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Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer

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Abstract

The aim of this study was to determine the patient's preference for oral UFT/leucovorin (LV) or intravenous (i.v.) 5-fluorouracil (5-FU)/LV chemotherapy in metastatic colorectal cancer and to compare 5-FU exposure with these two treatment options. A total of 37 previously untreated patients with advanced colorectal cancer were randomised to start treatment with either oral UFT 300 mg/m^2/day plus oral LV 90 mg/day for 28 days every 5 weeks or i.v. 5-FU 425 mg/m^2/day plus LV 20 mg/m^2/day for 5 days every 4 weeks. For the second treatment cycle, patients were crossed-over to the alternative treatment regimen. Prior to the first and after the second therapy cycle, patients were required to complete a therapy preference questionnaire (TPQ). The pharmacokinetics of 5-FU were determined by taking blood samples on days 8, 15 or 22 and 28 for UFT and on days 1 and 5 for i.v. 5-FU. 36 patients were eligible. 84% of the patients preferred oral UFT over i.v. 5-FU. After having experienced both treatment modalities, patients indicated taking the medication at home, less stomatitis and diarrhoea, and pill over injection as the most important reasons for their preference. The area under the plasma concentration curve (AUC) for 5-FU after UFT administration was 113 μM×min on day 8, 114 on day 15 and 98 on day 28; the peak levels (Cmax) were 1.2, 1.3 and 1.0 μM, respectively. The AUC for the 5-FU/LV courses was 3083 μM×min for day 1 and 3809 for day 5 ($P=0.002$). The Cmax was 170.1 and 196.2 μM ($P=0.06$) and the clearance 2.6 and 1.9 l/min, respectively ($P=0.002$). Patients with metastatic colorectal cancer clearly preferred oral over i.v. chemotherapy treatment. This choice was most importantly influenced by convenience and toxicity considerations. Although i.v. bolus 5-FU leads to higher peak 5-FU concentrations and AUC values compared with oral UFT, this pharmacokinetic advantage of i.v. 5-FU seems to translate mainly into higher toxicity as seen in large randomised studies comparing oral UFT/LV with i.v. 5-FU/LV. Oral UFT/LV compares favourably with i.v. 5-FU/LV in terms of toxicity and patient's preference and leads to prolonged 5-FU exposure, which is comparable to continuous i.v. 5-FU treatment.

Keywords: Patient's preference; Pharmacokinetics; Oral; UFT; 5-Fluorouracil; Leucovorin; Randomised crossover trial

1. Introduction

5-Fluorouracil (5-FU) is an integral component in the treatment of gastrointestinal cancer and other solid tumours. Only recently, insights into the molecular pharmacology of this drug have translated into more effective and less toxic administration schedules. Since 5-FU interferes with the replication and repair of nucleic acids, its efficacy is more pronounced in actively cycling cells. Even aggressively growing cancer cells have typically a doubling-time of days to weeks and means to prolong exposure to 5-FU have been shown to optimise its clinical activity [1].

Biochemical modulation with folinic acid (leucovorin (LV)) increases the dissociation half-life of the active metabolite of 5-FU, fluorodeoxyuridine monophosphate, with its target enzyme thymidylate synthase. In advanced colorectal cancer, two randomised studies

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have demonstrated a significant benefit in terms of survival and quality of life parameters if LV was added to 5-FU [2,3]. The major non-haematological toxicities of this combination are stomatitis and diarrhoea, which reached grade 3-4 intensity in 25 and 22% of the patients, respectively [2]. Although this toxicity is rarely fatal and can generally be avoided by reducing the 5-FU dose in the following treatment cycles, it inflicts substantial suffering upon the affected patients. In addition, the most frequently used treatment schedule (Mayo regimen) necessitates bolus injections on 5 consecutive days every 4 weeks.

Continuous intravenous (i.v.) infusion is another way to prolong exposure to 5-FU. In advanced colorectal cancer, continuous i.v. infusion has resulted in a significantly higher response rate and less toxicity, compared with i.v. bolus injections [4]. However, an important drawback of continuous i.v. infusion is the need for implantable access devices and portable infusion pumps. Implantable access devices may be associated with catheter-related complications and portable infusion pumps may severely limit the activity range of the patients. Clearly, the availability of an oral formulation of the drug would circumvent these problems, but 5-FU has shown incomplete and unpredictable absorption following oral administration [5].

UFT, a new oral fluoropyrimidine formulation, combines uracil and tegafur in a fixed molar ratio of 4:1. Tegafur as a prodrug is completely and rapidly absorbed after oral administration and converted to 5-FU by the hepatic microsomal system. Uracil inhibits the dihydropyrimidine dehydrogenase, the main catabolic enzyme of 5-FU, resulting in elevated and sustained concentrations of 5-FU in the body [6,7]. Two large phase III studies comparing oral UFT plus LV (UFT/LV) to i.v. bolus 5-FU plus LV (5-FU/LV) in advanced colorectal cancer have been completed [8,9]. Both treatments are equivalent in terms of efficacy parameters, although UFT plus LV has a more favourable toxicity profile.

Obvious advantages of oral over i.v. drug administration include avoiding painful injections, the possibility to take the drug at home and reduced drug administration costs. However, there are also patients who opt for i.v. treatment since they prefer to delegate the responsibility for drug administration to the health providing team. In a scenario-based study, 70% of the patients favouring i.v. treatment worried about their own compliance with medications [10]. Another potential advantage of i.v. treatment is that the drugs are generally administered only a few days per month compared with the more protracted oral administration. Patients are constantly reminded of their disease if they have to take anticancer pills once or even several times a day for long periods, which are typically only interrupted for 1 week at regular intervals.

To formally test the aspect of patient's preference for an oral fluoropyrimidine (UFT/LV) or i.v. 5-FU/LV (Mayo) regimen in advanced colorectal cancer, we performed the first prospective randomised crossover trial to date to examine this question. This design has the advantage of exposing patients to both treatment options before they are asked to make their choice of preferred regimen. Thus, each patient served as his or her own control for the impact of oral or i.v. treatment. In parallel, pharmacokinetic analyses were performed to compare plasma exposure to 5-FU with both fluoropyrimidine regimens in the first treatment cycle.

2. Patients and methods

2.1. Eligibility and patient evaluation

Eligible patients had histologically- or cytologically-confirmed advanced adenocarcinoma of the colon or the rectum, which was no longer amenable to surgical treatment. Other eligibility criteria were the ability to take oral medication, age over 18 years, World Health Organization (WHO) performance status 0-2 and a life expectancy of at least 3 months, absolute granulocyte count $\geqslant 2\times10^9$ cells/l, platelet count $\geqslant 100\times10^9$ cells/l, total bilirubin $\leqslant 1.5\times$upper limit of normal for the Institute (ULN) and creatinine $\leqslant 1.5\times$ULN. Patients with the following manifestations of disease only were excluded: lymphoedema, pleural effusion, ascites, bone marrow suppression, osteoblastic skeletal lesions. Other exclusion criteria were prior chemotherapy for advanced disease, clinical signs of central nervous system involvement, prior malignancies (excluding localised epithelial skin or cervical cancer), poor medical risk because of non-malignant systemic disease and treatment with other investigational drugs. Pregnant or breast-feeding women were not eligible, and sexually active fertile patients had to practise contraception. The protocol was approved by the local ethics review boards of all participating institutions, and all patients gave written informed consent before enrolment.

Pretreatment evaluation included a complete medical history and physical examination, complete blood count and chemistry profile, urine analysis, chest X-ray, a carcinoembryonic antigen (CEA) serum level and imaging examinations as required to assess all tumour parameters. A complete blood count was obtained weekly and serum chemistry profiles were obtained prior to the onset of each treatment cycle together with a physical examination and toxicity assessment. Patients had repeat CEA and radiological tumour parameter assessment at the end of the second treatment cycle once the Therapy Preference Questionnaire (see below) was completed. Thereafter, it was recommended to repeat tumour measurements every other treatment cycle.

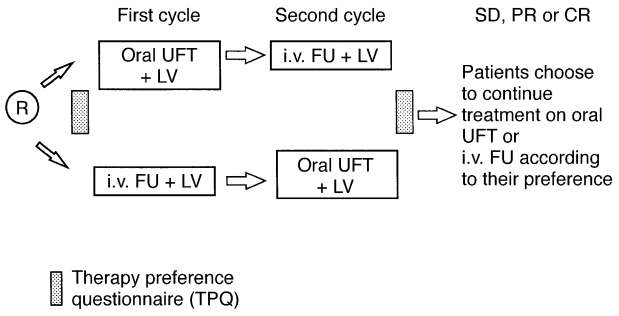

Fig. 1. Study design. R, randomisation; SD, stable disease; CR, complete response; PR, partial response; 5-FU, 5-fluorouracil; i.v., intravenous.

2.2. Design and treatment

The study design is depicted in Fig. 1. Patients were randomised at the New Drugs Development Office (NDDO) Oncology Headquarters to start treatment with either oral UFT/LV or i.v. 5-FU/LV. After randomisation, patients had to complete the pretreatment Therapy Preference Questionnaire (TPQ; see Appendix A). For the second treatment cycle, patients who had started on oral treatment received i.v. 5-FU/LV and *vice versa*. Plasma sampling for assessment of 5-FU exposure was performed at specific time-points (see below) during the first two treatment cycles. At the end of cycle 2, patients were asked to complete the post-treatment TPQ (Appendix B) before they were informed about the results of the tumour response assessment. Patients with stable disease (SD) or partial response (PR) after two treatment cycles, could continue on their regimen of choice thereafter. It was planned to include 30 evaluable patients in this study. For this purpose, additional patients were entered to substitute for patients failing to complete the first two treatment cycles and the TPQ.

Patients on UFT/LV received UFT 300 mg/m^2/day and LV 90 mg/day both given in three divided daily doses for 28 days followed by a 7-day drug-free rest period. UFT and LV were supplied in separate tablets by Bristol-Myers Squibb Oncology Europe (Brussels, Belgium). The UFT capsules contained 100 mg of tegafur, and the LV tablets contained 15 mg of (6*R,S*)leucovorin. The suggested times of administration were 0700, 1500 and 2300 h. For UFT, the daily dosages were rounded up or down to the nearest 100 mg. If the number of capsules to be taken per day did not evenly distribute between the three daily administration times, the greater number of capsules was taken in the morning and in the afternoon. With each dose of UFT, 30 mg LV was taken. The drugs had to be taken at least 1 h prior to or 2 h following food intake with one glass of water or juice. To have a measure of compliance, the patients had to record the intake of the study medication on a diary card. In addition, returned blisters (UFT) and bottles (LV) were controlled for remaining capsules and tablets.

Patients on 5-FU plus LV received LV 20 mg/m^2/day followed by 5-FU 425 mg/m^2/day both as a bolus injection on 5 consecutive days followed by a 23-day therapy-free rest period.

In the event of grade $\geqslant 2$ stomatitis or diarrhoea, treatment was withheld until toxicity recovered to grade $\leqslant 1$ or baseline. In case of grade 3-4 toxicity, the UFT or 5-FU dose was reduced by 50 mg/m^2/day in the following treatment cycle.

2.3. Patient preference

The patient's preference and strength of preference for oral and i.v. chemotherapy was assessed using a Therapy Preference Questionnaire (TPQ) (Appendices A and B). This instrument was designed for this study and its feasibility was assessed with this trial. The reasons behind a patient's preference were evaluated initially by directed questioning. Then, these reasons were assessed semiquantitatively.

Analyses of the responses for the items in the TPQ were exploratory. The outcome is summarised in frequency tables and descriptive statistics. The most important post-treatment question was whether oral UFT or i.v. 5-FU was the preferred treatment choice (Appendix B). Question 2 of the post-treatment TPQ measured the strength of the patient's preference. The scores from this scale were compared between preference groups to determine whether the strength of preference was different between patients choosing UFT or 5-FU. In addition, the reason for this choice was a main interest. The selection of UFT or 5-FU was the dependent variable in these analyses.

The features listed in the iterative ranking questions on both pretreatment and post-treatment forms were ranked by their overall scores in the two different groups; patients who preferred UFT and those who preferred 5-FU. A comparison was made of the relative importance of each feature to patients in the respective groups. For the pre-treatment TPQ, patients were asked to indicate the five most important features from a choice of 12 possible reasons (Appendix A), which could influence their choice of oral or i.v. treatment. In consecutive steps, patients had to limit their choice to the three, then the two and finally the one most important reasons from the selected features. The same procedure was followed for the post-treatment TPQ, where patients could select from 15 different reasons (Appendix B). A score was calculated to assess the 'relative frequency' with which the respective statements were chosen: Relative frequency = Number of patients choosing the respective statement (NPCRS) as one of the five most important reasons/(5×2) + NPCRS as one of the three most important reasons/(3×2) + NPCRS as

one of the two most important reasons/(2×2)+NPCRS as the most important reason/(1×1). This score includes the frequency with which a feature was selected as being important for the choice of i.v. or oral treatment. It also takes into consideration the different weight of a selected feature from being most important to being one out of the initial five selections. Only patients who completed the first two cycles of therapy and the TPQ were evaluable for the analysis of treatment preference.

2.4. Pharmacokinetics

For the oral UFT/LV regimen, blood samples were obtained on days 8, 15 or 22 and day 28 immediately before drug intake and at 0.5, 1, 1.5, 2, 3, 5 and 8 h after drug administration. On i.v. 5-FU/LV, blood samples were obtained on days 1 and 5 immediately before the onset of treatment and at 0.1, 0.3, 0.7, 1, 2, 5 and 8 h after drug administration. Blood specimens for pharmacokinetics were collected in heparinised tubes, placed on ice and centrifuged in a refrigerated centrifuge. Plasma was frozen at −80 °C until analysis. Pharmacokinetic parameters, including half-life, area under the plasma concentration-versus-time curve (AUC), and clearance were calculated using the WinNonLin (version 1.5). A patient was non-evaluable for pharmacokinetic analysis if three or more blood specimens were missing.

All pharmacokinetic analyses were performed by the laboratory of G.J. Peters at the Vrije Universiteit Medical Center (VUMC) in Amsterdam. 5-FU plasma concentrations were measured using gas chromatography coupled with mass spectrometry, as described previously [11,12] with a slight modification [13]. The following were added to 100 μl of plasma: 50 μl of 1 μmol/l 5-FU–$^{15}N_2$, 1 ml of Milli-Q water (Millipore, Bedford, MA, USA) and 100 μl of 2 mol/l Tris (pH 6). A calibration line of 5-FU was included in each set of measurements as well as a set of three quality controls in the range of the calibration line. The mean slope of the calibration line was 0.994. In case the intra-assay variation exceeded 15%, the samples were measured again. In the evaluable samples the overall intra-assay variation of the quality controls was −0.4±2.4%. The solution was extracted twice with 4 ml of diethylether/2-propanol (80/20, vol/vol). The organic fraction was blown to dryness under N_2 at 60 °C. The residue was reconstituted in 80 μL of acetonitrile and 10 μL of triethylamine, and 10 μl of pentafluorobenzylbromide was added. The mixture was left at room temperature for 15 min, at which time the derivatisation had reached a plateau. After the addition of 400 μl of 0.1 mol/l HCl, the solution was extracted once with 1 ml of hexane. The organic layer was blown to dryness under N_2 at 45 °C, and the residue was dissolved in 50 μl of hexane/propanon (3/1, vol/vol). From this sample, 1 μl was injected, with an injector temperature of 320 °C, into the gas chromatography/mass spectrometry system (VG30-250; Fisons, Weesp, The Netherlands). Chromatographic separation was carried out on a CPSil19CB column (internal diameter, 25 m×0.25 mm; film thickness, 0.25 μm) (Chrompack, Middelburg, The Netherlands) with an oven temperature gradient starting at 200 °C for 1 min and increasing by 20 °C/min to a temperature of 320 °C, which was maintained for 2 min. The ions for 5-FU and 5-FU–$^{15}N_2$ (m/z −309 and m/z −311, respectively) were recorded with negative ionisation detection and methane as the moderating gas.

3. Results

37 patients were randomised from six centres onto this study from 26 March 1998 until 23 July 1999 (Fig. 2). The characteristics of eligible patients are summarised in Table 1. One patient was ineligible because of elevated serum bilirubin level at study entry due to advanced disease. After two treatment cycles, the tumour response was evaluated to allow patients without signs of tumour progression to continue either oral or i.v. treatment. Tumour response was not a primary or secondary endpoint of this study, since it was assessed after only one cycle each of oral UFT and i.v. 5-FU in combination with LV. 5 patients were not evaluable for response due to early discontinuation of treatment

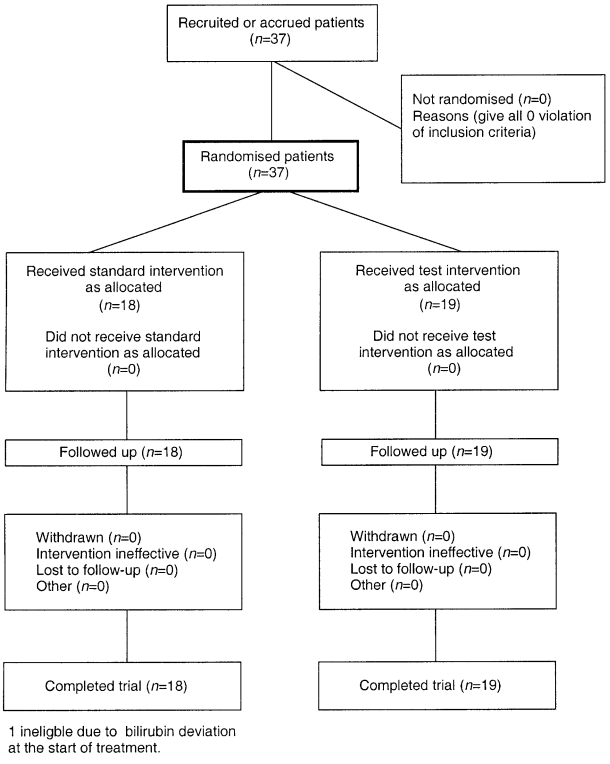

Fig. 2. Flow chart of the progress of patients through the trials (adapted from Ref. [22]).

Table 1
Characteristics of eligible patients according to study entry

Characteristics	Oral UFT ($n=19$)	i.v. 5-FU ($n=17$)
	No. (%)	No. (%)
Age (years)		
Median (range)	58 (33–73)	60 (39–82)
Sex		
Male	14	13
Female	5	4
Performance status		
WHO		
0	11	9
1	7	7
2	1	–
Unknown	–	1
Prior treatment for malignancy		
Prior surgery	18 (95)	16 (94)
Prior radiotherapy	3 (16)	2 (12)
Prior adjuvant chemotherapy	6 (32)	4 (24)
Response evaluation		
Patients evaluable for response	17	14
CR + PR	4	2
SD	11	8
PD	2	4
Therapy Preference Questionnaires		
Patients evaluable	17	14

i.v., intravenous; 5-FU, 5-fluorouracil; WHO, World Health Organization; CR; complete response; PR, partial response; SD, stable disease; PD, progressive disease.

because of toxicity [3], brain metastases diagnosed shortly after starting UFT/LV [1] and non-measurable disease [1]. The results of the response evaluation are summarised in Table 1. Overall, 6 out of 31 (19%; 95% Confidence Interval (CI): 7.45–37.47%) evaluable patients responded to the first two treatment cycles. Table 2 summarises the toxicities, which were experienced during the initial treatment course with i.v. 5-FU/LV and oral UFT/LV, respectively. Generally, patients experienced less stomatitis and haematological toxicity with UFT/LV.

3.1. Patient preference

31 out of the 36 patients were evaluable for the TPQ. The remaining 5 patients went off-study prior to the completion of the post-treatment TPQ. 3 of these patients went off-study due to toxicity, 1 patient was not evaluable because of early tumour progression and 1 other patient was not evaluable due to a technical artifact of the computed tomography (CT) scan.

Overall, 84% of the evaluable patients preferred the oral treatment with UFT/LV over i.v. 5-FU/LV. The treatment sequence did not influence the choice of regimen on which patients wished to continue treatment in cases of tumour response after two treatment cycles. Of the patients randomised to start treatment with UFT/LV, 88% preferred to continue therapy on this regimen compared with 79% of the patients who were randomised to 5-FU/LV first. On a 0–5 scale, the mean strength of preference was 4.12 for the choice of UFT/LV compared with 3.40 for patients preferring i.v. 5-FU/LV.

Table 2
Toxicity in the first treatment cycle with the respective therapy

Toxicity	Oral UFT ($n=31$)		IV 5-FU ($n=31$)	
	All grades	WHO 3/4	All grades	WHO 3/4
Nausea	10	0	9	0
Vomiting	7	0	4	1
Diarrhoea	10	0	12	1
Stomatitis	4	0	17	4
Leucopenia	3	0	18	6
Neutropenia	1	0	18	14

WHO, World Health Organization; i.v., intravenous; 5-FU, 5-fluorouracil.

As described in the Methods, scores were used to weight the relative importance of the features which patients indicated to influence their choice of treatment. The results of the pretreatment TPQ are summarised in Table 3. Before being exposed to any chemotherapy, patients were worried most about the possible occurrence of side-effects. It was considered desirable that a treatment would cause no infections, vomiting, or diarrhoea. Whether the medication could be given at home ranked only fourth after this concern for side-effects. The more specific question on treatment administration, whether it was important that the 'medication is a pill' reached only sixth place among possible factors influencing treatment preference. The results of the post-treatment TPQ are summarised in Table 4. Patients who preferred oral UFT/LV now indicated two features associated with the mode of administration among their four most important selection criteria. The experience of

Table 3
Factors to potentially influence patient preference assessed at pre-treatment TPQ

Factor	Relative frequency score
Does not increase your risk of infection	15.4
Does not make you vomit	15.2
Does not give you diarrhoea	11.8
The medication is taken at home	9.8
Does not cause painful sores in the mouth	9.1
The medication is a pill	7.4
Does not affect your mood	6.4
Does not interfere with your daily activities	6.3
Does not make you feel nauseated	3.8
Medicine is taken at doctor's office/hospital	2.0
Does not make you feel tired	1.6
Medication is given by injection	0.8

Table 4
Patient preference at post-treatment TPQ

Factor	Relative frequency score
The medication is taken at home	14.4
Does not cause painful sores in the mouth	10.5
Does not give you diarrhoea	8.0
The medication is a pill	7.8
Does not interfere with your daily activities	7.0
Does not make you vomit	6.1
Does not make you feel nauseated	4.5
Does not increase your risk of infection	4.0
Does not make you feel tired	3.2
Does not affect your mood	2.7
My cancer got better while taking it	2.5
Medicine is taken at doctor's office/hospital	0.8
I thought it was the stronger medicine	0.4
Others (family, friends) preferred it	0.4
Medication is given by injection	0

stomatitis, which is typically associated with i.v. 5-FU/LV, ranked second. Among the 5 patients who preferred i.v. 5-FU/LV, this choice was most importantly influenced by the fact that the treatment was given as an injection, followed by oral UFT/LV associated toxicity features. Interestingly, efficacy features such as "my cancer got better" or "I thought it was a stronger medicine" ranked overall very low as a reason for patient preference.

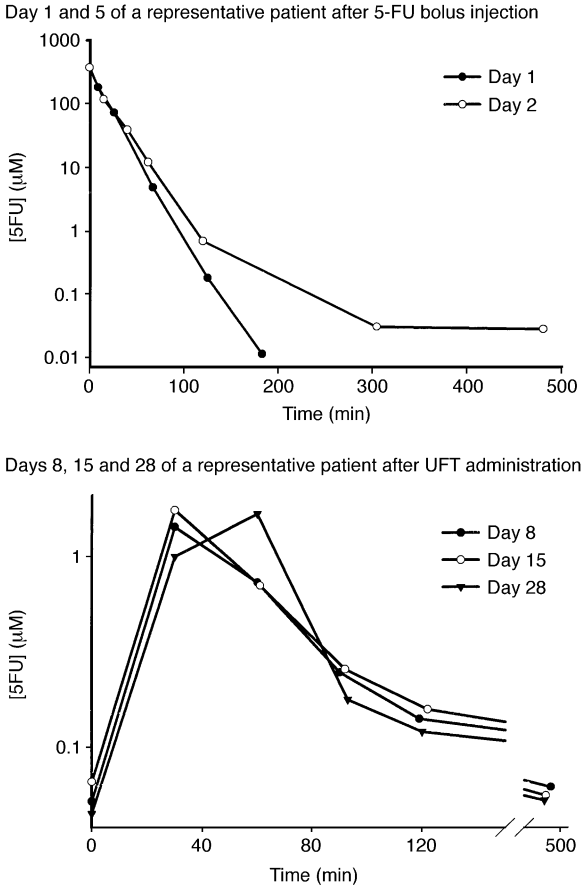

Fig. 3. Representative plasma 5-FU concentration versus time curve.

3.2. Pharmacokinetics

Blood samples for pharmacokinetic analysis of 5-FU after administration of either i.v. 5-FU/LV or oral UFT/LV were available for 35 patients. The UFT samples were not evaluable in 3 patients. Day 8 samples were missing from 3 patients, samples were also not available from 8 patients on day 15, 24 patients on day 22 and from 5 patients on day 28. From i.v. 5-FU, all samples were available and could be analysed. The results of the pharmacokinetic analyses are summarised in Table 5. With oral UFT, the mean AUC for 5-FU was 113 μM×min on day 8, 114 μM×min on day 15, 166 μM×min on day 22, and 98 μM×min on day 28. These values were not statistically different. With i.v. 5-FU, the mean AUC values for 5-FU were 3083 uM×min on day 1 and 3809 uM×min on day 5 ($P=0.002$, using a non-parametric one-tailed Wilcoxon test). Representa-

Table 5
Pharmacokinetic parameters of 5-FU after adminstration of UFT and 5-FU[a]

		AUC (μM×min)	Cmax (μM)	$T_{1/2}$ (min)	Clearance (l/min)
i.v. 5-FU					
Day 1	(35)[b]	3083±1756	170.1±107.4	10.5±2.1	2.6±1.6
Day 5	(35)	3809±1576	196.2±89.1	11.9±2.3	1.9±1.0
P (d1/d5)[c]		0.002	0.06	0.002	0.002
Oral UFT					
Day 8	(29)	113±80	1.2±0.9	36±25	
Day 15	(24)	114±65	1.3±0.8	27±9	
Day 22	(8)	166±113	1.2±0.7	45±28	
Day 28	(27)	98±39	1.0±0.7	36±21	

5-FU, 5-fluorouracil; i.v. intravenous; AUC, area under the plasma concentration curve; $T_{1/2}$, half-life.
[a] Results are means±standard deviation.
[b] Number of available samples.
[c] Probability of a statistical difference between day 1 and day 5.

tive examples of plasma 5-FU over time curves after oral UFT and i.v. 5-FU are depicted in Fig. 3.

The 5-FU peak levels were 1.2 μM on day 8, 1.3 μM on day 15, 1.2 μM on day 22, and 1.0 μM on day 28 with oral UFT. With i.v. 5-FU, the respective values were 170.1 μM on day 1 and 196.2 μM on day 5 ($P = 0.06$). This translated into an elimination half-life of 10.5 min on day 1 and 11.9 min on day 5 for i.v. 5-FU ($P = 0.002$). The difference of the day 1 and 5 clearance for i.v. 5-FU also reached statistical significance ($P = 0.002$).

4. Discussion

This is the only trial to date to assess the preference for oral or i.v. anticancer treatment in patients who experienced both routes of drug administration. It demonstrates a striking patient preference for oral compared with i.v. chemotherapy. The randomised crossover design of this study assured that the number of patients starting with oral or i.v. therapy, respectively, was balanced and that the choice of treatment sequence was unbiased. Since patients were asked to indicate the most important reasons for their choice before and after they actually experienced both oral and i.v. therapy, we were able to analyse their motives in more detail. Before the onset of chemotherapy, patients were most concerned about the possible side-effects of cancer treatment such as infections, vomiting or diarrhoea. This choice was dominated by the side-effects which are most commonly associated with anticancer treatment [14] and less familiar problems such as stomatitis were less frequently cited. The option of a treatment which could be given at home ranked only fourth after these toxicity concerns. The more specific choice of oral treatment was even less important to patients before they started therapy, since it ranked only sixth among factors which were considered influential for the preference of oral or i.v. treatment. Thus, the choice of chemotherapy-naïve patients was clearly dominated by the fear of toxicity, which reflects the prevalent perception of chemotherapy among patients and in the general population [14].

After experiencing both treatment options, patients more clearly indicated specific administration related features to influence their preference of oral or i.v. treatment. This is interesting in view of the pretreatment selection attitude, since oral UFT/LV and i.v. 5-FU/LV as administered in this study were not equitoxic. i.v. 5-FU/LV led to significantly more stomatitis and haematological toxicity, while oral UFT/LV was associated with slightly more diarrhoea and the same level of nausea/vomiting as the i.v. treatment. These results are corroborated by the two large phase III trials which established oral UFT/LV as equally effective, but safer compared with the i.v. Mayo regimen in metastatic colorectal cancer [8,9]. Still, the individual toxicity experience did influence the preference, since stomatitis and diarrhoea ranked second and third as potential factors to influence the choice of oral or i.v. treatment, respectively. At the pretreatment evaluation, stomatitis ranked only fifth after other better-known side-effects of chemotherapy and the possibility to take the treatment at home. Another indication that the individual toxicity experience had an influence on the choice of treatment was the fact that a disproportionally high incidence of diarrhoea and nausea/vomiting was observed among the few patients opting for i.v. 5-FU/LV in our study. The most frequently stated reasons to influence patient preference after experiencing both treatment choices were "I preferred to take the medication at home", "I had fewer mouth sores", "I had less diarrhoea" and "I preferred it was a pill". This change of attitude compared with their pretreatment selection indicates that patients became appreciative of the route of administration as a specific quality of an anticancer treatment only after experiencing the reality of both the oral and i.v. treatments.

Another trial suggesting a strong patient preference for oral treatment has been published by Liu and colleagues [10]. These investigators used scenario-based questionnaires in 103 patients who were likely to undergo palliative cancer treatment in the near future. In that study, 89% of the patients preferred oral chemotherapy. Only 10% preferred i.v. treatment, mainly because they did not want to deal with the drug administration themselves or because they worried about their own compliance. The major reasons to opt for oral treatment were convenience, fear of problems associated with the i.v. line or needles and a better environment for drug administration at home. However, patients in the trial by Liu and colleagues had no real chemotherapy experience and the questionnaire contained mainly questions, which linked side-effects to specific routes of administration only (e.g., "I would be concerned about vomiting up the pills") compared with the open questions in our questionnaire ("the treatment does not make you vomit"). Thus, the specific wording of the questionnaires might have strongly contributed to the fact that patient preference in the study by Liu and colleagues was more clearly influenced by administration issues compared with the fear of toxicity in our trial.

Interestingly, in the study by Liu and colleagues, most patients were not willing to sacrifice efficacy for convenience. 25% of patients refused to give up a mere 5% efficacy in terms of response rate and 34% were not willing to trade off even 1 month of response duration for convenience [10]. Our study did not include a formal trade-off analysis. However, efficacy features such as "my cancer got better" or "I thought it was a stronger medicine" ranked overall very low as a reason for

patient's preference. This suggests that efficacy was not a major issue for the choice of treatment. A possible explanation for this discrepancy is that the patient consent form of our study contained specific information about the palliative nature of the treatment. In addition, patients were informed that oral and i.v. treatment were probably equally effective. This may have made patients less concerned about a potential difference in efficacy. In contrast, the fact that a trade-off was suggested in the study by Liu and colleagues made the possibility of an efficacy difference between oral and i.v. treatment very real.

This is the only trial in the literature to compare 5-FU pharmacokinetics in patients receiving both the Mayo regimen (bolus i.v. 5-FU) and oral UFT. Bolus i.v. 5-FU led to a significantly higher 5-FU AUC indicating a higher 5-FU exposure compared with oral UFT. This held true even if the total 5-FU exposure was projected over a whole treatment cycle including the drug-free intervals. In addition, the 5-FU peak concentrations reached levels more than 100 times higher with i.v. 5-FU compared with oral UFT. Since large phase III studies have confirmed the higher toxicity and equal efficacy of i.v. 5-FU in comparison to oral UFT, this indicates that a high 5-FU exposure may not be necessary for tumour response, but may translate into toxicity. Our study was too small to correlate toxicity with 5-FU drug levels, although we observed that exposure to more than 5000 μM×min 5-FU was associated with toxicity for most of the patients. Toxicity, however, was not confined to patients with high drug exposure. It was not possible to see such an association with oral UFT, since blood sampling was typically not completed in patients experiencing major toxicity. Our results confirm the previously published saturable elimination for i.v. 5-FU, since AUC and 5-FU half-life significantly increased from day 1 to day 5 of i.v. drug administration. This has not been shown for the 5-day bolus administration schedule, but suggested for other forms of 5-FU administration [15]. Previous observations have shown that 5-FU elimination is not completed after 24 h, when the next i.v. 5-FU administration took place in our study [16]. 5-FU can still be present at levels up to 0.1 μM 24 h after injection. Theoretically, this 5-FU retention could translate into an AUC increase of 48 μM×min per day, accumulating to an AUC of 240 μM×min after 5 days. In addition, 5-FU can accumulate in tissue at 1–10 μM both as a free drug [12] and incorporated into RNA [11] and this fraction can be released into the plasma over time. This drug accumulation will increase with each administration as observed in our study over 5 days.

The concept that continuous exposure to 5-FU may make up for lower drug levels and may even be more beneficial in terms of efficacy has drawn much attention in view of the large variety of existing 5-FU administration schedules [1]. Preclinical experiments suggest that plasma 5-FU levels below 1 μM are sufficient to induce cytotoxicity in cancer cells if these low concentrations are maintained for a prolonged time period [1]. A meta-analysis of trials comparing bolus 5-FU administration to continuous infusion has demonstrated higher response rates, a slight increase in overall survival and less toxicity with continuous infusion 5-FU [4]. A 5-FU plasma steady-state concentration of 0.6 μM has been reached with continuous infusion of 250 mg/m^2/day 5-FU and increasing the dose to 2500 mg/m^2/day has led to a proportionally higher 5-FU level of 6.6 μM [17,18]. However, an important drawback of continuous i.v. infusion is the need for implantable access devices and portable infusion pumps. Our results demonstrate that oral administration of UFT translates into 5-FU drug levels which are comparable to the levels attainable with continuous infusion 5-FU. This is in accordance with the results of other studies demonstrating 5-FU peak levels of 1.4–2.3 μM and AUC values of 90–220 μM×min with 350–370 mg/m^2/day UFT [17,19]. Interestingly, in these patients, no accumulation of 5-FU was observed during the 28-day treatment period.

The hand–foot syndrome (palmar-plantar erythrodysesthesia) is a typical and very unpleasant side-effect of prolonged 5-FU administration by continuous i.v. infusion [20] or of other oral fluoropyrimidines such as capecitabine [7]. In view of the comparable 5-FU plasma concentrations achieved with all of these prolonged fluoropyrimidine administration options [21], it is remarkable that UFT administration is only rarely complicated by palmar-plantar erythrodysesthesia. Although this explanation is speculative at the moment, the inhibitory effect of uracil on dihydropyrimidine dehydrogenase might provide a protective effect against hand-foot syndrome. This suggests that some of the 5-FU catabolites are responsible for this toxicity. These metabolites may be excreted by sweat thus explaining the local preference for the palms of the hands and the soles of the feet. Provided equal efficacy, this lack of associated palmar-plantar erythrodysesthesia might be an advantage of UFT over other options for prolonged fluoropyrimidine administration.

This study shows a clear patient preference for oral chemotherapy in advanced colorectal cancer. The most important reasons for this choice were convenience and toxicity considerations of the patients, which were both in favour of oral UFT treatment. Although the pharmacokinetic analyses of our study clearly demonstrate higher peak 5-FU concentrations and AUC values with i.v. 5-FU/LV, this pharmacokinetic advantage did not translate in either higher toxicity or a beneficial effect on efficacy, in line with the results of large randomised studies comparing oral UFT/LV with i.v. 5-FU/LV. Thus, oral UFT/LV compares favourably with i.v. 5-FU/LV in terms of toxicity and patient preference and leads to prolonged 5-FU exposure, which is comparable to continuous i.v. 5-FU treatment.

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Appendix A. Pretreatment therapy preference questionnaire

Often there are several possible choices of medication to treat a single disease. In this study you will be taking two medications which we believe to be similar in their effect on this kind of cancer. When medications are being developed it is important to consider how well they fight disease, and it is also important to consider how well they work in other ways. In order to improve medications and make sure they deliver what you want, we need to understand what is important to you in a medication. To do this priority setting, we will ask you to examine a set of features that a medication might have and by a process of elimination reduce them to the most important ones. This will be done in four steps. Please do not jump ahead. Go through the steps one by one.

Here are 12 features you might want to have in a chemotherapy medication. Some of them are similar, but no two are exactly alike. Please read this list carefully.

A. Does not make you feel tired
B. The medication is given by injection
C. Does not interfere with your daily activities
D. Does not give you diarrhoea
E. The medicine is taken in a doctor's office or hospital
F. Does not increase your risk of infection
G. Does not make you nauseated
H. Does not cause painful sores in the mouth
I. The medication is a pill
J. Does not make you vomit
K. The medicine is taken at home
L. Does not affect your mood

Appendix B. Post-treatment therapy preference questionnaire

On the next few pages are some questions about your preferences in chemotherapy medication. In the last few months you have been treated with two different chemotherapy medicines and you have also had samples of your blood taken. When you are answering the questions on the next few pages please do not consider these blood samples or your visits to the hospital for them to be part of your treatment. Please try to think only about the medications, and how you felt while taking them, and disregard the blood samples which were drawn.

Question 1

You have taken two chemotherapy medications in the past two months, one in the first month and one in the second month. Please circle the medication that you prefer.

the first one the second one

Question 2

The numbers below represent how much you prefer the medication you chose in the question above, on a scale from 1 to 5. '1' means that you have very little preference and '5' means you strongly prefer this medication. Please circle the number which best represents how strongly you prefer the medication you chose.

1	2	3	4	5
no preference				strong preference

Question 3

We would like to get a better understanding of why you chose the medication you did in question 1. In order to do this, we will use a process similar to the one you completed at the beginning of the study. We will give you a list of reasons why you might have preferred the medication you chose. We would like you to tell us which of these items were reasons why you chose this medication and which were not. We will do this by a process of elimination. This will be done in four steps. Please do not jump ahead. Go through the steps one by one.

Please think about why you preferred the medication you choose over the other medication and then read this list carefully. Some of these statements may reflect how you felt, and some may not.

A. I vomited less
B. I had less diarrhoea
C. My cancer got better while taking it
D. I had fewer infections
E. I thought it was stronger medicine
F. I preferred taking the medication in the doctor's office or hospital
G. I preferred that it was a pill
H. The medicine interfered less with my daily activities
I. I preferred taking the medication at home
J. Others (my family or friends) preferred it
K. I preferred that it was an injection
L. I felt less tired
M. I had fewer mouth sores
N. I felt less nauseated
O. It affected my mood less

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