 5-FU had no discernable impact upon toxicity except for a slight increase in leukopenia. Eight patients on this combination complained of altered taste, primarily a metallic taste in the mouth.

There were three treatment-related deaths: one each on 5-FU alone, 5-FU plus thymidine, and MOF-Strept.

Therapeutic Results

Objective response rates are shown according to regimen in Table 3. None of the combination regimens showed a significant advantage to 5-FU used alone. It is noteworthy that while the MOF-Strept regimen had the highest regression rate, it was also the regimen with the lowest proportion of patients whose disease remained stable and the highest proportion of patients in whom the best response observed was tumor regression. Whereas 5-FU plus PALA was associ-

Table 3. Objective Response According to Regimen

Toxic Reaction	5-FU Alone (n = 37)	5-FU Plus PALA (n = 34)	5-FU Plus Thymidine* (n = 34)	5-FU Plus Levamisole (n = 40)	MOF-Strept (n = 38)
Best response (%)					
Regression	29.7	11.8	17.6	22.5	34.2
Stable	56.8	55.9	53.0	62.5	23.7
Progression	14.5	32.7	30.4	15.0	42.1
Duration of regression†					
Median (wk)	40	55	18.5	25	26
Range (wk)	5–65	5–151+	12–30	5–123	5–139+

*One patient refused observation and could not be evaluated.

†Measured from first day of therapy to last day of documented measurements meeting criteria for response.

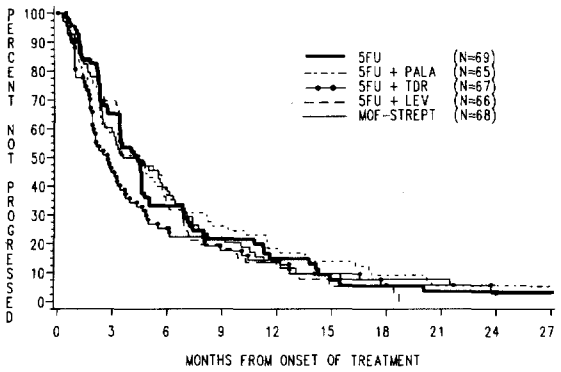

Fig 1. Intervals to disease progression according to treatment regimen.

ated with the lowest regression rate, these regressions were of the longest median duration. The intervals to disease progression are shown in Fig 1. The median interval to progression for all patients was 3½ months. There was no suggestion that any of the combination regimens performed in a superior fashion to 5-FU used alone, and it is unlikely that any could produce as much as a 50% increase in time to progression ($P < .05$) for each regimen *v* 5-FU alone. (These are two-sided *P* values obtained from a multivariate Cox analysis assessing consistency of the data with a hazard ratio of 1.5.)

Table 4 shows the association of a number of patient characteristics with survival. As would be expected, both performance status and the presence of measurable disease are highly predictive. Grade of anaplasia also proved to be a powerful prognostic predictor. This factor was imbalanced among our treatment regimens, but this imbalance clearly weighed against the 5-FU arm that had the lowest proportion of low-grade lesions and the highest proportion of highly anaplastic tumors. Sex ratios and patients with metastatic disease confirmed only by chest x-ray were also imbalanced in our study, but neither were important prognostic variables.

Figure 2 displays the patient survival according to treatment regimen. The median survival for all patients was 8¼ months. None of the combination regimens showed a significant superiority to 5-FU used alone. There is no reasonable possibility that a 50% (4 month) increase in survival could be obtained for any regimen in comparison with 5-FU alone. This was confirmed by a stratified Cox analysis, adjusting for

Table 4. Covariates and Their Predictive Value for Survival

	Median Survival (wk)	Two-sided Log-Rank (*P*)
Sex		
Male	38	.43
Female	34	
Age		
< 65 yr	35	.59
≥ 65 yr	38	
Performance score		
0–1	40	.011
2–3	24	
Measurable disease		
Yes	32	.007
No	37	
Site of primary		
Colon	36	.98
Rectum	34	
Confirmation of metastasis		
Histologic	36	.94
Chest x-ray	44	
Grade of anaplasia		
Low	55	<.0001
Median	38	
High	21	

key prognostic covariates, which indicated that the data were inconsistent with any combination regimen yielding a 50% increase in survival relative to 5-FU (ie, a hazard ratio of 1.5), wherefore 5-FU plus PALA, $P < .01$; 5-FU plus thymidine, $P < .0001$; 5-FU plus levamisole, $P < .01$; and MOF-Strept, $P < .05$.

DISCUSSION

The results of this study were singularly discouraging. In spite of the fact that the patients tested were in very good overall general condi-

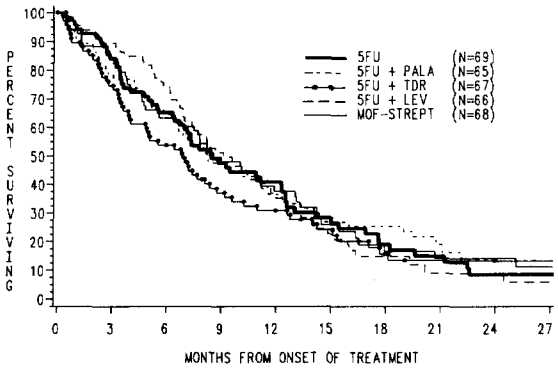

Fig 2. Survival according to treatment regimen.

tion with no previous chemotherapy exposure, none of our experimental regimens produced any meaningful advantage over therapy with simple 5-FU alone and none can be recommended for standard practice.

In each of the regimens we tested, drug dosages and scheduling were admittedly largely arbitrary. It is entirely possible that different proportionate representation of drug dosages or different scheduling could produce more favorable or less favorable results than we observed. Unfortunately, there is little in the way of reliably predictable animal model experimentation to serve as a foundation for rational dosage regimens in humans.

In designing the 5-FU–PALA regimen, we arbitrarily elected that both agents would be given at approximately equal proportions of the tolerable dose if each drug was used alone. This allowed for 60% of the full dose of both 5-FU and PALA to be administered. The dose-limiting mucocutaneous toxicity that we observed undoubtedly represented the additive effects of both agents. Our results were disappointing. Martin has pointed out that it might be possible to obtain the full biochemical modulating effect of PALA by using a considerably lower dose of this agent, thereby allowing the 5-FU dose to be increased to near full therapeutic levels.[9] Further exploration of the 5-FU–PALA theme might be justified on this basis.

With the 5-FU–thymidine combination, we observed a marked modulation of 5-FU effect with regard to both dose and toxicity. The total dose of 5-FU in this combination was only 12% of the dosage of 5-FU used alone that would produce a comparable degree of hematologic toxicity. Unfortunately, this modulation did not translate into the therapeutic gain predicted by animal models, and the neurotoxicity only rarely observed with 5-FU alone was made much more prominent.

Our experience with the 5-FU–levamisole combination was particularly discouraging in view of the early study of the University of Wisconsin, indicating that this combination could produce substantial survival improvement.[13]

In agreement with the New York Memorial Group,[14] and in contrast with the Gastrointestinal Tumor Study Group results,[16] we did record a moderately high response rate with the MOF-Strept combination. This, however, was purchased at the price of disagreeable nausea and vomiting and the additional toxic problems of thrombocytopenia. One cannot conclude that this regimen added to the quality of patient life; and since it did not add to duration of life, we must conclude that this regimen has little to recommend it.

An interesting sidelight of this study is the fact that grade of tumor anaplasia was found to be a powerful prognostic determinant, matching the more well-established performance status and presence or absence of measurable disease. The fact that all tissue was subjected to a common pathology review process may have produced sufficient uniformity of grading to allow this characteristic to be a useful predictor of survival.

Whereas the results of this study were negative, these should not discourage continued efforts to exploit the biochemical modulation approaches. We would hope this could be done more successfully with increasing knowledge of how best to apply the results of experimental models in the clinical settings.

APPENDIX

Other participating investigators in this study were: Allan Blair Memorial Clinic, Regina, Saskatchewan, Canada (J.M. MacIntoch, M.A. Poon, S. Rayson); Billings Clinic, Billings, Mont (W.D. Bowman, D.I. Twito); Creighton University, Omaha, Neb (P.S. Johnson); Duluth Clinic CCOP, Duluth, Minn (R.J. Dalton, R.D. Niedringhaus); Fargo Clinic CCOP, Fargo, ND (P.S. Etzell, R. Levitt, G.W. McCormack, L.A. Otteman); Grand Forks Clinic, Grand Forks, ND (A. Wax); Iowa Oncology Research Association CCOP, Des Moines, Iowa (L.D. Brown, S.F. Brunk, R.F. Morton, R.R. Shreck); Illinois Oncology Research Association CCOP, Peoria, Ill (J.B. Gerstner, M.H. Veeder); Mayo Clinic, Rochester, Minn (M.J. O'Connell, R.G. Hahn, L.K. Kvols, R.J. Reitemeier, J.R. Rubin, A.J. Schutt); Quain and Ramstad Clinic, Bismarck, ND (W.J. Gundlach, D.M. Pfeifle); Saskatoon Cancer Clinic, Saskatoon, Saskatchewan, Canada (C.D. Little, A.W. Maksymiuk); University of Nebraska Medical Center, Omaha, Neb (M.A. Kessinger, H.M. Lemon, M.A. Tempero); St Cloud Internists, St. Cloud, Minn (N.F. Reuter, H.E. Windschitl); Sioux Falls Community Cancer Consortium CCOP, Sioux Falls, SD (D.L. Elson, W. Fryda, R.A. Nelimark, L.K. Tschetter); Pathology Review Committee: John Barlow, Rapid City, SD; G.W. Cates, Saskatoon, Canada; John Edland, Omaha, Neb; Merrit Moon, Bismarck, ND; Daudur Rahman, Peoria, Ill; Subhash Vidyarthi, Duluth, Minn.

ACKNOWLEDGMENT

The authors express their gratitude to Joan Hilton, MPH, and Therese Hu, MS, for their valuable assistance in the conduct and analysis of this protocol.

REFERENCES

1. Martin DS, Stolf RL, Sawyer RC, et al: An overview of thymidine. Cancer 45:1117–1128, 1980

2. Rustum Y, as quoted by Martin DS, et al[1]

3. Woodcock TM, Martin DS, Damin LAM, et al: Combination clinical trials with thymidine and fluorouracil. Cancer 45:1135–1143, 1980

4. Kirkwood JM, Frei E III: 5-Fluorouracil (FU) with thymidine (TdR): A phase I study: Proc Am Assoc Cancer Res 19:151, 1978 (abstr)

5. Vogel SJ, Presant CA, Ratkin GA, et al: Phase I study of thymidine plus 5-fluorouracil infusions in advanced colorectal carcinoma. Cancer Treat Rep 63:1–5, 1979

6. Martin DS, Stolfi RL, Sawyer RC, et al: Therapeutic utility of utilizing low doses of N-(Phosphonacetyl)-L-aspartic acid in combination with 5-fluorouracil. Cancer Res 43:2317–2321, 1983

7. Rubin J, Purvis J, Britell JC, et al: Phase II study of PALA in advanced large bowel carcinoma. Cancer Treat Rep 65: 335–336, 1981

8. Van Echo DA, Diggs CH, Scoltock M, et al: Phase II evaluation of N-(Phosphonacetyl)-L-aspartic acid (PALA) in metastatic adenocarcinoma of the colon or rectum. Cancer Treat Rep 64:339–342, 1980

9. Carroll DS, Gralla RJ, Kemeny NE: Phase II evaluation of N-(Phosphonacetyl)-L-aspartic acid (PALA) in patients with advanced colorectal carcinoma. Cancer Treat Rep 64:349–351, 1980

10. Meshad MW, Evin TJ, Kufe D, et al: Phase I trial of combination chemotherapy with PALA and 5-FU. Cancer Treat Rep 65:331–334, 1981

11. Bedikian AY, Stroehlein JR, Karlin DA, et al: Chemotherapy for colorectal cancer with a combination of PALA and 5-FU. Cancer Treat Rep 65:747–753, 1981

12. Verhaegen H, DeCree J, DeCock W, et al: Levamisole therapy in patients with colorectal cancer, in Terry WD, Rosenberg SA (eds): Immunotherapy of Human Cancer. New York, Elsevier, 1982

13. Davis TE, Borden EC, Wolberg WH, et al: Levamisole and 5-fluorouracil in metastatic colorectal carcinoma. Proc Am Soc Clin Oncol 1:102, 1982 (abstr)

14. Kemeny N, Yagoda A, Braun D Jr, et al: Therapy for metastatic colorectal carcinoma with a combination of methyl CCNU, 5-fluorouracil, vincristine and streptozotocin (MOF-strept). Cancer 45:876–881, 1980

15. Kemeny N, Yagoda A, Braun D Jr: Metastatic colorectal carcinoma. A prospective randomized trial of methyl CCNU, 5-fluorouracil (5-FU), and vincristine (MOF) versus MOF plus streptozotocin (MOF-strept). Cancer 51:20–24, 1983

16. Gastrointestinal Tumor Study Group: Phase II study of MOF-strept (methyl CCNU, vincristine, 5-fluorouracil, streptozotocin) in advanced measurable colorectal carcinoma. Proc Am Assoc Cancer Res 23:149, 1982 (abstr)

17. Kaplan E, Meier P: Nonparametic estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958

18. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163–170, 1966

19. Cox DR: Regression models and life tables (with discussion). J R Stat Soc Series B 34:187–220, 1972

20. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549–556, 1979