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Treatment of Advanced Colorectal Cancer With Folinic Acid and 5-Fluorouracil in Combination With Cisplatinum

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51 patients with metastatic colorectal cancer (stage Dukes D) were treated with intravenous (i.v.) infusion on days 1, 3, 5, 8 and 16 with folinic acid (200 mg/m²) and 5-fluorouracil (600 mg/m²), and on days 1, 8 and 16 with cisplatinum (25 mg/m² i.v.); cycles were repeated every 4 weeks. All 51 patients were evaluable for toxicity and response criteria. 26 patients had objective responses (3 complete responses, 5.9%; 23 partial responses, 45.1%), relative risk 51% (95% confidence intervals 36.7–65.0%). Response duration ranged from 4 to 28.0 months (median 16.8). Overall median survival of all patients included was 14.7 months (range 3.0–33.0). Toxicity of WHO grade III, requiring dose reduction, occurred in 9 (18%) patients. The regimen described here appears to be active, safe and well tolerated for treatment of patients with advanced colorectal cancer.

Key words: colorectal cancer Dukes D, chemotherapy, folinic acid, 5-fluorouracil, cisplatinum, objective response rate, survival time, toxicity
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INTRODUCTION

TREATMENT OF advanced colorectal cancer is still considered a major problem in oncology. For more than 30 years 5-fluorouracil (5-FU) monotherapy was generally accepted as an active agent for treatment of metastatic disease, despite the fact that response rates in the range of only 10–20% have been achieved [1].

In recent years, several attempts have been made to improve treatment results by combining 5-FU with other agents. One of these treatment approaches is the use of 5-FU together with folinic acid (FA) [2, 3]. This treatment regimen is based on *in vitro* studies which have shown an increased tumour cell kill [4]. The mechanism underlying the increased anti-tumoral activity of 5-FU and FA is probably a pharmacological manipulation of the intracellular pathway of 5-FU [5].

Several randomised trials, comparing 5-FU with 5-FU plus FA, have demonstrated two to four times higher response rates with the combination in metastatic colorectal cancer. Despite these higher response rates, survival improvement appears to be modest at best, not exceeding more than a few months [6].

Further attempts to increase the therapeutic potential of 5-FU have been made by combinations with cis-platinum (CDDP).

Preclinical studies have provided evidence for a synergistic antitumoral activity of CDDP in combination with 5-FU. The basis for this effect seems to be, as is the case for FA, an increase of intracellular levels of reduced folates, which potentiate the action of 5-fluorodeoxyuridine monophosphate by forming a convalent tertiary complex with thymidilate synthase [6–8]. Alternatively, evidence exists that 5-FU modulates the repair of platinum–DNA adducts, thereby potentiating the antitumoral activity of CDDP [9]. With this regimen, response rates in the range of 40–60% have been achieved, which suggests increased antitumoral activity of this combination in patients with advanced colorectal cancer [10, 11]. However, preliminary reports of ongoing randomised trials comparing 5-FU monotherapy with the combination of 5-FU and CDDP have not yet shown any significant difference in response rates between these treatment arms [12].

In a pilot study, we have demonstrated that the three-drug combination including CDDP, 5-FU and FA is a safe and active regimen for treatment of metastatic colorectal cancer [13]. The purpose of the present study was to extend these initial findings with regard to therapeutic efficacy in patients with palliatively resected metastatic colorectal cancer. Furthermore, we investigated the influence of the addition of CDDP infusion on the pharmacokinetics of 5-FU within the 3–60 min postinfusion period.

PATIENTS AND METHODS

Patients

51 previously untreated (except with surgery) patients with biopsy-proven and pathologically confirmed adenocarcinoma of the colon or rectum, classified Dukes D stage, were entered in this study. Patients were required to have at least one bidimensionally measurable lesion for evaluation of therapy responses. Additionally, patients were required to be of less than 75 years of age, to have a performance status of ≤ 2 on the ECOG scale and a life expectancy of at least 3 months. Further inclusion criteria were a leucocyte count $> 3.5 \pm 10^9$/l and $> 120 \times 10^9$/l platelet counts, total bilirubin < 34 μmol/l, serum creatinine < 140 μmol/l, creatinine clearance of 50 ml/min for 1.73 m^2 or more.

Patients with isolated bone metastases or malignant ascites as their only disease manifestation were not entered in this study. Furthermore, patients with severe cardiac disease or with a history of prior other invasive carcinoma or severe infections were ineligible.

Pretreatment evaluation and follow-up

Before initiation of therapy, all patients underwent a complete medical history and physical examination. Laboratory studies included complete blood count (CBC) with differential and platelet count, haematocrit (HTK), haemoglobin (Hb), blood urea nitrogen (BUN), creatinine and liver function tests. These tests were repeated in weekly intervals during therapy. Carcinoembryonic antigen (CEA) levels and serum electrolytes were determined before and during therapy. Pretreatment examinations also included chest X-ray, abdominal sonography, computed tomography, and bone scan, and were repeated at 4–8-week intervals during therapy, to enable assessment of measurable disease and, by this, response to therapy.

Study design and treatment

This was an open single arm study. Therapy cycle consisted of an infusion (30 min) of 200 mg/m^2 FA (Leucovorin Calcium, Ebewe, Vienna) followed by a 2-h infusion of 600 mg/m^2 5-FU (Hoffmann La-Roche, Vienna) on days 1, 3, 5, 8 and 16. CDDP (Ebewe) was given on days 1, 8 and 16 at a dose of 25 mg/m^2 by a 1-h infusion after FA/5-FU, using standard conditions for adequate hydration. Treatment was performed on an outpatient basis and cycles were repeated every 4 weeks.

The doses and time intervals of FA and 5-FU were chosen according to previous studies by Löffler and colleagues [14], in which this combination was found to be effective [15]. In order to reduce possible side-effects, the total dose of CDDP (75 mg/m^2) was divided in three single doses of 25 mg/m^2 each. Moreover, results of our pilot study have shown tolerability and antitumoral activity of this three-drug regimen in patients with metastatic colorectal cancer [13]. The study protocol was reviewed and accepted by the hospital's ethical committee. Before entering the study, patients had to give verbal informed consent.

Pharmacokinetic data assessment

In order to determine whether addition of CDDP to FA+ 5-FU results in an alteration of pharmacokinetic behaviour of 5-FU, blood samples were drawn from 6 patients at respective time intervals. Plasma was separated and kept frozen at −20°C (< 3 months) for 5-FU analysis.

On day 1, after termination of 5-FU infusion, at times 0, 3, 5, 10, 20, 30, 40, 50 and 60 min, plasma samples were obtained for determination of baseline levels. On day 16, plasma sampling was performed in the same patients, at identical time intervals following 5-FU administration, during CDDP infusion.

5-FU levels were measured by selective high liquid pressure chromatography as described previously [16].

Area under the curve (μg/ml during 50 min; AUC_{0-50}), plasma half lives ($t_{1/2}$ elimination) and plasma concentration of 5-FU ± CDDP were determined.

Criteria for response

Responses were assessed according to the WHO criteria in at least 4-week intervals [17]. Complete response (CR) was defined as the disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. Partial response (PR) was defined as a reduction of > 50% in the sum of the products of the diameters of the measurable lesion(s), without evidence of new lesions for two consecutive evaluations separated by at least 4 weeks. The same criteria were used whether single or multiple lesions were evaluated. Progressive disease (PD) was defined as an increase of > 25% in the area of the measurable lesion(s) or the appearance of new lesions. Patients with tumours not meeting these criteria for response or progression were considered stable. Response duration was measured from the onset of response until disease progression; duration of stable disease (SD) was calculated from the first day of therapy until progression. Survival was determined from the first day of treatment until death.

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Statistical methods

Cumulative survival was determined according to Kaplan and Meier [18]. The 5-FU plasma concentration time values fitted into a two-compartment open model by a nonlinear least square regression analysis. Computer-assisted iterations were performed by means of a modified Gauss–Newton method (regression of the residuals into the partial derivatives of the models). Estimations of plasma half life were based on the regression model $y = b_0 * e(-b1 * t)$ and computed according to the formula $t_{1/2} = \ln(2)/b1$. Subgroup observations were calculated by means of the non-parametrical Kruskal–Wallis test. When the two sets of data were derived from identical patients, Student's *t*-test was applied for paired data.

RESULTS

Patients' characteristics

51 consecutive patients (29 male and 22 female) with diagnosis of Dukes' D colorectal cancer were entered into this study. Details are presented in Table 1. With regard to metastatic sites, 14 (27.5%) patients had liver involvement only, whereas 72.5% of the patients presented more than one site of metastatic disease.

Response to treatment

All 51 patients entered were evaluable for both response and toxicity criteria. The total number of cycles given was 306, with a median number of 6 (range 3–12). In 3 patients (5.9%) CR and in 23 (45.1%) PR have been documented. The overall response rate (CR+PR) achieved was 51% with a 95% confidence interval of 36.7–65.0%. Stabilisation of the disease (SD) was documented in 12 (23.5%) patients and PD in 13 patients (25.5%).

The median duration of response in patients with CR+PR was 16.8 (4.0–28.0) months. Median survival time (estimated by life table analysis) of patients experiencing objective remissions was 18.2 months (range 6.0–32.0). In patients with SD or PD, median survival was 8.5 months (range 3.0–14.0). The overall median survival was 14.7 months (range 3.0–33.0) (Figure 1).

Toxicity

All 51 patients evaluated for response were also assessed for toxicity (WHO criteria) (Table 2). In general, side-effects of therapy were tolerable, and in all patients except one, treatment was not interrupted due to toxicity. In 6 patients, haematological toxicity exceeded grade 2.

With regard to non-haematological toxicity, vomiting was the most frequent side-effect with ≥ grade 2 occurring in 20 (39.2%) patients. 14 patients experienced diarrhoea (5 grade 3). Other toxicities were of low grade (Table 2). Dose reduction by 25% was required in 9 patients (18%) (5 patients with diarrhoea grade 3, 1 patient with grade 4 and 3 with leukopenia grade 3).

Table 1. Patients' characteristics

	No. of patients	Per cent
Included	51	100.0
Evaluable	51	100.0
Male	29	56.9
Female	22	43.1
Mean age (62.4 years)		
> 50	8	15.7
50–69	31	60.8
≥ 70	12	23.5
Metastatic sites		
Liver	14	27.5
Liver and other	8	15.7
Lung and other	9	17.6
Abdominal and pelvic masses	12	23.5
Other sites	8	15.7
Performance status (ECOG scale)		
0	30	58.8
1	14	27.4
2	7	13.7

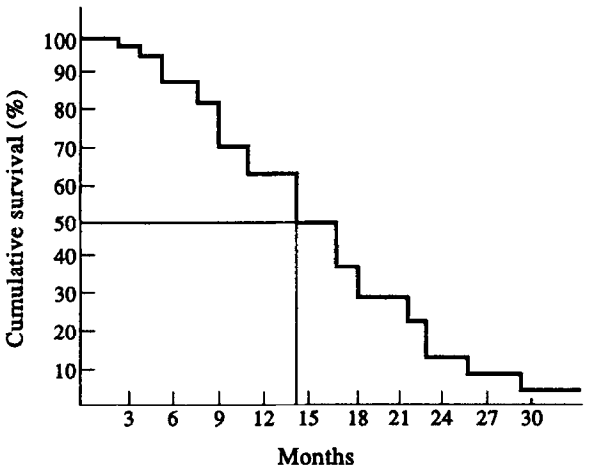

Figure 1. Probability of survival (Kaplan–Meier). Median survival 14.7 (3.0–33.0+) months.

Pharmacokinetics of 5-FU

Plasma levels of 5-FU were measured in 6 patients with or without CDDP infusion. Figure 2 shows the kinetics of 5-FU clearance from peripheral blood, i.e. median 5-FU plasma concentrations during the 40 min after termination of FA + 5-FU + CDDP and FA + 5-FU infusion. All differences observed are highly significant; the fitted exponential functions for FA + 5-FU + CDDP and FA + 5-FU show a dose-dependent pattern of clearance under both conditions.

The median value of the AUC (AUC μg/ml during 50 min) for FA + 5-FU + CDDP was 299.0 (range 123.6–354.4) and for FA + 5-FU 94.4 (range 47.6–164.9). This difference is significant ($P < 0.01$, Kruskal–Wallis test).

Applying non-linear regression models, the resulting

Table 2. Toxicity (WHO)

Toxicity	Grade 1	2	3	4	Total (%)
Non-haematological					
Diarrhoea	2	7	5		14 (27)
Stomatitis	4			1	5 (10)
Vomiting	7	18	2		27 (53)
Alopecia		7	9		16 (31)
Neurol periph	4				4 (8)
Renal toxicity	1				1 (0.2)
Haematological					
Leucopenia		8	4	1	13 (25)
Thrombopenia	2	2		1	5 (10)
Anaemia	3	2			5 (10)

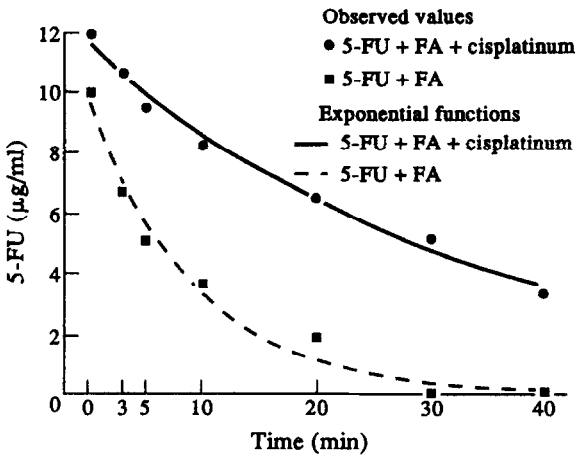

Figure 2. Kinetics of 5-FU clearance. Median 5-FU plasma concentration during the first 40 min after termination of infusions of FA + 5-FU + CDDP (circles) and FA + 5-FU (squares). All observed differences are highly significant; the fitted exponential function (solid line FA + 5-FU + CDDP, dotted line FA + 5-FU) show dose-dependent patterns of clearance under both conditions.

exponential functions could be defined as $y = 11.5292^* e(0.0293^*t)$ and $y = 9.6463^* e(-0.1061^*t)$ for FA + 5-FU + CDDP and FA + FU, respectively. The estimated half-life of 5-FU was 23.7 min for the combination FA + 5-FU + CDDP and 6.5 min for FA + 5-FU.

To minimise circadian changes of 5-FU kinetics, therapy was started in all patients in the morning (before 8 a.m.). No changes in renal and liver functions were observed between days 1 and 16, which might have influenced pharmacokinetics of drugs administered during this period.

DISCUSSION

The principle of biochemical modulation is now extensively used for treatment of advanced malignancies, especially in order to improve response rates to 5-FU. However, so far no standard combination regimen has been established according to dose and time sequence for both agents. Doses for FA range from 20 to 500 mg/m^2, and for 5-FU from 250 to 1200 mg/m^2 [12]. In this study we used an intermediate dose regimen for these two drugs, i.e. 200 mg/m^2 FA and 600 mg/m^2 5-FU given on days 1, 3, 5, 8 and 16 and repeated every 4 weeks according to Löffler [14]. The total dose of 75 mg/m^2 of CDDP was divided into three single doses of 25 mg/m^2 in order to avoid increased toxicity by the additional combination with CDDP. This regimen was found to be effective in our pilot study in combination with CDDP [13].

In the present study, 26 (51%) of 51 included and evaluated patients with metastatic colorectal cancer showed objective tumour responses (CR+PR). The initial performance status of a patient did not predict response to therapy. There was no significant difference in frequency and quality of objective remission with regard to performance status 0, 1 or 2. Our data compare favourably with results obtained by others with the 5-FU/FA combination therapy in advanced colorectal cancer. Documented remissions in these studies were in the range of 27 to 50% [2, 3, 6]. Results of randomised prospective studies have demonstrated increased response rate with this combination in comparison to 5-FU monotherapy (16–48% combination therapy versus 5–23% 5-FU). However, only two of these 10 studies have shown increased overall survival [6, 12].

There are now data available from five randomised studies comparing 5-FU alone to CDDP + 5-FU for therapeutic efficacy for advanced colorectal cancer [19]. Out of these studies, four did not show any difference in response rates between these two treatment arms. In a study by Kemeny, however, significant differences in response rates between 5-FU (3%) and combination arm (25%) were achieved, but no difference with regard to survival times was reported. Factors that may have influenced low response rates to 5-FU in this study have not been identified [19].

Our treatment results suggest that the inclusion of CDDP in the combination 5-FU/FA has led to an increased therapeutic activity. With regard to survival data, no firm conclusion can be drawn due to the phase II character of this study. However, overall median survival compares favourably with studies using 5-FU combination therapy in colorectal cancer.

The possible mechanism underlying this favourable response rate by this combination has also been addressed. The administration of CDDP resulted in an increased AUC value for and plasma half-life of 5-FU. These pharmacokinetic data contribute to the notion that CDDP addition leads to a biochemical modulation of this antimetabolite, i.e. increased levels of reduced folates result in an inhibition of thymidilate synthase [7].

However, other mechanisms should also be considered with regard to increased activity of this combination. Recently, Esaki and colleagues have demonstrated in *in vitro* studies that the synergistic cytotoxic activity of the 5-FU + CDDP combination was detected only when 5-FU preceded CDDP exposure [9]. According to their investigations, this enhanced activity appears to be caused by a modulation of the repair of CDDP-induced interstrand cross-links by 5-FU. Therefore, one might assume that both these described mechanisms are contributing to the antitumoral activity also observed *in vivo*.

Data of a phase II study using the combination of 5-FU + FA + CDDP in somewhat different doses and application schemes in advanced colorectal cancer have also been recently presented by other authors [15, 20]. These investigators concluded that, according to remission rates, i.e. 26.6% [20] and 38% [15], this regimen seems to be active for treatment of advanced colorectal cancer.

Treatment results with this three-drug combination regimen have to be confirmed by randomised studies in order to demonstrate an advantage over the 5-FU + FA combination with regard to response rates and survival times in patients with advanced colorectal cancer.

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Sex Hormone Levels in Postmenopausal Women With Advanced Metastatic Breast Cancer Treated with CGS 169 49A

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30 postmenopausal patients with metastatic breast cancer were treated with three different doses of fadrozole hydrochloride (CGS 169 49A), a non-steroidal competitive aromatase inhibitor. The effect of 0.5, 1 and 2 mg given twice daily upon the levels of oestrogens, their androgen precursors and upon the concentration of sex hormone binding globulin (SHBG) was investigated after 1 and 3 months and then every 3 months until progression of disease. A significant reduction in the serum concentration of oestrone ($P < 0.0001$) was obtained at all doses. Also, the serum concentration of oestrone sulphate was significantly reduced ($P < 0.001$). However, after 1 month, the concentration was significantly different from pretreatment levels ($P < 0.01$) only at the 4 mg daily dose. A decline was also observed in the concentration of SHBG ($P < 0.05$), with a concomitant elevation of the percentage non-SHBG-bound oestradiol. The androgens, testosterone and dehydroepiandrosterone sulphate, were unaltered during treatment, while androstendione was significantly elevated at the 2 mg daily dose ($P < 0.001$).
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INTRODUCTION

HORMONES ARE often implicated in various aspects of genesis and growth of cancer. Malignant cells tend to lose their ability to differentiate, but some malignant tumours retain their responsiveness to the specific hormones that are necessary for growth and maintenance of function in the normal tissue from which the tumour originated. Oestrogens are considered to be important in the development of breast cancer, although they are not directly carcinogenic. The growth of a proportion of human breast carcinomas is dependent on oestrogens, and this oestrogen dependency has led to the use of several therapeutic regimens aimed at reducing oestrogen production. In postmenopausal women, extra glandular tissues such as fat, muscle and skin are considered to be principal sites of oestrogen production from adrenal androgen precursors [1–3]. No consistent differences in serum levels of oestrogens in women with or without breast