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Dose-effect Relationship of Bolus 5-Fluorouracil in the Treatment of Advanced Colorectal Cancer

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The effect of different dose intensities of 5-fluorouracil (5-FU) in advanced colorectal cancer was investigated. A total of 312 patients were randomized to receive 400 mg/m^2 (group A), 500 mg/m^2 (group B) or 600 mg/m^2 (group C) of 5-FU with leucovorin 60 mg/m^2 on two consecutive days every second week. Treatment continued to progression. Pharmacokinetic analyses with calculation of the area under the concentration (AUC) were performed in 91 patients. The primary endpoint was survival, and secondary endpoints were time to disease progression, toxicity and, if the disease was measurable, tumour response. The study was well balanced in the three groups with respect to a number of patient characteristics. Crude survival as estimated by Kaplan–Meier plots was not statistically significantly different ($p = 0.07$) but tended to show the best results in the intermediate dose group (median survival 10, 12.5 and 10 months, respectively). Analyses of time to progression or death showed significant differences among the three groups ($p = 0.02$) with the longest progression-free interval in the intermediate group receiving 500 mg/m^2. The objective response rates were 23%, 39% and 28%, respectively ($p = 0.02$). The actual/projected dose intensity (mg/m^2/week) was 92%, 92% and 84%, respectively. AUC did not correlate with response or survival. The frequency of severe side effects in group C was significantly higher than that of groups A and B. The study indicated that an increase from 800 to 1000 mg/m^2 of bolus 5-FU fortnightly improved the treatment results but a further increase only worsened the toxicity.

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Fluorouracil (5-FU) is still the drug of choice in the treatment of colorectal cancer. This applies to the treatment of advanced disease as well as treatment in the adjuvant situation after surgery. Despite its long history, there is no general agreement concerning the best schedule or the optimal dose for this treatment. The conventional five days' schedule has a high risk of toxic effects, especially bone marrow toxicity, compared with both continuous infusion and weekly or fortnightly schedules. Furthermore, the injection time of bolus 5-FU appears to be of major importance. In a previous study (1) we demonstrated that a true bolus injection (≤ 3 min) has a higher response rate than short-time infusion (15 min) without any significant increase in side effects.

The optimal dose and dose intensity also need further clarification. It has been claimed that 5-FU has a steep dose-effect curve mainly based on retrospective studies (2). In discussions on the dose-effect relationship, at least three parameters should be considered. The total dose (mg/m^2) may be applied in the adjuvant situation, e.g. in a randomized study of treatment duration with the same dose intensity. One example is treatment for 6 versus 12 months. The concept is less applicable in advanced disease when the treatment is given until progression. An intended total dose cannot be decided by the investigator, but is directed by the time to progression. The dose intensity (mg/m^2/week) is probably a more valid concept. The basic idea behind it is to increase the drug dose per time unit to overcome relative resistance, and it can be applied in both the adjuvant situation and the treatment of advanced disease. However, the dose intensity cannot be used without reservations. It may be increased either by increasing

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the dosage per course and keeping the interval constant or by reducing the interval and keeping the dosage constant. Both strategies increase the dose intensity but may well have different effects. If the dose-effect curve is steep within the dose range used, a substantial increase in tumour cell kill would be expected with an increase in the administered dosage. On the other hand, a reduction of the treatment interval may be advantageous in rapidly proliferating tumours. Furthermore, dose intensity is probably not always the best parameter to elucidate the dose-effect relationship. There is a wide interindividual variability in 5-FU pharmacokinetics, which of course may blur a relation between dose intensity and effect. The area under the concentration (AUC) versus time curve is a measure of drug exposure and it should probably replace milligrams per square metre, at least when discussing some drugs, especially concerning the association between dose and toxic side effects where it may be a more reliable parameter.

The objective of the present randomized study was to investigate the effect of different 5-FU dose intensities. A dose of 1000 mg/m^2 fortnightly is well tolerated by most patients (3). Our aim was to study the possible effect of a decrease and an increase of 20% of dose intensity with survival as the primary end point. Secondary endpoints were time to progression, response rate and toxic side effects. We also sought to investigate whether AUC was a more reliable parameter than dose expressed as milligrams per square metre.

MATERIAL AND METHODS

The study included 312 patients with recurrent colorectal cancer (local and/or metastatic) over the period January 1995–June 1998. The diagnosis was histopathologically verified in all cases. Inclusion criteria were also age ≤ 75 years, measurable or evaluable disease and informed consent according to the Helsinki II Declaration. Patients with serum bilirubin > 40 mmol/L, a Karnofsky index ≤ 40 or a previous malignant disease were excluded. Previous adjuvant chemotherapy was allowed only if treatment was terminated at least 12 months before protocol entrance. The patients were required to have an adequate bone marrow function as indicated by WBC $\geq 3 \times 10^9$/L and thrombocytes $\geq 100 \times 10^9$/L. The pretreatment evaluation included full history, clinical examination, chest x-ray and abdominal ultrasonography/CT scan.

Treatment

The patients were randomized to receive one of the following treatments. Regimen A: 5-FU 400 mg/m^2 and leucovorin 60 mg/m^2. Regimen B: 5-FU 500 mg/m^2 and leucovorin 60 mg/m^2. Regimen C: 5-FU 600 mg/m^2 and leucovorin 60 mg/m^2. The treatment was given on two consecutive days every second week as a rapid bolus injection (≤ 3 min.). Leucovorin was administered approx. 0.5 h after 5-FU. Response was evaluated after 2 months (4 courses) and then every second month for the following period, according to WHO criteria. The treatment continued until progression or unacceptable toxicity. Recording of toxicity (WHO scale) variables was performed at every course. The 5-FU dose was reduced to 75% for grade-2 haematological toxicity on the first day of a course and further reduced to 50% in case for grade-3 haematological toxicity. The 5-FU dose was reduced by 10% if grade 2 diarrhoea or stomatitis was registered and by one dose step for grade 3 or 4 stomatitis or diarrhoea. Protocol treatment of patients was stopped if hospitalization because of diarrhoea was necessary on two consecutive courses.

Calculation of 5-FU dose intensity

The dose intensity in the three treatment groups was calculated according to the method described in detail by Longo et al. (4). The actual dose intensity for each patient was calculated as milligrams/square meter per week. Based on the individual values, the mean actual received dose intensity of 5-FU was calculated for each of the three regimens after 2, 4, and 8 courses. The same calculations were performed for the whole treatment course and compared with the projected dose intensity.

Pharmacokinetics

Blood samples for 5-FU analysis were obtained from 91 patients during the first course of chemotherapy. A blood sample was drawn approx. 10 min after start of the bolus injection. The samples were prepared by centrifugation and stored at -20°C until analysis. 5-FU was measured by high performance liquid chromatography (HPLC) according to the method described in detail elsewhere (5). The detection limit was 1 μM/L and the intra- and interassay coefficients of variation were 3.0% and 3.8%, respectively. Assuming a monoexponential decay of 5-FU in plasma samples not taken exactly 10 min after the start of the bolus injection were calculated to the 10 min value using the time constant published by Moore et al. (6). Thus, samples could be drawn between 10 and 20 min after start of the injection. The area under the concentration versus time curve was calculated according to the formula published by Moore et al., $AUC = C_0 \times 0.43 + 4.33$.

Statistics

A sample size of 300 patients was decided upon to detect a survival difference of 15%, with a significance level of 5% and a power of 80%. Before each comparison of the different treatment groups, a χ^2 test or Kruskal–Wallis test, whichever was the more appropriate, was performed to exclude that a possible difference among the groups could be explained by a different distribution of important

patient characteristics. The survival was calculated as Kaplan–Meier plots and analysed for differences using the log-rank test. The survival analyses were performed on the intention-to-treat basis. Differences in response rates and toxic side effects were analysed by χ^2 tests. Linearity of a continuous explanatory variable in the Cox's regression model was checked as described by Thomsen (7), with two/three breakpoints for piecewise linear function of the variable at 33.3, 50, 66.6, and 75 percentiles of the variable distribution.

RESULTS

Patient and treatment characteristics

For various reasons, 13 patients were not started on treatment: 6 patients refused treatment after randomization and 2 patients died before treatment had started; 3 patients underwent major surgery and were never started on treatment; a major protocol violation was registered in 2 patients. The numbers of patients eligible for the different analyses are presented in Fig. 1.

Some of the patient and treatment characteristics are listed in Table 1. The study was well balanced regarding a number of different prognostic parameters. Most patients had disease recurrence, with the liver as the most frequent site of metastases. Approximately 90% of the patients had measurable tumours. Only a minor fraction had previously received adjuvant chemotherapy. The mean number of chemotherapy courses was highest in group B, indicating a longer overall treatment time. Dose reduction occurred more frequently in groups B and C than in group A ($p = 0.01$) and treatment delay because of toxic side effects was necessary more often in group C than in the other two groups ($p = 0.02$).

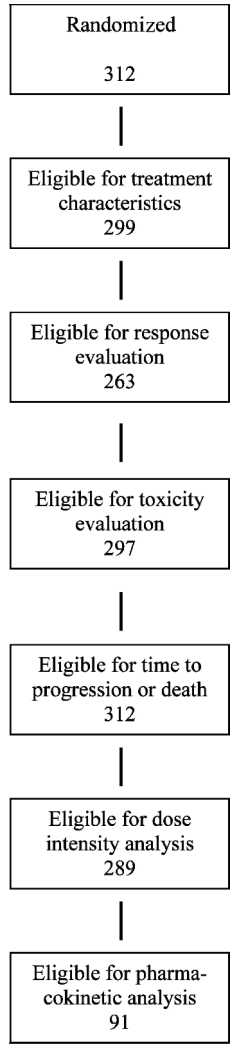

Fig. 1. Flowchart showing the number of patients available for different subset analyses.

Response

The response rate according to the WHO criteria is recorded in Table 2. The table includes 263 patients with measurable tumour receiving at least four courses of chemotherapy. The overall response rates in the three groups were 23% (15%–33%, 95% CL), 39% (29–49%, 95% CL), and 28% (18%–39%, 95% CL), respectively. The response rate for group B was significantly different from that for group A ($p = 0.02$), but not from that for group C. If the response rates were calculated on the randomized population, the corresponding rates would be 21%, 34%, and 22%, respectively.

Progression-free survival

Progression-free survival is depicted in Fig. 2. Patients without registered progression were considered to have progression on the date of death. The median values were 4.8, 7.2, and 6.4 months, respectively. The Kaplan–Meier plots indicated that group B had a longer progression-free interval than groups A and C, the difference being statistically significant ($p = 0.02$).

Survival

The crude survival of all randomized patients ($n = 312$) according to treatment group is shown in Fig. 3. The median survival was identical in groups A and C (10 months), but 12.5 months in group B. The difference in overall survival is marginally significant ($p = 0.07$). The 2-year survival rates for the three groups were 11%, 17%, and 5%, respectively.

Toxicity

One death from toxicity was recorded in group B. The patient experienced grade-4 leucopenia during the first course and died despite aggressive antibiotic treatment. The risk of diarrhoea increased with increasing dose (Table 3), but it was also the case that more than half of the patients did not experience any significant diarrhoea. Similar findings applied to stomatitis. Leucopenia was recorded in only a small number of the patients in groups

Table 1

Patient and treatment characteristics

Variable	Group A n = 98	Group B n = 103	Group C n = 98
Age (years)			
Median	63	62	63
Range	36–72	33–75	30–79
Gender			
Male	56	65	56
Female	42	38	42
Site (primary tumour)			
Colon	57	61	59
Rectum	41	42	39
Disease category			
Primarily advanced	24	26	22
Recurrence	74	77	76
Recurrence			
Local recur. only	4	6	2
Metastatic	65	64	72
Local and metastatic	5	7	2
Metastases			
Liver	72	72	69
Lung	27	26	27
Other	29	47	34
Measurable tumour	93	93	86
Tumour size			
Median	5.9	5.9	5.1
Range	1–17	1–25	1–15
Method for assessment			
x-ray	14	8	14
UL	40	45	32
CT	40	42	43
Other	4	8	9
Hb (start of treatment) (mmol/L)			
Mean	7.7	8.0	7.7
Range	5.1–10.4	5.8–10.2	5.1–10.3
Pre. adjv. chemotherapy	7	9	9
Number of series			
Median	11	13	11
Range	1–41	2–36	1–30
Dose reduction	8	16	28
Treatment delay	2	5	14

A and B but increased to 24% in group C. Infection, usually caused by leucopenia, also occurred at a lower frequency in groups A and B than in group C. The different risks of toxicity according to treatment group became more obvious when only the severe grades (3 or 4) were considered. In Fig. 4 it is shown that there was only a minimal difference between groups A and B, but a steep increase occurred when the dose intensity was raised to 600 mg/m^2/week (group C). This pattern applied to all four parameters analysed and the difference is statistically significant ($p < 0.05$). No major thrombocytopenia was

Table 2

Objective response

Variable	Group A N = 92		Group B n = 91		Group C n = 80	
	No.	%	No.	%	No.	%
CR	2	2	8	9	5	6
PR	19	21	27	30	17	21
NC	43	47	41	45	39	49
PD	28	30	15	17	19	24

Abbreviations: CR = complete remission; PR = partial remission; NC = no change; PD = progressive disease.

recorded. Mild alopecia was seen in 6% of the patients and 10% complained of eye infection, but although the frequency tended to increase with dose, there was no significant difference among the treatment groups with respect to these two parameters. This also applied to 'hand-foot' syndrome, which occurred in approx. 10% of the patients.

Dose intensity

Dose intensity levels in the three treatment groups after 2, 4 and 8 courses are presented in Fig. 5. The figures indicate a high compliance in all three groups for the first four months. Thus, the first two response evaluations were based on dose intensities close to those intended. For the most part, dose reduction and treatment delay occurred later in the course of treatment, especially with respect to group C. Taking the whole treatment course into account, it was found that the dose intensities were 368, 460 and 504 mg/m^2/week. The difference is statistically significant ($p < 0.01$). Group A and B received approximately the planned dose intensity (actual/projected dose intensity), 92% for both groups. In group C, dose reduction and treatment delay occurred more frequently, which explains that this group received 84% of the planned dose intensity when the whole treatment course was taken into account.

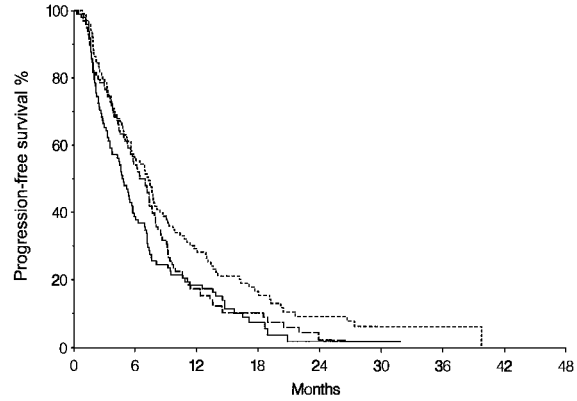

Fig. 2. Progression-free survival according to treatment group. The plots indicate a significant difference ($p = 0.02$) between group B (500 mg/m^2) and the other two groups. Key: — 400 mg/m^2. --- 500 mg/m^2. – – – 600 mg/m^2.

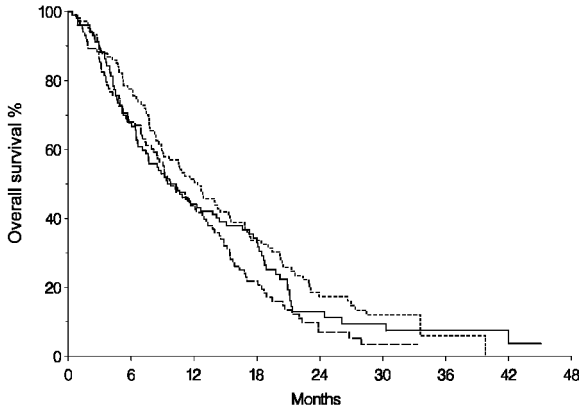

Fig. 3. Overall survival according to treatment group. The difference is marginally significant ($p = 0.07$). Key: — 400 mg/m^2. ---- 500 mg/m^2. – – – 600 mg/m^2.

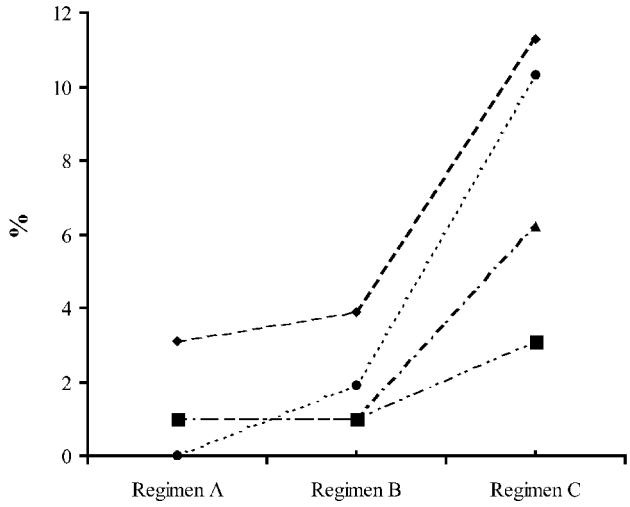

Fig. 4. Risk of grade 3 or 4 toxicity in the three treatment groups. The difference is statistically significant for all four parameters ($p < 0.05$). Key: --◆-- Diarrhoea. --●-- Leucopenia. --▲-- Infection. --■-- Stomatitis.

Pharmacodynamics

The AUC ranged from 17 to 778 μM/h. The mean value for group A was 77 and for groups B and C 107 and 145, respectively (Table 4)—a statistically significant difference ($p = 0.0001$). Following statistical analysis according to the Cox model as described in the section on statistics, the values were divided into two groups with AUC < 100 and ≥ 100. The response rates in these two groups (45 and 46 patients, respectively) were 23% and 29%, respectively. The median time to progression was 6.1 months and 7.4 months and the median survival 10.8 months in both groups. The risk of toxic side effects appeared to be higher in the group with an AUC ≥ 100. Thus the frequency of any diarrhoea in the two groups was 20% and 37%, respectively ($p = 0.07$). Leucopenia occurred in 9% and 13%, respectively.

Table 3

Important side effects

Variable	Regimen A n = 97		Regimen B n = 103		Regimen B n = 97	
	No.	%	No.	%	No.	%
Diarrhoea						
None	76	78	70	68	55	57
Grade 1–4	21	22	33	32	42	43
Stomatitis						
None	78	80	75	27	39	60
Grade 1–4	19	20	28	73	58	40
Leucopenia						
None	95	98	95	92	74	76
Grade 1–4	2	2	8	8	23	24
Infection						
None	94	97	96	93	84	87
Grade 1–4	3	3	7	7	13	13

DISCUSSION

The dose-effect relationship is crucial in the treatment of cancer patients with cytostatic drugs. It is well known that the effect on normal tissue, e.g. bone marrow, increases with increasing dose, but the relation between dose and effect needs clarification regarding the anticancer effect. The problem cannot be solved in retrospective studies for a number of reasons; e.g. patients receiving the highest dose and with the longest survival times may be the group with the best prognostic characteristics. This issue calls for prospective studies, but there is a dearth of published studies of well-designed, randomized trials. A number of randomized studies in ovarian cancer (8) clearly failed to show any beneficial effect of an increase of total dose or dose intensity of cisplatin (9) or carboplatin (10). On the other hand, a recent randomized study of adjuvant combi-

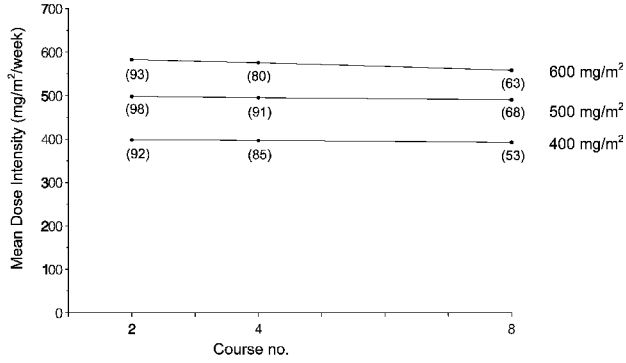

Fig. 5. Actual received dose intensity after 2, 4 and 8 courses according to treatment group. The number of patients is given in parentheses. The mean values for group A are 398, 396 and 392 mg/m^2/week, for group B 498, 495 and 490 mg/m^2/week and for group C 582, 575 and 558 mg/m^2/week.

Table 4

Calculated AUC in the three treatment groups. The mean values are significantly different

Group	No. of patients	AUC	
		Mean	Range
A	26	77	17–162
B	31	107	51–215
C	34	145	43–778

$p = 0.001$.
Abbreviation: AUC = area under the concentration.

nation chemotherapy in breast cancer indicated a more beneficial effect with a moderate or high-dose regimen than with a low-dose intensity regimen but there was no difference in disease-free or overall survival between the moderate and high-dose regimens (11).

The relation between dose and effect of 5-FU in the treatment of colorectal cancer has not been sufficiently clarified. In the adjuvant situation a higher total dose does not appear to improve the effect, as prolongation of treatment beyond 6 months does not result in a more favourable rate of survival (12). However, the total dose of 5-FU within the first 3 months may be of importance, as indicated by a retrospective analysis (13). In advanced colorectal cancer, the results of a phase II trial suggest that there is a better response rate when evaluating the dose intensity of 5-FU given as 8 h of continuous infusion (14). In their study, Larsson et al. (15) indicated that bolus injection ($<$ 3 min) resulted in a higher AUC and a higher response rate compared with short-time infusion.

The dose intensity used in the present study is within the range of other current bolus regimens. The dose intensity in the Mayo regimen (425 mg/m^2 5 days monthly) is 531 mg/m^2/week and that of the Machover regimen (370 mg/m^2 5 days monthly) is 463 mg/m^2/week.

The results presented here indicate that a moderate increase in dose intensity from 400 to 500 mg/m^2/week improves the response rate and prolongs the progression-free interval. The response was decided by the investigators in the present study and not verified by independent review since response was not the primary endpoint. This means that the rates should be viewed with caution, but any misrecording is likely to have the same effect in the three treatment groups and cannot explain the difference. The escalation can be carried out with only a minimal worsening of the toxicity. Consequently, the planned dose intensity can be maintained over a long period in almost all patients, resulting in a high ratio (92%) between actually received and projected dose intensity.

On the other hand, a further increase in dose intensity caused a significantly higher toxicity without improvement in response rate, progression-free interval or survival. Dose reduction and treatment delay occurred more frequently resulting in a lower relative dose intensity, but, even so, the group accomplished 84% of the planned dose intensity. The rather small difference in dose intensity between groups B and C indicates that the dose-effect curve is steep in that range with respect to toxicity.

In agreement with other studies, a considerable interindividual variability of 5-FU pharmacokinetics was observed. The method used for calculation of AUC was based on the single-sample method published by Moore et al. (6). In the original publication this method was shown to give a reliable estimate compared to actual measured AUC. In the present work a clear difference between the mean values was found in the three treatment groups, suggesting the reliability of the method. A significant increase in 5-FU exposure as expressed by AUC did not improve the treatment results. There was a hint of increased toxicity but not to a statistically significant level. There was no indication that a higher AUC prolonged the progression-free interval or the survival time.

In conclusion, the present study shows that an increase in 5-FU dose intensity from 400 to 500 mg/m^2/week improved the treatment results in advanced colorectal cancer but a further dose escalation only increased the toxicity. A dose of 1000 mg/m^2 fortnightly (Nordic regimen) can be given with a very low level of toxicity and the effect as expressed by a median survival of 12.5 months seems equal to other more toxic schedules (16).

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