Modulation of Fluorouracil by Leucovorin in Patients With Advanced Colorectal Cancer: Evidence in Terms of Response Rate

By the Advanced Colorectal Cancer Meta-Analysis Project*

Purpose: A meta-analysis was performed on nine randomized clinical trials that compared fluorouracil (5-FU) with 5-FU plus intravenous (IV) leucovorin (LV) for the treatment of advanced colorectal cancer.

Design: The analysis was based on the most recently updated individual patient data from all trials. The end points of interest were tumor response and overall survival.

Results: Therapy with 5-FU plus LV administered either as weekly or monthly regimens showed a highly significant benefit over single-agent 5-FU in terms of tumor response rate (23% v 11%; response odds ratio (OR), 0.45; $P < 10^{-7}$). This increase in response did not result in a discernable improvement of overall survival (survival OR, 0.97; $P = .57$). The large number of patients who did not respond to treatment in both groups, and cross-overs from 5-FU alone to 5-FU plus LV are discussed as plausible explanations for the lack of a survival difference.

Conclusion: These results confirm the advantage of 5-FU plus leucovorin over 5-FU alone in terms of objective tumor response. They also suggest that in planning future trials, tumor response should not be considered a valid surrogate end point for survival in patients with advanced colorectal cancer.

J Clin Oncol 10:896-903. © *1992 by American Society of Clinical Oncology.*

FLUOROURACIL (5-FU) is still considered the standard drug for the treatment of advanced colorectal cancer. However, response rates to 5-FU alone are generally less than 20%, and many 5-FU–containing combination regimens have either failed to improve these results significantly or have been associated with an increase in morbidity.

Experimental studies[1-3] have shown that the cytotoxic activity of 5-FU can be potentiated by folinic acid (leucovorin [LV]). Fluorodeoxyuridylate (FdUMP), one of the metabolites of 5-FU, binds to thymidylate synthase in the presence of 5-10 methylene tetrahydrofolate (CH_2FH_4). This interaction leads to the formation of a covalent ternary complex, and to the inhibition of thymidylate synthase. It was postulated that in some human tumors, the amount of folate may be insufficient to permit optimal cytotoxicity of 5-FU.[4] LV, a mixture of stereoisomers ([6R,S]-5-formyltetrahydrofolate), can increase the intracellular concentration of CH_2FH_4, and stabilize the ternary complex.[2]

Early phase I and II trials[4-6] suggested that the combination of 5-FU and LV might enhance the activity of 5-FU in patients with advanced colorectal carcinoma. Randomized phase II or III trials were subsequently performed. At the time of writing, 10 randomized clinical trials comparing 5-FU alone to intravenous (IV) LV and 5-FU had been completed to confirm the promising results reported in phase II trials (Table 1). These trials included more than 1,500 patients. To date, seven of these trials have been published.[7,12,19] Six trials[7-11,19] reported a significantly higher tumor response rate in patients receiving the combined treatment. In two of these trials, overall survival was significantly improved,[8,11] while a trend toward longer survival was reported in two others.[7,9]

These studies showed that the combination of IV LV and 5-FU may give higher tumor response rates than 5-FU alone in patients with advanced colorectal carcinoma. However, the possible benefit of this combination on overall survival was still doubtful, and there was no consensus about the best dose/schedule of administration for 5-FU and LV.

Meta-analysis is a useful tool to address these complex issues. Its main advantage lies in the possibility of ascertaining treatment benefits that are too small or too erratic to be demonstrated in individual trials. Therefore, it is particularly suited to the analysis of overall survival in cancer patients. Moreover, meta-analysis

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Submitted September 6, 1991; accepted February 3, 1992.

Supported by Ligue Nationale Française Contre le Cancer, Fondation Française pour la Recherche sur le Traitement du Cancer, Faculté de Médecine de Créteil, and Cyanamid-Lederle.

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0732-183X/92/1006-0005$3.00/0

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Table 1. Randomized Clinical Trials of 5-FU Alone v 5-FU Plus IV LV in Patients With Advanced Colorectal Carcinoma

Institution	5-FU	5-FU + LV	No. of Patients
GITSG[9]*	5-FU 500 days 1-5, every 28 days	5-FU 600 day 1 + LV 500 2-hour infusion	113
		day 1, every 7 days	115
		5-FU 600 day 1 + LV 25 day 1, every 7 days	115
		5-FU 1,000 day 1 + LV 25-250-500 day 1, every 21 days	39
NCOG[12]	5-FU 12 mg/kg/d days 1-5 then 15 mg/kg/d day 1, every 7 days	5-FU 400 days 1-5 + LV 200 days 1-5, every 28 days	55
			107
GOIRC[18]	5-FU 13.5 mg/kg/d days 1-5, every 28 days	5-FU 400 days 1-5 + LV 200 days 1-5, every 28 days	90
			91
GISCAD[19]	5-FU 400 days 1-5, every 28 days	5-FU 400 days 1-5 + LV 200 days 1-5, every 28 days	90
			92
Genova[17]	5-FU 600 day 1, every 7 days	5-FU 600 day 1 + LV 500 2-hour infusion day 1, every 7 days	73
			75
Toronto[8]	5-FU 370 days 1-5, every 28 days	5-FU 370 days 1-5 + LV 200 days 1-5, every 28 days	64
			66
City of Hope[7]	5-FU 370 days 1-5, every 28 days	5-FU 370 days 1-5 + LV 500 24-hour infusion days 0-$5^{1/2}$, every 28 days	40
			39
RPCI[10]*	5-FU 450 days 1-5 + 5-FU 200 days 6-11, every 39 days	5-FU 600 day 1 + LV 500 2-hour infusion day 1, every 7 days	23
			30
Bologna[16]	5-FU 600 day 1, every 7 days	5-FU 600 day 1 + LV 200 day 1, every 7 days	30
			34
NCCTG/Mayo Clinic[11]†	5-FU 500 days 1-5, every 35 days	5-FU 370 days 1-5 + LV 200 days 1-5, every 28-35 days	70
			69
		5-FU 370 days 1-5 + LV 20 days 1-5, every 28-35 days	73

NOTE. Treatment groups other than 5-FU or 5-FU + LV are not shown. Doses are expressed in milligrams per meter squared per day, and the mode of administration is bolus unless otherwise specified.

Abbreviations: GITSG, Gastrointestinal Tumor Study Group; RPCI, Roswell Park Cancer Institute; NCOG, Northern California Oncology Group; GOIRC, Italian Oncology Group for Clinical Research; GISCAD, Italian Group for the Study of Digestive Tract Cancer; NCCTG, Northern Central Cancer Treatment Group.

*The 5-FU + LV regimens in these trials consisted of 6 weekly doses followed by a 2-week rest.

†Not included in the meta-analysis (see Discussion).

provides an exhaustive and unbiased evaluation of all available evidence, and may clarify on-going controversies or suggest directions for future studies.

This report presents a detailed meta-analysis of nine randomized trials comparing 5-FU alone with IV LV and 5-FU. Trials that compared different schedules of 5-FU plus LV without a group receiving single-agent 5-FU as a control were not considered.[13,14] The end points of interest were tumor response and overall survival.

DESIGN

Data Collection

This meta-analysis was based on individual patient data provided by the principal investigator of each trial. A list of items was requested for every randomized patient, whether eligible or not, assessable or not, and properly followed-up or not (Table 2). This list was sent to the principal investigators in November 1990. All data were sent to a coordinating office by May 1991 and were extensively checked and discussed with the principal investigators in May and June 1991. Individual patient data from the North Central Cancer Treatment Group (NCCTG)/Mayo Clinic trial[11] were not made available, and thus, could not be included in the main analyses presented. However, the published results of this trial contained enough information on response and survival to include it in additional analyses.

Treatment Comparisons

The only comparison of interest was that of 5-FU alone versus IV LV and 5-FU. Treatment arms with additional drugs (methotrexate, cisplatin) were not included in the analysis.[10-12]

Tumor Response Criteria

All patients considered in the meta-analysis had measurable disease. There were no major differences between trials with respect to patient eligibility. Four of 578 patients in the 5-FU alone group, and six of 803 patients in the 5-FU plus LV group had received a chemotherapy before entering the trial, and were included in the present meta-analysis.

Tumor responses were analyzed as reported by the investigators. The response criteria were essentially identical in all trials[15]; a complete response (CR) was defined as the disappearance of all detectable tumor, and a partial response (PR) was defined as a 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable disease without new lesions. In

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Table 2. Information Requested for Every Randomized Patient, Whether Eligible or Not, Assessable or Not, and Properly Followed-Up or Not

Patient identification
Date of randomization
Eligibility
Treatment assigned by randomization
Age at randomization (years)
Sex
Performance status*
Primary tumor site (colon or rectum)
Prior radiotherapy in metastatic areas
Location of disease (on-study)
Overall response status with the first allocated treatment
Cross-over to another treatment arm (yes or no)
Second treatment arm (if cross-over)
Date of death or last visit
Survival status
Cause of death, if applicable

*Eastern Cooperative Oncology Group scale.

the Gastrointestinal Tumor Study Group (GITSG) trial,[9] a 30% decrease in hepatomegaly, measured by the sum of the measurements below the xiphoid and the costal margin at the midclavicular lines, was considered a PR. The minimum required response duration was usually 8 weeks, sometimes 4 weeks.[7,12] For the purposes of the meta-analysis, tumor responses were categorized into three groups: CR, PR, and no response. Minimal response, stable disease, progressive disease, and any doubtful case were classified as no response.

Survival

Survival was defined as the time from randomization to the date of death, whatever its cause. Four trials[7,10,12,16] allowed a cross-over from 5-FU to 5-FU plus LV after progression on 5-FU alone. A separate survival analysis was performed without these four trials, in addition to the overall analysis. Moreover, each principal investigator was asked to provide an estimate of the number of patients who were crossed-over or who received another treatment after the study was completed.

Grouping of Trials According to Dose/Schedule

There was some heterogeneity in treatment schedules between the various trials listed in Table 1. However, the treatment schedules showed similarities that led to informative analyses. The trials were broadly categorized into three groups according to the initially prescribed doses of 5-FU and the modalities of administration of LV.

The first group consisted of trials adding a weekly administration of LV to 5-FU (weekly regimen). The initial dose intensity of 5-FU was approximately 2,400 mg/m^2 per month; LV was usually given at the dose of 500 mg/m^2 every 7 days (ie, a monthly dose of 2,000 mg/m^2). There were four such trials (608 patients): GITSG,[9] Roswell Park Cancer Institute,[10] Bologna,[16] and Genova.[17] The dose of LV was lower in the Bologna trial (200 mg/m^2 every 7 days),[16] and in one arm of the GITSG trial (25 mg/m^2 every 7 days).[9]

The second group consisted of trials of LV and 5-FU given as 5-day courses every 28 days (monthly regimen). The initial dose intensity of 5-FU was between 1,850 and 2,000 mg/m^2 per month, and LV was usually given at the dose of 200 mg/m^2 per day on days 1 to 5 every 28 days (ie, a monthly dose of 1,000 mg/m^2). There were three such trials (391 patients): City of Hope,[7] Toronto,[8] and Italian Group for the Study of Digestive Tract Cancer (GISCAD).[19] Continuous infusion of LV was used in the City of Hope trial.[7] In the Toronto trial,[8] all patients received the same dose of 5-FU for the first course, with subsequent dose increase in the 5-FU alone arm to maintain equal toxicity in the two regimens. However, the difference in terms of 5-FU dose intensity between the two treatment arms remained relatively small during the first six courses.

The third group consisted of trials using a higher dose of 5-FU as control. The initial dose intensity of 5-FU was 2,400 to 2,500 mg/m^2 per month in the 5-FU alone group, and 2,000 mg/m^2 per month in the 5-FU plus LV group. LV was given at the dose of 200 mg/m^2 per day on days 1 to 5 every 28 days. There were two such trials (343 patients): Northern California Oncology Group (NCOG)[12] and Italian Oncology Group for Clinical Research (GOIRC).[18]

The GITSG trial[9] had a treatment arm with an increase of LV. This arm, which was stopped early, did not fit into either of the previously described groups and was only considered in the overall meta-analysis.

Statistical Analysis

All analyses were based on individual patient data. The analyses of treatment effect were based on comparisons of treatment groups within the same trial, avoiding any comparisons of patients in one trial with patients in another. Response data were analyzed through a Mantel-Haenszel test,[20] and survival data through a stratified log-rank test.[21]

Summary results were presented graphically in terms of odds ratios (ORs) and their confidence interval (CI) (see details below).[22] An OR between 0 and 1 indicated that 5-FU plus LV was better than 5-FU alone, while an OR greater than 1 indicated that 5-FU plus LV was worse than 5-FU alone.

Survival curves were estimated using the Kaplan-Meier method.[23] The logistic regression model was used to adjust the comparison of tumor response rates for prognostic factors.[24] The Cox regression model was used to adjust the comparisons of survival times for prognostic factors.[25]

Methods for Meta-Analysis

The statistical method used to combine several trials is based on the classical notion of stratification.[20] The method may be used to analyze binary outcomes such as therapeutic responses as well as survival times.[26] Essentially, the method consists of estimating a treatment effect within each trial, and then overall. The simplest method is to express the treatment effect as an OR. The response OR is defined as:

$$\frac{\text{probability of failing to treatment/probability of responding to treatment}}{\text{probability of failing to control/probability of responding to control}}.$$

The survival OR is defined as:

$$\frac{\text{death rate on treatment/survival rate on treatment}}{\text{death rate on control/survival rate on control}}.$$

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Technically, to estimate these ORs, three quantities must be available for each individual trial: O, which is the number of untoward events observed in the treatment group; E, which is the number of events that would be expected in the treatment group if there were no difference between treatment and control; and V, the variance of the number of events.

In the analysis of therapeutic response, O is the number of patients who do not respond to therapy in the treatment group, and E and V are the hypergeometric expectation and variance, respectively. Specifically, E is given by $p(N - R)$, where p is the proportion of patients randomized to the treatment group, N is the total number of patients in the trial, and R is the total number of responses in the trial. With the same notations, V is given by $p(1 - p)R(N - R)/(N - 1)$.[27]

In the analysis of survival, O is the number of deaths in the treatment group, and E and V, are the log-rank expectation and variance, respectively.[27]

Once O, E, and V are available for each trial, the OR can be estimated within each trial by $\exp[(O - E)/V]$, with associated 95% CIs given by $\exp[(O - E)/V \pm 1.96/\sqrt{V}]$. ORs in individual trials are presented graphically as squares of which the area is proportional to the variance (or weight) of each trial.[22] The treatment effect is statistically significant in an individual trial if the CI of the OR does not include 1, or equivalently if the χ^2 test statistic $(O - E)^2/V$ exceeds 3.84 (the 95% critical value of the χ^2 distribution with one degree of freedom).

When n trials are combined, the overall OR, its associated CI, and the corresponding χ^2 test statistic are given by similar formulas with O, E, and V replaced by the summation of the corresponding quantities over the n trials considered.

A statistic for heterogeneity between n trials can be computed as the sum of χ^2 statistics in the n individual trials minus the overall χ^2 statistic. This statistic can be compared with a χ^2 distribution with $(n - 1)$ degrees of freedom.[22]

RESULTS

In the nine clinical trials considered in the present meta-analysis, 1,381 patients were randomized. The mean follow-up was 13 months. The patient characteristics are listed in Table 3. The treatment arms were well balanced within each trial regarding prognostic features.

There were notable differences in patient characteristics among the trials: the Bologna trial[16] included many patients with poor performance status; the NCOG trial[12] and the City of Hope trial[7] included few patients with liver metastases only; the NCOG trial[12] included few patients with a rectal primary location (Table 3).

Analysis of Tumor Response

Objective tumor responses were observed in 64 of 578 (11%) patients allocated to 5-FU (15 CRs plus 49 PRs), and 181 of 803 (23%) patients allocated to 5-FU plus LV (24 CRs plus 157 PRs).

The response ORs are shown in Fig 1 for individual trials and overall. The ORs for individuals trials ranged from 0.18 to 1.21 and were statistically less than unity in seven of the trials, the exceptions are the NCOG trial[12] and the GOIRC trial,[19] whose ORs were 1.03 and 1.21, respectively. The overall response OR was 0.45 (95% CI, 0.34 to 0.60). The overall test for treatment effect was highly significant ($P < 10^{-7}$). The test for heterogeneity was also statistically significant ($P = .023$), confirming

Table 3. Patient Characteristics

	Treatment	No. of Patients (% eligible)	Dates	Male (%)	Median Age (years)	PS < 2 (%)	Primary Colon (%)	Metastasis (%)		Cross-over (%)
								Liver Only	Lung Only	
GITSG[9]	5-FU	113 (95)	1984-87	62	64	89	81	38	8	—
	5-FU + LV	269 (97)	1984-87	62	63	87	83	35	7	
NCOG[12]	5-FU	55 (98)	1984-87	62	64	95	95	16	9	35
	5-FU + LV	107 (100)	1984-87	64	65	95	88	18	7	
GOIRC[18]	5-FU	90 (97)	1986-89	54	62	89	63	47	11	—
	5-FU + LV	91 (97)	1986-89	49	62	88	64	42	9	
GISCAD[19]	5-FU	90 (100)	1987-89	49	60	76	80	46	9	—
	5-FU + LV	92 (100)	1987-89	60	61	82	64	39	2	
Genova[17]	5-FU	73 (100)	1984-90	48	62	89	51	53	8	—
	5-FU + LV	75 (100)	1984-89	60	61	81	48	47	12	
Toronto[8]	5-FU	64 (97)	1984-86	61	63	87	56	58	9	—
	5-FU + LV	66 (100)	1984-86	58	63	91	50	52	6	
City of Hope[7]	5-FU	40 (100)	1983-86	40	55	80	75	13	5	77
	5-FU + LV	39 (92)	1983-87	49	63	82	82	3	3	
RPCI[10]	5-FU	23 (96)	1983-85	87	61	96	74	22	4	22
	5-FU + LV	30 (100)	1984-85	80	62	80	63	30	3	
Bologna[16]	5-FU	30 (100)	1986-89	50	65	27	57	23	10	10
	5-FU + LV	34 (100)	1986-90	76	58	26	53	44	9	
Total	5-FU	578 (98)	1983-90	56	63	84	71	40	9	10
	5-FU + LV	803 (98)	1983-90	61	62	84	71	35	7	

Abbreviation: PS, performance status.

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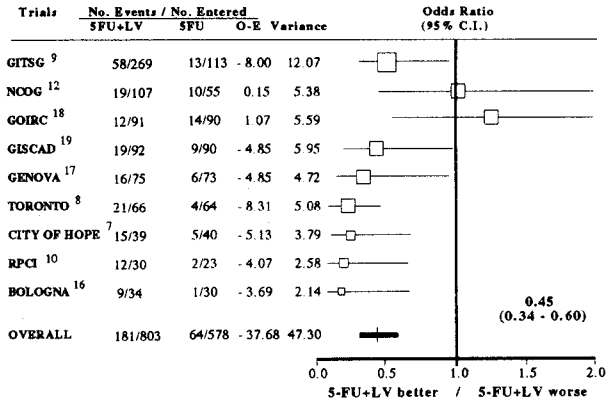

Fig 1. Response ORs in individual trials and overall. Test for treatment effect: $\chi^2 = 30.02$ (1 df); $P < 10^{-7}$. Test for heterogeneity: $\chi^2 = 17.77$ (8 df); $P = .023$.

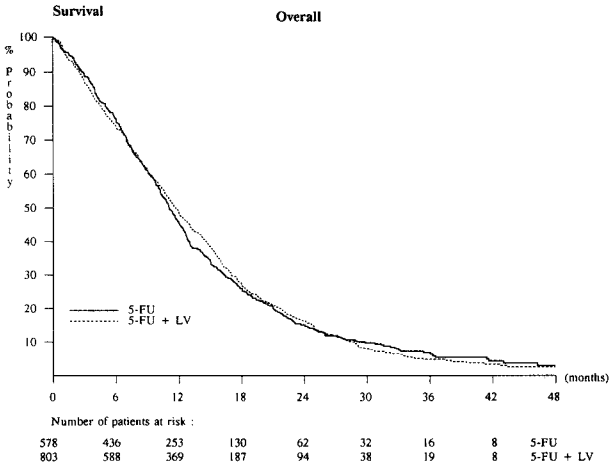

Fig 2. Overall survival.

the difference observed between the NCOG and GOIRC trials and all others.

The response ORs were 0.36 (95% CI, 0.24 to 0.55) for the four trials adding weekly LV, 0.29 (95% CI, 0.17 to 0.48) for the three trials adding monthly LV, and 1.12 for the two trials using a higher 5-FU dose as a control regimen (95% CI, 0.62 to 2.02; Table 4). The tests for treatment effect were highly significant in favor of 5-FU plus LV both in the trials adding weekly LV ($P < 10^{-5}$) and in those adding monthly LV ($P < 10^{-5}$), but far from significant in the trials using a higher 5-FU dose as a control ($P = .71$).

The analysis of the prognostic value of sex, age ($<$ or $>$ 60 years of age), performance status (Eastern Cooperative Oncology Group 0-1 v $>$ 1), primary site (colon v rectum), prior chemotherapy, prior radiotherapy, and localization of metastases (liver only v others) showed none of these factors to be significant predictors for tumor response. When all of the factors and treatment (5-FU v 5-FU plus LV) were simultaneously taken into account in a logistic regression model, treatment was the only variable retained in the model ($P < 10^{-9}$).

Table 4. Response and Survival ORs for the Different Groups of Trials and Overall

	Response ORs (95% CI)	Survival ORs (95% CI)
Trials adding weekly LV*	0.35 (0.24-0.55) $P < 10^{-5}$	0.90 (0.75-1.07) $P = .22$
Trials adding monthly LV†	0.29 (0.17-0.48) $P < 10^{-5}$	0.89 (0.71-1.12) $P = .32$
Trials using a higher-dose 5-FU as control‡	1.12 (0.62-2.02) $P = .71$	1.22 (0.96-1.55) $P = .10$
Overall	0.45 (0.34-0.60) $P < 10^{-7}$	0.97 (0.86-1.09) $P = .57$

*GITSC,[9] RPCI,[10] Bologna,[16] Genova.[17]
†City of Hope,[7] Toronto,[8] GISCAD.[19]
‡NCOG,[2] GOIRC.[18]

Analysis of Survival

Overall survival curves for the nine trials together are depicted in Fig 2. There was no survival advantage of 5-FU plus LV over 5-FU alone ($P = .57$). Median survival was 11.0 months for 5-FU alone, and 11.5 months for 5-FU plus LV. The lack of difference persisted when the trials with cross-overs were excluded from the analysis ($P = .51$).

Survival ORs are shown in Fig 3 for individual trials and overall. None of the individual trials showed a statistically significant advantage of 5-FU plus LV in terms of survival: the CIs of individual ORs all crossed the unity (no difference) line. The overall survival OR was 0.97 (95% CI, 0.86 to 1.09).

There was no statistically significant survival advantage of 5-FU plus LV in trials of weekly 5-FU plus LV

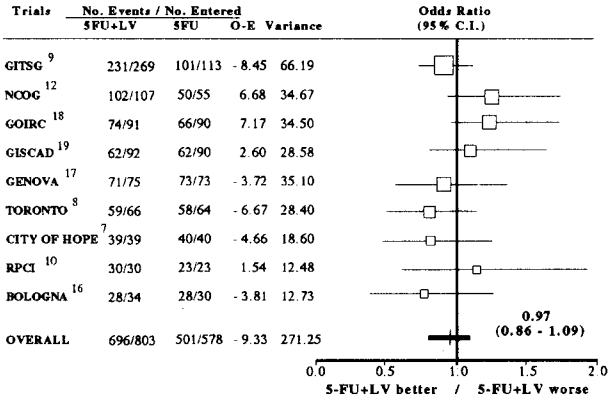

Fig 3. Survival ORs in individual trials and overall. Test for treatment effect: $\chi^2 = .32$ (1 df); $P = .57$. Test for heterogeneity: $\chi^2 = 8.33$ (8 df); $P = .41$.

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($P = .22$), nor in trials of monthly courses ($P = .32$). In trials using a higher 5-FU dose as a control regimen, the survival difference was in the opposite direction, but again this was not statistically significant ($P = .10$).

The analysis of individual prognostic factors showed that patients with a good performance status and those with metastases confined to the liver had a significantly better prognosis in terms of survival ($P < 10^{-9}$ and $P = .046$, respectively). When all factors and treatment were simultaneously taken into account in a Cox regression model, performance status remained as the only factor of prognostic importance ($P < 10^{-9}$).

DISCUSSION

Despite several phase I and II trials and the enrollment of more that 1,500 patients in 10 randomized clinical trials, the advantage of the modulation of 5-FU by LV in patients with advanced colorectal cancer is still debated. Although the advantage of adding LV to 5-FU to enhance tumor response may seem to be established, several questions remain. The differences between the various trial protocols and the accumulation of sometimes conflicting results make it difficult to draw any definite conclusions.

Meta-analysis is an attempt to overcome these difficulties. By pooling data from all studies without comparing the patients of one study with those of another, it increases the likelihood of detecting small but worthwhile treatment benefits. Differences among the trials are not necessarily a disadvantage, providing that these trials all address essentially the same question. In the case presented, even though there were obvious variations in treatment protocols, a straightforward grouping of the trials could be defined on the basis of the dose/schedule of 5-FU and LV.

The present meta-analysis confirmed the advantage of 5-FU plus LV over 5-FU alone in terms of objective tumor response; the overall response rate of 5-FU plus LV was more than twice that of 5-FU alone (23% *v* 11%; OR, 0.45; $P < 10^{-7}$).

The benefit of 5-FU plus LV in terms of objective tumor response was observed both in trials of weekly LV (OR, 0.36) and in trials of monthly LV (OR, 0.29). Because the planned dose of LV was generally higher in trials adding weekly LV than in those adding monthly LV (2,000 *v* 1,000 mg/m^2 LV per month), these results do not suggest a dose-response relationship within the range considered. However, this approach to the role of LV dose intensity is not based on a direct comparison of randomized groups and, therefore, is of limited value. A proper comparison of low-dose LV (20 mg/m^2 on days 1 to 5 every 4 to 5 weeks) versus high-dose LV (500 mg/m^2 weekly six times every 8 weeks) was recently performed in a randomized trial by the NCCTG/Mayo Clinic.[14] The response rates were 33% in the low-dose LV arm, and 28% in the high-dose LV arm. The first results of this trial did not seem to indicate any response or survival difference between the two regimens.

In the present series of trials, there was no advantage of 5-FU plus LV in terms of tumor response in trials using a higher dose of 5-FU as a control (OR, 1.12). In these trials, the advantage of the modulation of 5-FU by LV may have been obliterated by the difference in dose of 5-FU between the two arms.

The highly significant overall advantage of 5-FU plus LV in terms of tumor response rate did not lead to any discernible advantage in terms of survival. Among the nine analyzed trials, only the Toronto trial had shown a statistically significant advantage in survival for patients treated with 5-FU plus LV[8]; with more follow-up, the survival advantage was no longer statistically significant.

The following four hypotheses can be proposed to explain the absence of benefit of 5-FU plus LV in terms of survival: First, the duration of tumor responses may have been too short to lead to a benefit in terms of survival. Although the duration of response in individual patients had not been made available for most trials, there is evidence that the median duration of tumor response to 5-FU plus LV generally exceeds 6 months.[4,7,9-11,19] This duration should be sufficient to expect a survival benefit. Second, the response rate of 5-FU plus LV, although significantly better than that of 5-FU alone, could still be too small to affect survival. In fact, three of every four patients did not respond to the 5-FU plus LV regimen. Therefore, the number of patients with an objective response may have been too small to have a significant impact on overall survival, even though almost 1,400 patients were included in this meta-analysis. Third, the CR rate was under 3% in both treatment groups, with no significant difference between 5-FU plus LV (3%) and 5-FU alone (2.6%). Such CR rates may be too low to lead to an increase of survival. Finally, patients not responding to 5-FU alone were switched to the 5-FU plus LV group in four trials.[7,10,12,16] When these trials were excluded from the analysis, no advantage of 5-FU plus LV in terms of survival was apparent ($P = .51$). Except for these formally planned cross-overs, little information could be obtained on treatments given in second-line. According to all of the principal investigators, less than 20% of patients with a tumor progression after 5-FU alone could receive a second-line chemotherapy. Most of them received 5-FU plus LV and may have had a response to this regimen.[28]

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Thus, second-line treatments may have obscured any small-to-moderate impact of 5-FU plus LV on survival.

No data from the published NCCTG/Mayo Clinic trial[11] were included in the previously mentioned analysis. This trial had six treatment arms, and included 429 patients. A total of 212 patients were randomized to 5-FU alone, 5-FU plus high-dose LV, and 5-FU plus low-dose LV. Among these patients, 111 had measurable disease. The objective tumor response rates were 10% in the 5-FU–alone arm, 26% in the 5-FU plus high-dose LV arm ($P = .04$), and 43% in the 5-FU low-dose LV arm ($P = .001$). These results are fully consistent with our conclusions regarding the advantage of 5-FU plus LV on tumor response. The NCCTG/Mayo Clinic trial also identified a statistically significant advantage of both high-dose and low-dose LV in terms of survival ($P = .037$ and $P = .050$, respectively). Although these results seem to be at variance with our own conclusions regarding the lack of a survival benefit of 5-FU plus LV, the survival advantage in the NCCTG/Mayo Clinic trial was limited to patients with nonmeasurable disease. Thus, this trial does not add evidence that 5-FU plus LV prolongs survival in patients with measurable disease. In the NCCTG/Mayo Clinic trial, the survival OR for all eligible patients, with or without measurable disease, was 0.72 (95% CI, 0.50 to 1.03) in the 5-FU plus high-dose LV arm, and 0.74 (95% CI, 0.52 to 1.06) in the 5-FU plus low-dose LV arm. Adding this information to our meta-analysis provides an overall survival OR of 0.92 (95% CI, 0.83 to 1.02). Although this is still not significantly different from unity ($P = .14$), it is clearly more encouraging that the value of 0.97 found among the nine trials previously analyzed. It is quite possible, although still speculative, that a true survival improvement can be achieved by 5-FU plus LV in the less advanced stages of the disease. By contrast, in the more advanced stages such as those included in the present trial, further research is undoubtedly required to enhance CR rates and survival. The impressive benefit of 5-FU modulation in terms of tumor shrinkage should motivate continued laboratory work as well as clinical trials in that direction.

The present meta-analysis focuses on response and survival data, even though other end points, including toxicity, are relevant in the choice of a chemotherapy regimen. However, no attempt was made to collect and analyze toxicity data. Indeed, the power of meta-analysis to detect minor differences may not be needed to compare the treatment toxicities of regimens that differ substantially in their activity. Additionally, the heterogeneity among trials in the reporting of toxicity, in the frequency of evaluation, and in the amount of supportive care would have made a meta-analysis of toxicity data rather problematic.

In conclusion, this meta-analysis confirms that 5-FU plus IV LV offers a definite advantage over 5-FU alone in terms of tumor response rate for patients with advanced colorectal cancer. This benefit was observed in trials using both weekly and monthly administration of LV. However, no benefit was observed in overall survival. The large number of patients who did not respond to treatment, and cross-overs from 5-FU alone to 5-FU plus LV are possible explanations for this lack of difference. On a more general level, our results indicate that an improvement in the response rate of patients with measurable disease does not automatically translate into a survival benefit. Tumor response should not be considered a valid surrogate end point for survival in planning future clinical trials in advanced colorectal cancer.[29]

ACKNOWLEDGMENT

We thank all collaborators for providing individual patient data. The collaborators were: P. Creaven, N. Petrelli, Y. Rustum, P. Burke (Roswell Park Cancer Institute, Buffalo, NY and Gastrointestinal Tumor Study Group); F. Valone, B. Brown, R.W. Carlson (Northern California Oncology Group); M. Bacchi, F. Di Costanzo (Italian Oncology Group for Clinical Research); G. Luporini, R. Labianca, G. Pancera, B. Cesana (Italian Group for the Study of Digestive Tract Cancer); M.T. Nobile, R. Rosso, M.R. Sertoli, A. Sobrero (Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy); C. Erlichman, S. Fine, T. Gadalla (Princess Margaret Hospital, Toronto, Canada); A. Wong (Tom Baker Cancer Clinic, Calgary, Canada); J.H. Doroshow (City of Hope National Medical Center, Duarte, CA); A. Martoni, A Cricca, F. Pannuti, M. Casadio (Ospedale Policlinico G. Orsola-M. Malpighi, Bologna, Italy); D. Machover (Hôpital Tenon, Paris, France); P. Piedbois and J.P. Le Bourgeois (Hôpital Henri Mondor, Créteil, France); and M. Buyse (European Organization for Research and Treatment of Cancer, and International Institute for Drug Development, Brussels, Belgium).

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