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ORAL FTORAFUR VERSUS INTRAVENOUS 5-FLUOROURACIL

A comparative study in patients with colorectal cancer

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Abstract

The toxicities of oral Ftorafur (1 g/m^2/day 1–21) and intravenous 5-fluorouracil (5-FU) (500 mg/m^2/day 1–5) were compared in a prospective randomized study in patients with colorectal cancer. The treatment courses were repeated every 6th week. Leucopenia was more common after 5-FU. Leucocyte nadir in connection with first treatment cycle was on average seen on day 15 in patients receiving 5-FU and on day 28 in patients receiving Ftorafur. Significantly more patients on 5-FU developed stomatitis. There was no difference in the number of patients with diarrhea or nausea/vomiting. Median survival and response rates were not significantly different after the two treatment schedules.

Key words: Chemotherapy; colorectal cancer, Ftorafur, 5-FU.

Patients with advanced colorectal cancer often receive 5-fluorouracil (5-FU) given intravenously (i.v.) as bolus injection or as prolonged infusion. The average reported response rate is about 15–20%, with a range of 8–80% (10, 11, 13, 15). No single agent or multiple drug therapy has shown to be superior to 5-FU (10, 13, 15). 5-FU given as bolus injection causes bone marrow toxicity as well as gastrointestinal (GI) toxicity (nausea, vomiting, diarrhea, stomatitis), with bone marrow toxicity as dose limiting factor. When 5-FU is given as constant infusion the hematologic toxicity is markedly reduced while the GI toxicity is still present, with stomatitis as dose limiting factor (13).

Ftorafur (1-(tetrahydrofuran-2-yl)-5-FU), a fluorinated pyrimidine analog to 5-FU, is slowly metabolized in the organism to 5-FU and other derivatives with cytotoxic activity (5, 9, 12). If Ftorafur is given i.v. as bolus injection it has dose-dependent GI toxic effects (nausea/vomiting, anorexia, diarrhea, stomatitis) and toxic effects (dizziness, headache) but only minor hematologic toxicity, with GI and CNS toxicities as dose limiting factors. These toxic effects can be reduced by giving Ftorafur slowly as prolonged infusion (8, 12, 14). Pharmacologic studies have shown that Ftorafur administered orally is reliably absorbed from the GI tract, and that the toxic effects are diminished this way (6–8, 14). Ftorafur given orally produces only minimal hematologic toxicity, with GI toxicity as dose limiting factor (2, 14).

The reduced bone marrow toxicity is comparable with the low bone marrow toxicity of continuously infused 5-FU in accordance with the belief that orally administered Ftorafur is slowly metabolized to 5-FU among other metabolites (1, 4).

Intravenously given Ftorafur has shown antitumor activity equal to 5-FU against colorectal cancer (2). This prospective study was designed to compare the survival from start of chemotherapy and toxicity of orally daily administered Ftorafur with those of i.v. administered 5-FU. The WHO criteria for toxicity and response were employed (16).

Material and Methods

Eligibility criteria included histologically proven inoperable, advanced or recurrent colorectal cancer, normal blood cell counts, measurable disease, serum bilirubin $\leq$25 mol/l, serum creatinine $<$120 mol/l, performance status (WHO) $\geq$3, no previous chemotherapy with 5-FU/Ftorafur and at least 4 weeks between other types of previous cancer chemotherapy and entrance to this study. Hemoglobin, blood leucocytes (WBC) and thrombocytes were counted once a week while renal and liver function tests were repeated prior to each treatment cycle.

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Table 1

Patient characteristics

	Ftorafur	5-FU
Patients randomized (No.)	30	30
Refusing treatment	1	1
Protocol violations	3	2
Lost to follow-up	0	3
Evaluable patients	26	24
Age		
Median (years)	55	59
Range (years)	32–76	27–74
Sex		
Male (No.)	13	11
Female (No.)	13	13
Performance status (WHO)		
Median	1	1
Range	0–3	0–3
No. of courses given	84	75
Mean SEM	4.1±0.9	3.3±0.4
Median	3	3
Range	1–10	1–11
Patients with		
local/inoperable rectal cancer	1	0
disseminated rectal cancer	12	11
local/inoperable colon cancer	3	4
disseminated colon cancer	10	9

The majority of the patients had disseminated disease, with metastases to the liver and lungs (Table 1).

The patients were randomized to treatment with either 5-FU or Ftorafur. 5-FU was administered as i.v. bolus injection, 500 mg/m^2/day during day 1–5. Ftorafur was administered orally as 1 g/m^2/day during day 1–21 in 2 or 3 daily doses for 21 days. Treatments were repeated every 36th day.

The toxicity and survival rates after the 2 schedules were evaluated in patients who fulfilled the above mentioned criteria and who had not received previous cancer chemotherapy. They received at least one treatment cycle with 5-FU or Ftorafur.

The treatment was stopped if a patient developed intractable toxic side effects or if the patient had progressive disease during the treatment.

Statistics. Fischer's exact test and chi-square test were used to test the differences in toxic side effects. Student's t-test (paired and non-paired) were used to test differences between the clinical-chemical parameters. Survival rates in the 2 treatment groups were estimated by the Kaplan-Meier method, and the significance of the difference in survival was examined with log-rank test.

Results

Sixty patients were primarily included in the study and randomized (Table 1). However, 2 patients, one in each group, abstained from treatment and 3 patients, all on 5-FU, were lost to follow-up. One patient had received previous cancer chemotherapy and 3 patients on Ftorafur had abnormal blood tests (data on pretreatment serum-bilirubin were not available). Two patients on Ftorafur did not complete one treatment cycle because of toxic effects (one patient developed stomatitis and one patient developed diarrhea). One patient on Ftorafur and one patient on 5-FU discontinued treatment during first cycle due to deteriorating general condition.

The number of courses and the toxicity are summarized in Tables 2 and 3. Fig. 1 shows the white blood cell counts (WBC) on day 8, 14, 21, 28 and 36 after start of first treatment. There were no significant differences between the 2 groups in mean WBC and blood platelet counts before start. The lowest registered WBC during all courses was significantly lower in patients on 5-FU than in patients on Ftorafur ($p<0.01$). Also the lowest registered value of blood platelet count was significantly lower in patients on 5-FU ($p<0.05$). The total number of courses with WBC toxicity grade 1 (WHO) was significantly different between the 2 groups. In patients on 5-FU 38 courses were followed by toxicity grade 1 or more (19 courses with toxicity grade 2 or more) while no toxicity was observed in patients on Ftorafur ($p<0.0005$). There was no difference in the number of courses with hematologic toxicity between the 2 schedules with regard to blood platelets.

Table 2

Average initial and nadir values (× 10^9/l) for WBC and platelet counts during any treatment cycle

	WBC count		Platelet count	
	Initial count	Nadir count	Initial count	Nadir count
Ftorafur				
Mean±SEM	9.5±0.9	6.3±0.5	458±50	231±19
Median	8.7	5.8	398	242
Range	4.9–23.5	4.2–13.2	200–1 070	99–482
5-FU				
Mean±SEM	9.5±0.7	3.4±0.3	417±26	182±14
Median	9.3	2.9	403	175
Range	4.2–10.3	0.8–5.9	241–724	34–312

Table 3

Non-hematologic toxicity

	Ftorafur		5-FU	
	No.	%	No.	%
Patients with				
mucositis	1	4	7	29
nausea/vomiting	12	50	5	21
diarrhea	4	17	9	39
cutaneous affection	2	8	0	

Table 4

Treatment results

	Ftorafur		5-FU	
	No.	%	No.	%
Partial response	1	4	1	4
Stable disease	11	42	6	25
Progression	11	42	11	46
Not evaluable/not evaluated	3	12	6	25

During the first treatment course WBC on day 14 was significantly lower in patients on 5-FU than in patients on Ftorafur ($p<0.001$). WBC was significantly lower on day 28 ($p<0.01$) and on day 36 ($p<0.02$) in patients receiving Ftorafur than in patients on 5-FU. The nadir value for WBC in patients on 5-FU was registered on day 14, and on day 28 for patients on Ftorafur. In patients on 5-FU WBC, when compared with WBC before start, was significantly lower on day 8 and 15 ($p<0.001$) and on day 21 ($p<0.02$). On day 28 and 36 the WBC was significantly higher than the pretreatment value (Fig. 1). In patients on Ftorafur WBC was significantly lower than pretreatment values on day 21 and 28 ($p<0.01$) and on day 36 ($p<0.05$).

The non-hematologic toxicity is shown in Table 4. There was no significant difference in the number of patients with nausea/vomiting or diarrhea between the 2 groups, but a significantly greater number of patients on 5-FU developed stomatitis during the treatment ($p<0.05$). Two patients receiving Ftorafur got cutaneous symptoms; in one patient diffuse melanosis, and in the other Stevens-Johnson syndrome which appeared after 4 treatment courses. No neurologic toxicity was seen. Response rates after the two treatment regimens are summarized in Table 4.

There was no difference in median survival between patients receiving 5-FU (211 days) and patients receiving Ftorafur (209 days). When comparing the survival of patients receiving at least one full cycle the median survival for patients on 5-FU was 166 days, and for patients on Ftorafur 211 days, the difference not being statistically significant.

Discussion

The GI toxicity of the 2 drugs was nearly identical. One patient on Ftorafur had to stop treatment because of stomatitis and another due to diarrhea, similar to previously reported observations (1).

Our study failed to demonstrate hematologic toxicity after Ftorafur while moderate to severe hematologic toxicity was observed after 5-FU. No neurological toxicity was seen in our patients while in other studies with nearly the same treatment schedules mild CNS toxicity has been reported (2). The response rates in our study were low, compared to results reported by other authors. This can partly be explained by the fact that many of our patients who initially were regarded as having measurable disease either died before evaluations had been made or were not retrospectively evaluable concerning the tumor response. If the efficacy of the treatment was measured by median survival of the patients no difference was observed between the 2 treatment regimens.

Ftorafur is a chemotherapy agent with only minimal hematologic toxicity when given as scheduled in this study. This advantage could make it useful in combination

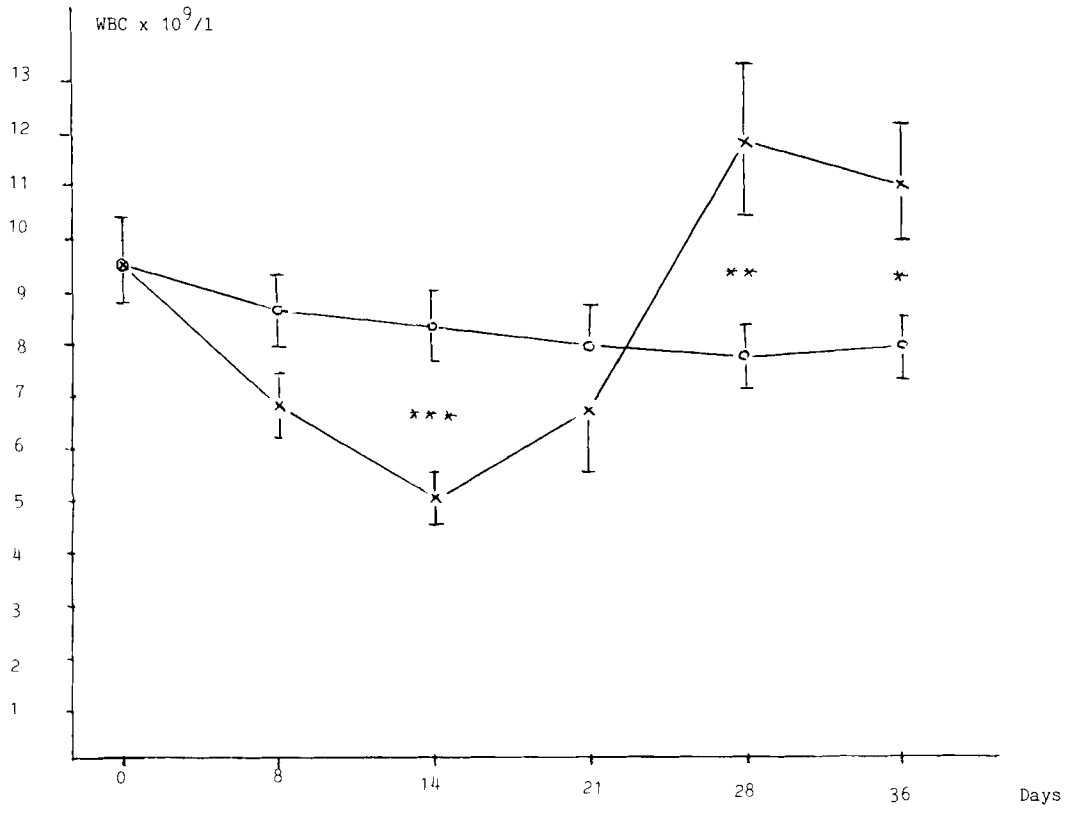

Figure. WBC ± SEM day 8, 14, 21, 28 and 36 after start of first treatment. 5-FU (×) and Ftorafur (o). (* $p<0.02$, ** $p<0.01$, *** $p<0.001$.)

with myelosuppressive drugs in efforts to develop more effective treatment schedules.

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