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Original Paper

5-Fluorouracil (5-FU) Continuous Intravenous Infusion Compared with Bolus Administration. Final Results of a Randomised Trial in Metastatic Colorectal Cancer

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The aim of this Phase III, balanced randomised trial was to compare continuous intravenous infusion (CVI) of 5-FU with bolus (B) administration for metastatic colorectal cancer (CRC). One hundred and fifty-five non-pretreated patients were randomised to receive CVI 5-FU at a dose of 750 mg/m^2/day (d), 7 d every 21 d (n = 77), or bolus 5-FU 500 mg/m^2/d × 5 d every 28 d (n = 78). Incremental dose escalation at 50 mg per step was recommended in the absence of toxicity. All the patients had measurable metastatic disease (M), particularly, liver and a good performance status (WHO grade 0–1). Dose intensity was significantly higher in CVI than in the bolus group: 1369 mg/m^2/week versus 558 mg/m^2/week (P = 0.0001). Grade II–IV stomatitis was more frequent in the CVI group (31% versus 9%; P < 0.0001) as was hand and foot syndrome (14% versus 3%; P < 0.001). Diarrhoea (22% versus 12%) and grade III granulocytopenia (2% versus 6%) were comparable. Responses were more frequent in the CVI (26%) than in the bolus group (13%) (P < 0.04); progression-free survival was higher for the CVI group (P = 0.04), but there was no statistical difference in overall survival (median: 10 months (m) compared to 9 m), and 1 year survival (SD) 42% (6%) versus 40% (6%). In the multivariate analysis, survival was better for patients with a good PS, well-differentiated adenocarcinomas and a primary tumour without serosal extension. In conclusion, with a higher dose intensity, CVI 5-FU improved tumour control, but not overall survival. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

FOR OVER 40 years, 5-FU (5-fluorouracil) has been the principle drug used for the treatment of advanced colorectal adenocarcinomas. Compelling evidence has demonstrated that higher doses yield higher response rates [1], but no trial has been able to demonstrate any benefit to the length and quality of life when doses are increased. Continuous venous infusion (CVI) is one of the simplest ways of increasing the total dose administered and is well tolerated. It also prolongs the duration of contact between 5-FU and the tumour which enhances 5-FU's efficacy according to experimental evidence [2]. Some trials have partially confirmed these assertions [3–5], but others were negative [6–8]. To determine the optimal dose and duration of CVI, we conducted a phase I–II trial [9] testing a 7 day every 21 day (1 week on, 2 weeks off) CVI of 5-FU; in this trial the optimal dose was 750 mg/m^2/day 5-FU and a 21% response rate was observed. This report concerns the phase III trial conducted thereafter which compared this infusion schedule to conventional bolus infusion in a randomised multicentric study.

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PATIENTS AND METHODS

One hundred and fifty-five patients were enrolled in 14 centres between August 1987 and April 1990, 83% of whom were entered by 6 centres. Patients were allocated to receive CVI 5-FU (77 pts) or conventional bolus IV 5-FU (78 pts) by balanced randomisation, every 4 patients, which was stratified by centre.

Protocol

CVI was administered through a central venous line connected to a subcutaneous port. 5-FU was administered at 750 mg/m^2 daily for 7 days every 21 days; a dose increment of 50 mg/m^2/day was allowed in the absence of toxicity above WHO grade 2 [10]. If toxicity exceeded grade 2, a reduction of 250 mg/m^2/day was planned. The IV bolus of 5-FU was chosen at the conventional dose of 500 mg/m^2/day 5 days every 28 days [4], to be reduced by 25% in case of toxicity greater than grade 2.

Patients

All had proven metastatic colorectal cancer with at least one measurable lesion. They were to have non-pretreated unresectable lesions. Their informed consent was obtained prior to inclusion and was followed by a complete examination including a clinical examination and blood tests (blood count, ionogram, urea, creatinine, liver enzymes, bilirubin, CEA (carcino embryonic antigen) determinations). A chest X-ray was used to measure lung metastases, completed by a thoracic (computer tomography) CT scan. Abdominal ultrasonography was used to measure liver metastases or lymph node involvement and completed by a CT scan.

Lesions were considered measurable if they had two perpendicular diameters of more than 2 cm.

Evaluation and statistical analysis

Overall survival was the main endpoint. Secondary endpoints studied were progression-free survival (PFS) and tumour response. PFS was calculated from the date of randomisation to the date of progression or death. Tumour responses were evaluated every 8 weeks according to WHO criteria [10]. A complete response (CR) was defined as the absence of any detectable tumour lasting more than 4 weeks and determined by CT scan; partial response (PR) corresponded to a decrease of at least 50% in the sum of the products of the two largest perpendicular diameters of each measurable lesion without the appearance of new lesions and lasting for more than 4 weeks; stabilisation (S) corresponded to a decrease in the sum of the previously described products <50% or an increase of <25%. Progression was defined as an increase of >25% or the appearance of new tumoural lesions.

Sample size. It was estimated that a minimum of 150 patients would be necessary to demonstrate an increase of the one year survival rate from 30% in the bolus group to 60% in the continuous group, with a type I error of 5% and a type II error of 5%.

Statistical methods. Comparisons were tested by the chi-squared test and Student's *t*-test. Survival curves were estimated by the Kaplan–Meier method [11], 95% confidence intervals were calculated by Rothman's method [12] and survival curves were compared using the logrank test [13] and Cox's regression model [14]. All the patients randomised were taken into account in the analysis (intention to treat analysis), even those who never received chemotherapy.

Table 1. Main characteristics of the patients

Characteristics	CVI 5FU $n = 77$	Bolus 5-FU $n = 78$
Sex: M/F	55/45%	55/45%
Age (years) mean (SD)	61 (10)	61 (9)
PS (WHO grade)		
0	50%	34%
1	42%	56%
2	8%	10%
Site of primary tumour		
right + transverse	29%	24%
left + sigmoid	38%	41%
rectum	33%	35%
Extension of the primary		
serosal invasion	87%	84%
lymph nodes	80%	78%
Degree of differentiation		
well/mild	91%	84%
poor	9%	16%
Excision of primary tumour	90%	85%
Metastatic sites		
Measurable		
liver	70%	71%
lung	25%	24%
abdominal mass	25%	18%
other	16%	16%
Non-measurable		
pleura	0%	3%
peritoneum/pelvis	14%	10%
bones	4%	3%
other	4%	4%
CEA level (ng/ml): median (range)	66 (0–20 500)	67 (1–15 008)

RESULTS

The main characteristics of the 155 patients randomised in the trial are reported in Table 1. There was no significant difference between the two groups with respect to these characteristics, especially to performance status (PS), extension and histology of the primary, and the site and number of metastases. Eight patients never started their chemotherapy; 5 in the CVI group and 3 in the bolus group; 6 because of early death or deterioration of their PS after randomisation and 2 because of subsequent refusal of the proposed treatment (1 CVI and 1 bolus).

Table 2. Description of treatment of evaluable patients

Characteristics	CVI ($n = 72$)	Bolus ($n = 75$)	*P* value
Treatment duration (d) median (range)	197 (2–761)	138 (4–579)	ns*
No. of cycles	7 (1–32)	5 (1–21)	0.03
Dose intensity (mg/m^2/week) (range)	1369 (140–6140)	558 (126–1204)	0.0001
Second-line chemotherapy	33 (46%)	45 (60%)	
mitomycin C	19	24	ns
5-FU + folinic ac	4	8	
other	10	13	

*ns: non significant.

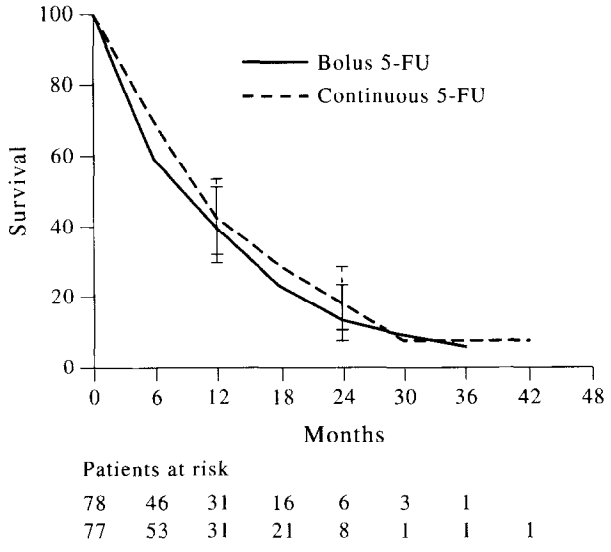

Figure 1. Overall survival for patients receiving bolus ($n = 77$) or continuous IV infusion ($n = 78$) of 5-FU.

As planned in the study design, the CVI group received a statistically higher dose intensity of 5-FU (Table 2); this was related to a higher number of cycles administered ($P = 0.03$) with a higher 5-FU dose intensity ($P = 0.0001$) administered in the CVI group. 46% of patients in the CVI group and 60% in the bolus group received second-line therapy.

The time between randomisation and the present analysis ranged from 18 to 50 months and the mean duration of follow-up was 35 months; 2 patients were lost to follow-up from the CVI group.

The overall survival curves are presented in Figure 1, and were not significantly different ($P = 0.6$); the 1- and 2-year survival rates (SD) were 42% (6%) and 17% (5%) in the CVI group and 40% (6%) and 13% (4%) in the bolus group, respectively; the median survival was 10 [1] months in the CVI group compared to 9 [2] months in the bolus group. There was a slightly better control of tumour progression in the CVI group with 44% of patients with PD or deceased at 3 months compared to 66% in the bolus group, and a statistically higher PFS in the CVI group compared to the bolus group: 27% and 14% at one year, respectively (Figure 2; $P = 0.04$).

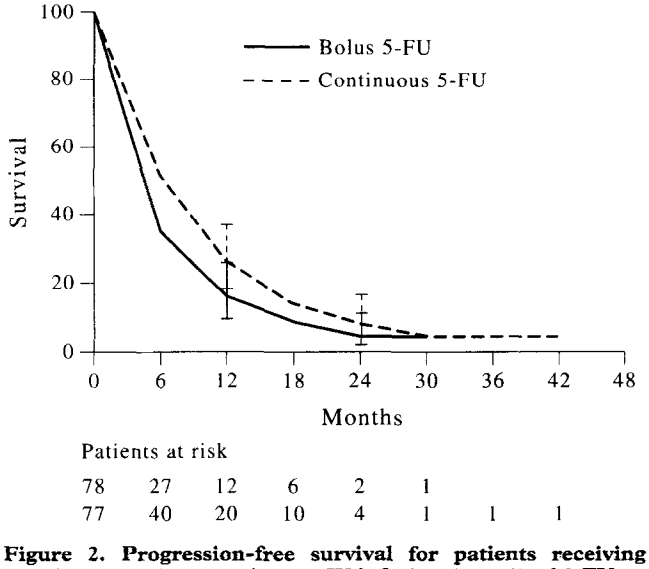

Figure 2. Progression-free survival for patients receiving bolus ($n = 77$) or continuous IV infusion ($n = 78$) of 5-FU.

Table 3. Responses of patients

Responses	CVI $n = 77$ (%)	B $n = 78$ (%)
Complete (CR)	3 (4)	0 (0)
Partial (PR)	17 (22)	10 (13)
Objective responses (CR + PR)	20 (26)*	10 (13)
Stabilisation (SD)	32 (42)	31 (40)
Progression (PD)	11 (14)	26 (33)
Non-evaluable (NE) (early death or no chemotherapy)	14 (18)	11 (14)

*CR + PR versus SD + PD + NE: $P < 0.04$

18% of patients in the CVI group and 14% in the bolus group were not evaluable for response as they never received the chemotherapy prescribed due to rapid death or a deteriorated PS; however, they were kept in the denominator for calculation of the response rate. The response rate (Table 3) was higher ($P = 0.04$) in the CVI group than in the bolus group (26% versus 13%), with 80% of the responses observed at 2 months (respectively 16/20 for the CVI and 8/10 for the bolus group). There were 3 complete responses in the CVI group and none in the bolus group. No difference was noted between the two groups in the performance status at 3 months. None of the patients who received second-line chemotherapy, in particular none of the 43 patients who received bolus intravenous mitocmycin C, attained an objective response.

Toxicity (Table 4) did not differ for granulocytopenia and diarrhoea between the two groups, but stomatitis and hand and foot syndrome were more frequent and severe in the CVI group at 3 months ($P = 0.0001$ and 0.001, respectively).

In the univariate analysis, sex and age were not significant prognostic factors. The site of the primary tumour was of borderline significance (poorer prognosis for right colon cancer; $P = 0.055$). PS ($P = 0.03$), location of metastases (lung/liver/abdomen; $P = 0.01$), the number of metastatic

Table 4. Toxicity observed at 3 months in evaluable ($n = 64$ CVI; $n = 65$ bolus)

WHO grade	9	1	2	3	4	2–4 %
Granulocytes						
CVI	59	4	1	0	0	2
Bolus	55	6	2	0	3	6
Stomatitis						
CVI	35	9	8	11	1	31
Bolus	57	2	4	2	0	9
Diarrhoea						
CVI	40	10	13	1	0	22
Bolus	46	11	6	2	0	12
Hand and foot syndrome						
CVI	43	12	8	1	0	14
Bolus	59	4	2	0	0	3

Table 5. Prognostic factors of patients entered in the trial comparing 5-FU IV bolus (B) and continuous IV infusion (CVI). Multivariate analysis (Cox model analysis)

Variable	Relative risk of death	*P*
Performance status (2 versus 0–1)	3.5	0.001
Degree of differentiation (poor versus well or mild)	2.6	0.004
Parietal extension of primary (serosal invasion: yes versus no)	1.9	0.019

sites (unique/multiple; $P = 0.01$), the degree of differentiation ($P = 0.001$) and the stage of the primary (serosal involvement: $P = 0.02$; lymph node invasion: $P = 0.01$) significantly influenced survival whatever the treatment. The multivariate analysis demonstrated that only three of these variables independently influenced survival, namely PS, degree of differentiation and parietal extension of the primary (Table 5).

DISCUSSION

In spite of the interesting results regarding tumour control, this study failed to demonstrate an advantage on overall survival with CVI compared with bolus 5-FU, which was the main endpoint of this study. This was not related to an underestimation of 1-year survival in the control group which was expected to be 30% and was actually 40%, but was related to a lower survival rate in the CVI group, which was expected to be 60% at 1 year, as in our phase II trial [9], but was actually only 42%. This lack of difference illustrates that 5-FU administered by CVI is unable to increase significantly survival; this is perhaps related to biological factors of resistance, such as the level of thymidylate synthase expression or dihydropyrimidine dehydrogenase.

This study demonstrated a modest superiority of 5-FU CVI over bolus 5-FU in terms of the response rate and for the control of tumour progression. This is consistent with other studies (summarised in Table 6), where the response rate was higher for patients receiving CVI, although the difference was significant in only 3 of them [3, 4, 8]. The more logical explanation for this increased tumour response rate is the increased dose intensity allowed by the mode of administration of 5-FU by continuous infusion (Table 6). It supports the concept of a relationship between dose intensity and tumour response advocated by Hryniuk a few years ago [1]. However, one cannot exclude the possibility that continuous infusion increases the probability of 5-FU reaching cells in S phase, related to a longer exposure; it may also act in a totally different manner from that of bolus administration by inhibiting RNA synthesis in parallel with the inhibition of DNA synthesis as emphasised by Sobrero [15]. Thus the relative efficacy of 5-FU CVI would not be only due to the total amount of 5-FU administered per week, but also to the continuous mode of administration.

A disadvantage of this study is that the 5-FU was not used in combination with folinic acid (FUfol), but bolus 5-FU was routinely used when this trial was designed and was the control arm in many randomised trials [4, 5, 16]. Although FUfol may become the standard treatment for metastatic colorectal cancer [16, 17], its activity was not superior to 5-FU CVI in 2 randomised trials [5, 18]. Thus, 5-FU CVI can be considered as one of the optimal or better methods of administering 5- FU. However, continuous infusions are more complicated and more expensive than bolus administration and cannot be considered as a 'standard' protocol. There is a clear need to develop more active combinations, such as 5-FU CVI combined with oral folinic acid [19], or using shorter duration of infusion or combination with new agents, such as oxaliplatin or irinotecan to improve the efficacy of 5-FU-based chemotherapy in colorectal cancers.

Concerning tolerance, this study confirms that CVI is feasible as an outpatient treatment when ambulatory pumps connected to a subcutaneous access are used. As in other studies using protracted 5-FU CVI [4], we found a higher rate of stomatitis and hand–foot syndrome which may have decreased a potential amelioration in the quality of life in approximately 30% of the patients. Research aiming at the improvement of tolerance is clearly needed and chronomodulation is perhaps a way of lowering this toxicity [20].

Three prognostic factors independently influenced overall survival: PS, degree of differentiation and extension of the primary, and there was no imbalance between the 2 groups of patients treated in our study for these factors (Table 1). Due to their impact on survival, these factors should be

Table 6. Trials comparing continuous IV 5-FU infusion to bolus administration in colorectal cancer

Study	No. of patients	5-FU CVI protocol (mg)	5-FU bolus (mg)	Dose intensity (mg/m^2/week) CVI/bolus	Response: CVI/bolus	Median survival (months)
Seifert [3]	70	30/kg/d1–d5/4w	12/kg/d1–d5/4w	1545 vs 618	44% vs 22%	6 vs 2†
Lokich [4]	179	300/m^2/d until PD	500/m^2/d1–d5/5w	2100 vs 500	30% vs 7%	11.2 vs 10.3 (ns)
Weinerman [8]	185	350/m^2 2w/4	400/m^2/d1–d5/4w	1312 vs 531	12% vs 8% (ns)	ns
Hansen [6]	485	300/m^2/d until PD	500/m^2/d1–d5 then 1/w	2100 vs 600	27% vs 19% (ns)	13 vs 10.5 (ns)
Isacson [7]	22	600/m^2/d1–d5/3w + fol ac	600/m^2/d1–d5/3w + fol ac	1000 vs 1000	36% vs 18%	10 vs 8 (ns)
Leichmann [5]		300/m^2/d1–d28 q35 d	500/m^2 d1–5 q35 d	1680 vs 500	29% vs 29%	14 vs 15
		200/m^2/d1–d28 q35 d + fol ac 20/m^2 i.v. q7 d	425/m^2 d1–d5, q28 + fol ac 20/m d1–d5 q28	1120 vs 531	26% vs 27%	14 vs 14
This study	155	750/m^2/d1–d7 d/3w	500/m^2/d1–d5/4w	1369 vs 558	26% vs 13%*	10 vs 9 (ns)

CVI, continuous intravenous infusion; B, bolus administration; RR, objective response rate (WHO criteria); q, every. *$P < 0.05$. †Unbalanced prognostic factors between the two arms. ns = non significant. vs = versus.

used in future prospective trials where they may help to optimise the patients stratification.

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