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Doxifluridine (5'-dFUrd) in patients with advanced colorectal carcinoma

A phase II study

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Summary. *Infusion of 5'-dFUrd (2.0–3.0 g/m² over 1 h on days 1–5 every 3rd week) resulted in one partial response in 21 patients with advanced and progressing colorectal cancer. No patient had received chemotherapy before the 5'-dFUrd trial. Hematological and gastrointestinal toxicity were generally mild. In 4 patients peripheral neurotoxicity was diagnosed during treatment, whereas transient cerebellopathy was observed in one. Cardiac side effects (repeated angina pectoris following 5'-dFUrd infusion) led to discontinuation of treatment after two courses in one patient. It is concluded that 5'-dFUrd at the above doses is not superior to conventional 5-FU treatment in colorectal cancer. Neurological and cardiac side effects are rare but may be a problem in individual patients.*

Introduction

For many years the antimetabolite 5-fluorouracil (5-FU) has been the standard treatment for metastatic colorectal cancer, with a response rate about 20% [6]. Combination chemotherapy has not significantly improved the therapeutic results.

In 1976 a derivative of 5-FU was synthesized: Doxifluoridine (5'-deoxy-5-fluorouridine, 5'-dFUrd). It is thought that 5'-dFUrd is converted to 5-FU inside the cells by a nucleoside phosphorylase [4]. This enzyme has an especially high activity in several tumor cell types. The drug should therefore have a better therapeutic efficacy and a lower toxicity than 5-FU.

In a phase II study the drug (4 g/m² × 5, 3- to 4-week interval) showed promising effects in patients with advanced colorectal cancer, indicating superiority compared with 5-FU [2]. In this and other studies, the clinically significant side effects were mucositis, myelotoxicity, neurotoxicity, and cardiotoxicity, especially if total doses of 15 g/m² or more over a 3-week period were given [1–3, 8, 10]. The mode of IV administration of 5'-dFUrd (push injection versus infusion) is believed to influence the frequency and the degree of toxicity, and especially of cardiotoxicity. It is claimed that the drug should preferably be administered by prolonged infusion rather than by rapid injection.

The present study was therefore undertaken to evaluate the effect and toxicity of lower doses of 5'-dFUrd given by 1 h infusion to previously untreated patients with measurable metastatic colorectal cancer. A 5-day infusion schedule was chosen as this is the mode of administration most often used for 5-FU.

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Patients and methods

Three Norwegian hospitals entered 22 patients with advanced colorectal cancer. None of the patients had previously received cytostatic treatment. All had progressive disease measurable by ultrasound, CT scan, chest X-ray and/or clinical examination. All patients gave their informed oral consent before entry on this trial. The patients' characteristics and the type of indicator metastases are given in Table 1.

The initial dosage was 5'-dFUrd 2 g/m² administered daily on days 1–5. The drug was infused IV over 1 h dissolved in 1000 ml 5% glucose. The cycle was repeated (up to six times) at 3-week intervals. The daily dose could be increased by 0.5 g/m² after two treatment cycles if no toxicity or only grade 1 toxicity (WHO) [9] was observed. The dose could further be increased by 0.5 g/m² 5'-dFUrd daily after the fourth cycle, depending on the frequency and degree of toxicity.

Patients were evaluable for response after at least two treatment courses. Evaluation of response after each second course was based on the WHO criteria [9]. In general, treatment was discontinued if progressive disease was demonstrated after two cycles or if not more than 'no change' was observed after four courses. Some patients, whose general condition improved during treatment despite the absence of an objective response, continued on treatment at the discretion of the investigator.

The toxicity was assessed after each cycle. Blood samples were analyzed routinely on day 22 (before the next treatment cycle) but not during the treatment-free interval. Serum CEA was analyzed according to methods previously described [5]. In addition, 13 patients underwent electromyography and an examination by a neurologist prior to each cycle and on discontinuation of treatment.

Results

A total of 84 cycles with 5'-dFUrd were given, the mean dose per cycle being 12.5 g/m². Twenty-one patients were evaluable for response after the second course. One patient refused further treatment after the first cycle.

Table 1. Patient characteristics

		Number of patients
Total		22
Mean age (years)	61.4	
Males/females		9/13
Performance status (WHO)		
	0	6
	1	9
	2	7
Mean:	1.05	
Prior surgery		
	No	4
	Curative	12
	Palliative	6
Prior radiotherapy		3
Histological grade		
	G1	4
	G2	9
	G3	3
	Unknown	6
Type	Colon carcinoma	7
	Carcinoma of the sigmoid colon	5
	Rectal carcinoma	10
Indicator lesions		
	Lung metastases	8
	Liver metastases	16
	Metastatic lymphnodes	3
	Subcutaneous nodes	2
	Primary tumour	1
	Other	3

Table 2. Side effects by cycle

Cycle	1	2	3	4	5	6
No. of patients	22	21	15	13	8	5
Mean dose (g/m^2)	10.3	11.9	13.1	13.3	14.2	14.7
Nausea/vomiting	4	3	4	3	3	1
Diarrhoea	0	1	2	2	4	1
Peripheral neurotoxicity	2	4	3	3	2	1
Central neurotoxicity	0	0	1	1	0	0
Cardiac toxicity	1	1	0	0	0	0
Infection	1	0	0	1	0	0

After the second course one patient with a locally recurrent colon cancer was classified as partial responder. This response (>50% reduction of an abdominal mass measurable by computer tomography), lasted for 12 weeks (from start of treatment). On assessment after the fourth cycle the tumor was found to have regained its initial size. In general, increases of serum CEA were most often seen in patients who progressed objectively. Three patients had a significant (≥50%) decrease of an elevated pretreatment serum CEA. Two of these were finally classified in the no change group, and one was classed in the disease progression group (according to tumor measurements and WHO criteria).

Based on the evaluation on day 22 only grade 1 hematological toxicity or none at all was observed in most of the patients. However, there was a tendency for the thrombocyte count to fall. Nausea and vomiting (grade 1–2) increased as the number of courses increased, possibly due to the increased dose per cycle (Table 2). The same tendency was observed for diarrhea (grade 1–2), which generally lasted until day 10–15 in each cycle. In one patient diarrhea and vomiting led to a dose reduction after the fourth course. One patient with a necrotizing locally recurrent rectal cancer developed septicemia after the first and fourth cycles, treated by antibiotics and incision of a pelvic abscess both times.

Clinical peripheral neuropathy grade 1, verified by electromyography, was observed in four patients, starting after the first or second cycle and persisting during the treatment, but without progression. After the third course one patient developed transient clinical symptoms of cerebellopathy.

One patient developed angina pectoris during cycles 1, 2, and 3, leading to premature discontinuation of treatment on day 4 of the third cycle.

Case report. Female patient 59 years, no previous history of cardiopathy. 5'-dFUrd treatment (2 g/m^2) was started owing to liver metastases from a colonic cancer. She developed angina pectoris 3–4 h after the 5'-dFUrd infusion

on day 3 of cycle 1, day 2 of cycle 2, and days 2 and 3 of cycle 3. Dyspnea on physical activity on days 4 and 5 of cycle 1, but not during the subsequent cycles. During the attacks of angina pectoris, which lasted for 4–6 h, she took paracetamol which was helpful. No alterations were revealed by repeated ECG examinations, which remained normal. No significant increase of serum ALAT, γ-GT, or LDH was found on day 4 of the third cycle. Further 5'-dFUrd treatment was discontinued on day 4 of cycle 3. After discontinuation of 5'-dFUrd, the patient remained free of angina pectoris attacks during the followup period of 13 months.

Discussion

In a similar study in patients with advanced colorectal cancer, Abele et al. [2], observed 7 objective remissions among 27 patients treated with 5'-dFUrd (4 mg/m^2 on days 1–5) [2]. Remissions were seen only in patients with rectosigmoid cancer. In the present study the only partial remission was seen in a patient with a locally recurrent cancer of the ascending colon. The observed decrease of serum CEA in 3 patients may indicate a subclinical antitumour effect on selected clones in the heterogenous tumour cell population. The low response rate in the present study compared with the study of Abele et al. is probably due to the low dose of 5'-dFUrd in the present trial (2 g/m^2 on days 1–5). Indeed, the only partial response was observed in a patient in whom the initial dose was recalculated to be 2.8 g/m^2 on days 1–5. On the other hand, dose escalation was undertaken in this study (up to 3 mg/m^2) in 9 patients, without obtaining any response. Thus, 5'-dFUrd used at the above doses does not seem to be superior to the standard treatment with 5-FU in the response rate.

No dose-limiting hematological toxicity was observed, but the start of the fourth cycle had to be delayed for a week in one patient with thrombocytes at 70×10^9/l on day 22 of cycle 3. With 4 mg/m^2 on days 1–5 leukopenia and thrombopenia must be expected in 50% and 25% of the patients, respectively [2, 3]. The frequency and severity of the gastrointestinal side effects also appeared to be dose-related, and were a clinical problem if doses above 3 g/m^2 were given.

The clinical symptoms of peripheral neurotoxicity were generally mild. They were only observed in the 4 of the 13 patients who underwent detailed examinations by a neurologist. On the other hand, a 5th patient had grade III central neuropathy with major clinical symptoms. It could not be stated definitely how far the developement of central or peripheral neuropathy was an effect of worsening general condition in the patients or whether it was solely a side effect of 5'-dFUrd, or whether both these factors were involved. Nevertheless, if higher doses of 5'-dFUrd are used neurotoxicity may become a major side effect. Cardiac toxicity is another serious side effect, observed in this study in one patient.

The above major side effects (central neurotoxicity, cardiac side effects) have also been described by other authors working with 5'-dFUrd and/or 5-FU [2, 3, 7]. In most of these studies 5'-dFUrd is given at higher doses and by rapid infusion. The toxic effects are believed to be dependent on the occurrence of 5'-dFUrd metabolites. The production of these metabolites may be decreased if 5'-dFUrd is administered as a slow infusion rather than as a bolus injection or rapid infusion. However, the present study showed that such toxicity does still occur, though at a lower frequency, if a 1 h infusion is used.

In conclusion, 5'-dFUrd at a dose of 2 g/m^2 on days 1–5, repeated 3-weekly, shows only weak antitumor activity in patients with advanced colorectal cancer (1 partial remission in 21 patients). The subjective and objective toxicity is generally mild at the above dose. However, one should be aware of cardiotoxicity and cerebellar toxicity in individual patients. How far the frequency and severity of these adverse effects can be reduced by slow IV infusion, especially if higher doses of 5'-dFUrd are given, has yet to be determined.

References

1. Abele R, Alberto P, Seematter RJ, Germano G, Heintz R, Bollag W (1982) Phase I clinical study with 5'-deoxy-5-fluorouridine, a new fluoropyrimidine derivative. Cancer Treat Rep 66: 1307–1313
2. Abele R, Alberto P, Kaplan S, Siegenthaler P, Hofmann V, Ryssel HJ, Hartmann D, Holdener EE, Cavalli F, for the Swiss Group for Clinical Cancer Research (SAKK) (1983) Phase II study of doxifluridine in advanced colorectal adenocarcinoma. J Clin Oncol 1: 750–754
3. Abele R, Kaplan E, Grossenbacher R, Schmid HJ, Cavalli F (1984) Phase II study of doxifluridine in advanced squamous cell carcinoma of the head and neck. Eur J Cancer Clin Oncol 20: 333–336
4. Bollag W, Hartmann HR (1980) Tumour inhibitory effects of a new fluorouracil derivate: 5'-deoxy-5-fluoridine. Eur J Cancer 16: 427–432
5. Börmer O (1982) A direct assay for carcinoembryonic antigen in serum and its diagnostic value in metastatic breast cancer. Clin Biochem 15: 128–132
6. Davis HL (1982) Chemotherapy of large-bowel cancer. Cancer 50: 2638–2646
7. Gottlieb JA, Luce JK (1971) Cerebellar ataxia with weekly 5-fluorouracil administration. Lancet 138–139
8. Hurteloup P, Metz R, Cappelaere P, Keiling R, Fumoleau P, Armand JP, Mathe G. A phase II trial of 5'deoxy-5-fluorouridine (5'-dFUrd) for advanced solid tumours. Preliminary results. 13th International Congress of Chemotherapy, Vienna 1983, SE 12.1.20, part 259, pp 31–34
9. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
10. Van Oosterom AT, ten Bokkel Huinink WW, v. d. Burg ML, Vrisendorp R, Boven E (1983) Phase II study with 5'-deoxy-5-fluorouridine (5'-dFUR) in patients with advanced resistant ovarian cancer. 2nd European Conference on Clinical Oncology, November 1983, Amsterdam, Abstracts NB 05-31

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