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A Phase I–II Study of 14-days Continuous Infusion of 5-Fluorouracil with Weekly Bolus Leucovorin in Metastatic Colorectal Carcinoma

Harm A.M. Sinnige, Afien G. Nanninga, Rene C.J. Verschueren, Dirk Th. Sleijfer, Elisabeth G.E. de Vries, Pax H.B. Willemse and Nanno H. Mulder

A consecutive phase I and phase II study of a 14-days continuous infusion schedule of 5-fluorouracil with weekly bolus injection leucovorin was performed in 10 and 21 patients, respectively. Chemotherapy courses were repeated every 4 weeks. 1 patient in the phase I study was pretreated, all the others had no prior chemotherapy. 300 mg/m^2 continuous infusion of 5-fluorouracil for 14 days could not be combined with any dose of leucovorin 20–200 mg/m^2 without severe toxicity, mainly gastrointestinal. A 5-fluorouracil dose of 200 mg/m^2 day for 2 weeks, combined with weekly bolus injection of 200 mg/m^2 leucovorin was found to be feasible. The phase II study was performed at this dose level. In 21 patients a response rate of 5/21 [23.8%, 95% confidence interval (CI) 8.2–47.1%] was observed, and the overall response rate was 8/29 (27.6%, 95% CI 12.7–47.2%). Responses were observed in patients with liver (4), lung (1), abdominal (1), and multiple (2) metastases. Median survival was 14.5 months. Toxicity was low, mucositis WHO grade 1–2 being most frequent (36/113 courses = 31.9%). Patients' acceptance of this continuous infusion schedule was generally good.
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INTRODUCTION

COLORECTAL CARCINOMA continues to be a major health problem in western countries, representing 15% of all cancers and constituting one of the major causes of neoplastic mortality. Metastatic colorectal carcinoma carries a bleak prognosis, estimated median survival time in untreated patients was found to be 10.5 months [1]. There are few therapeutic options, and 5-fluorouracil is considered to be the most effective agent. It shows an unsatisfactory level of remissions (8–25%). These remissions are usually partial and not lasting (average duration: 7–8 months). Effects on survival, if any, are marginal [2–4].

Several modifications enhance the efficacy of 5-fluorouracil [4]. Among these are continuous infusion schedules which have an improved response rate and decreased toxicity compared to bolus 5-fluorouracil but not an improved survival [5, 6]. Biochemical modulation of 5-fluorouracil involves the pharmacological manipulation of its intracellular metabolic pathway: 5-fluorouracil exerts its effect by incorporation into RNA and/or DNA and/or by direct inhibition of thymidylate synthase (TS), a critical enzyme in the synthesis of DNA. It has become apparent that one of the limiting factors of TS inhibition is the availability of 5,10-methylene tetrahydrofolate cofactor. Resistance to 5-fluorouracil has been attributed to relative deficiency of this folate cofactor. Exogenous folate in the form of leucovorin may reverse resistance. The exposure of tumour cells to leucovorin in cell culture systems can result in increased intracellular levels of reduced folates and in increased cytotoxicity [7–9]. Several randomised clinical studies confirmed the efficacy of leucovorin combined with 5-fluorouracil in terms of enhancement of tumour response but also of toxicity [10–15]. The optimal dose, route and schedule of drug administration of leucovorin has not yet been established [13, 14, 16, 17].

In the present study, the most promising adaptations, continuous infusion of 5-fluorouracil and co-treatment with leucovorin, are combined. A phase I study aimed at determining the maximum tolerated dose of leucovorin with a fixed dose of 5-fluorouracil was followed by a phase II study in patients with disseminated colorectal cancer.

PATIENTS AND METHODS

Eligibility criteria for the phase I study were: histologically proven end-stage disseminated colorectal cancer, Karnofsky performance status >60, age 21–75 years, leucocytes $>3 \times 10^9$/l, platelets $>100 \times 10^9$/l, creatinine <130 μmol/l, bilirubin <35 mmol/l, diseases, other than the malignancy, not controllable with outpatient treatment, and an expected survival of 2 months or more. Additional eligibility criteria for the phase II part of the study were: measurable or evaluable histologically documented advanced colorectal cancer and no prior chemotherapy. Informed consent was obtained from all patients and the study was approved by the local medical ethical committee.

Treatments

5-Fluorouracil and leucovorin were obtained commercially. For continuous drug infusion an implanted venous access port (Infuse-A-Port™) and a portable pump (Graseby Medical MS 16A syringe driver) were used as described previously [18]. A 20 ml Luer-lock syringe with 5-fluorouracil was connected to the port via an extension tube and a right angle Huber point needle. The syringe was replaced with freshly prepared 5-

Correspondence to N.H. Mulder.
N.H. Mulder, H.A.M. Sinnige, A.G. Nanninga, D. Th. Sleijfer, E.G.E. de Vries and P.H.B. Willemse are at the Department of Internal Medicine; and R.C.J. Verschueren is at the Department of Surgery, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands.
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Table 1. Patients' characteristics at entry of treatment

	Phase I (n = 10)	Phase II (n = 21)
Median age (range)	49 (35–57)	55 (31–69)
Male/female	2/8	14/7
Prior chemotherapy	1	0
Prior radiotherapy	1	0
Site of primary tumour		
Colon	9	16
Rectum	1	5
Site of metastasis		
Liver	5	9
Lung	0	1
Liver + lung	2	1
Liver + retroperitoneum	0	3
Multiple	0	5
Others	3	2

fluorouracil every day. Except for implantation of the venous access device and initial patient instructions, the treatment was on an out-patient basis.

Initial dose of 5-fluorouracil was 300 mg/m^2 day for 14 days. Leucovorin was administered as an intravenous bolus injection on days 2 and 8. Initial dose of leucovorin was 200 mg/m^2 on each day (= 400 mg/m^2/course). Courses were repeated every 4 weeks. Dose escalation of leucovorin was to proceed if no unacceptable toxicity occurred in 3 patients. Unacceptable toxicity was defined as any WHO grade 3 or 4 toxicity [19] except for alopecia. Toxicity was evaluated on day 7, 15 and 28 after the start of chemotherapy. The study was designed to be followed by a phase II study at the appropriate dose. Evaluation of response in both studies was done after each two treatment courses. In case of progressive disease (PD) treatment was stopped. In case of stable disease (SD) treatment was continued until a maximum of six courses. When partial remission (PR) occurred, treatment was continued until no further reduction of tumour was observed. Criteria for CR were: the disappearance of all perceptible tumour and for PR at least 50% reduction in product of largest perpendicular diameter of the indicator lesion with no increase in the size of other measurable disease and no appearance of new lesions. Remissions had to last for a minimum of 4 weeks. SD was defined as no change in size of measurable lesion or a decrease in tumour size by less than 50% or an increase of a quarter with no appearance of new lesions; SD required a minimum of 8 weeks duration. PD was the appearance of any new lesions and/or growth of any existing lesion by more than a quarter from the start of the treatment.

During the phase II study, evaluation of toxicity, following WHO guidelines [19], was performed every 2 weeks.

Survival times were calculated using the Kaplan–Meier method.

RESULTS

10 patients were entered into the phase I study and 21 patients into the subsequent phase II study. Patients' characteristics are summarised in Table 1. In the phase I study, toxicity appeared to be unexpectedly high at the first leucovorin dose level, requiring de-escalation of leucovorin dose. This was performed in individual patients per course by halving the leucovorin dose. 54 courses were given, median per patient: 5.5 (range 1–8). WHO toxicity per dose range of leucovorin is given in Table 2. Hand–foot syndrome occurred in 40 out of 54 courses. No relationship between leucovorin dose and occurrence or grade of hand–foot syndrome was observed. Haematological toxicity was not observed. No hospitalisation was needed because of toxicity. There were no toxicity related deaths.

8 out of these 10 patients were evaluable for response after at least two courses. 1 patient stopped treatment after one course because of toxicity, the second patient had a lesion in an irradiated area. 1 patient had a CR during 18 weeks and 2 patients had a PR, both lasting 12 weeks [response rate 37.5%, 95% confidence interval (CI) 8.5–75.5%]. Responses occurred in 2 patients with liver metastases and 1 patient with an intra-abdominal metastasis. The other 5 patients had SD with a median duration of 16 weeks (range 16–36 weeks). Responses in these 8 patients occurred only at the 200 mg/m^2 leucovorin dose level. Median survival of all patients in the phase I study was 13 months (range 2–25+). No reduction in grade and incidence of toxicity could be reached by de-escalation of the leucovorin dose (Table 2).

Therefore, the study was continued as a phase II study with 5-fluorouracil at a level of 200 mg/m^2 per day, while leucovorin was maintained at weekly 200 mg/m^2. At this dose level 21 new patients were entered. 113 courses were administered in total, median per patient: 6 (range 1–12). Toxicity at the dose used in the phase II study was remarkably less severe and is summarised in Table 3. In addition, hand–foot syndrome was observed in 19 courses and conjunctivitis in nine courses. No dose adjustment nor hospitalisation was necessary for toxicity. There were no treatment related deaths. One patient developed a vena brachiocephalica thrombosis related to the implanted venous access port.

In these 21 patients one CR lasting 52+ weeks and four PR's (lasting 14+, 22, 26+ and 48+ weeks, respectively) were observed (response rate: 23.8%, 95% CI: 8.2–47.1%). These responses occurred in patients with liver (2), lung (1) and multiple (2) metastases. In 12 patients SD occurred with a median duration of 16 weeks (range 8–34 weeks).

Median survival in the phase II part of the study was 14.5 months.

DISCUSSION

Various ways are known to improve efficacy of 5-fluorouracil. Continuous infusion allows constant exposure of tumour cells to the drug over the course of one or more doubling times, and leucovorin addition diminishes 5-fluorouracil resistance by providing reduced folates, necessary for increasing TS inhibition. Thus, combining continuous infusion and leucovorin addition may enhance the duration and degree of TS inhibition. An early dose finding study with continuous infusion of 5-fluorouracil established 300 mg/m^2/day as a dose that could be given for up to 60 days with limited toxicity [20]. At least nine phase III trials compared 5-fluorouracil bolus injection with 5-fluorouracil bolus injection with leucovorin. Six of these trials are clearly positive in terms of response rates in favour of 5-fluorouracil plus leucovorin treatment, and three trials showed also an improvement in survival [21]. Gastrointestinal toxicity is the most frequent complication when leucovorin is added to 5-fluorouracil. No optimal dose of leucovorin is evident from the literature, but five of the above-mentioned nine studies used 200 mg/m^2/day in a 5 day schedule every 4–5 weeks. Three other studies used 500 mg/m^2 leucovorin in a weekly schedule.

Table 2. Toxicity in phase I study

Weekly leucovorin dose	<50 mg/m²	50–100 mg/m²	100–200 mg/m²	>400 mg/m²
Number of courses	6	8	38	2
Mucositis				
Grade 0	0	0	8	0
Grade 1–2	2	2	18	0
Grade 3–4	4	6	12	2
Nausea and vomiting				
Grade 0	4	2	31	1
Grade 1–2	2	4	6	1
Grade 3–4	0	2	1	0
Diarrhoea				
Grade 0	4	5	20	2
Grade 1–2	2	1	13	0
Grade 3–4	0	2	5	0

$n = 10$.

Table 3. WHO toxicity of the phase II study

Number of courses	113
Mucositis grade 1–2	36
Mucositis grade 3–4	0
Nausea and vomiting grade 1–2	9
Nausea and vomiting grade 3–4	0
Diarrhoea grade 1–2	6
Diarrhoea grade 3–4	0

5-Fluorouracil 200 mg/m²/24 h for 14 days, and leucovorin bolus injection 200 mg/m² on day 2 and 8.
$n = 21$.

We therefore chose to start with a weekly bolus injection of leucovorin of 200 mg/m².

The combination of continuous infusion and leucovorin at the initial dose levels led to an unexpectedly high toxicity with grade 3–4 digestive tract toxicity in 18 out of 38 courses (47%), mucositis grade 3–4 being most frequent (12/38 courses = 32%). Lowering the leucovorin dose did not alleviate this toxicity (Table 2). Thus, whereas 300 mg/m²/day 5-fluorouracil can be continuously infused for up to 60 days [5], no leucovorin can be added in a 2 week schedule at the same dose without severe and unacceptable toxicity. This is in accordance with recent dose finding studies of continuous infusion of 5-fluorouracil with leucovorin [22–24]. These findings demonstrate the modulating capacity of leucovorin, as it decreases the maximal acceptable dose of continuously infused 5-fluorouracil. Noteworthy, de-escalation of leucovorin dose did not lead to reduction of toxicity, and thus the modulating capacity of leucovorin, appeared not to be dose dependent. This is in agreement with the ongoing discussion on the optimal dose of leucovorin when combined with bolus 5-fluorouracil [13, 14, 16, 17]. At present, data do not suggest a clear leucovorin dose relationship with effect on response and survival. As all responses (3/8 patients = 37.5%) occurred in the 200 mg/m² leucovorin dose level, we decided to lower the 5-fluorouracil dose to 200 mg/m²/day for 14 days and keep the leucovorin at 200 mg/m² weekly. On this schedule toxicity was remarkably less severe, and generally acceptable. Mucositis grade 1–2 was most frequent, occurring in 31.9% of the courses. Hand–foot syndrome occurred in 16.8% of the courses. Myelosuppression was not observed.

In the phase II part of the study we observed a 23.8% response rate, and the overall response rate of this phase I and II study is 27.6% (8/29). A recent comparison of bolus schedules of 5-fluorouracil and leucovorin with continuous 5-fluorouracil schedules without leucovorin shows similar response rates (29 vs. 30%) and survival (46 vs. 40 weeks), however, toxicity, specially life-threatening diarrhoea, is greater in the bolus schedules [21]. Response rates of our study are in agreement with these studies indicating that the addition of leucovorin does not dramatically influence response rates of continuous infusion. Although another phase II study of continuous infusion 5-fluorouracil with weekly leucovorin reported higher response rates [25], it remains to be answered in phase III studies whether 5-fluorouracil continuous infusion regimens combined with leucovorin are superior in terms of response rates, survival and toxicity to 5-fluorouracil plus leucovorin bolus regimens.

In conclusion, the optimal dose rates for 2 weeks continuous infusion of 5-fluorouracil combined with weekly bolus leucovorin are 200 mg/m²/day and 200 mg/m², respectively. Although toxicity of 5-fluorouracil is increased by leucovorin, this effect is not dose dependent. This regimen has a comparable antitumour response to other 5-fluorouracil/leucovorin regimens in colorectal cancer and has minimal toxicity.

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A Double-blind Study of the Efficacy of Metronidazole Gel in the Treatment of Malodorous Fungating Tumours

M. Bower, R. Stein, T.R.J. Evans, A. Hedley, P. Pert and R.C. Coombes

A double-blind placebo-controlled trial was undertaken to assess the value of topical metronidazole gel preparation in the palliation of the offensive odour of fungating tumours. This 5 day trial was followed by a 6 day period during which all patients received the active gel. Subjective odour assessments were performed by both patients and medical staff. 11 patients were entered and the randomisation was then halted because of an obvious overall benefit over the whole 11 days. There was a non-significant trend in favour of the active treatment during the initial double-blind placebo-controlled phase of the trial, and no side-effects were observed.
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INTRODUCTION

THE OFFENSIVE odour of fungating tumours is distressing for both patients and their carers, and arises as a consequence of colonisation of a necrotic tumour by anaerobic bacteria. Oral metronidazole has been shown to inhibit anaerobic colonisation [1] and reduce the associated odour of these tumours [2–4]. However, continuous therapy is necessary as organisms rapidly regrow when the treatment is stopped, oral metronidazole frequently causes nausea and vomiting, and the ban on alcohol necessary with oral metronidazole may further impair patients' quality of life [5]. Topical application of metronidazole would circumvent these problems and we have therefore conducted a double blind randomised study to assess its efficacy.

PATIENTS AND METHODS

Patients were randomised for an initial treatment period of 6 days into one of two parallel groups receiving either 0.8% metronidazole gel (Tillotts Laboratories) 1g/cm^2 lesion or placebo gel applied daily. This double-blind randomised placebo-controlled trial period was followed by an open assessment period of 5 days when all patients received active gel. Doses varied between 3.75 and 15 g per day depending on lesion sizes but were constant for each patient. None of the patients received antitumour therapy or antibiotics within the 4 weeks preceding and for the duration of the trial.

The odour of the lesion was graded daily by the patient and by one investigator (AH) at home visits, using visual analogue