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Patient preference for oral or intravenous chemotherapy: A randomised cross-over trial comparing capecitabine and Nordic fluorouracil/leucovorin in patients with colorectal cancer

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ABSTRACT

Until recently, flourouracil (F) and leucovorin (L) had been considered the standard therapy for patients with colorectal cancer. However, several studies have shown that oral therapy with UFT/L or capecitabine is as effective as intravenous (i.v.) therapy and in addition it is claimed that patients prefer oral to i.v. therapy as long as efficacy is not compromised. In a previous crossover study by Borner et al., it was shown that 26 out of 31 patients preferred oral therapy with UFT/L to i.v. FL (Mayo regimen) [Borner M, Schöffski P, de Wit R, et al. Patient preferences and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002;**38**:349–58]. The objective of the present study was to investigate patient preference between i.v. FL and oral capecitabine using the design described by Borner.

The Nordic FL schedule is a bolus regimen with efficacy comparable to other i.v. regimens and at the same time a very tolerable and easy administered regimen. We randomised 60 patients with colorectal cancer (53 patients received adjuvant therapy and seven patients received palliative therapy) to start therapy with either oral capecitabine or Nordic bolus FL. After 6 weeks of therapy (two courses of capecitabine or three courses of Nordic FL) patients were crossed over to the other regimen. After having completed 12 weeks of therapy the patients (49 evaluable patients) were asked to choose one of the regimens for a further 12 weeks of therapy.

Patients had more side-effect when treated with capecitabine and a total of 30 out of 49 (61%) preferred the Nordic FL regimen and 19 (39%) preferred capecitabine.

We conclude that patients prefer the regimen with less toxicity and that it is of minor importance whether the medication is administrated orally at home or i.v. at the hospital.

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1. Introduction

For more than 40 years a combination of 5-Flourouracil (*F*) and Leucovorin (*L*) has been the most extensively used chemotherapy regimen for patients with colorectal cancer (CRC) both as adjuvant and palliative treatment.[1,2] Many different schedules of F with different doses of L have been developed. F has been given as a continuous infusion, as prolonged infusion (24–48 hours), as a bolus injection (1–5 consecutive days) or as a combination of both.[1,2] In general, bolus regimens are an easier and cheaper way to administer FL.

In the United States, the Mayo regimen (bolus on 5 consecutive days, repeated every 4 weeks) has for many years been the standard regimen serving for comparison with newer regimens.[1,2] However, randomised trials have shown that many other regimens have comparable efficacy (response rate – RR, time to progression – TTP and overall survival – OS) with less toxicity. Therefore, the Mayo regimen is not used as standard treatment anymore. In Europe, modulated infusion regimens are preferred; the most commonly used approach is probably the de Gramont regimen that combines bolus with infusional FL.[1] Numerous studies have been conducted to establish the optimal *F* regimen but without reaching consensus.

The Nordic FL regimen was developed to be an effective and tolerable bolus regimen. The Nordic FL regimen consists of a 3 min bolus injection of *F* followed 30 min later by bolus *L* for 2 consecutive days every 2 weeks. The Nordic FL has not been compared directly to other *F* regimens but from phase III studies, efficacy (RR, TTP, and OS) is comparable to other FL regimens and toxicity is low.[3–6]

Capecitabine (Xeloda) is an oral drug that is converted into *F* in a cascade of three enzymatic steps. Capecitabine was rationally designed to generate *F* preferentially in tumour tissue through exploitation of higher intramural concentrations of thymidine phosphorylase.[7] Side effects are primarily diarrhoea and hand-foot syndrome.

Randomised studies have shown that oral therapy with UFT/L[8–10] or capecitabine[11,12] is as effective as bolus FL therapy. Capecitabine is a well-established alternative to intravenous (i.v.) FL both in the adjuvant and the palliative setting.[2,11,12]

Because of the convenience of oral therapy most patients would be expected to prefer oral rather than i.v. therapy. Initial research showed that patients prefer oral chemotherapy[13] as long as efficacy is not compromised. The principal reasons for these preferences include the convenience of treatment at home, reduced hospitals visits, and avoidance of problems with i.v. lines, as for example, infections.

These results were confirmed in a study by Borner and colleagues.[14] In a cross-over study patients were randomised to oral therapy followed by i.v. therapy or vice versa. After being treated with both regimens patients were asked about their preference and 26 of 31 (84%) preferred oral therapy. However, one explanation to this remarkable result might be that the Mayo regimen (perhaps the most toxic i.v. regimen) was more toxic[16,17] than the UFT/L regimen (perhaps the least toxic regimen).[8,9]

The objective of the present study was to investigate in a randomised trial patient preference between i.v. FL and oral capecitabine using the design described by Borner and colleagues.[14]

2. Patients and methods

In this randomised cross-over study patients received three cycles of Nordic FL followed by two cycles of capecitabine (or visa versa), and patients were asked about their preference (Fig. 1). We planned to include 60 patients, 30 patients receiving adjuvant therapy and 30 patients receiving palliative therapy. However, combination chemotherapy became standard for disseminated disease soon after initiation of our study[2] and therefore we only included seven patients with metastatic disease.

2.1. *Selection of patients*

We included patients with histologically proven adenocarcinoma of the colon or the rectum who were planned for FL-based therapy (oral or i.v. therapy). Other inclusion criterion were the ability to take oral medication, age > 18 years, performance status 0–1, life expectancy of at least 3 months and adequate organ functions (neutrophile count > 1.5×10^9/l, platelet count > 100×10^9/l, bilirubin < 1.25 × upper normal limit (UNL), creatinine < 1.5 × UNL and transaminases < 3 × UNL. However, in patients with liver metastases, total bilirubin was allowed to be 1.5 × UNL and transaminases < 5 × UNL. Patients had given written informed consent and the study was conducted in accordance with the Declaration of Helsinki and the Danish National Ethics Review Board.

Patients were excluded if they had received prior chemotherapy, if they had known involvement of the CNS, chronic diarrhoea or any other serous illnesses like significant

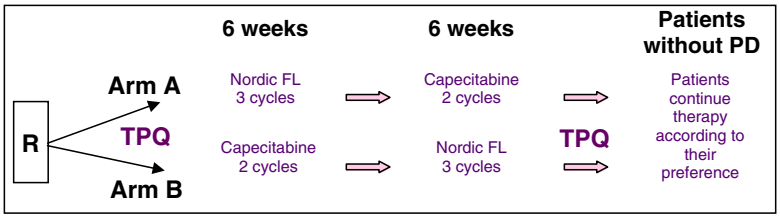

Fig. 1 – Summary of study design – patient preference for oral or i.v. chemotherapy: a randomised crossover trial comparing capecitabine and Nordic fluorouracil/leucovorin in patients with colorectal cancer.

heart disease or cardial infarction within 3 months. Patients were not allowed to receive any other experimental treatment while in the study. Females were not to be included if they were pregnant or lactating. Contraception was required throughout treatment for females of childbearing potential.

2.2. *Treatment and design*

2.2.1. *Intravenous therapy*

The Nordic FL regimen consisted of *F* 500 mg/m^2 i.v. as bolus (3 min) followed 30 min later by *L* (folinic acid) 60 mg/m^2 i.v. bolus (3 min). Both drugs were given day 1 and 2 every 2 weeks.

2.2.2. *Oral therapy*

Capecitabine 1250 mg/m^2 was administered twice daily (total 2500 mg/m^2/day) for 14 days followed by 1 week of rest. After 6 weeks of treatment (two cycles of capecitabine or three cycles of Nordic FL) the patients were crossed over to the other treatment.

The capecitabine dose and FL doses were reduced to 80% for all grade 3 or 4 haematologic and nonhaematologic toxicities. Therapy was withheld until evidence of haematologic recovery and recovery of all nonhaematologic toxicities to baseline or grade 1.

Before the first dose of chemotherapy and after 12 weeks of therapy (two cycles of capecitabine and three cycles of Nordic FL) the patients were asked to complete a Therapy Preference Questionnaire (TPQ). We used the same TPQ as used by Borner[14] but translated into Danish. After 12 weeks patients were asked to choose which of the two regimens they preferred for an additional 3 months. After completion of 6 months of therapy the patients were asked whether they would still prefer the desired regimen.

Therapy was given for 24 weeks unless there was any sign of progression or severe toxicity or the patient wanted to discontinue the therapy. Treatment related toxicity was evaluated according to NCI-CTC version 2.0.

2.3. *Statistics*

Patient preferences were analysed with a Sign test. If 21 out of 30 patients (70%) preferred one treatment from the other this was considered to be significant ($p = 0.04$). Data were summarised in frequency tables and Firsher's test was used to analyse correlations between discrete variables.

3. Results

From December 2002 to December 2003, 60 patients were randomised in five Danish departments. Patient characteristics are listed in Table 1. Chemotherapy was discontinued prematurely during the first 12 weeks of therapy in eleven cases, due to clinical or radiological progression (three patients with metastatic disease), toxicity while receiving FL ($n = 1$) or toxicity while receiving capecitabine ($n = 6$). In addition, one patient did not fill in the TPQ. Thus 49 patients (arm A $n = 23$, arm B $n = 26$) completed at least 12 weeks of chemotherapy and filled in the TPQ before the first course of chemotherapy and after 12 weeks of therapy.

Table 1 – Characteristics of 60 randomised patients

Characteristic	Arm A Nordic FL Capecitabine $n = 30$	Arm B Capecitabine Nordic FL $n = 30$
Age, years		
Median, range	63 (45–79)	69 (36–81)
Adjuvant therapy	26	27
Palliative therapy	4	3
Sex		
Female	14	15
Male	16	15
WHO performance status		
0	26	24
1	4	6
Completed 12 weeks of therapy and filled in Preference Questionaire	23	26

Abdominal ultrasound or CT-scan was performed after 3 months to ensure that there was no sign of progressive disease.

Before the first course of chemotherapy, patients were asked about different factors that might influence their preference for therapy (Table 2), but we did not ask the patients specifically whether they would prefer either i.v. or oral therapy.

After 12 weeks of therapy, 30 patients (61%) preferred Nordic FL and continued with i.v. therapy for a further 3 months whereas 19 patients (39%) preferred capecitabine and continued with oral therapy for an additional 3 months, Table 3 ($p = 0.11$).

At the end of 6 months of therapy four patients stated that they would have chosen the other regimen. Three patients in

Table 2 – Factors that might influence patient preference assessed before therapy ($n = 56$ patients)

	Relative frequency
Does not increase your risk of infection	18 (32%)
Does not make you vomit	25 (45%)
Does not give diarrhoea	24 (43%)
The medication can be taken at home	22 (39%)
Dose not cause painful sores in the mouth	19 (34%)
The medication is a pill	19 (34%)
Does not affect your mood	18 (43%)
Does not interfere with your daily activities	29 (52%)
Dose not make you feel nauseated	18 (43%)
Medicine is taken at hospital	10 (18%)
Does not make you feel tired	25 (45%)
Medication is given by injection	3 (5%)
Does not cause pain	24 (43%)

Table 3 – Patient preference, *n* = 49

Randomisation group	No. of patients preferring oral therapy (%)	No. of patients preferring i.v. therapy (%)
Arm A		
Nordic FL × 3 followed by capecitabine × 2: *n* = 23	7 (30%)	16 (70%)
Arm B		
Capecitabine × 2 followed by Nordic FL × 3: *n* = 26	12 (46%)	14 (54%)
Total, *n* = 49	19 (39%)	30 (61%)

arm B would have chosen oral therapy and one patient in arm A would have chosen Nordic FL.

The treatment sequence did to some degree influence the patients' preference. In arm B (patients commencing with capecitabine) 46% preferred to continue with oral therapy while in arm A (patients commencing with Nordic FL) only 30% of patients preferred to continue with oral therapy.

The median strength of preference was high for both regimens (most often grade 4 or 5).

After 12 weeks of therapy there were several different factors of importance that determined what kind of treatment the patients chose.

The major reasons for a preference of oral therapy included. 'I preferred a pill' and 'I preferred taking the medication at home'.

On the other hand, the major reasons for a preference of i.v. therapy were 'I had less diarrhoea', 'I felt less nauseated', 'I felt less tired' and 'Medicine interfered less with my daily activities'.

Both regimens were well-tolerated (Table 4). It seems as if the treatment sequence does influence toxicity. In patients randomised to arm A (Nordic FL followed by capecitabine) only two cases of grade 3 toxicity were noticed during Nordic FL but 11 cases of grade 3 toxicity were seen during capecitabine (diarrhoea = 5, hand-foot syndrome = 4, nausea = 1, vomiting = 1) ($p = 0.05$). In contrast, the total number of grade 3 toxicities in patients randomised to arm B (capecitabine follow by Nordic FL) did not differ between capecitabine (5/26) and Nordic FL (4/26).

4. Discussion

The present work compared patient preference when capecitabine was compared with a less toxic i.v. FL regimen (Mayo regimen). The optimal FL regimen has yet to be established and there has not been consensus of which FL regimen is the most effective with the least toxicity. The Nordic FL regimen has not been compared directly with other FL regimens and is therefore not well known outside the Nordic countries. However, several phase III studies indicate that efficacy (RR, TTP, and OS) is comparable to other FL regimens and toxicity is low.[3–6]

Several randomised studies and pooled analysis have demonstrated that adjuvant FL increases 5-year overall survival in patients with colon cancer Dukes C[1,2] and comparable results can be obtained with either capecitabine or UFT/L.[1] Even though the Nordic Fl regimen has not been

Table 4 – Worst toxicities per patient during the first 6 weeks of therapy (two cycles of capecitabine and three cycles of Nordic FL or vice versa), *n* = 49 evaluable patients

	Nordic FL		Capecitabine	
	All grades	Grade 2/3	All grades	Grade 2/3
Arm A: Nordic FL × 3 followed by capecitabine × 2, n = 23				
Nausea	14	1	12	3
Vomiting	12	1	12	4
Diarrhoea	9	2	15	6
Stomatitis	9	0	10	2
Hand foot syndrome	5	1	20	13
Thrombocypenia	0	0	0	0
Neutropenia	5	1	2	2
	Capecitabine		Nordic FL	
Arm B: Capecitabine × 2 followed by Nordic FL × 3, n = 26				
Nausea	8	1	7	1
Vomiting	7	1	6	1
Diarrhoea	9	5	10	4
Stomatitis	4	0	5	0
Hand foot syndrome	10	7	12	5
Thrombocypenia	0	0	0	0
Leucopenia	1	1	2	1

compared to other regimens, a recent study indicates that comparable results can be obtained with the Nordic FL regimen.[15]

Liu and colleagues documented that cancer patients clearly preferred oral chemotherapy for their palliation rather than i.v. treatment just by asking them.[13] Borner and colleagues[14] confirmed these results in a randomised crossover trial and found that patients preferred oral therapy (UFT/L) to i.v. therapy (Mayo regimen). The reasons for this preference, after being exposed to both treatments, were primarily lower toxicity and home administration.[14] The Mayo regimen is probably the most toxic FL regimen and perhaps side-effects are not comparable to the side-effects of oral UFT/L.

In a recent cross-over study by Twelves and colleagues[18] patients were randomised to receive oral capecitabine or i.v. FL (Mayo regime or de Gramont as inpatient or de Gramont as outpatient). Before treatment, most patients (79%) expressed a preference for oral therapy and only 4% preferred i.v. therapy. Following completion of both treatments 58% of patients retained their preference for oral treatment, 31% preferred i.v. therapy and 10% were ambivalent. The most interesting part was that there was a difference between the groups receiving the two regimes. Among patients randomised to the Mayo regimen, 86% preferred oral treatment after receiving one course of oral therapy and one course of i.v. therapy. Among patients receiving the de Gramont schedule, fewer patients (inpatients 62% and outpatients only 50%) retained their preference. The de Gramont regimen is better tolerated than the Mayo regimen[16] and therefore these results could imply that patients prefer the regimen with the fewest side-effects.

In the present study 30 patients (61%) preferred and continued with the Nordic FL regimen. We observed a lower toxicity profile for the i.v. FL as compared with the oral capecitabine. Major reasons for preference for i.v. treatment were less diarrhoea, less nausea and less fatigue. Our results are very similar to the results obtained by Twelves and colleagues who reported that half of their patients receiving the deGramont schedule as outpatients preferred i.v. therapy.[18] In accordance with the results of Twelves and colleagues, it seems that patients prefer the regimen with the least toxicity.

Rocha Lima and colleagues[19] also randomised patients to oral (UFT/L) or i.v. therapy (5 days regimen) but in contrast to the Mayo regimen, the daily dose of F was reduced from 425 mg/m^{2}to 350 mg/m^2. Despite this fact, results were similar to the Borner data. The majority of patients (18 out of 20) chose oral therapy. They concluded that patients chose the oral regime because of the lower toxicity and because of convenience. Again, the results and conclusion imply that the degree of side-effects seems to play an important role for the patient preference and not only the fact that oral therapy offers a lot of convenience.

In summary, we believe that patients prefer the regime with least toxicity and that it is of minor importance if the medication is administrated at the hospital or at home. By giving the patients a choice between oral or i.v. treatment, patients often sense a feeling of control over the treatment and thereby control of their life.

Conflict of interest statement

None declared.

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