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Original Paper

Bolus Injection (2–4 min) Versus Short-term (10–20 min) Infusion of 5-Fluorouracil in Patients with Advanced Colorectal Cancer: a Prospective Randomised Trial

B. Glimelius,[1] A. Jakobsen,[2] W. Graf,[3] Å. Berglund,[1] C. Gadeberg,[2] P. Hansen,[4] M. Kjaer,[5] N. Brunsgaard,[5] E. Sandberg,[6] B. Lindberg,[7] H. Sellström,[8] T. Lorentz,[9] L. Påhlman,[3] and B. Gustavsson[10] for the Nordic Gastrointestinal Tumour Adjuvant Therapy Group

[1]Department of Oncology, Akademiska sjukhuset, Uppsala, Sweden; [2]Department of Oncology, Veile Sygehus, Denmark; [3]Department of Surgery, Akademiska sjukhuset, Uppsala, Sweden; [4]Department of Oncology, Århus; [5]Department of Oncology, Aalborg; [6]Department of Oncology, Esbjerg, Denmark; [7]Department of Surgery, Kungälv; [8]Department of Surgery, Säffle; [9]Department of Surgery, Ludvika; and [10]Department of Surgery, Östra sjukhuset, Gothenburg, Sweden

The use of bolus 5-fluorouracil (5-FU) as a short-term infusion over 10–30 min is increasing at the cost of a push injection, mainly due to practical advantages. Since even a short prolongation of the administration time results in lower 5-FU peak and area under the curve (AUC) levels, there might be a risk of decreased efficacy. The aim of this study was to compare a rapid intravenous (i.v.) 5-FU injection and a short-term 5-FU infusion with respect to objective responses and toxicity in patients with advanced colorectal cancer. 203 patients with measurable advanced colorectal cancer were randomised to bolus 5-FU either as an injection for 2–4 min or as a short-term infusion lasting 10–20 min. In both groups, the 5-FU dose was 500 mg/m^2 and leucovorin 60 mg/m^2 was given 40 min after the start of 5-FU. Treatment was given on two successive days every other week until progression. Objective tumour regression was seen in 27/100 (27%) in the injection group and in 13/103 (13%) in the infusion group ($P = 0.02$). Severe toxicity was rare and did not differ significantly between the groups. Progression-free survival tended to be longer in the injection group ($P = 0.07$), but overall survival did not differ between the groups. Bolus 5-FU should be administered as a rapid i.v. injection rather than as a short-term infusion, since the former rate of administration results in a higher response rate without being significantly more toxic. **© 1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

5-FLUOROURACIL (5-FU) is the most widely used drug in the treatment of patients with colorectal cancer [1]. It is also extensively used in other tumour types. If 5-FU is combined with leucovorin (LV) or methotrexate, the clinical effect is enhanced. In advanced colorectal cancer, the combined treatment usually results in an objective tumour regression in approximately 25–30% [1–3]. A great number of treatment schedules exists, but which is optimal is not known [4]. Two principal methods of intravenous (i.v.) administration have been used, i.e. a bolus injection or a continuous infusion for one or several days. While the rate of administration during continuous infusion has been well defined, the exact method for bolus injection is usually not precisely described. The use of short-term infusions for 10–30 min by mini-bags, has, in many instances, replaced the push injection using a syringe, promoted by commercial and hygienic interests and claims of increased tolerability. It is not known how common this increase in administration time is, although it is likely that

Correspondence to B. Glimelius.
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this modification has become the rule rather than the exception. However, it is not known if the anti-tumour effects are compromised by a prolongation of the administration time. A retrospective analysis of a recent Nordic multicentre trial [5] revealed that a short-term infusion was followed by a lower response rate and a somewhat decreased incidence of side-effects as compared to a rapid injection [6].

Considering the rapid catabolism of 5-FU and its fast disappearance from the circulation [7], it is conceivable that a short-term infusion could result in a lower cytotoxic effect. A recent study also showed that 5-FU peak levels and area under the curve (AUC) values are lowered after a short-term infusion of 15 min compared to an i.v. injection of 3 min [8]. The clinical impact of the rate of 5-FU administration during bolus injection has not, to our knowledge, previously been studied in a controlled trial. In spite of this lack of knowledge, it has recently been stated that a rapid injection is preferable to a short-term infusion [9]. Considering the widespread use of 5-FU both in the palliative and adjuvant settings, this hypothesis deserves to be tested in a controlled trial. The most rapid way to test this issue is to study objective response rates in advanced measurable disease.

The present study was designed to compare bolus 5-FU given as a 2–4 min injection or as a 10–20 min infusion with respect to objective response rates and toxicity. These times were selected since they adhere to general clinical routines of giving a 5-FU bolus dose of 750–1000 mg either as an injection of 15–20 ml over 2–4 min or as an infusion lasting 10–20 min using a 50–100 ml mini-bag.

PATIENTS AND METHODS

Study population

Patients with recurrent or primarily uncurable, histopathologically verified colorectal cancer and bidimensionally measurable disease were eligible after informed consent. Exclusion criteria were: age ≥ 75 years, previous chemotherapy, other primary tumours, except basal carcinoma of the skin or a cervix cancer *in situ*, S-creatinine ≥ 120 μmol/l, or S-bilirubine ≥ 40 μmol/l. 203 patients were included between October 1993 and May 1995 at 11 participating Scandinavian centres (five in Denmark and six in Sweden). Patients were randomly allocated to one of two parallel treatment groups which were well balanced with respect to patient characteristics of potential prognostic importance [10] (Table 1).

Table 1. *Patient's characteristics*

	Bolus injection ($n = 100$)	Short-term infusion ($n = 103$)
Sex		
Men	44 (44)	59 (57)
Women	56 (44)	44 (43)
Mean age (years) (range)	58 (27–75)	60 (29–75)
Site		
Colon	68 (68)	62 (60)
Rectum	32 (32)	41 (40)
Mean no. of tumour sites (range)	1.1 (1–4)	1.1 (1–2)
B-haemoglobin (g/L) (range)	115 (78–155)	116 (77–155)
Metastases		
Hepatic	69 (69)	63 (61)
Lung	16 (16)	22 (21)
Peritoneal	5 (5)	3 (3)
Local growth	5 (5)	7 (7)
Miscellaneous	13 (13)	12 (12)

Figures are number of patients and (percentages) unless otherwise indicated.

Treatment and evaluation of treatment effects

All patients received i.v. 5-FU 500 mg/m^2 and LV 60 mg/m^2 as an i.v. push injection 30–40 min after the start of 5-FU administration [5]. The protocol stated that 5-FU was injected for 3 (range 2–4) min with a syringe in the injection group, whereas 5-FU was infused using a mini-bag system for 15 (10–20) min in the infusion group. The exact outfit of the mini-bag system was not determined in the protocol, but 5-FU could be infused by gravity or an infusion pump. Treatment was given on two successive days every other week until progression. The first response evaluation was carried out after four courses (2 months) and repeated evaluations after every four courses, as previously described [5]. If the treatment was interrupted, repeated evaluations were performed every second month until disease progression. Tumour regression had to be present at two consecutive evaluations to qualify as a response. The index lesions, i.e. the three largest measurable lesions, were assessed with computed tomography (CT) scans, ultrasonography, X-ray, or, rarely, palpation for determination of area. Objective responses were evaluated according to UICC criteria [11] and toxicity according to WHO criteria [12]. Briefly, a complete remission (CR) implied disappearance of all disease, a partial remission (PR) was present when the area had decreased by at least 50% without the appearance of new lesions. Stable disease (SD) was present when the change in size was between a 50% decrease and a 25% increase and designated SD4 when the disease stabilisation lasted for a minimum of 4 months and SD2 when the duration was between 2 and 4 months. In all other instances, progressive disease (PD) was recorded. All responses were independently reviewed. Second-line therapy after progression on 5-FU + LV was permitted. The date of tumour progression was recorded as the date of radiologically verified tumour enlargement, or, in a few cases, when this was clinically evident.

Statistical methods

A sample size of 120 patients was decided upon to be able to detect an increase in response rate from 10% after short-term infusion to 30% after bolus injection with a significance level of 5% and a power of 80%. The final number of randomised patients outnumbered the planned sample size, since the present trial continued to accrue patients while waiting for the authorities' approval of a new trial. Differences in proportions were evaluated using the χ^2-test with Yates correction and numerical differences by Student's *t*-test. Survival curves were constructed by the actuarial method and differences between the curves were assessed by the log rank test. All analyses were performed on the intention-to-treat basis.

RESULTS

Objective responses

There were 27/100 (27%) objective responses in the injection group compared to 13/103 (13%) in the infusion group ($P = 0.02$, χ^2-test). There was a larger proportion of patients with SD4 in the infusion group (Table 2).

Table 2. Objective responses in the bolus injection and short-term infusion groups

	Bolus injection ($n = 100$)	Short-term infusion ($n = 103$)
Complete response	4 (4)	1 (1)
Partial response	23 (23)	12 (12)
Stable disease (4 + months)	23 (23)	35 (34)
Stable disease (2–4 months)	16 (16)	12 (12)
Progressive disease	33 (33)	43 (42)

Table 3. Toxicity in the bolus injection and short-term infusion groups

WHO grade		Bolus injection ($n = 100$)	Short-term infusion ($n = 103$)
Leucopenia	I–II	9 (9)	6 (6)
	III–IV	0 (0)	2 (2)
Thrombocytopenia	I–II	2 (2)	2 (2)
	III–IV	0 (0)	0 (0)
Nausea	I–II	5 (5)	7 (7)
	III–IV	0 (0)	0 (0)
Stomatitis	I–II	27 (27)	20 (19)
	III–IV	1 (1)	0 (0)
Diarrhoea	I–II	24 (24)	36 (35)
	III–IV	6 (6)	1 (1)
Alopecia	I–II	5 (5)	3 (3)
	III–IV	0 (0)	0 (0)
Conjunctivitis	I–II	6 (6)	8 (8)
	III–IV	0 (0)	0 (0)

Toxicity

The average number of treatment courses was 8.3 (range 0–22) in the injection group and 8.6 (1–21) in the infusion group. Severe toxicity was rare, but grade 3–4 diarrhoea tended to be more common in the injection group (6/100 versus 1/103, $P = 0.11$, χ^2-test). There was no treatment related mortality. Mild diarrhoea was the most frequent toxicity, followed by stomatitis, with no differences between the treatment groups (Table 3). Dose reductions due to toxicity, mainly stomatitis and/or diarrhoea, were necessary in 11 patients (11%) in the injection group and in 9 patients (9%) in the infusion group ($P = 0.76$, χ^2-test), after a median of three and four courses, respectively.

Time to progression and survival

The median time to progression was 5.5 (range 0.6–24.3) months in the injection group, and 4.2 (0.5–22.3) months in the infusion group ($P = 0.07$, log rank test, Figure 1). The median survival after randomisation was 9.5 (0.6–30) months in the injection group and 9.5 (0.8–29) months in the infusion group ($P = 0.73$, log rank test, Figure 2).

DISCUSSION

Short-term infusion using mini-bags is a practical and, for hospital staff, a safe method for administration of chemotherapeutic agents, since the drug is kept in a closed system and nurses can leave the patient while infusing the drug. These aspects may explain the growing world-wide popularity of this mode of administration over the last 5–10 years. For other cytotoxic drugs, such as doxorubicin, it has also been shown that this form of administration does not impair the therapeutic effect; in fact it has therapeutic advantages due to a reduction in side-effects [13].

This study indicates that the efficacy of 5-FU is less when the drug is infused for approximately 15 min as compared to a rapid injection over 3 min. The results in the injection arm are in agreement with previous studies using the same regimen. The differences with respect to response rates in this prospective study were also in agreement with the findings of a previous retrospective study [6]. There is also a pharmacokinetic rationale for this finding, since both peak levels and AUC values are reduced with the former rate of administration [8]. This can probably be explained by the limited capacity of the 5-FU degrading enzyme dehydropyrimidine-dehydrogenase. Following a rapid injection of the drug, the enzyme capacity might be saturated allowing relatively more 5-FU to be anabolised and activated.

The results of the retrospective study created great uncertainty among clinicians and nurses at several hospitals where mini-bags were used for all chemotherapy infusions. In

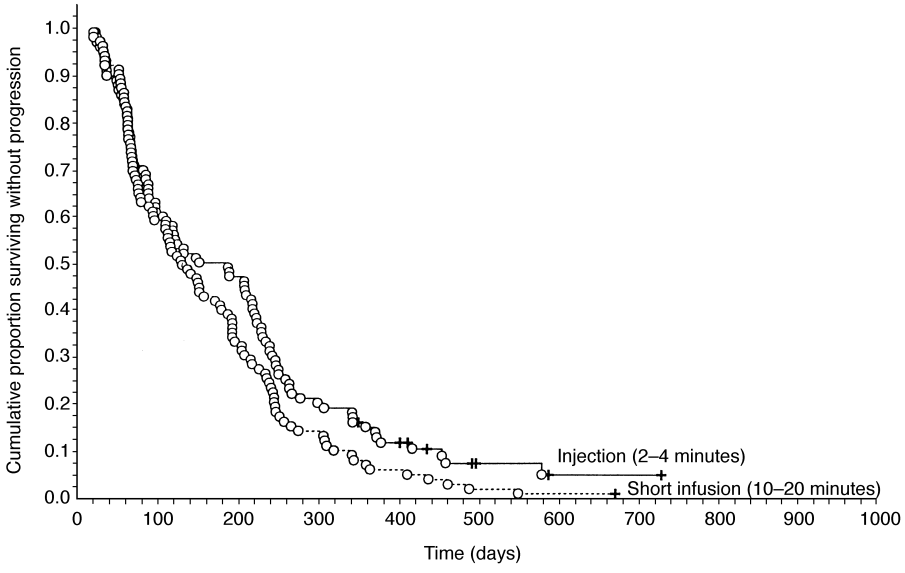

Figure 1. Time from randomisation to progression in the injection and infusion groups ($P = 0.07$, log rank test).

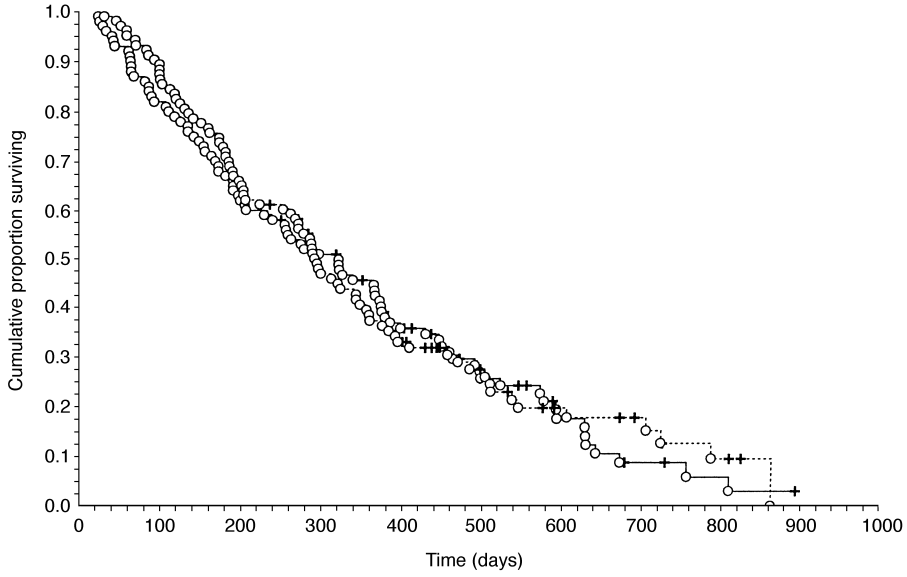

Figure 2. Time from randomisation to death in the injection (solid line) and infusion (broken line) groups ($P = 0.73$, log rank test).

certain hospitals where, for legal reasons, it was not possible for a nurse to give a patient chemotherapy through a syringe, routines were developed to use a 50 ml mini-bag in an attempt to minimise the infusion time to 5 min. Owing to the practical and widespread importance of the issue, it was not considered appropriate to rely on retrospective data, even if supported by pharmacokinetic evidence. We, therefore, initiated a very pragmatic randomised multicentre study with objective responses and toxicity as primary end-points, i.e. measures reflecting a cell kill effect. In spite of its relevance in the palliative situation, a quality of life evaluation was not included in order to keep it as simple as possible. Survival was not an end-point, although the data are presented, since second line therapy was used at most of the participating hospitals. The two treatment groups were also not selected to maximise any therapeutic difference, but to adhere to general clinical routines. Pharmacokinetic evidence would, for example, indicate that an i.v. push injection over 1–2 min theoretically would give better results than the 2–4 min interval actually used in the study in order to be able to use a 50 ml mini-bag. The short infusion time was also in the lower range of what actual measurements at several hospitals showed when using 100 ml mini-bags, i.e. 10–40 min [6, 8].

A somewhat unexpected finding, and in contrast with our earlier study, was that the gain in therapeutic activity by the use of a rapid injection did not appear to be accompanied by an increased incidence of side-effects, as conventionally recorded by physicians. It is, however, known that certain adverse effects are under-reported by doctors [6]. Since the enhanced effect of 5-FU when given as a rapid injection did not result in an apparent increase in toxicity, this form of administration is also likely to be superior from a palliative point of view. The result of this study may be valid regardless of the indication for treatment, palliative or adjuvant. Actually, the result of the present study, although tested in advanced disease, probably has its greatest relevance in the adjuvant situation.

A commonly used 5-FU/LV regimen was originally reported to give a response rate of 30–40% [14, 15]. Lower response rates have usually been seen in subsequent trials [2, 4, 16–18]. The insufficient knowledge about how bolus 5-FU is administered world-wide in clinical trials, together with the strong trend towards inferior results when prolonging the administration time, even by as little as 10–15 min, should call for careful reinterpretation of recent studies, where bolus 5-FU regimens have given unexpectedly poor results as compared with investigational drugs [16, 19]. This also relates to studies where bolus 5-FU has been compared with prolonged continuous 5-FU infusion [20–22]. However, the present study does not allow any conclusions about the efficacy of prolonged continuous 5-FU infusions since the short-term infusion is a type of bolus infusion. A recent review article about the activity of different administration times of 5-FU suggests caution in selecting a dose and infusion time of 5-FU, since it is possible that even a 15 min 5-FU infusion acts differently than a rapid i.v. push, i.e. the former may relate more to inhibition of thymidylate synthase and the latter more to incorporation into RNA [23].

In conclusion, this study has shown that bolus i.v. 5-FU should be given as a rapid i.v. injection rather than as a short-term infusion, since the former rate of administration results in a superior tumour cell kill effect without being significantly more toxic.

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