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A Randomized Comparison of Doxifluridine and Fluorouracil in Colorectal Carcinoma

PIERRE ALBERTO,* BERNADETTE MERMILLOD,† GHISLAINE GERMANO,‡ SUSANNA KAPLAN,§ WALTER WEBER,‖ RUDOLF JOSS,¶ BRUNO SPATI,** GEORGES MARTZ†† and FRANCO CAVALLI‡‡

**Division of Oncology, University Hospital, 1211 Geneva 4, Switzerland, †Statistician, Division of Informatics, University Hospital, 1211 Geneva 4, Switzerland, ‡Hoffmann-La Roche & Co. Ltd, Basel, Switzerland, §Division of Oncology, San Giovanni Hospital, 6500 Bellinzona, Switzerland, ‖Division of Oncology, University Hospital, 4056 Basel, Switzerland, ¶Institute of Clinical Oncology, Inselspital, 3010 Bern, Switzerland, **Division of Oncology, Dept. Medicine C, Kantonsspital, 9000 St. Gallen, Switzerland, ††Division of Oncology, University Hospital, 8000 Zürich, Switzerland and Swiss Group for Clinical Cancer Research, Division of Oncology, Hospital San Giovanni, 6500 Bellinzona, Switzerland*

Abstract—*In a randomized study 52 patients with advanced colorectal cancer and measurable lesions were treated with doxifluridine 4000 mg/m² or fluorouracil 450 mg/m² i.v. on 5 consecutive days over 3 weeks. None had prior fluoropyrimidines except two who received adjuvant fluorouracil. Partial responses with a duration ranging from 259 to 406 days were observed in five patients treated with doxifluridine and two patients treated with fluorouracil. Toxic reactions were evaluated in 88 doxifluridine courses and 105 fluorouracil courses. The most frequent adverse effects were neurotoxicity (48% of patients) and mucositis (43%) for doxifluridine, leukopenia (48%) and nausea/emesis (37%) for fluorouracil. Mucositis, diarrhea, nausea, emesis and skin reactions were observed in both treatment groups. Fluorouracil produced neurotoxic effects in 26% of patients. Reversible cardiac dysfunctions were observed in four patients treated with doxifluridine, expressed by ectopic ventricular beats (2) precordial pains (1) and ventricular fibrillation (1). This latter toxicity justified the premature interruption of the study. Doxifluridine is an active agent in colorectal cancer. Compared to fluorouracil it produces, when used i.v., a lower myelosuppression and a greater incidence of neurological and cardiac toxicity.*

INTRODUCTION

SINCE the introduction of 5-fluorouracil (5-FU) new fluoropyrimidines have been developed in the search for a more effective and less toxic antitumor treatment. Doxifluridine (5′-deoxy-5-fluorouridine, dFUR) was synthesized by Cook *et al.* in 1976 [1]. Its molecular structure consists of a 5-FU molecule attached to a pseudopentose. Due to the missing hydroxyl group in the position 5′, this compound cannot be directly metabolized in DNA or RNA synthesis, but may serve as a 5-FU prodrug in the cell following cleavage by a pyrimidine phosphorylase [2]. Pyrimidine phosphorylase activity is higher in fluoropyrimidine-sensitive animal tumors than in normal tissues, particularly bone marrow [3–6]. In cultured human tumors, a correlation has been observed between the ability to metabolize dFUR to 5-FU and the antitumor effect [7]. Using an *in vitro* clonogenic assay method, Armstrong and Cadman have compared the cytotoxicity of dFUR and 5-FU in several human tumor cell lines and bone marrow [8]. They found that the growth suppressive concentration of dFUR was 1–5 times higher than that of 5-FU for the tumor cell lines and more than 10 times higher for the bone marrow. As myelosuppression is generally the dose-limiting toxicity of 5-FU in humans, these observations suggest that dFUR could be administered at a higher dose than 5-FU with a better therapeutic ratio.

In a phase I trial using a daily schedule with rapid intravenous injections for 5 consecutive days [9], doses were escalated up to 5 g/m² and granulocytopenia as well as stomatitis were found to be dose-limiting. Other toxic effects consisted of nausea/vomiting, central nervous system (CNS) symptoms and electrocardiogram (ECG) changes. Disease-oriented phase II studies using a similar schedule with 4 and 3 g/m²/day in good- and poor-risk patients showed antitumor activity in colorectal [10], oropharyngeal [11], ovarian [12] and breast cancer [13]. The dose-limiting toxicities encoun-

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Address for reprints: P. Alberto, Division of Oncology, University Hospital, 1211 Geneva 4, Switzerland.

tered in these trials were leukopenia, stomatitis and cerebellar ataxia. A few patients experienced cardiac toxicity as indicated by ECG alterations, anginal chest pains and arhythmia.

This randomized study was initiated to assess and to compare the antitumor effectiveness and drug tolerance of dFUR and 5-FU in patients with advanced colorectal cancer. This study was undertaken within the framework of the Swiss Group for Clinical Cancer Research (SAKK). Initially, the trial was intended to be a large schedule phase III trial with approx. 300 patients. Unfortunately, the accrual was interrupted because of severe cardiac toxicity in one patient allocated to the dFUR treatment arm. For this reason, a statistically significant comparison of antitumoral activity is not possible. The present data allow for a comparison of toxic effects and tolerable doses of the two fluoropyrimidines.

PATIENTS AND METHODS

Selection of patients

All patients had histologically proven adenocarcinoma of the colon or the rectum with measurable or evaluable lesions [14]. The criteria of eligibility included a WHO index >4, white blood cell (WBC) count >4000/mm^3, platelet count >100,000/mm^3 as well as normal bilirubin and creatinine levels. None of the patients had received prior fluorpyrimidine therapy except for adjuvant chemotherapy discontinued >6 months before entering the study. Patients with fever, infectious disease, cardiac arhythmia or a history of myocardial infarction and angina pectoris were not eligible. Informed consent was obtained from all patients according to institutional policy.

Study design

Patients were randomly allocated to received dFUR or 5-FU using a computer generated random list with a 1:1 distribution in both arms. At least two courses of either drug were given, unless there was clear evidence of rapid disease progression after a single course of treatment.

Drug therapy

Both drugs were administered by rapid intravenous (i.v.) injection daily for 5 consecutive days every 3 weeks. The doses of dFUR and 5-FU were 4000 and 450 mg/m^2, respectively. Retreatment was postponed in case of severe non-hematologic adverse reactions or in the absence of full hematologic recovery. Provisions were given for dosage reductions according to nadir blood count during previous cycle. The dose was reduced to 3000 mg/m^2 for dFUR and to 350 mg/m^2 for 5-FU in the case of a WBC nadir between 3000 and 3999/mm^2, and to 2000 mg/m^2, respectively 250 mg/mm^2 for a WBC nadir between 2000 and 2999/mm^3 or platelet nadir count between 75,000 and 99,999/mm^3. If the nadir counts were <2000/mm^3 and/or <75,000/mm^3, treatment was postponed until the next planned treatment cycle.

Doxifluridine was supplied by F. Hoffmann-La Roche (Basle) in vials containing 1000 mg of pure substance as a 10% sodium salt. Doxifluridine had to be prepared immediately prior to use, vials were dissolved with 10 ml of sterile water for injection. Fluorouracil is commercially available in 5-ml vials at 250 mg.

Treatment and follow-up

At baseline, a complete physical examination with documentation of measurable or evaluable lesions, complete blood cell counts, renal and liver functions, ECG and X-rays of the lesions were required. Thereafter, physical examination and blood cell counts were scheduled weekly and the other observations every three weeks. In case of cardiac toxicity, ECG and serum creatine kinase activity were repeated at short intervals until full recovery.

RESULTS

This study was terminated with 52 eligible patients only when a patient, with no history of cardiac disease, developed a ventricular fibrillation 6 h after the third dFUR injection in cycle one. The patient was resuscitated and his cardiac rhythm reversed to sinus rhythm by electric cardioversion (400 J). Electrocardiographic signs of anterolateral myocardial ischemia were recorded after cardioversion and persisted for a few days. Elevated serum creatine kinase concentrations were recorded which could have been produced by the cardioversion or the external cardiac massage. Serum potassium was 3.8 mmol/l immediately after resuscitation and remained unchanged for 2 days thereafter. During the following months, the cardiac rhythm was checked regularly by ECG and remained normal. The patient's condition slowly deteriorated due to tumor progression and he died without clinical evidence of cardiac failure on March 1984. No *post mortem* was performed.

Patient characteristics are illustrated in Table 1. Twelve patients went off study before receiving a second treatment cycle. Reasons for early treatment discontinuation in the dFUR group were four early non-toxic deaths, four massive tumor progressions, one cardiac toxicity, one cutaneous toxicity and one patient refusal. In the 5-FU group, there was one toxic death. Patients who were assessed as early non-toxic deaths (on days 4, 8, 22 and 24) were considered non-evaluable for drug-induced toxicity.

Objective tumor responses were seen in both treatment group (Table 2). Five patients responded

Table 1. *Patient characteristics according to treatment*

	dFUR	5-FU
No. of eligible patients	25	27
Mean age (years)	63	60
No. of males/females	11/14	16/11
Performance status 1/2/3/4	8/9/7/1	14/9/3/1
Prior adjuvant 5-FU treatment	2	0
Site of primary tumor:		
rectum	5	8
sigmoid	8	10
colon	13	8
colorectal	0	1
Site of indicator lesions		
liver	14	16
lung	5	7
deep abdominal mass (CT scan)	3	4
local recurrence	2	1
other	4	3
Mean duration of treatment (days)	103	119

Table 2. *Response to treatment*

Agent	Measurable lesions	Time to progression
dFUR	Liver, abdominal lymph nodes	406 days
dFUR	Liver, skin	290
dFUR	Liver	282*
dFUR	Liver	303
dFUR	Liver	309
5-FU	Liver	259
5-FU	s/clavicular lymph nodes	282

*Radiotherapy of residual liver lesions after day 142.

to dFUR for a median duration of 303 days (range 282–406) and two patients responded to 5-FU for 259 and 282 days. Responses were mainly achieved in patients with liver indicator lesions.

Toxic effects

In the dFUR and the 5-FU group, 88 and 105 courses were fully evaluable for drug-induced adverse reactions, respectively (Table 3). A maximum of 13 courses were administered to patients in the dFUR arm vs. 11 courses in the 5-FU arm. Nine dFUR cycles were delayed due to prolonged toxicity: leukopenia in five patients, neurological disturbances in three and mucositis in one patient. Twenty-four 5-FU cycles were similarly delayed, due to leukopenia in 21 cases and to mucositis, diarrhea and thrombocytopenia in one patient. In the dFUR arm, the most frequent adverse reactions were neurotoxicity, primarily CNS, and mucositis (Table 4). In the 5-FU group, the most frequent adverse effect was leukopenia. Nausea, vomiting and diarrhea were observed in approx. 30% of patients in both groups. Alopecia was more frequent in 5-FU patients. Unexpected was the relatively high incidence of neurologic disturbances encountered in the 5-FU group (26%). Toxic agranulocytosis accompanied by severe infection was the cause of death of one patient treated with 5-FU.

Cardiac toxicity was observed in 19% (4/21) of the patients treated with dFUR and was always reversible. Three patients had ECG changes which showed ectopic ventricular beats (two cases) and ventricular fibrillation (one case). The remaining patient had a normal ECG but complained of precordial pains. None of the patients who received 5-FU experienced cardiac dysfunction.

In the dFUR group, the dominant neurotoxicities were ataxia or dizziness. The other neurologic effects were confusion, aphasia, ageusia or loss of food taste and peripheral paresthesia. In the 5-FU group, four patients reported dizziness. Interestingly, ageusia was also observed in one patient. The toxic role of 5-FU could not be ascertained in two patients complaining of fatigue or hearing defect. Toxic signs and symptoms were reversible in all patients regularly followed-up.

Two cases of transient skin rashes were seen in the dFUR group and one patient developed, during the first dFUR course, a severe edema of the face and the hands with burning dysesthesia. A similar episode of edema and dysesthesia in the face was encountered in the 5-FU group. The patient spontaneously recovered without treatment interruption. The other case was of skin discoloration at the infused veins during the last treatment cycle.

Table 3. Treatment cycles evaluable for toxicity and % of due dose

Cycle sequence	dFUR No. of cycles	Mean % of due dose	Cycle sequence	5-FU No. of cycles	Mean % of due dose
1	21	94.0	1	27	99.5
2	15	91.8	2	22	97.1
3	8	93.5	3	16	89.2
4	8	97.1	4	13	90.0
5	6	81.2	5	7	95.3
6	7	85.7	6	7	93.6
7	6	83.3	7	5	90.8
8	4	75.0	8	3	98.0
9	4	75.0	9	3	98.0
10	4	75.0	10	1	94.0
11	3	66.7	11	1	94.0
12	1	73.0			
13	1	29.0			
Total	88	87.1		105	95.0

Table 4. Adverse reactions in evaluable patients

Toxic effects	dFUR $n = 21$ No. of patients	%	5-FU $n = 27$ No. of patients	%
Neurologic	10 (2)	48	7 (0)	26
Mucositis	9 (1)	43	8 (1)	30
Nausea/vomiting	8 (1)	38	10 (1)	37
Diarrhea	7 (1)	33	8 (1)	30
Leukopenia*	5 (0)	24	13 (1)	48
Cardiac	4 (1)	19	0	
Skin	3 (1)	14	2 (0)	7
Thrombocytopenia†	2 (0)	10	6 (2)	22
Alopecia	2 (0)	10	9 (0)	33
Sepsis	0		2 (1)	7

() No. of patient with WHO 3–4 toxicity.
*No. of patients with WBC <2500 (1500)/mm^3.
†No. of patients with platelets <100,000 (50,000)/mm^3.

DISCUSSION

This trial compared dFUR and 5-FU given on a 5 consecutive day schedule repeated every 3 weeks. The overall drug adverse reactions produced by dFUR and 5-FU were approximately equivalent. Doxifluridine was less myelosuppressive but had a higher incidence of neurologic alterations, cardiovascular events and mucositis. Approximately half of the patients treated with dFUR experienced various forms of neurologic toxicity. The most frequent was described as fatigue, abnormal gait, vertigo or dizziness. Objectively, these signs and symptoms correspond to cerebellar ataxia. Peripheral neuropathy as expressed by paresthesia was also observed but rare. Interestingly enough, some form of neurotoxicity was even noted in 26% (7/27) of the patients treated with 5-FU. This suggests that a mild form of 5-FU neurotoxicity might be a frequent but generally undetected adverse event. Alteration of food taste was seen in two patients, one in each treatment arm. These patients received no prior platinum coordination complexes. To our knowledge, ageusia has not yet been reported during fluoropyrimidine treatment. The 'metallic taste' described by Ansfield *et al.* in three out of 65 patients treated with tegafur could be related to the same neurotoxicity [15]. Neurotoxicity was always found to be reversible in patients observed during a sufficiently long period of time after therapy.

Cardiotoxicity was observed in four patients treated with dFUR. The most severe consisted of a ventricular fibrillation. Cardiac toxicity, a rare event with 5-FU [16–18], was observed in previous dFUR studies using the same treatment schedule [9–11]. No cardiologic alterations were observed in 42 patients with malignant melanoma [19].

A peculiar type of skin reaction was seen in one patient in each treatment group. It consisted of

erythema accompanied by burning dysesthesia. This adverse reaction is probably related to the one observed with 1-hexylcarbamoyl-5-fluorouracil and described as a sensation of warmth, particularly in the perineum and often accompanied by vesical and rectal tenesmus [20], and to the palmo-plantar erythrodysesthesia reported with 5-FU [21].

In conclusion, this randomized study has confirmed the antitumor activity of dFUR in colorectal cancer and has provided more precise information concerning the dose and the dose-limiting toxicity of this fluoropyrimidine derivative compared to 5-FU. The most interesting characteristic of dFUR is its low myelosuppressive effect, which is probably due to the low activity of pyrimidine phosphorylase in the bone marrow. However, the results of the present study indicate that this good hematologic tolerance cannot be fully exploited, as non-hematologic adverse reactions appear at a dose still tolerable in the bone marrow. Despite this limitation, dFUR can be administered at a dose level significantly higher than that of 5-FU, even if the difference in the molecular weight is taken into account. This could be compatible with a higher therapeutic effect. Further studies will show whether other treatment schedules could improve the tolerance, particularly regarding the neurological and cardiovascular toxicities.

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