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Phase I Study of Oral Doxifluridine Using Two Schedules

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INTRODUCTION

DOXIFLURIDINE (5'-deoxy-5-fluorouridine, dFUR), a metabolic prodrug of 5-fluorouracil (FU), raised interest due to its low hematologic toxicity. The pyrimidine phosphorylases required for the transformation of dFUR into FU are present in tumors and various normal tissues, including the intestinal mucosa, the liver and the kidney, but practically absent from the bone marrow [1, 2]. Preclinical and clinical studies have confirmed that dFUR has a lower myelosuppressive effect than FU [3, 4]. The clinical toxicity and antitumor activity of intravenous (i.v.) dFUR have been extensively studied by our group as well as by others [4–10]. Doxifluridine is active in FU-sensitive tumors, especially in colon, rectum [4, 5, 7], head and neck [8], and breast cancer [9]. The drug was inactive in malignant melanoma [10]. The clinical use of i.v. dFUR as a bolus injection or short term infusion has been limited because of more severe and more frequent neurological toxicity compared to FU as well as unexpected cardiotoxicity. Neurological manifestations were dose-limiting factors and mostly defined as cerebral ataxia, tiredness, weakness and less frequently peripheral neuropathy. Cardiotoxicity, although rare, included precordial pain, ventricular dysrhythmia and ventricular fibrillation [4].

The bioavailability of oral dFUR is high and reproducible compared to that of FU [11–13]. In Japan, dFUR was developed as an oral capsule and was active in the same panel of tumors as that of the i.v. form. Ota and Kimura reviewed the Japanese experience with oral dFUR and reported the toxic effects at a dose of 800 mg/m^2 per day [14]. The most frequent adverse reactions were diarrhea (19%), nausea (13%), anorexia (13%) and leukopenia (7%). Neither cardiac nor neurological toxicities were reported except tiredness. It was of interest to initiate in Europe a Phase I trial of oral dFUR in order to evaluate the tolerance of this compound. Preliminary results were presented in abstract form [15].

PATIENTS AND METHODS

Adult patients aged between 20 and 75 years with histologically proven advanced solid tumors were eligible to participate in the study. Women with childbearing potential were excluded. Written informed consent was required. At baseline, a WHO performance status of ≤ 2, no digestive malabsorption, no active cardiac disease or neurological dysfunction were required. All patients had leukocyte counts of ≥ 4000/cmm and a platelet count of $\geq 120{,}000$/cmm. Serum bilirubin and serum creatinine levels were <17 μmol/l and <120 μmol/l respectively. Other laboratory requirements were the evaluation of transaminases, alkaline phosphatase, calcium, sodium, potassium and bicarbonates. Laboratory parameters and clinical examinations were repeated weekly during the first part of the study and every 2 weeks during the second part of the study. Whenever possible tumor measurements were taken before, during and at the end of treatment. An electrocardiogram (ECG) was performed at baseline in all patients and repeated every 3 weeks thereafter. In the first part of the study,

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patients underwent radionuclide angiography to evaluate the left ventricular function at baseline, week 6, week 12 and at the end of dFUR treatment. Gated blood pool technique was used with *in vivo* red cells labeled with 20–25 mCi ^{99}mTc, 16 frame/cycle, 300 s time acquisition on 64 × 64 matrix LAO 45° projection. Bicycle ergometry was performed in a supine position. No radiotherapy or antineoplastic agents were allowed within 4 weeks prior to study entry. No folates or folate antagonists were given during the administration of dFUR.

Doxifluridine was supplied by the Pharma Division of F. Hoffmann-La Roche & Co. Ltd, Basle, Switzerland as 5, 10 and 20 ml vials containing 125, 250 and 500 mg of water-soluble free acid solution of dFUR. Vials were diluted in a sweet non-alcoholic beverage in order to palliate the bitter taste of the compound.

The study was conducted in two parts. In part I, dFUR was given 4 × per day for at least 3 consecutive weeks, depending on the tolerance. The starting dose was 250 mg × 4 per day escalated to 375 mg × 4 per day. In part II, dFUR was given 3 × per day for 14 consecutive days repeated every 4 weeks, depending on the time taken to recover from toxicity. The starting dose was 500 mg × 3 per day escalated to 750–500–750 mg per day and 750 mg × 3 per day. No attempt was made to adjust the dosage to body surface or body weight. At least three patients were entered at each dose level. The maximum tolerable dose was defined as the dose which caused any cardiotoxicity, neurotoxicity of WHO Grade 3 or 4 in one patient or any other toxicity of WHO Grade 3 or 4 in more than one patient. Dose escalation was stopped when the maximum tolerable dose was reached. Treatment was discontinued in patients who experienced either cardiac or neurologic toxicity of any grading or any other toxicity of WHO Grade 3 or 4.

RESULTS

Twenty-three patients entered the trial (Table 1), 14 men and nine women. Their median age was 58 years with a range between 27 and 73 years. Eleven patients had colorectal adenocarcinoma, six had cancer of the breast, the remaining six patients had cancer of the pancreas (one), kidney (one), head and neck (one), non-small cell lung (one), and two patients with unknown primary. Seven patients had prior radiotherapy alone, five were treated with radiotherapy and chemotherapy, two had chemotherapy alone, whilst nine patients entered with no previous medication or radiotherapy.

Table 1. *Patient characteristics*

Total No. of patients	23*
Males/females	14/9
Performance status	
WHO 0	9
WHO 1	9
WHO 2	5
Prior treatment	
Radiotherapy alone	7
Chemotherapy alone	2
Radiotherapy + chemotherapy	5
None	9

*Three patients were entered in both Parts I and II of the study.

Ten patients entered part I and were given therapy for at least 20 days, whilst all patients in part II (17) had at least one full cycle of 14 days. Three patients were treated in both part I and part II and contributed for seven treatments with a free interval of 4 weeks or more between treatments. None of them belonged to the 2.25 g/d group.

The most frequent nonhematologic toxicities (Table 2) were diarrhea (nine patients), nausea/vomiting (seven patients) and abdominal pain (six patients). At the highest dose level reached, all three patients in part I and four out of five patients in part II discontinued treatment because of toxicity. In part I, one patient stopped treatment due to toxicity lower than WHO grade 3. No significant hematologic toxicity was encountered (Table 3). One patient suffered from icterus with elevated bilirubin (80 μmol/l) and transaminases (ALAT 168, ASAT 187). However, this was due to gallstones and appeared to be drug-unrelated. Left ventricular ejection fractions at rest and during supine submaximal exercise (35–42 watt) remained unchanged and within normal range after 6 or more weeks of treatment. The three patients treated in both parts I and II received cumulative doses of dFUR of 160, 165 and 202 g over periods of 204, 246 and 256 days respectively. At these high cumulative doses neither cardiac or neurologic toxicity nor evidence of cumulative hematologic or oral mucosal toxicity were observed.

Reporting therapeutic results is not the aim of this study. However we just mention two partial responses observed in patients with colorectal cancer. One patient had lung and lymph node metastases and received dFUR at doses of 1.5 g/day in part I and 2.0 g/day in part II. The second patient had lung metastases and was treated at a dose of 2.25 g/day in the second part of the study.

CONCLUSIONS

The results of this phase I study of oral dFUR have shown that the observed toxicity was reproducible and dose-related. The results also confirmed that dFUR is active in colorectal carcinoma. The neurologic and cardiac toxicity encountered in previous clinical studies of intravenous dFUR were not observed in this trial. The toxicity of the oral form was essentially digestive, including diarrhea, muco-

Table 2. Non-hematological toxicity

	Part I		Part II		
	1.0 g/d	1.5 g/d	1.5 g/d	2.0 g/d	2.25 g/d
Total No. of patients	7	3	5	7	5
Nausea/vomiting	2	1	1 (1)	2 (1)	1 (1)
Diarrhea	2	3 (2)	1 (1)	1 (1)	2 (1)
Abdominal pain	2 (1)	1	0	1 (1)	2 (1)
Mucositis	0	0	0	1 (1)	1 (1)
Icterus	1	0	0	0	0
Dyspepsia	1	0	0	0	0
Dehydration	0	1 (1)	0	0	0
Fatigue	0	0	1	0	0
Vertigo	0	0	1	0	0
Aphtae	0	0	0	1	0
Fever	0	0	0	0	1
Paresthesia	0	0	0	0	1 (1)
Dysphagia	0	0	0	1 (1)	0

( ) No. of patients who experienced WHO Grade 3 or 4 toxicity.

Table 3. Hematologic toxicity

	Part I		Part II		
	1.0 g/d	1.5 g/d	1.5 g/d	2.0 g/d	2.25 g/d
Total No. of patients	7	3	5	7	5
Leukocyte nadir ($\times 10^3/mm^3$)					
Median value	4.7	3.5	4.5	7.5	4.5
Range	2.5–9.7	2.4–4.3	2.8–8.0	2.6–13.5	3.5–5.5
Platelet nadir ($\times 10^3/mm^3$)					
Median value	194	147	145	180	206
Range	144–348	111–168	73–199	120–357	75–332

sitis and to a lesser extent vomiting. Myelosuppression was rare and consisted mainly in mild leukopenia and thrombocytopenia. The maximum single daily dose was 1.5 g continuous treatment, with a duration of approx. 4 weeks before toxicity. Alternatively, a dose of 2.25 g daily × 14 days every 4 weeks is tolerable. This cyclic treatment allows recovery from toxic symptoms, while maintaining a high dosage.

Our results suggest that oral dFUR, a fluoropyrimidine with low myelosuppressive effect, could be substituted for intravenous FU in cyclic combination chemotherapy programs, particularly for breast and gastrointestinal cancer.

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