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Phase I/II tolerability/pharmacokinetic study with one-hour intravenous infusion of doxifluiridine (5'-dFUrd) 3 g/m² VS 5 g/m² QD × 5 per month

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Summary. Eighteen patients with advanced solid cancer were treated with daily 5'-dFUrd infusions given over 1 h on days 1–5 of a 4-week cycle. Nine patients received 3 g/m² 5'-dFUrd daily and another nine patients 5 g/m². One patient on 5 g/m² 5'-dFUrd was not fully evaluable for tolerability due to early death (progressive disease) 4 weeks after the first cycle. A total of 48 cycles was given. The gastrointestinal and hematological toxicity was generally mild (grade 1–2). Central neurotoxicity (ataxia, unsteadiness, diplopia, dysarthria, sometimes confusion) was observed in 7 of 8 patients on 5 g/m² 5'-dFUrd leading to premature discontinuation of treatment in 3 patients (after 2 cycles). Only 3 of the 9 patients in the 3 g/m² group had slight signs of cerebellopathy. Typically, the reversible neurological side effects started at the end of the 2nd week of a cycle. The serum elimination kinetics of 5'-dFUrd and its metabolites 5-FU and 5'-dFUH$_2$ have been investigated in the serum and showed very low intra- and interindividual variations. Peak concentrations of the 5'-dFUrd at the end of the infusion approximated 500 μmol/l and 1000 μmol/l for the 3 g/m² and 5 g/m² group, respectively. The peak of the serum 5-FU was reached at the same time, the ratio 5-FU/5'-dFUrd being around 10%. The elimination half-life time for 5-FU was protracted by a factor of 2–3 compared with the direct injection of 5-FU.

Monthly infusion of 5'-dFUrd 5 mg/m² per day on days 1–5 lead to an unacceptable frequency and degree of neurological toxicity. Similar infusions of 5'-dFUrd 3 g/m² per day on days 1–5 were well tolerated.

Introduction

5-Fluorouracil (5-FU) is widely used in cancer chemotherapy. Doxifluidine (5'-dFUrd) is a 5-FU prodrug which is converted to 5-FU after cleavage by a pyrimidine phosphorylase [3]. This conversion occurs predominantly in tumor cells. In early clinical studies response rates were achieved with intravenous doxifluridine in colorectal (26%), head and neck (25%), breast (37%), and ovarian carcinomas (23%), [1, 2, 9, 11]. Moreover, some patients who were resistant to 5-FU responded to 5'-dFUrd. Mild to moderate leukopenia represented the most frequent hematological toxicity (about 50%) [1, 9, 11], especially in patients with prior cytostatic treatment [11]. Using intravenous bolus injections (4 g/m² daily × 5) Abele et al. [1] observed neurological and cardiac side effects in respectively 33% and 12% of the patients. Hurteloup et al. [9] applied large single doses (12.5 mg/m² weekly) over 6 h. These authors found a 38% neurotoxicity rate and cardiac toxicity in 1% of the patients.

This phase I/II study was undertaken to evaluate the tolerability of 1-h intravenous (i.v.) 5'-dFUrd infusions and to study the serum pharmacokinetics of the drug and its metabolites using two different dose schedules of 5'-dFUrd, given over 5 days. It was anticipated that the serum levels of the unchanged drug and its metabolites could be lowered by slowing the rate of the intravenous administration and by giving the total dose of 5'-dFUrd over 5 days. A slow application rate is probably also more consistent with the pharmacological properties of an antimetabolic agent and a prodrug. The increase of the time of the intravenous application would hopefully lead to a reduction of the clinical toxicity of 5'-dFUrd without decrease of the anti-tumor activity.

Patients and methods

Eighteen patients (8 males, 10 females, median age 62 years) (Table 1) with histologically confirmed malignant advanced solid tumors entered the study. Fifteen patients had colorectal carcinoma and 6 were resistant to prior i.v. 5-FU treatment. All cytostatic treatment and extensive radiotherapy had been discontinued for at least 4 weeks prior to trial entry.

Eligible patients had to have a life expectancy of more than 6 months and a performance status of more than 60% (Karnofsky scale). Cases with clinically manifest myocardial disease or patients treated previously with neurotoxic or cardiotoxic drugs were excluded. All patients gave their informed consent.

Patients were randomized according to a computerized random number list to receive 1-h intravenous infusions of 5'-dFUrd at single doses of 3 or 5 g/m² daily for 5 days at a 4-week interval for 3 months. In patients with progressing disease after two cycles or those with excessive toxicity the 5'-dFUrd treatment was discontinued before giving the third cycle. Nine patients were scheduled to receive 3 g/m² daily and 9 patients 5 g/m².

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Table 1. Patient details

Characteristic	Number of patients		
	3 g/m² (n=9)	5 g/m² (n=9)	Total (n=18)
Females/Males	4/5	6/3	10/8
Median age (years)	62	62	62
Diagnosis			
Adenocarcinoma of sigmoid	4	–	4
Adenocarcinoma of caecum	1	–	1
Adenocarcinoma of rectum	3	7	10
Renal cell carcinoma	–	1	1
Carcinoid, unknown primary	–	1	1
Carcinomatosis, unknown primary	1	–	1
5-FU resistant	4	2	6
Indicator lesions	9	8	17
Lung metastases	6	4	10
Liver metastases	3	5	8
Lymph node metastases	1	1	1
Abdominal/retroperitoneal tumor	1	1	2

Tolerability. The following clinical parameters were evaluated before and 4 weeks after each cycle: weight, performance status, general clinical status, and cardiac function (blood pressure, ECG). The left ventricular ejection fraction was determined by equilibrium radionuclide ventriculography [12]. A multiple gated acquisition was used with 16 frames per cycle. Measurements were done by a Siemens counterbalance gamma camera, ZLC 7500S. Red blood cell labelling with ^{99m}Tc was performed in vivo [13]. Values below 50% were considered to be pathological.

Prior to each cycle and at treatment discontinuation, a complete neurological examination was performed considering peripheral neurotoxicity, encephalopathy, and cerebellopathy. Electroencephalograms and electromyelograms were obtained simultaneously. The results were scored according to a previously described scoring system [8]. A "Total Central Neurotoxicity Score (TCNS)" was calculated, comprising central and peripheral neurotoxicity.

Blood cell counts and liver and kidney function tests were performed routinely on days 1 and 5 of each cycle, on days 15 and 22 of the first cycle, and 4 weeks after the third cycle. Hematological and biochemical toxicity was assessed accoridng to the WHO criteria [10]. The patients' creatinine clearance was calculated as previously described [14].

Pharmacokinetics. To evaluate the serum elimination kinetics of the parent drug and its metabolites 5-FU and 5'-dFUH$_2$, blood samples were drawn at defined intervals over a 6-h period from the start of 5'-dFUrd infusion on days 1 and 5 of cycle 1 and day 5 of cycle 3. In addition single pre- and post-infusion serum samples were obtained on days 1 and 5 of cycle 2 and on day 1 of cycle 3. Plasma samples' work-up involved protein precipitation with saturated ammonium sulfate solution and extraction with ethyl acetate. Separation and quantification of 5'-dFUrd and 5-FU was achieved with HPLC using ion-pair formation and UV detector.

The limit of the determination of 5'-dFUrd and 5-FU was 0.2 and 0.1 μg/ml plasma. The reproducibility of the 5'-dFUrd and 5-FU assay in plasma was equal to 8.7% and 6.4%, respectively [5, 6]. Another metabolite, 5'-dFUH$_2$, was quantified by GC/MS-SIM after pentylation of the plasma extract using pentyliodine. [^{15}N$_2$]-FUH$_2$ was used as an internal standard.

The sensitivity of the method was around 100 ng 5'dFUH$_2$/ml plasma and the reproducibility was better than 5% for concentrations larger than 1 μg/ml.

Tumour response evaluation. In 13 patients with measurable disease, the response was assessed according to the WHO criteria [10] after treatment with three cycles of 5'-dFUrd.

Results

Tolerability

All 18 patients were evaluable for toxicity, though the neurotoxicity was not assessable in one patient with carcinoid syndrome (on 5'-dFUrd 5 g/m²), who died 4 weeks after the first cycle due to progressive disease. Severe toxicity caused early termination of the trial (after two cycles) in three patients on 5 g/m². The observed clinical and hematological adverse effects are summarized in Table 2.

Leukopenia was a clinical problem in only one patient on 5 g/m², who developed a grade 4 leukopenia with severe infection after the third cycle. In all other patients both dose levels were without clinically significant bone marrow toxicity. In particular, no case of thrombopenia was observed.

Gastrointestinal (GI) adverse effects were reported in two-thirds of the patients in each dose group. Except for one patient on 5 g/m², all GI effects were mild to moderate and never necessitated delay or cessation of 5'-dFUrd. Nine of the eleven patients with gastrointestinal side effects had nausea alone. Additional mild to moderate diarrhoea, vomiting, stomatitis, and decreased appetite were observed in two individuals. No drug-related changes of

Table 2. Clinical and hematological adverse effects during 5'-dFUrd treatment

	Number of patients	
	3 g/m² (n=9)	5 g/m² (n=9)
Any	6	9
Cardiac[a]	–	
Gastrointestinal[a]	6	5
Neurological (any)	3	7[c]
Alopecia (grade 1–2)[b]	1	1
Conjunctival dryness	–	1
Mouth soreness (grade 1)[b]	–	2
Leukopenia		
Grade 0[b]	6	1
Grade 1	1	1
Grade 2	1	5
Grade 3	1	1
Grade 4	0	1

[a] for grading see text
[b] According to the WHO criteria
[c] of eight evaluable patients

Table 3. Central neurological side-effects in 17 patients treated with 5'-dFUrd

		Number of patients	
		3 g/m²	5 g/m²
Number of evaluable patients side-effects		9	8
Cerebellopathy			
Slight:	Unsteadiness without clinical findings	2	2
Moderate:	Moderate ataxia	1	2
Marked:	Disabling ataxia (of truncus and extremities)	0	3
Additional symptoms:	Double vision/nystagmus	1	2
	Dysarthria	0	1
Encephalopathy			
Slight:	Somnolence or hyper-irritability lasting less than 3 days	1	0
Moderate:	Moderate difficulties in concentration and memory, >3 days	1	1
Marked:	Marked confusion and disturbance of memory	0	2
EEG-dysrhythmia			
Slight, generalized		1	1
Moderate, generalized		1	0
Marked, generalized		0	1

the hepatic or renal function were observed in either of the groups.

One case of possibly drug-related clinical cardiotoxicity was observed in a patient receiving 5 g/m². This 68-year-old female had "slight hypoxic ECG changes" at baseline and during week 4 of the first cycle. The serum creatinine phosphokinase levels were normal at that time. At the end of the third week of cycle 2, she developed severe clinical signs of encephalopathy and cerebellopathy. One week later there were low voltage ST wave changes on the ECG which were probably ischemic in origin, associated with temporarily elevated creatinine phosphokinase levels and tachycardia. The left ventricular ejection fraction remained unchanges (above 50%) in spite of the ECG changes. The cardiological findings could theoretically also be related to a concurrent pneumonia. 5'-dFUrd was discontinued after cycle 2. All neurological and cardiological effects had resolved 6 weeks after 5'-dFUrd discontinuation.

There were no other drug-related hematological or biochemical abnormalities in any of the patients. In particular, the values for the left ventricular ejection fraction remained unchanged during 5'-dFUrd treatment.

Three of the patients receiving 5 g/m² developed a marked central neurotoxicity with disabling ataxia and confusion (Table 3), with marked EEG changes in two of them, neccessitating termination of the treatment after the second cycle. Mild to moderate degrees of central neurotoxicity was seen in four of the patients on 5 g/m² and in

Table 4. Creatinine clearance (ml/min), total central neurotoxity score (TCNS), area under the curve, and maximal serum concentration (μmol/liter) (for 5'-FUrd, 5FU and 5'-FUH_2) in patients receiving 5'-dFUrd by 1-h infusion

(a) 3 g/m² daily × 5

Patients *n*	Creatinine clearance	Area under the curve			Maximal serum concentration			TCNS
		5'-dFUrd	5-FU	5'-$dFUH_2$	5'-dFUrd	5-FU	5'-$dFUH_2$	
1	101	112.0	18.0	10.0	409	64.0	24.3	6
3	101	84.5	3.7	14.5	264	20.0	32.0	3
6	71	157.0	6.0	16.2	424	35.9	35.9	0
8	74	130.0	6.6	13.0	433	38.5	31.7	0
11	79	105.0	4.8	13.3	369	28.7	34.7	1
12	77	87.5	3.3	9.4	322	23.6	28.6	0
14	96	93.3	5.6	9.0	296	39.5	27.4	1
16	60	126.3	4.3	16.0	399	31.1	39.3	0
17	64	150.0	8.3	12.0	405	38.2	28.4	0

(b) 5 g/m² daily × 5

Patients *n*	Creatinine clearance	Area under the curve			Maximal serum concentration			TCNS
		5'-dFUrd	5-FU	5'-$dFUH_2$	5'-dFUrd	5-FU	5'-$dFUH_2$	
2	57	310	18.5	25.0	671	80.0	51.0	5
4	59	290	10.0	22.5	724	44.7	40.6	2
5	61	214	12.5	13.5	622	63.0	87.9	1
7	79	266	14.0	19.0	758	67.6	42.9	7
9	103	225	10.5	16.0	652	52.8	42.2	0
10	48	251	11.6	12.2	802	62.8	34.4	1
13	50	254	10.6	15.3	715	52.6	32.5	n.e.[a]
15	95	202	13.0	7.1	701	77.6	19.3	2
18	80	305	9.6	20.6	838	62.1	43.4	9

[a] *n.e.*, not evaluable

three patients on 3 g/m^2. The symptoms of neurotoxicity generally started at the end of the second week of the cycle with ataxia, dysarthria, and sometimes confusion, becoming more pronounced with an increasing number of cycles; full recovery was attained within 4–8 weeks after discontinuation of treatment. Patients with slight, generalized dysrhythmia on pretreatment EEG, seemed to represent a high risk group for central neurotoxicity. One patient in either group developed slight peripheral neurotoxicity.

No correlation was found between the calculated initial creatinine clearance, the TCNS, and pharmacokinetic parameters as the "area under the curve" and the "maximal serum concentration" of 5'-dFUR and its metabolites (Table 4).

Tumour response

In the 13 patients evaluable for response after three cycles, no remission was observed. Stable disease was seen in 5 patients in each treatment group.

Serum pharmacokinetics

The serum elimination kinetics of 5'-dFURrd and 5-FU and 5'-dFUH$_2$ did not change during the treatment period as shown by the very low intra-individual variability (Fig. 1). Inter-individual variability also proved to be surprisingly low. In many instances the elimination profiles of two different patients are superimposable. The ratio 5-FU/5'-dFUrd was about 10% at the end of the intravenous infusion.

Discussion

Neurotoxicity, bone marrow suppression, and cardiotoxicity have been described as the major side effects of chemotherapy with 5'-dFUrd given as single i.v. infusions of 10 or 12.5 g/m^2 with 2- to 3-week intervals or as bolus i.v. injections of 3 or 4 g/m^2 5'-dFUrd daily over 5 days every 3–4 weeks [1, 2, 8, 10]. A previous study from our group has shown that even lower doses (2 g/m^2 daily $\times$5) in 15–20 min i.v. infusions may cause cardiotoxicity and neurotoxicity in individual patients [7]. As there was very limited therapeutic response in colorectal carcinoma with this low dose, an increase of the total monthly dose of 5'-dFUrd was warranted, if this would not lead to increased toxicity.

The present study shows that daily doses of 5 g/m^2 5'-dFUrd given over 5 days in a 1-h i.v. infusion lead to an unacceptably high incidence of severe central neurotoxicity (3 of 8 patients). Bone marrow suppression was a less severe and less frequent complication representing mainly grade 1–2 leukopenia. Bone marrow suppression was, however, more frequent in the 5 g/m^2 group and became life-threatening in one patient on 5 g/m^2.

The transient low voltage ST changes on ECG with simultaneous creatinine phosphokinase elevation in one patient on 5'-dFUrd (5 g/m^2) has most probably to be regarded as treatment-induced cardiotoxicity. The risk of cardiotoxicity, though rare, should thus not be overlooked during treatment with 5'-dFUrd. The present study thus could not prove that 1-h infusions of 5'-dFUrd are less toxic for the patient than bolus injections.

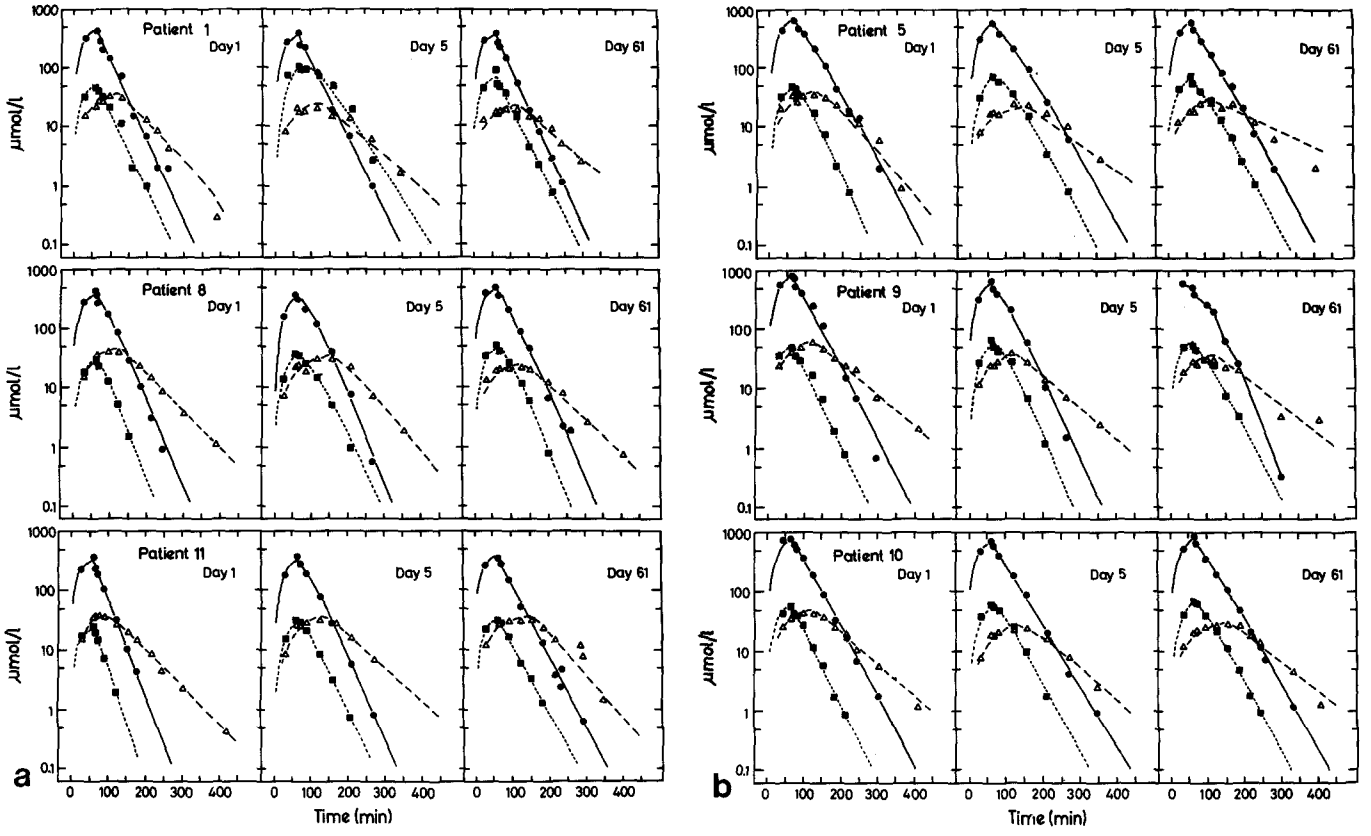

Fig. 1 a, b. Serum elimination profiles in patients on treatment with 5'-dFUrd, given by 1-h intravenous infusions. ●———●, 5'-dFUrd; ■·····■, 5FU; ▲------▲, 5'-dFUH$_2$. **(a)** 3 g/m^2; **(b)** 5 g/m^2 5'-dFUrd

No response was seen in the present study. However, one has to consider that this trial primarily was designed to assess the tolerability and the pharmacokinetic profiles and not the efficacy of 5'-dFUrd. Only 13 patients could be evaluated for response (after three cycles). Furthermore, one-third of patients had progressed on 5-FU previously, thus probably representing a bad risk group for response to 5'-dFUrd. Larger phase 2–3 studies with 5'-dFUrd should be performed to show 5'-dFUrd's efficacy and its claimed advantage in comparison to 5-FU, e.g., in colorectal cancer.

The great intra- and inter-individual reproducibility of the serum profiles for 5'-dFUrd, 5-FU, and 5'-dFUH$_2$ indicates a significant predictability of the elimination kinetics. However, in patients on 5'-dFUrd treatment no clear correlation has been detected between the shape of the elimination curves in serum samples and the observed toxicity in the individual patients. Nor has there been any clear correlation between the serum pharmacokinetics of 5'-dFUrd, 5-FU, and 5'-dFUH$_2$ and the patients' renal function, as suggested by de Brujn et al. [4]. One theoretical advatage of 5'-dFUrd treatment compared to 5-FU therapy may be that the elimination time of performed 5-FU seems to be protracted after intravenous application of 5'-dFUrd [6]. The absolute serum levels of 5'-dFUrd and 5-FU, measured after a 1-h infusion of the drug, were similar to those obtained previously by bolus injections [4].

Based on this comparative phase I study, we conclude that 5'-dFUrd treatment with 5 g/m^2 daily $\times$ 5 given by 1-h infusion and at 4 week intervals caused unacceptable toxicity. Single 1-h infusions of 3 g/m^2 $\times$ 5 in patients without pretreatment neurological disorders seem to represent an acceptable treatment schedule with minimal side-effects.

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