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Clinical Evaluation of Ftorafur (Pyrimidine-deoxyribose N_1-2′-Furanidyl-5-fluorouracil)[1]

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SUMMARY

Ftorafur, a possible sustained-release formulation of 5-fluorouracil, was administered to 27 patients with metastatic cancers. The majority of patients had adenocarcinoma, most of which (60%) arose from the gastrointestinal tract. Ftorafur was given i.v. at doses ranging from 1 to 3 g/sq m/day for 5 days, repeated every 2 to 3 weeks. Gastrointestinal (68%) and neurological (17%) toxicities were the most common side effects encountered in this study and became dose limiting at doses greater than 2 g/sq m/day for 5 days. Myelosuppression (7%) was infrequent. Other toxicities included weakness (20%), chills and fever (8%), and phlebitis (1%). Of 24 evaluable patients, 4 (17%) responded (1 complete and 3 partial remissions). Responses were seen in 1 of 8 carcinomas of the lung, 1 of 5 carcinomas of the stomach, 1 of 3 carcinomas of the colon, and 1 of 1 carcinoma of the jejunum. The duration of response ranged from 4 to 58 weeks. The results of this study resemble somewhat those obtained with the laborious 5-day continuous i.v. infusion of 5-fluorouracil. Daily doses of 2 g/sq m for 5 days, repeated every 3 weeks, produced significant antitumor effect and tolerable toxicity.

INTRODUCTION

Ftorafur is an antimetabolite synthesized in the Soviet Union, and it is closely related to 5-FU[3] and 5-fluorourodeoxyuridine (Chart 1). Chemically, it is a pyrimidine-deoxyribose N_1-2′-furanidyl-5-fluorouracil. The spectrum of antineoplastic activity of this compound in animal tumor systems is similar to 5-FU, but it is far less toxic. For example, the dose lethal to 50% of mice is 1000 mg/kg for Ftorafur, compared with 250 mg/kg for 5-FU (1, 3).

Clinical studies performed in the Soviet Union demonstrated the efficacy of this compound in the treatment of a variety of human adenocarcinomas. Daily i.v. doses of 30 mg/kg every 12 hr, to a total of 30 to 40 g, produced a greater than 25% tumor regression in patients with carcinomas of the breast (86%), stomach (31%), colon (33%), and rectum (44%). Ftorafur compared favorably to 5-FU and had the advantage of being less toxic (1, 3).

Preliminary pharmacological studies of Ftorafur suggest that this compound is metabolized to 5-FU, which is believed to be the active component. This transformation is rather slow so that a sustained release of 5-FU is obtained following a single dose of Ftorafur, thus, mimicking the continuous i.v. infusion of 5-FU (2, 8). The administration of 5-FU by continuous infusion has resulted in significant reduction of its myelosuppressive toxicity without decreasing its efficacy (4, 6). Consequently, the administration of Ftorafur could be of practical advantage. This study was designed to evaluate the efficacy and toxicity of Ftorafur administered by intensive 5-day i.v. courses.

MATERIALS AND METHODS

Adult cancer patients admitted to the Department of Developmental Therapeutics of the University of Texas M. D. Anderson Hospital and Tumor Institute were the subjects of this study. All patients had histological proof of metastatic cancer, preferentially adenocarcinoma of the gastrointestinal tract, who could be benefited by therapy with a fluoropyrimidine derivative. Prior therapy, including 5-FU, did not preclude patients from entering this study as long as patients were completely recovered from its toxicity.

Patients were informed of the investigational nature of the study, and signed informed consent forms were obtained according to institutional policies. Ftorafur was obtained from the Soviet Union through the Division of Cancer Treatment of the National Cancer Institute. The drug was administered in 5-day courses by i.v. infusion. The initial dose of Ftorafur was 1 g/sq m daily for 5 days. During subsequent courses of treatment, the dose of Ftorafur was increased by a factor of 0.5 g/sq m/day until reaching the maximal tolerable dose. Each dose of Ftorafur was given dissolved in 100 to 200 ml of 5% dextrose solution over a 1-hr period and with the patient in the recumbent position. Courses of therapy were usually repeated every 2 to 3 weeks, depending on complete recovery from toxicity. Patients were observed closely during the period of drug administration and their vital signs were checked immediately prior to, during, and immediately after each dose of Ftorafur. All side effects noticed during the period of drug administration, as well as those developing between courses of therapy, were recorded.

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[3] The abbreviations used are: 5-FU, 5-fluorouracil; CNS, central nervous system.

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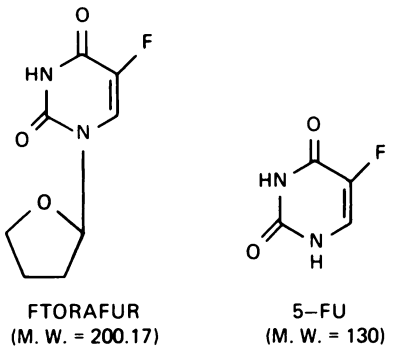

FTORAFUR (M. W. = 200.17) 5-FU (M. W. = 130)

Chart 1. Comparative chemical structure of Ftorafur and 5-FU. M.W., molecular weight.

Complete blood counts were performed twice weekly; urinalysis and SMA-100, once weekly. Appropriate radiological examinations as well as radioisotope-scanning procedures were usually performed after every 2 to 3 courses of treatment.

Tumor measurements were recorded at least every 3 weeks. Patients were considered to have achieved complete remission upon disappearance of all symptoms and signs of cancer. Patients were considered to have achieved a partial remission if there was a 50% or greater reduction in the product of the 2 largest diameters of measured lesions. In addition, no lesion increased in size simultaneously, nor did any new lesions appear. Patients were considered to have achieved stability of disease when there was no further growth of a previously rapidly growing tumor for at least 4 weeks, or when there was a response less than partial remission or minimal progression. Patients were considered to have increasing disease (failures) when there was an unequivocal increase of at least 50% in the size of any measured lesion. The development of new lesions also constituted increasing disease.

RESULTS

Twenty-seven adult patients with a variety of cancers received Ftorafur. There were 15 females and 12 males. Their median age was 57 years (range, 24 to 73 years). Patients had the following diagnoses: adenocarcinoma of the lung, 8; adenocarcinoma of the stomach, 5; adenocarcinoma of the colon, 5; adenocarcinoma of the pancreas, 3; adenocarcinoma of the breast, 2; and 1 patient each with adenocarcinoma of the jejunum, adenocarcinoma of unknown primary, hepatoma, and melanoma. Five patients received intensive prior chemotherapy: 1 patient each with carcinoma of the lung, colon, stomach, and breast, and 1 patient with melanoma. Three of these patients were previously treated with 5-FU, and 2 patients, 1 each with carcinoma of the colon and stomach, had tumors considered resistant to 5-FU. The remaining patient had carcinoma of the lung and did not have a clear history of disease progression during prior 5-FU therapy. Other agents given to patients with prior chemotherapy included: cyclophosphamide, phenylalanine mustard, methotrexate, vincristine, nitrosoureas, and dimethyltriazenoimidazolecarboxamide.

The doses of Ftorafur administered, as well as the number of patients treated at each dose, are presented in Table 1. Initial doses of Ftorafur ranged from 1 to 2.5 g/sq m/day for 5 days. However, they were escalated subsequently to 3 g/sq m/day for 5 days. The greatest number of patients received doses of 2 and 2.5 g/sq m.

The most common side effects encountered in the study, as well as their relationship to the dose of Ftorafur administered, are presented in Tables 2 and 3. Gastrointestinal toxicities were most frequent and were dose limiting (Table 2). The frequency and severity of nausea and vomiting were directly related to the dose of Ftorafur administered. They were mild at doses of 1 and 1.5 g/sq m, became prominent at 2 g/sq m, and certainly intolerable at larger doses. They occurred during the 5 days of treatment and occasionally persisted for 2 to 3 days thereafter. There were 8 episodes of mucositis, all of which developed at doses of 2 g/sq m or larger. Esophagitis occurred in 3 patients and stomatitis in 5. They were very mild, occurring in the 2nd week of treatment and lasting for 2 to 4 days. Diarrhea of moderate degree occurred during only 2 courses of treatment and at the lowest doses (1 to 1.5 g/sq m).

Neurological toxicity, although infrequent, was another important side effect of Ftorafur therapy (Table 2). Ataxia and dizziness occurred during 12 courses in 5 patients receiving doses of 2 g/sq m or greater. They were more common at the larger doses and prevented further dosage escalation. They usually occurred 5 to 10 days after completion of therapy and lasted for 3 to 5 days. Less common neurological side effects included 6 episodes of anxiety and confusion, 1 of lethargy, 1 of retrograde amnesia, and 1 of severe headache. All developed immediately after a dose of Ftorafur, lasted for 2 to 4 hr, and most occurred when doses of 2.5 g/sq m were given. An episode of anxiety and confusion and 1 of severe headache occurred immediately after a 1st dose of Ftorafur at 1.5 g/sq m in a patient with adenocarcinoma of the lung with brain metastases.

Hematological toxicity was infrequent and occurred in 7% of all courses of therapy (Table 3). Only 5 patients developed this toxicity. Neutropenia occurred during 2 courses and thrombocytopenia, during 7 courses. Hematological toxicity occurred only when the daily dose of Ftorafur was 2 g/sq m or greater. The degree of neutropenia and thrombocytopenia was extremely mild. The lowest neutrophil count was 1,200 cu mm and the lowest platelet count was 50,000 cu mm. They occurred during the 2nd week of therapy and lasted for 3 to 5 days. Two of the episodes of thrombocytopenia that occurred at 2.5 g/sq m were probably related to

Table 1

Patients entered at each dose level of Ftorafur

Patients were entered initially at the lowest dose level of 1 g/sq m. Subsequent entries and dose escalations were performed according to information on toxicities obtained during the study.

Dose (g/sq m/day for 5 days)	Patients entered	
	Initially	Subsequently
1	8	0
1.5	4	7
2	11	13
2.5	4	20
3	0	7

Table 2

Gastrointestinal and neurological toxicities of Ftorafur, relationship to dosage

The development of different gastrointestinal and neurological side effects is expressed in percentage related to the total number of treatments administered at each dose level.

Dose (g/sq m/ day for 5 days)	No. of treatments	Nausea and vomiting (%)	Mucositis (%)	Diarrhea (%)	Ataxia and dizziness (%)	Confusion and anxiety (%)	Severe headache[a] (%)
1	8	25	0	13	0	0	0
1.5	11	55	0	9	0	9[a]	9
2	45	78	9	0	7	0	0
2.5	52	65	6	0	10	12	2
3	7	100	14	0	57	0	0
Total	123	68	7	2	10	6	2

[a] They occurred in a patient with adenocarcinomas of the lung and brain metastases.

Table 3

Hematological toxicity of Ftorafur

Represents all episodes of granulocytopenia and thrombocytopenia observed during the administration of Ftorafur at each dose level.

		Granulocytopenia		Thrombocytopenia	
Dose (g/sq m/ day for 5 days)	No. of treatments	No. of cases	Lowest ($\times 10^3$)/day	No. of cases	Lowest ($\times 10^3$)/day
1	8	0		0	
1.5	11	0		1	53/15
2	45	1	1.2/9	1	116/12
2.5	52	1	1.2/14	5[a]	50/7
3	7	0		0	

[a] Diffuse intravascular coagulation could have been responsible for 2 episodes.

diffuse intravascular coagulation. There were no infections and bleeding complications related to the occurrence of neutropenia and thrombocytopenia.

Other toxicities occurred following 26% of the courses of therapy and were dose related. The most common was weakness following 20 courses of therapy. It was characterized by tiredness of variable severity, which usually occurred in the 2nd week of treatment and lasted from 5 to 10 days. The frequency and severity of weakness correlated with the dose of Ftorafur. There were 7 episodes (11%) at the dose of 2 g/sq m or less, and 13 episodes (22%) at doses larger than 2 g/sq m. There were 10 episodes (8%) of chills and fever which usually occurred immediately after a dose of Ftorafur and lasted from a few minutes to 3 hr. There was 1 episode of phlebitis at 3 g/sq m. One patient with a history of bronchial asthma had one of his attacks immediately after a dose of 1.5 g/sq m. There were no biochemical alterations that could be attributed to the administration of Ftorafur.

The antitumor efficacy of Ftorafur is presented in Table 4. Four patients (17%) had greater than 50% reduction in measurable lesions. One patient with adenocarcinoma of the colon achieved a complete remission, and 3 patients, 1 patient each with adenocarcinoma of the lung, stomach, and jejunum, achieved partial remissions. The patient with adenocarcinoma of the lung was the only responder among patients previously treated with 5-FU. However, the tumor of this patient was not considered to be resistant to 5-FU prior to starting Ftorafur therapy. There were 9 patients whose disease stabilized while on Ftorafur. With the exception of a patient who responded to a dose of 2.5 g/sq m, all other responses were seen among patients receiving doses of Ftorafur of 2 g/sq m either initially or following dosage escalation. Response occurred within the 1st 3 courses of therapy. The duration of response ranged from 4 to 58 weeks. The shortest was in the patient with adenocarcinoma of the lung who achieved a partial remission. The longest was in the patient with adenocarcinoma of the colon who achieved a complete remission. The duration of disease stability ranged from 4 to 50+ weeks with a median of 9 weeks.

DISCUSSION

Our studies with Ftorafur have confirmed the preliminary information from the Soviet Union on the potential usefulness of this compound. When administered in 5-day courses, Ftorafur demonstrated antitumor effect and tolerable toxicity.

Gastrointestinal and neurologic (CNS) toxicity prevented dosage escalation above 2 g/sq m for 5 days. Although they occurred at lower doses, they became intolerable at doses greater than 2 g/sq m. Nausea and vomiting were the most common manifestations of gastrointestinal toxicity and occurred in 68% of the treatments. Neurological toxicity (17%), although less common than the gastrointestinal toxicity, was of particular importance. It was characterized mainly by ataxia and dizziness, and was also seen more commonly at doses of 2 g/sq m or greater. Postural hypotension occurred in none of these patients, although it has

Table 4
Response to Ftorafur therapy
Antitumor efficacy of Ftorafur in relation to tumor category and dose of drug producing response.

Diagnosis	No. of patients	Remission[a]	Stable	Dose of response (g/sq m/day for 5 days)	Duration of response (wk)
Adenocarcinoma of lung	8	1 PR	2	2	4; 9, 6+
Adenocarcinoma of stomach	5	1 PR	3	2	23; 50+, 16, 4+
Adenocarcinoma of pancreas	3	0	2	2; 2.5	27, 23
Adenocarcinoma of colon	3	1 CR	1	2	58; 4
Others[b]	5	1 PR	1	2	14; 6
Total	24	4	9	2; 2.5	4–58

[a] CR, complete remission; PR, partial remission.
[b] One case each of jejunum adenocarcinoma (PR), hepatoma, adenocarcinoma of unknown origin, breast, and melanoma.

been observed by other investigators in patients receiving rapid infusions of Ftorafur (7). One possible explanation for the development of CNS side effects in our patients is the high concentration of drug in the brain tissue that may occur following a dose of Ftorafur. Recent pharmacokinetic studies of Ftorafur in beagle dogs and in humans at our institution have revealed that Ftorafur readily crosses the blood-brain barrier and that the cerebrospinal fluid concentration could be as high as 75% that of the plasma (5). These observations are of major clinical importance in view of the potential benefits that may derive from using Ftorafur in the therapy of patients with primary or metastatic brain tumors. In fact, Soviet studies have already shown some degree of efficacy of this compound in certain primary brain tumors (1).

The absence of significant myelosuppressive toxicity during our study was also of major importance. In this regard, the results obtained with single daily doses of Ftorafur are similar to those previously reported with continuous i.v. infusion of 5-FU (4, 6). This observation was not surprising in view of the fact that in animals and in humans Ftorafur is extensively degraded to 5-FU, which is believed to be the active component (2, 8). This transformation is rather slow so that a sustained release of 5-FU is obtained following a single dose of Ftorafur. A reflection of the slow metabolism of Ftorafur is given by the pharmacokinetic studies of Ftorafur conducted at our institution, demonstrating that the median half-life of 50 mg/sq m of ^{14}C-labeled Ftorafur in humans is 18.6 hr, as opposed to 0.5 hr for 5-FU (5).

The results of the 5-day intensive course schedule of Ftorafur administration used in this study appeared somewhat similar to the daily schedule of administration used by Soviet investigators. Unfortunately, the antitumor effect could not be adequately compared in view of their different criteria for evaluating response. However, it would seem clear from all studies that Ftorafur is inactive in patients with tumors that are resistant to prior 5-FU therapy. The toxicities encountered in all studies have been similar, although a higher degree of CNS toxicities was observed in our study. The lack of significant myelosuppressive toxicity is comparable to what is seen with the continuous infusion of 5-FU. This is a distinct advantage over the rapid i.v. injection of 5-FU which causes myelosuppression in 30% of patients (6). Other toxicities that are significantly less common with Ftorafur are diarrhea, stomatitis, and dermatitis.

The antitumor efficacy of Ftorafur could only be firmly established by studying a larger number of patients. However, the results of this study suggest that a 5-day intensive course schedule of Ftorafur at 2 g/sq m/day, repeated every 3 weeks, is well tolerated and could be efficacious for the treatment of human adenocarcinomas. A short daily infusion of Ftorafur for 5 consecutive days appears equivalent to the 5-day continuous 5-FU infusions that are being investigated as a method for achieving full effectiveness of 5-FU without myelosuppression. This observation suggests that Ftorafur might be used in combination with myelosuppressive agents without a major reduction in dosage. In addition, the capability of Ftorafur of readily crossing the blood-brain barrier needs further investigation. At this time, detailed therapeutic clinical and pharmacological studies of Ftorafur at different schedules of administration, alone and in combination with other agents and in comparison to 5-FU, are being conducted at our institution. Preliminary results of these studies are encouraging.

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