Eur J Cancer Clin Oncol, Vol. 25, No. 11, pp. 1543–1548, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Phase I–II Trial of Doxifluridine (5′DFUR) Administered as Long-term Continuous Infusion Using a Portable Infusion Pump for Advanced Colorectal Cancer

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Abstract—*Doxifluridine, a new fluoropyrimidine analog, was administered to 21 patients with advanced colorectal carcinoma. The starting dose was 1.0 g/m² given over 24 h for 90 consecutive days as a continuous infusion. Due to severe skin reactions (hand-foot syndrome), the dose was reduced stepwise to 0.75 g/m²/day. Twenty patients were evaluable for efficacy, one had an early non-toxic death. Seven out of 20 (35%) showed a partial response; disease stabilization was observed in 10 patients (50%) and three showed progressive disease after 3 months of treatment. All 17 patients who achieved a partial response or a stabilization of disease were treated until progressive disease was documented and some had therapy up to 46 weeks. Toxicity was minimal and mainly defined as hand-foot syndrome which occurred in 50% of the patients of whom three experienced severe reaction. There was no myelosuppression, renal or liver dysfunction, no cardiac alterations and only one patient experienced severe dizziness. Doxifluridine is active in advanced colorectal carcinoma when the drug is given as a continuous infusion for 90 consecutive days at a daily dose of 0.75 g/m².*

INTRODUCTION

DOXIFLURIDINE (5-deoxy-5-fluorouridine, 5′dFUR) is a fluoropyrimidine derivative with significant antitumor activity in animal models [1]. Its chemical structure consists of a 5-fluorouracil molecule attached to a pseudo-pentose. This cytotoxic agent has a particular strong tumor-inhibiting effect in mice on the Crocker's sarcoma S-180, the Lewis lung carcinoma and a chemically induced squamous cell carcinoma of the skin [2, 3]. In these *in vivo* experimental tumor models, the therapeutic index of 5′dFUR is 10–15 times higher than that of 5-fluorouracil and other fluoropyrimidine derivatives.

Disease-oriented phase II trials have demonstrated activity in a variety of solid tumors including ovarian cancer [4], colorectal cancer [5–8], malignant melanoma [9], head and neck cancer [10] and breast cancer [11] when the drug is administered at a daily × 5 schedule as a 1-h infusion or as a bolus injection. Oral administration showed definite activity in advanced breast cancer and some activity in colorectal cancer [12, 13].

The resistance of many tumors to cytotoxic drugs may be due in part to some inherent characteristics of the tumor cells as well as to the pharmacokinetic features of the drug. The circadian rhythm of tumor growth and the small proportion of cells in cycle may preclude optimal drug effect by standard intermittent bolus regimens. In addition, cytocidal plasma drug levels may be transient for a rapidly metabolized drug. Some chemotherapeutic drugs due to their pharmacokinetic behavior are more effective when administered by continuous infusion instead of i.v. bolus injection. Included in this category are cytosine arabinoside, 5-fluorouracil and bleomycin [14–16]. For other drugs mainly toxic effects are decreased by the use of continuous infusion dose schedules. These drugs include cisplatin, vinblastine and etoposide [17–19].

Previous studies of 5-fluorouracil administered by continuous infusion date back to the early 1960s when Sullivan *et al.* studied protracted intravenous and intraarterial infusion of the fluoropyrimidines [20, 21]. These studies suggested that the maximum tolerated dose of 5-fluorouracil increased

Accepted 15 June 1989.
This study was supported by Hoffmann-La Roche Inc., Basle, Switzerland.

when the drug was delivered as a continuous infusion. More recently Lokich *et al.* [22, 23] demonstrated the favorable effect of 5-fluorouracil administered by continuous infusion.

Despite numerous clinical trials using different cytotoxic drugs, drug combinations and regimens for the treatment of advanced colorectal carcinoma are not satisfactory up to now [24]. The fluorinated pyrimidines are still the most promising drugs suggesting response rates of 20–25%. For this reason we started a phase I–II trial with a long-term continuous infusion of doxifluridine using a Cormed portable external infusion pump. The aim of this study was

— to assess the acceptability to the patients of such a therapeutic procedure,
— to evaluate the maximum tolerated dose and long-term toxicity of doxifluridine,
— to test the usefulness and risk of the external catheter system for such a treatment, and
— to study the efficacy of this therapy in terms of response and response duration.

Table 1. Patient characteristics

Total number of patients	21
Number of evaluable patients	20
Early non-toxic death	1
Males/females	11/10
Age (years)	
Median	56
Range	(41–70)
Karnofsky performance status	
100	14
90	4
80	3
Primary tumor	
Sigmoid	9
Colon	8
Rectum	4
Indicator lesions	
Liver	15
Lung	8
Lymph nodes	5
Peritoneum	1
Local	1
Bone	1
Prior treatment	
Surgery	20
None	1

PATIENTS AND METHODS

All patients had pathologically proven adenocarcinoma of the colon, rectum or sigmoid not amenable to surgery. Other eligibility criteria included advanced disease with measurable and/or evaluable lesions, a performance status on the Karnofsky scale of at least 60%, white blood cell (WBC) count >4000/cmm, platelet count >120,000/cmm, serum bilirubin <1.5 mg/dl, serum creatinine <1.4 mg/dl or creatinine clearance >70 ml/min, and a life expectancy of >6 months. No anticancer treatments were allowed within 4 weeks prior to entry into the study. Patients with active cardiac and/or neurological disease were excluded. Informed consent was obtained according to legal and institutional regulations. This study was started in January 1985 and completed in July 1987. The patient characteristics and the type of indicator metastases are given in Table 1.

The drug was supplied by Hoffmann-La Roche, Basle, Switzerland, in sterile vials containing 1 or 5 g lyophilized pure substance. The compound is a white crystalline powder, water-soluble, light- and oxygen-stable. The drug was dissolved in 60 ml sterile water for injection and the final solution was administered intravenously for 90 consecutive days using a Cormed portable external infusion pump with a 60 ml polyvinyl chloride plastic bag. The patient was hospitalized for the first treatment week in order to place the catheter surgically under local anesthesia and to be instructed by the hospital staff on the use of the pump. The pump was placed in a holster which was worn as a shoulder harness or at the belt line. After 1 week, the patient was discharged from the hospital and received a mini-bag set for 1 week treatment; each mini-bag was replaced on a daily basis, every day at the same time.

Initially, the starting dose was 1.0 g/m^2 given over 24 h for 90 consecutive days as a continuous infusion—rate and doses were escalated by 500 mg increments. Due to intolerable skin reactions after the treatment of three patients, the initial dose was set to 0.75 g/m^2/day. There were also provisions for treatment modifications according to cardiac or central nervous system alterations as well as according to 'hand-foot syndrome' [25, 26]. This syndrome, which is seen in association with continuous infusion of doxorubicin and 5-fluorouracil, is characterized by exquisitely tender plaques on the foot pads and palmar surfaces, marked by central pallor and a ring of surrounding erythema. We used the following grading of severity of hand-foot syndrome in absence of a WHO definition:

mild: taut, shining skin, tingling of skin,
moderate: erythema, tenderness,
severe: desquamation of skin, pain.

The trial protocol called for monthly measurements of evaluable lesions which were performed by CT scan, X-ray or ultrasound. Responses were defined according to the WHO criteria [27]. The duration of response was calculated from onset to progressive disease for complete response and from the start of treatment to progressive disease for partial response and disease stabilization. Patients still being responders or having a stable disease

Table 2. Response and duration of response (n = 20)

Type of response	No. of patients responding (%)	Duration of response, median (range)
Partial	7 (35)	210 days (195–322)
Stable	10 (50)	146 days (90–195)
Progressive	3 (15)	

after the first 3 month treatment period were treated until progressive disease was documented. Patient activity was assessed at each visit by using the Karnofsky performance scale. Laboratory parameters were evaluated on a weekly basis.

RESULTS

All but one patient completed at least 3 months treatment. One patient died on day 28 due to surgical problems (secondary suture deficiency). Of the 20 remaining patients evaluable for efficacy, there were seven partial responses, 10 disease stabilizations and three progressive diseases. At the end of the study in July 87 only five patients had died, all for causes unrelated to doxifluridine. There was an overall response rate of 33.3% among all entries and 35% among evaluable patients (Table 2).

Only three patients developed progressive disease on therapy. Responses were observed in 3/7 patients with lung lesions, 3/7 with liver lesions and 1/7 with peritoneal surface lesions. Of the three patients with initial high dose (1 g/m^2/day) two partial remissions and one stable disease was achieved. Of all patients in whom baseline plasma CEA levels were elevated and monitored nine patients had decreasing levels to less than 50% of baseline of whom seven had objective tumor regression and two had stable disease. In 1/7 patients definitively responding to therapy after 3 months, treatment was interrupted for patient convenience for 24 days. At the follow-up time, tumor regrowth was documented and secondary responses were obtained with retreatment.

The duration of continuous doxifluridine therapy ranged from 28 to 322 days with a median of 159 days. The cumulative dose varied according to the duration of treatment and ranged from 67.5 to 288.75 g.

Adverse reactions were analyzed in 21 patients. Based on a weekly count, none of the patients experienced myelosuppression, liver or renal dysfunction. No cardiac alterations were noted at all. No side-effects were seen in two patients. Eight patients showed mild side-effects (Table 3).

Eight patients experienced predominantly mild and moderate hand-foot syndrome and three patients had severe reactions (Table 3).

The initial dose of 1 g/m^2/day was administered to three patients and was modified after a 3 (1 pt) and 8 (2 pt) week treatment period due to severe hand-foot syndrome. The dose was reduced to 0.75 g/m^2/day. All the remaining 18 patients received a fixed dose of 0.75 g/m^2/day which was a safe dose as only mild to moderate adverse reactions were encountered.

The date of first occurrence of hand-foot syndrome (HFS) ranged from 13 to 91 days from the beginning of the trial. For the three patients who experienced severe hand-foot syndrome described as desquamation and pain of the skin, the total cumulative dose at the time of the onset of severe symptoms was 49 g/m^2 for two patients and 67 g/m^2 for the third. The severity of hand-foot syndrome decreased rapidly after dose reduction and disappeared after treatment end without permanent sequalae.

of continuous infusion therapy involving the catheter site placement are detailed in Table 4. Of the 21 patients entering this trial, five had developed clinical evidence of axillary/subclavian vein thrombosis. Two patients received a new catheter because local fibrinolysis was not successful. To prevent this complication we decided to add heparin 5000 IE in the mini-bag with the daily dose of doxifluridine.

In 3408 catheter days only two local infections occurred which could not be confirmed by culture,

Table 3. Non-hematologic adverse reactions (n = 21)

Adverse reactions	WHO	No. of patients with 1	2	3	4	Total(%)
Stomatitis		2	0	0	0	2 (10%)
Diarrhea		0	2	0	0	2 (10%)
Fatigue		0	1	0	0	1 (4.7%)
Nausea/vomiting		0	1	0	0	1 (4.7%)
Eye burning		0	0	1	0	1 (4.7%)
Dizziness		0	0	1	0	1 (4.7%)
	mild	moderate		severe		
Hand-foot syndrome	4	4		3		11 (52.3%)

Table 4. Catheter complications

	No. of patients
Thrombosis of catheter site (axillaris, subclavia)	5
new implantation of catheter	2
local fibrinolysis	3
Catheter dislocation	1
Catheter break	1
Infection local	2

but they did present erythema, tenderness and warmth.

The median duration of survival for all patients was 11.8 months, for the seven patients with partial remission 14.3 months, the patients with no change only 7.8 months.

DISCUSSION

5-Fluorouracil has become the standard form of chemotherapy for advanced colorectal cancer. Tumor response is variably reported but generally in the 15–20% range with a modest to minimal impact on survival. During the last years many trials have been instituted to improve the treatment results of 5-fluorouracil by combining it with other cytostatic agents and new fluoropyrimidine analogs [24, 28] were introduced. Doxifluridine was synthesized in 1976 in the search for more effective and less toxic treatment. Preliminary studies with bolus intravenous injections, 1 and 6 h intravenous infusions have indicated that doxifluridine is active in a variety of refractory tumors even when used as a single agent. In a randomized trial doxifluridine was compared with 5-fluorouracil as rapid intravenous injection showing slightly better response rates for the doxifluridine treatment (20% partial response) versus the 5-fluorouracil treatment (7% partial response). However, tolerability was unsatisfactory due to neurotoxicity and in the case of bolus injections cardiotoxic side-effects were observed [4, 6, 8, 11, 25]. Because of unacceptable side-effects with bolus intravenous injection and short infusions of doxifluridine, we therefore decided to start a long-term infusion study. By slowing the rate of administration of doxifluridine it might be possible to decrease the plasma levels of the metabolites with a reduction in toxicity but without a corresponding decrease of tumor responses.

Due to their pharmacokinetic behavior some cytotoxic drugs are more effective and less toxic when administered by continuous infusion. Comparative clinical trials of continuous infusion versus bolus or short intermittent therapy have suggested that at least for 5-fluorouracil and for vindesine the continuous infusion schedule is superior [15, 29] to intravenous treatment in terms of antitumor effects. A randomized trial to compare directly the tumor response rate for the bolus versus the continuous infusion of 5-fluorouracil was done by Lokich *et al.* [30]. They observed in 25/32 patients 30% remission rates (four complete response, 21 partial response) using 5-fluorouracil infusion side and 8% remission rates in 76 patients using 5-fluorouracil bolus.

The current recommended dosage of doxifluridine given by 1 h infusion for 5 days per 28 day treatment cycle was 20–25 g/m^2 per month, even by bolus injections. By oral administration the total acceptable monthly dose was 21 g/m^2. During the constant infusion the maximal tolerated monthly dosage was 22.5 g/m^2. Thus the use of continuous infusion does not provide any significant increase in monthly dosage compared to the continuous intravenous rates of administration.

Side-effects seem to be dependent on the mode of application. The dose-limiting toxicity in intravenous injection treatment is central neurotoxicity and myelosuppression, while the main side-effects in oral administration are gastrointestinal. The hand-foot syndrome which occurred in 11 of 21 patients was the major dose-limiting adverse effect of doxifluridine given by continuous intravenous infusion. The results indicate that a daily dose of 1 g/m^2 per 24 h by continuous infusion is unacceptable due to the frequency and severity of hand-foot syndrome. The 0.75 g/m^2/day dose appears to be well tolerated and produces either no or only a mild–moderate form of hand-foot syndrome.

This toxicity is similar to studies of long-term continuous infusion of 5-fluorouracil [22, 26] and 6 h infusion with doxifluridine [25]. The etiology of the hand-foot syndrome is unknown. We observed during the continuous infusion an increase of serum zinc levels between weeks 3 and 4 in five patients with hand-foot syndrome. Molina *et al.* [31] described the increase of serum zinc level under 5-fluorouracil treatment. These results indicate that alterations of zinc metabolism can occur during treatment with pyrimidines. High zinc concentrations in the serum might play a pathophysiological role in developing the hand-foot syndrome.

The reported complications of the therapeutic procedure of continuous infusion therapy involving the catheter site placement occured mainly at the beginning of this trial.

Our results in this trial with 35% partial response and a survival rate of 14.3 months for the responder demonstrated the efficacy of continuous infusion.

These results are similar to the reported trials with continuous infusion of 5-fluorouracil in advanced colorectal tumors [30, 32]. The present study shows slightly higher response rates for the treatment of colorectal tumors with continuous

infusion in comparison to short infusion or bolus injection of doxifluridine or 5-fluorouracil, while there seems to be no advantage in survival rates.

Continuous infusion therapy represents an alternative in the delivery of chemotherapy of cancer. For long-term infusion therapy patients have to be selected for good performance status and willingness to be involved in technical aspects of applications. While patient compliance was high this treatment cannot be considered as standard treatment because of the high costs of the pump and the necessity of patients' collaboration.

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