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A combination of 5-fluorouracil and thymidine in advanced colorectal carcinoma

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Summary. *Concurrent administration of thymidine (TdR) has been shown to increase the antitumor activity of 5-fluorouracil (5-FU) in various experimental models. The clinical response rate, side-effects, and toxicity of 5-FU und TdR were evaluated in 27 patients with advanced colorectal carcinomas. Each 6-day treatment course consisted of an IV loading dose of TdR (405 mg/kg, over 30 min), followed by continuous IV infusions of 5-FU (7.5 mg/kg per day for 5 days), and TdR (216 mg/kg per day for 6 days); courses were repeated every 4 weeks. The overall partial response rate was 4.5%, or 16.7% in patients with no prior 5-FU chemotherapy. Short-lived stable disease was seen at an overall rate of 27.3%, half of these patients with prior 5-FU chemotherapy. Myelotoxicity occurred in 64% of the patients, but this was dose-limiting in only 20%. Gastrointestinal and neurological symptoms were mild and infrequent. There was one case of treatment-related death due to sepsis secondary to leukopenia. It is concluded that the concurrent IV administration of 5-FU and TdR does not improve the response rate over that obtained with 5-FU alone.*

Introduction

5-Fluorouracil (5-FU) is the chemotherapeutic agent that has been most widely used for advanced colorectal carcinoma. Although it has been used systemically in a variety of regimens, both as a single agent and in combination with other agents, no significant improvement has been achieved in the 15%–20% response rate to this agent or in the 27- to 32-week median survival of the patients [6].

Various metabolites have been combined with chemotherapeutic agents in an attempt to improve their selectivity by sensitizing tumor cells and desensitizing normal host cells to the antimetabolite. The simultaneous administration of thymidine (TdR) and 5-FU has shown to prevent the inhibition of DNA synthesis secondary to thymidylate synthetase block by the 5′-monophosphate of the deoxyribonucleoside of 5-FU (FdUMP), and to increase the incorporation of 5-FU into defective tumor RNA. This results in an enhanced anticancer activity in murine colon carcinoma [4, 5,7]. Phase I studies of 5-FU and TdR have been carried out in patients with inoperable, advanced solid tumors of various histological origins [3, 10, 11]. No conclusions were reached regarding antitumor response rates in two of these phase I studies [3, 10].

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In a previous paper [1], we described the effects of TdR coadministration on the pharmacokinetics and metabolism of 5-FU in patients with advanced colorectal carcinoma. The present paper describes the clinical response rate, side-effects, and toxicity of 5-FU and TdR chemotherapy in advanced colorectal carcinoma.

Materials and methods

Patients were considered eligible if they had histologically confirmed inoperable recurrent or metastatic colorectal carcinoma, and initial WBC > 4,000, platelet count > 150,000, serum bilirubin < 2.5 mg/dl, serum creatinine < 1.5 mg/dl, and creatinine clearance > 60 ml/min. All patients underwent pretreatment baseline evaluation, which included liver scans, bone scans and radiographic studies pertinent to the site involved with metastatic disease.

Each 5-FU, TdR treatment course lasted 6 days. Each course consisted of a loading dose of TdR (405 mg/kg), administered IV over 30 min, followed 2 h later by continuous IV infusions of 5-FU (7.5 mg/kg per day for 5 days) and TdR (216 mg/kg per day for 6 days). The chemotherapeutic agents were administered by a volumetric infusion pump and each course was repeated every 4 weeks. The 5-FU dose was subject to an increase or decrease by 20%–50% in subsequent courses depending on toxicity.

Patients were evaluated after the second course of treatment and after each additional course. Weekly WBC and platelet counts were determined after the completion of each course. Patients were evaluated by physical examination, complete blood count, blood chemistry, chest X-ray and tomograms, and liver, bone, brain, and CAT scans. Criteria for discontinuation of treatment were progresson of disease and/or severe toxicity.

The criteria for response were defined as follows:

Complete response, disappearance of all lesions according to physical examination and/or radiographic studies or nuclear scan testing for a minimum of 4 weeks.

Partial response, a 50% decrease in the diameters of all measurable lesions for longer than 1 month; no new lesions or any increase in previous lesions.

Minor response, objective decrease in measurable lesions > 25% but < 50% or regression of greater magnitude but of short duration.

Stable disease, no change in any of the measurable lesions. All patients were evaluated with respect to drug tolerance and response to treatment. Also, all of the patients were followed till the time of their death.

Patient population

A total of 27 patients entered the study, 7 of whom had not received any prior chemotherapy. The remaining 20 patients had received prior chemotherapy: 4 patients 5-FU, 11 patients 5-FU combination, 5 patients a drug other than 5-FU. Therefore, 15 patients had received prior 5-FU chemotherapy and 12 patients had not.

The patients in the two groups (5-FU versus no previous 5-FU) did not significantly differ with respect to sex and mean age (Table 1).

Table 1. Sex and age distribution of patients

	Overall	Prior 5-FU	No prior 5-FU
Sex			
Male	16/27 (59%)	9/15 (60%)	7/12 (58%)
Female	11/27 (41%)	6/15 (40%)	5/12 (42%)
Age			
Range	38–76	61–72	38–76
Mean	58	57	60

Table 2 illustrates the patients' metastatic involvement of various sites. It is noteworthy that 6 of 27 patients had single-site metastasis [in 5, the liver (P.A., B.S., A.P., W.D., A.H.); and in 1, the lung (J.M.)].

Table 3 compares the extent of metastatic disease in the various groups of patients.

Reactions and toxicity

A total of 58 courses of treatment were administered: 28 courses to 14 patients with prior 5-FU chemotherapy and 30 courses to 12 patients with no prior 5-FU.

One patient (R.D.) had a severe reaction to the IV bolus of TdR and was not treated. He is evaluable only for tolerance to TdR.

One patient (C.B.) was considered to have a poor performance status, and his dosages of 5-FU and TdR were considerably lower than the protocol requirements; he is therefore partially evaluable for tolerance and toxicity, but not for response.

Two patients (C.A., J.B.) were withdrawn by their families after the first course and neither is evaluable for response. One of them (C.A.) did not have weekly CBCs and is therefore evaluable only for tolerance and not for toxicity.

There was one case of death directly attributable to the treatment. A patient (A.B.) who had had no prior chemotherapy developed severe leukopenia and died of sepsis 2

Table 2. Extent of metastatic involvement

	Liver	Lung	Extrahepatic intra-abdominal	Bone	Brain	Soft tissue
Prior 5-FU						
C. A.	+		+	+		+
P. A.	+					
C. B.	+	+				
J. B.		+	+			
R. D.		+	+			+
W. E.	+	+				
J. E.	+	+	+			+
A. G.		+			+	
P. M.	+	+				
J. M.		+				
E. P.	+		+			
J. R.		+	+			
B. S.	+					
T. S.		+		+		
V. V.	+	+		+		
No prior 5-FU						
Other agents						
A. B.	+	+				
G. H.		+	+			
W. H.	+					+
M. M.	+	+			+	
A. P.	+					
No prior chemo						
A. J. B.	+	+				
P. C.	+	+				
W. D.	+					
E. F.	+	+				+
A. H.	+					
M. R.	+	+				
G. R.		+	+			

weeks after his second course. He is therefore not evaluable for response.

With regard to tolerance to TdR alone, one patient (R.D.) developed a severe systemic reaction consisting of hypotension and generalized myalgia, which repeated itself after repeated attempts at IV administration of TdR. Three additional patients (P.A., T.S., W.D.) had mild side-effects, possibly associated with TdR, which were all transient. One patient (P.A.) had mild headache and dizziness after the IV bolus of TdR; a second patient (T.S.) complained of backache; and a third patient (W.D.) complained of headache and of 'tingling' in his arms and chest.

Overall, TdR-associated side-effects occurred in 4 of 27 patients (14.8%).

Tolerance to 5-FU and TdR can be summarized as follows:

Nausea and vomiting. These were usually mild, not always recurring in all courses of treatment and often not persistent throughout any course of treatment. Only two patients (J.R., V.V.) (both with prior 5-FU chemotherapy) suffered severe nausea and emesis.

Diarrhea. Only two patients complained of mild diarrhea; one patient (W.D.) was affected only during his second of six courses, and the other (P.C.) before and after his second course.

Stomatitis. Five patients (J.B., V.V., A.B., W.H., W.D.) developed stomatitis, which was usually mild. Only one patient (J.B.) (prior 5-FU chemotherapy) had severe stomatitis.

Alopecia. Three patients (P.A., J.B., A.J.B.) complained of alopecia; two of them (P.A., J.B.) had prior 5-FU chemotherapy.

Dizziness. Eight patients (P.A., C.B., W.E., J.E., P.M., J.M., T.S., V.V.), all with prior 5-FU chemotherapy, complained of dizziness, which was usually mild and transient, lasting only during the course of treatment or part of it.

Hyperthermia. This is a rare and questionable side-effect of 5-FU, TdR treatment. Three patients (P.C., W. D., E.F.), none of whom had received prior chemotherapy, experienced an elevation in body temperature during treatment. One patient (P.C.) had bronchopneumonia at the time, which responded to antibiotic treatment; two patients (W.D., E.F.) had short elevations of temperature with no apparent causes.

Table 5 illustrates the side-effects and their incidences in the various groups of patients.

Marrow toxicity. (25 patients were evaluable for marrow toxicity.) The dose-limiting toxicity of 5-FU, TdR chemotherapy was marrow toxicity. The effect was more frequently noted

Table 3. Extent of metastatic involvement

	Overall	Prior 5-FU	No prior 5-FU	
			Other agents	No prior chemotherapy
Liver	19/27 (70.4%)	9/15 (60%)	4/5 (80%)	6/7 (85.7%)
Lung	19/27 (70.4%)	11/15 (73.3%)	3/5 (60%)	5/7 (71.4%)
Intraperitoneal	8/27 (29.6%)	6/15 (40%)	1/5 (20%)	1/7 (14.3%)
Soft tissue	5/27 (18.5%)	3/15 (20%)	1/5 (20%)	1/7 (14.3%)
Bone	3/27 (11.1%)	3/15 (20%)	–	–
Brain	2/27 (7.4%)	1/15 (6.7%)	1/5 (20%)	–
≥ 2 systems involved	21/27 (77.8%)	12/15 (80%)	4/5 (80%)	5/7 (71.4%)
Only 1 system involved	6/27 (22.2%)	3/15 (20%)	1/5 (20%)	2/7 (28.6%)

Table 4. Incidence of myelotoxicity

	Range	Overall	Prior 5-FU	No prior 5-FU	
				Other agents	No prior chemotherapy
Leukopenia	(900–4,000)	16/25 (64%)	9/13 (69.2%)	3/5 (60%)	6/7 (57.1%)
Thrombocytopenia	(60,000–150,000)	6/25 (24%)	3/13 (23%)	2/5 (40%)	1/3 (14.3%)

Table 5. Incidence of side-effects

	Overall	Prior 5-FU	Other agents	No prior chemotherapy
Nausea	13/26 (50%)	10/16 (71.4%)	2/5 (40%)	1/7 (14.3%)
Vomiting	8/26 (30.7%)	7/14 (50%)	1/5 (20%)	–
Dizziness	8/26 (30.7%)	8/14 (57.1%)	–	–
Stomatitis	5/26 (19.2%)	2/14 (14.3%)	2/5 (40%)	1/7 (14.3%)
Alopecia	3/26 (11.2%)	2/14 (14.3%)	–	1/7 (14.3%)

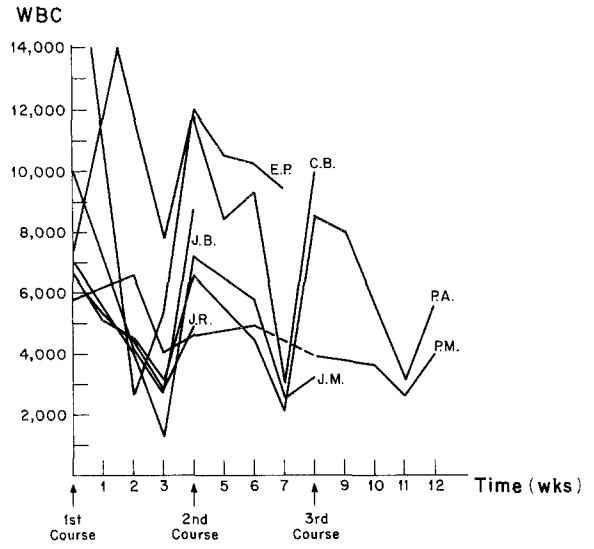

Fig. 1. WBC toxicity with 5-FU and thymidine in patients with prior 5-FU chemotherapy. Nadir WBC counts were reached 3 weeks after each course of treatment, with recovery achieved within 1 week thereafter. - - - - -, no interval WBC counts drawn

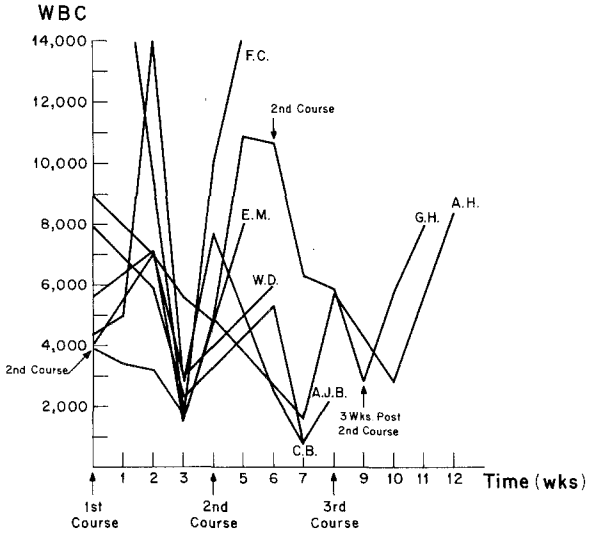

Fig. 2. WBC toxicity with 5-FU and thymidine in patients with no prior 5-FU chemotherapy. Nadir WBC counts were reached 3 weeks after each course of treatment, with recovery occurring within 1 week thereafter. Patients with no prior 5-FU chemotherapy illustrate the same pattern of leukopenia and subsequent recovery as patients who had received prior 5-FU

in the WBC than in the platelet count (16 patients versus 6 patients). Nadir WBC counts were reached 3 weeks after a course of 5-FU and TdR, with recovery of the counts within 1 week (Figs. 1 and 2). Only four patients (P.A., P.M., J.R., A.B.) needed a decrease in the dosage of 5-FU because WBC counts had not recovered by the time of their next course of treatment. Three of these patients (P.A., P.M., J.R.) had prior 5-FU chemotherapy. One patient (A.B.; no prior 5-FU) had severe leukopenia and died of sepsis 2 weeks after his second course of 5-FU, TdR but did not have a drug dose reduction.

In half the cases of thrombocytopenia (three patients), platelet counts paralleled WBC counts in both suppression and recovery, while in the remaining half platelet suppression and recovery preceded the changes in WBC counts by 1 week. The incidence of myelotoxicity in the various patient groups is illustrated in Table 4.

Response

Twenty-two patients were evaluable for response. One patient with no prior 5-FU (W.D.) showed partial remission after his second course and then stayed in a state of stable disease until after his sixth course, when minimal progression was noted and the patient was changed to another protocol. This constitutes an overall partial response rate of one of 22 patients (4.5%) or one of six patients with no prior 5-FU chemotherapy (16.7%). Six patients received three courses of treatment because they were considered to have stable disease at the time of evaluation after their second course. However, in all these patients the disease progressed after their third course. This constitutes an overall rate of stable disease of six of 22 patients (27.3%), half of them with prior 5-FU chemotherapy (3 of 11 patients; 27.3%), one patient with prior chemotherapy other than 5-FU (1 of 5 patients; 20%), and two patients with no prior chemotherapy (2 of 6 patients; 33.3%).

All patients were followed up until their death. The mean period from the last course of 5-FU, TdR until death was 6.5 months for patients with prior 5-FU chemotherapy and 9.3 months for those with no prior 5-FU chemotherapy. The patient (A.B.) who died as a direct result of treatment-associated complications is excluded.

Discussion

The coadministration of TdR changes the pharmacokinetics and metabolism of 5-FU, with a resultant prolongation of its serum half-life [3, 11] and an increased incorporation into RNA tumor cells [1, 4, 5, 7]. According to experimental studies, both toxicity and antitumor effect of 5-FU are enhanced. The antitumor effect is more enhanced, thus resulting in a favorable net effect [9]. Our present clinical trial, like earlier clinical studies, failed to produce this result.

The primarily gastrointestinal toxicity of 5-FU was changed by the coadministration of TdR to one of myelotoxicity. Gastrointestinal toxicity was reduced both in incidence and in severity and may be regarded as mild side-effects rather than dose-limiting toxicity. All previous clinical studies have noted this phenomenon [2, 3, 5, 10, 11]. In those of our patients who had received prior 5-FU chemotherapy, gastrointestinal side-effects were more frequently encountered and tended to be more severe than in those who had not received prior 5-FU.

Alopecia was relatively infrequent and also tended to occur in patients with prior 5-FU chemotherapy. A transient spiking temperature was a rare side-effect, which was noted in two patients who had no apparent source of infection. Neurological side-effects are known to accompany 5-FU and TdR chemotherapy. The prolonged severe neurotoxicity described by Woodcock et al. [11] was not observed in our study, but mild transient dizziness was encountered in eight patients, all of whom had prior 5-FU chemotherapy. Neurological symptoms may well be related primarily to TdR itself. Four patients (14.8%) reacted to the IV bolus of TdR with myalgia, dizziness, headache, and paresthesias. Except for one severe reaction, with hypotension and generalized myalgia, all other reactions were mild and transient.

Myelotoxicity was seen in 64% of our patients, with no significant relationship to prior chemotherapy. The suppressing effect was noted primarily on WBC counts and to a much lesser extent on platelet counts (16 versus 6 patients). Nadir WBC counts were seen 3 weeks after treatment, and recovery usually occurred within the next week. Only four patients needed a drug dose reduction of 5-FU at the time of their next course because WBC counts had not yet recovered. A fifth patient had no dose reduction although it was indicated, and together this constitutes a 20% (5 of 25 patients) dose-limiting myelosuppression rate.

Platelet nadirs showed a tendency to precede WBC nadirs by 1 week and also recovered within the following week. Kirkwood et al. have also noted this phenomenon [3].

Prior 5-FU chemotherapy had no significant effect on myelotoxicity. The high incidence and severity of marrow suppression clearly contradict the idea that TdR could protect normal bone marrow against toxicity while enhancing the antitumor effect of 5-FU [9].

Only one of 22 evaluable patients showed a partial response of 6 months' duration (4.5% overall partial response rate or 16.7% for patients with no prior 5-FU chemotherapy).

We do not consider the six patients who appeared to have stable disease at 2 months as unequivocal evidence of antitumor activity of 5-FU and TdR. The accuracy of the criteria for evaluating these patients' measurable disease (especially liver scan) is questionable regarding minimal change, and in all six patients the disease was found to have progressed 1 month later.

It seems that the increased incorporation of 5-FU into colorectal carcinoma RNA fails to enhance its antitumor activity [2, 11]. Similar conclusions have been expressed by Ellims [2] and Woodcock et al. [11]. This is opposed to the optimistic results obtained in several experimental tumor studies [4, 5, 7, 8].

One could conclude that the concurrent IV administration of 5-FU and TdR is not indicated for the treatment of advanced colorectal carcinoma based on the data presented. However, it must be borne in mind that randomized controls were not used in this study and that the therapeutic results that appear to be equivalent to those in historical controls were obtained with only 25%–30% of the historical dose of 5-fluorouracil alone. Under the historical control conditions employed for comparison, concomitant 5-FU and TdR merely did not improve the therapeutic index of 5-FU. However, comparison with randomized controls might yield a different conclusion.

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