Original article _____

The impact of adding low-dose leucovorin to monthly 5-fluorouracil in advanced colorectal carcinoma: Results of a phase III trial

M. M. Borner, M. Castiglione, M. Bacchi, W. Weber, R. Herrmann, M. F. Fey, O. Pagani,
S. Leyvraz, R. Morant, B. Pestalozzi, S. Hanselmann & A. Goldhirsch for the Swiss Group for
Clinical Cancer Research (SAKK)

Bern, Switzerland

Summary

Purpose: A wide variety of fluorouracil (FU)-plus-leucovorin (LV) dose schedules are in clinical use for the treatment of advanced colorectal cancer. Only the monthly low-dose LV-plus-FU regimen, as used by the North Central Cancer Treatment Group, has demonstrated a lasting survival benefit as opposed to FU alone (J Clin Oncol 1989; 7: 1407–1417). The Swiss Cancer Group adopted this regimen for a confirmatory phase III trial but used the same dose-intensity of fluorouracil in both treatment arms.

Patients and methods: Patients with inoperable or metastatic colorectal cancer were randomized to receive monthly FU 400 mg/m^2/day plus LV 20 mg/m^2/day as intravenous push daily for five days, or FU alone.

Results: Three hundred nine of the 310 patients randomized were eligible and included in the analysis. The objective response rate for patients with measurable disease was 9% with FU alone and 22% with FU-plus-LV ($P = 0.0001$). The median progression-free survival was 3.9 *versus* 6.2 months ($P = 0.003$)

and the overall survival 10 *versus* 12.4 months ($P = 0.02$). The major prognostic factors for survival were performance status, weight loss, and disease symptoms. WHO > 2 toxicity, consisting of stomatitis ($P = 0.001$), diarrhea ($P = 0.001$), and nausea ($P = 0.001$), was more pronounced for FU-plus-LV, without fatal events.

Conclusions: This is the largest published randomized trial to compare FU-plus-LV to FU alone in advanced colorectal cancer. It confirms the survival benefit obtained from biomodulating monthly FU with low-dose LV. The toxic effects of FU-plus-LV were acceptable to most patients, and they responded well to FU dose reductions. In the absence of an ideal dose-intense FU monotherapy regimen, monthly FU with low-dose LV provides a simple and economical means by which to achieve adequate FU efficacy in the treatment of advanced colorectal cancer.

Key words: colorectal cancer, fluorouracil, low-dose leucovorin, phase III trial, survival benefit

Introduction

Fluorouracil (FU) is still the standard treatment for advanced colorectal cancer, against which new drugs and combinations have to be compared. However, despite decades of clinical experience with this drug, its optimal administration schedule has yet to be determined [1]. Biochemical modulation with folinic acid (leucovorin [LV]) has been clearly shown to increase the biological effect of FU. A meta-analysis of phase III trials comparing different schedules of FU modulated by LV *versus* FU alone has demonstrated the significantly higher response rate of 23% for the combination as opposed to 11% for FU monotherapy [2]. However, this increase in response did not translate into a discernible improvement of overall survival [2]. As for FU alone, different schedules of FU-plus-LV are in clinical use and were included in the meta-analysis.

The most popular administration schedules of FU-plus-LV are the weekly regimens and daily-times-five courses every 28 days (monthly regimen). A direct com-

parison of weekly and monthly FU-plus-LV administration has shown no clear advantage for one schedule over the other [3]. Another open question is the LV dose required to obtain optimal modulation of FU activity. With the monthly regimen, low- and high-dose LV (20 and 200 mg/m^2) have yielded similar results [4, 5], while the situation is apparently more controversial with the weekly regimen [6, 7]. An important aspect is the fact that LV adds significantly to the costs of this treatment.

The only trial so far to demonstrate a lasting significant survival benefit with FU and LV compared to FU alone was published by Poon et al. of the North Central Cancer Treatment Group (NCCTG)/Mayo Clinic [4, 5]. Their regimen in the modulated treatment arm was monthly FU-plus-low-dose-LV, which led to both a survival benefit and an improvement of various quality-of-life (QoL) parameters. The study is unique because of the beneficial effect from modulated FU on clinically relevant endpoints and the use of a monthly FU-plus-low-dose-LV schedule. Therefore, in 1991 the Swiss Group for Clinical Cancer Research (SAKK) started this con-

firmatory phase III trial in which FU was given monthly at 400 mg/m^2 for five days throughout the entire treatment period to achieve equal FU dose intensity for both treatment arms. This allows a direct assessment of the biomodulatory effect of LV on FU. In the Poon study, FU alone (500 mg/m^2) was repeated every five weeks as was FU (425 mg/m^2)-plus-LV after the first two treatment cycles [4]. Thus, the FU dose intensities in the monotherapy arms of our study and the Mayo Clinic trial were identical. We were reluctant to increase the dose of modulated FU to 425 mg/m^2, since FU at a dose of 400 mg/m^2 caused significant toxicity in our randomized pilot study [8]. Furthermore, a fatality occurred in a previous study of this group using FU alone at a dose of 450 mg/m^2 [9].

Patients and methods

Eligibility criteria

Patients were required to have histologically-confirmed inoperable locally advanced or metastatic colorectal cancer. Disease was defined as either bidimensionally measurable or non- measurable. All patients were ambulatory (Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3). Previous chemotherapy was not allowed except for adjuvant chemotherapy which had been terminated $\geq$ one year before study entry. Adequate organ function was required. All patients provided voluntary informed consent. The study protocol was approved by the local ethics committees of the participating institutions.

Treatment

Patients were stratified according to the presence or absence of measurable disease and disease symptoms and randomized to FU alone or FU-plus-low-dose-LV. FU alone: FU was given by rapid IV push at 400 mg/m^2/d for five consecutive days with courses repeated every 28 days. FU-plus-low-dose-LV: leucovorin was given at 20 mg/m^2/day immediately followed by FU at 400 mg/m^2/day. Both drugs were given by rapid IV bolus injection daily for five consecutive days with courses repeated every four weeks. The FU dose was decreased by 25% if grade 3 toxicity according to WHO criteria had occurred in the previous treatment cycle. Dose escalation of FU by 10% per step was recommended in instances of non-hematological toxicity <grade 2 and nadir blood counts of > 2000 leucocytes/μl and > 100.000 platelets/μl [10]. The intent was to escalate the FU dose to produce comparable toxicity in the two treatment arms.

Endpoints and response criteria

Endpoints of the study were overall survival, time-to-treatment-failure, progression-free survival, objective response for patients with measurable disease, palliative effects as suggested by Poon et al. [4], and toxicity. Treatment failure was defined as cessation of treatment because of disease progression, clinical deterioration, treatment refusal, toxicity, or death. The type of first failure was evaluated and recorded for each patient. Progression-free survival was defined as the time between randomization and clinical deterioration, progression or death. Patients who discontinued treatment by choice or because of toxicity were followed and monitored for progression. The intervals were calculated from day of randomization until occurrence of the event. Complete response (CR) required the total disappearance of all tumor initially observed, with no new areas of disease. Partial response (PR) was defined as a greater than 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable

indicator lesions. Progressive disease (PD) was a greater than 25% increase in the products of the longest perpendicular diameters of any area of known malignant disease. Radiological tumor measurements were performed at every second treatment cycle. At study entry, the presence or absence of disease symptoms was assessed. At the start of each treatment cycle the patient was asked whether these symptoms were still present or had disappeared during study participation.

Statistical analysis

The computation of sample size was made with the aim of achieving sufficient power for the comparison of the treatment arms in terms of survival. Assuming an exponential survival distribution, a median survival improvement from 30 to 45 weeks and, with the significance level for the log-rank test set at 5% and the power at 90%, a target number of 300 patients was estimated. The study was closed after the accrual of 310 patients in November 1995. The efficacy analyses included all eligible patients and used the 'intent-to-treat' approach. The safety analysis included all treated patients. The chi-square or the Fisher's exact tests were used for contingency tables (StatXact, Cytel Corporation, Cambridge, MA). The Wilcoxon rank sum test was used for ordered categorical tables (types of toxicities).

Time-to-treatment-failure (TTF), progression-free survival (PFS), and overall survival (OS) were estimated according to the Kaplan–Meier product limit method [11]. The validity of the proportional hazard assumption was tested [12] and since there was evidence of an increasing hazard ratio over time for these parameters, the Gehan–Wilcoxon was applied instead of the log-rank test for treatment comparison in terms of TTF, PFS and OS. The prognostic importance of clinical variables with respect to progression-free survival and overall survival was assessed using the log-rank test [13]. Stratified analyses to adjust for covariates were calculated as described [4]. This method of covariate adjustment was used because of the treatment interactions with the covariates, which prevented the use of an unstratified Cox proportional hazards model. Of the two prospectively defined stratification factors, measurability was not considered because of the small number of patients with non-measurable disease. Unless otherwise noted, significance indicated P-values ≤ 0.05. All P-values given are two-sided. No adjustment for multiple comparisons was performed.

Results

Patient characteristics and treatment summary

Between 5 February 1991 and 20 November 1995, 310 patients were accrued to this trial. Only one patient was ineligible, because FU had been given in the adjuvant setting. Six patients were inevaluable for toxicity, since they received no protocol treatment due to unexpected deterioration of their physical conditions after randomization. The characteristics of the 309 eligible patients are displayed in Table 1. The variables listed were distributed without significant differences between the two treatment arms. The median age was 63 years (range 26–82 years) in the monotherapy arm and 62 years (range 27–81 years) in the FU-plus-LV arm. Slightly fewer than half of the patients had symptoms attributed to malignant disease. Almost 90% of the patients had measurable disease.

The median number of treatment cycles was 4 in the FU monotherapy arm and six in the FU-plus-LV arm. The protocol recommended intensification of the FU dose (see 'Patients and methods') to produce equal tox-

Table 1. Characteristics of eligible patients.

Characteristic	FU alone, $n = 157$ (%)	FU + LV, $n = 152$ (%)
Sex		
Male	63	60
Female	37	40
Symptomatic	45	43
Measurable disease	89	88
Performance score (ECOG) 0.1	90	88
Weight loss in previous six months > 10%	21	22
Site of primary		
Colon	71	69
Liver involvement	76	70
Multiple metastatic sites	51	52
Tumor-free interval < six months	65	59
Adjuvant chemotherapy	5	9

Table 2. Toxicity.

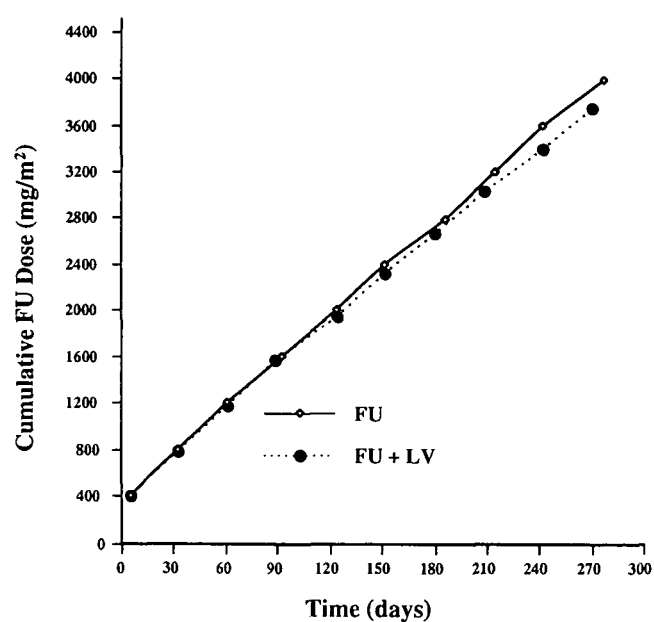| Toxicity	Fu alone, $n = 155$ (%)		Fu + LV, $n = 148$ (%)
Stomatitis			
1	19		19
2	12		23
3	3	0.0001[a]	22
4	0		3
Diarrhea			
1	22		18
2	14		30
3	5	0.0001	21
4	1		1
Nausea/vomiting			
1	32		34
2	15		23
3	1	0.007	7
4	1		1
Alopecia			
1	5		23
2	3		8
3	1	0.0001	5
Other toxicity			
1	12		14
2	17		24
3	7	0.0001	10
4	1		4

[a] Wilcoxon rank sum test significance level.

Figure 1. Mean cumulative dose of FU in the respective treatment arm.

icity in both treatment arms. FU doses were increased ≥ 10% at least once in 41% of the patients in the mono-therapy arm and in 31% of those in the FU-plus-LV arm ($P = 0.07$). However, restricting the analysis to patients without toxicity, the appropriate FU dose increase was performed in only 23% and 20% of these patients, respectively, suggesting a poor compliance with the dose increase recommendations. FU doses were decreased ≥ 10% at least once in 27% of the patients in the monotherapy arm and in 57% of those in the FU-plus-LV arm ($P = 0.0001$). The cumulative plot of the dose received is displayed in Figure 1. In the monotherapy arm, the dose intensity of FU remained largely constant over the treatment period, suggesting a good tolerance of the therapy. In the FU-plus-LV arm the dose intensity of FU decreased slowly over time, suggesting the impact of toxicity and the need for dose modifications. Since the treatment intervals remained largely unaffected over time in both treatment arms it can be

assumed that patients recovered from toxicity in due time.

Toxicity

Adding LV to FU resulted in a significant increase in WHO grade ≥ 2 stomatitis, diarrhea, nausea, alopecia, and other, mainly hematological, toxic effects (Table 2). Weekly blood counts were not required in this trial. No fatal toxicities were observed. In 17 patients with FU-alone treatment was discontinued due to refusal or toxicity compared to 26 patients on FU-plus-LV ($P = 0.14$).

Progression-free survival and time-to-treatment-failure

Two hundred ninety-seven patients had progressed or died at the time of this analysis. The distribution of progression-free survival according to treatment regimen is illustrated in Figure 2. Events occurred later with the combined treatment, but this effect disappeared after about 18 months. The median progression-free survival time was 3.9 months for FU and 6.2 months for FU-plus-LV ($P = 0.003$). The six-month failure-free actuarial survival was 38% for FU and 52% for FU-plus-LV. Performance status, weight loss, symptoms at study entry, and tumor-free interval were the factors most significantly associated with progression-free survival. The significant advantage of FU-plus-LV was confirmed adjusting for disease measurability, symptoms, and weight loss (stratified test: 8.18, $P < 0.01$). The median time-to-
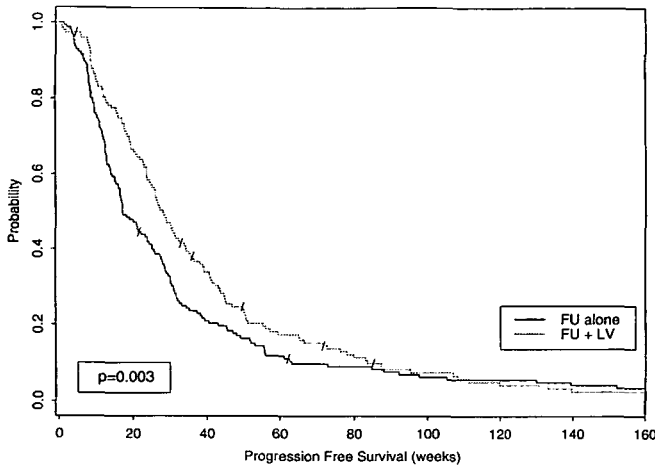
Figure 2. Progression-free survival according to treatment arm. The P-value refers to the Gehan–Wilcoxon test.
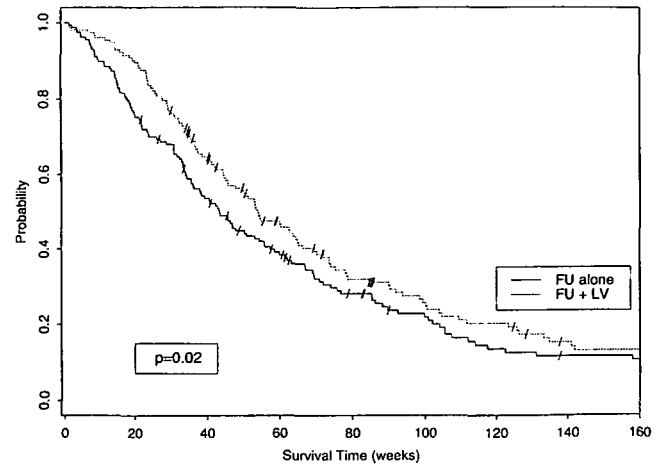

Figure 3. Overall survival according to treatment arm. The P-value refers to the Gehan–Wilcoxon test.

Table 3. Response rates: Patients with measurable disease at baseline.

Clincal response	FU alone, $n = 139$ (%)	FU + LV, $n = 134$ (%)
CR + PR	9	22
95% confidence interval	5–13	15–29
SD	29	34
PD	40	25
Inevaluable for response	22	19

Table 4. Covariates predictive for survival.

Factor	Deaths/total	Median survival (days)	Two-sided log-rank (P-values)
Symptomatic			
No	126/174	486	0.0001
Yes	124/135	256	0.0001
Performance status			
0	116/154	486	0.0001
≥ 1	134/155	261	0.0001
Weight loss (%)			
< 5%	137/177	455	0.0001
≥ 5%	113/132	240	0.0001
Tumor free interval[a]			
< six months	157/192	283	0.001
> six months	93/117	439	0.001
Peritoneal involvement			
Yes	53/62	252	0.008
No	197/247	373	0.008
Age group			
< 60 years	98/121	382	0.03
> 60 years	152/188	304	0.03
Measurable disease			
No	28/36	376	0.07
Yes	222/273	336	0.07
Site of primary			
Colon	181/217	320	NS
Rectum	69/92	382	NS
Sex			
Female	95/119	335	NS
Male	155/190	352	NS
Lung involvement			
Yes	64/75	355	NS
No	186/234	350	NS
Liver involvement			
Yes	183/226	328	NS
No	67/83	434	NS

[a] Time from diagnosis of primary until progression.
Abbreviation: NS – not significant.

treatment-failure was 3.9 months for FU and 5.5 months for FU-plus-LV ($P = 0.02$). As expected, time-to-treatment-failure roughly corresponded to the median number of cycles in the respective treatment arm.

Objective tumor response

Clinical response was evaluated in the 273 patients with measurable disease (Table 3). FU-plus-LV yielded a significantly higher response rate than FU alone ($P = 0.0002$). A conservative approach for response evaluation was chosen since all measurable but non-evaluable patients entered the denominator as unresponsive to treatment. The median response duration was seven months for FU and 10 months for FU-plus-LV ($P = 0.46$).

Overall survival

Two hundred fifty patients have died at the time of this analysis. The median follow-up for patients while alive was three years. FU-plus-low-dose-LV provided a significant survival advantage over FU alone ($P = 0.02$). The median overall survival was 12.4 and 10 months and the one-year actuarial survival 53% and 43%, respectively. Survival distributions for the study patients according to treatment arm are illustrated in Figure 3. Prognostic covariates predictive of overall survival are summarized in Table 4. Performance status, weight loss, symptoms at study entry, and tumor-free interval were the factors most significantly associated with overall

survival. When adjusted for performance status, weight loss, and symptoms at study entry, the significant survival advantage of FU-plus-LV was confirmed (stratified

Table 5. Exploratory evaluation of impact of toxicity on survival according to treatment.

Treatment arm	Overall survival, toxicity (WHO) grade		Two-sided log-rank (P-values)
	≤2 (months)	≥2 (months)	
Stomatitis			
FU	9.3	15.4	0.04
FU + LV	11.5	14.4	0.04
Diarrhea			
FU	8.8	19.8	0.006
FU + LV	10.5	14.9	0.06
Nausea/vomiting			
FU	9.9	11.6	0.07
FU + LV	14.7	10.5	0.01

Table 6. Comparative palliative effect.

Effect	FU	FU + LV	P-value (chi-square test)
Disease symptoms			
No. evaluable	69	63	
% disappeared	42	65	0.009
Gain of weight gain ≥ 5%			
No. evaluable	151	146	
% improved	38	26	0.03
Improvement in performance status			
No. evaluable	155	148	
% better	27	27	
% equal	59	63	0.62
% worse	14	10	

test: 7.43, $P < 0.01$). We were also interested in whether patients with relevant toxicity had more benefit from the treatment or whether, on the contrary, toxicity had a negative impact on outcome. In both treatment arms, patients with WHO grade ≥2 diarrhea or stomatitis lived longer than patients without toxicity (Table 5). However, nausea and vomiting had a negative impact on survival in the FU-plus-LV arm.

Palliative effects

Improvement in performance status, symptomatic improvement, and weight gain were proposed as surrogate quality-of-life measuremens in the study of Poon et al. [4]. Our results using the same parameters are summarized in Table 6. We confirmed the beneficial effect of FU plus LV on disease symptoms, but performance status was not affected. Weight was negatively affected by FU-plus-LV, suggesting an impact of gastrointestinal toxicity.

Discussion

Despite a convincing biochemical rationale for the biomodulation of FU with LV, only a single randomized trial has thus far shown a lasting survival benefit from FU-plus-LV over FU alone in advanced colorectal cancer [4, 5]. Additional attractive features of modulated FU in that study were the demonstration of a beneficial impact on different quality-of-life parameters and the use of an economical LV dose. Thus, the monthly FU-and-low-dose-LV regimen favored by the NCCTG/Mayo Clinic team seems to be the most attractive chemotherapy for advanced colorectal cancer at this point.

However, a meta-analysis of randomized trials comparing FU alone to FU-plus-LV in advanced colorectal cancer failed to confirm a survival benefit for the combination despite a significantly higher response rate. For this meta-analysis, trials using widely differing dose schedules of FU and LV were lumped together. The assumption that these regimens have similar therapeutic potency might not be valid, and the effect of trials using a potent FU-plus- LV regimen could have been blurred by trials using an ineffective regimen. It has been speculated that even small differences in the duration of the FU injection could affect outcome in terms of efficacy and toxicity [1]. In addition, individual patient data from the NCCTG/Mayo Clinic were not included in the meta-analysis. A post hoc analysis including the NCCTG/Mayo Clinic overall results changed the hazard ratio and the p-value for a survival benefit from modulated FU from 0.97 ($P = 0.57$) to 0.92 ($P = 0.14$). This indirect evidence of the superiority of monthly FU-plus-low-dose-LV over FU alone rendered a second independent trial testing the same hypothesis highly desirable.

This is the largest study published to date of a comparison of FU-plus-LV and FU alone in advanced colorectal cancer. Despite minor schedule and dosing differences between it and the NCCTG/Mayo Clinic trial, we obtained very similar results in terms of overall survival and progression-free survival. This result is particularly reassuring, since close to 90% of our patients had measurable disease, which was identified as an adverse prognostic factor in both studies. Another important adverse prognostic factor in our study was the presence of disease symptoms at the start of study treatment. This result provides indirect evidence that it might be detrimental to postpone treatment in colorectal cancer until symptoms occur. This is in agreement with the findings of the NORDIC group, which randomized patients to early treatment or treatment delay until symptoms occurred and thus was not affected by a length of time bias [14].

We chose the same initial dose level of FU for both treatment arms of our study to assess the true impact of LV in terms of tumor response and toxicity. Despite *in vitro* data suggesting the need for LV serum concentrations of > 10 μM for optimal FU biomodulation, the impact of this low LV dose on the toxicity of FU was striking. In addition, the NCCTG/Mayo Clinic compared 20 mg/m²/day LV to 200 mg/m²/day LV in combination with FU and found no increased clinical effect with the higher LV dose [4, 5]. The significant toxicity of monthly FU-plus-low-dose-LV [4, 5, 15],

however, leads to the question of whether this grade of toxicity is acceptable considering the modest survival benefit with this palliative treatment. Although disease symptoms were significantly more often abolished by the combined treatment, we were not able to confirm a clinical benefit for FU-plus-LV over FU monotherapy in terms of weight gain and improvement of performance status as described by Poon et al. [4]. However, treatment refusal due to toxicity was rare in both treatment arms and the median number of treatment cycles was six in the combination arm compared to four with FU alone, suggesting that patients accepted the toxicity of the combined regimen. This might have been helped by the fact that FU dose reductions led to a decrease of toxicity during the course of treatment with FU-plus-LV. Interestingly, in our evaluation patients suffering ⩾ grade 2 stomatitis or diarrhea had longer survivals in both treatment arms. The median survival doubled for patients treated with FU alone suffering ⩾ grade 2 diarrhea. This is even more surprising in view of the possible adverse impact of this toxicity pattern in terms of nutritional and performance status. Being aware of the bias of post hoc comparisons, these results seem to suggest a critical dose level for FU, which is associated with both efficacy and toxicity. Nausea and vomiting had a negative impact on overall survival in patients treated with FU-plus-LV. This could have been related to the fact that peritoneal disease, which was associated with this type of toxicity, was an adverse prognostic factor for overall survival.

A crucial question is whether the effect seen for FU-plus-LV could also be obtained by increasing the dose intensity of FU alone [16]. Valone et al. of the NCOG compared a dose-intensive FU regimen to monthly FU-plus-LV (200 mg/m^2/day) in advanced colorectal cancer [17]. The dose intensive FU regimen led to higher hematological and non-hematological toxicity and the authors state that FU-plus-LV had the better therapeutic ratio of benefits versus toxicity. Laufman et al. designed an interesting randomized, double-blind study to achieve equitoxicity between FU monotherapy and FU-plus-high-dose-oral-LV [18]. They found a higher response rate with the combination, which did not translate into prolonged survival. The equitoxic FU doses were 472 mg/m^2/wk in the monotherapy and 420 mg/m^2/wk in the combined treatment arm. The dose intensity of FU was 500 mg/m^2/wk for both treatment arms in our study. This suggests that our FU-plus-LV arm had a higher relative FU dose intensity than the FU monotherapy arm. Although dose intensification was recommended in the absence of relevant toxicity, these recommendations were only observed in a small proportion of the eligible patients. Many clinicians obviously considered a dose increase too risky for their patients. In other cases, FU had to be discontinued due to treatment failure before an adequate toxicity level was achieved.

It is debatable for many published trials comparing FU alone to FU-plus-LV whether the optimal dose intensity of the FU monotherapy arm has been achieved

[16]. Surprisingly, this question has never been resolved although FU was introduced into clinical use four decades ago. Thus, it is doubtful that this problem will be solved in the near future. We would reason that modulating monthly FU with low-dose LV is a feasible and pragmatic means by which to increase the efficacy of FU. This approach is safe, since we observed no fatalities in our large trial and the toxicity of this treatment responded well to FU dose modifications or to the omission of LV. However, the patients should be informed about the greater chances of their suffering side effects from FU-plus-LV and be given the option of making an informed decision against the use of LV. The monetary argument against LV loses importance in view of the falling prices for this drug and the low LV dose used in this regimen. Despite the vast experience with FU alone and in combination with LV in the treatment of advanced colorectal cancer, the question of the optimal FU dose schedule still needs to be answered.

Acknowledgement

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Correspondence to:
M. M. Borner, MD
Institute of Medical Oncology
Inselspital
3010 Bern
Switzerland