Efficacy of Intravenous Continuous Infusion of Fluorouracil Compared With Bolus Administration in Advanced Colorectal Cancer

By the Meta-analysis Group In Cancer

Purpose: **The administration of fluorouracil (5-FU) by continuous intravenous infusion (CI) is an alternative to the bolus administration of 5-FU in patients with advanced colorectal cancer. Although more than 1,200 patients have been enrolled onto randomized trials that compared these two treatment modalities, there is still no definitive evidence of an advantage of 5-FU CI, and the magnitude of this advantage, if any, is also controversial. A meta-analysis was performed to assess this benefit in terms of tumor response and survival, and to compare the toxicity profiles of these two modalities of administration of 5-FU.**

Design: **Individual data of 1,219 patients included in six randomized trials served as the basis for this meta-analysis, which was conducted by an independent secretariat in close collaboration with the investigators.**

Results: **Tumor response rate was significantly higher in patients assigned to 5-FU CI than in patients assigned to 5-FU bolus (22% v 14%; overall response odds ratio, 0.55; 95% confidence interval [95% CI], 0.41 to 0.75; $P = .0002$). Overall survival was also significantly higher in patients assigned to 5-FU CI (overall hazards ratio [HR], 0.88; 95% CI, 0.78 to 0.99; $P = .04$), although the median survival times were close. Multivariate analyses showed that randomized treatment and performance status were the only two significant predictors of tumor response, whereas the same plus primary tumor site were independent significant predictors of survival (patients with rectal cancer did somewhat better). Grade 3 or 4 hematologic toxicity was more frequent in patients assigned to 5-FU bolus (31% v 4%; $P < 10^{-16}$), whereas hand-foot syndrome was more frequent in the 5-FU CI group (34% v 13%; $P < 10^{-7}$).**

Conclusion: **5-FU CI is superior to 5-FU bolus in terms of tumor response and achieves a slight increase of overall survival. The hematologic toxicity is much less important in patients who receive 5-FU CI, but hand-foot syndrome is frequent in this group of patients.**

J Clin Oncol 16:301-308.

APPROXIMATELY 50% of patients with colorectal cancer have metastatic or nonoperable disease at the time of diagnosis, or will develop metastases or a local recurrence in the following months. Fluorouracil (5-FU) is still considered as the standard treatment for patients with incurable colorectal cancer, but tumor response rates and survival durations are low when 5-FU is given alone as an intravenous bolus injection. In the past 15 years, biomodulation of 5-FU by leucovorin (LV) or by methotrexate (MTX) has been extensively explored. These biomodulations allow doubling of tumor response when compared with 5-FU bolus alone, without a major impact on survival duration.[1,2]

The activity of 5-FU is relatively S-phase–dependent and the half-life in serum is short. Thus, prolonged infusion may expose a relatively larger proportion of tumor cells to 5-FU. Moreover, extending the time of infusion is attractive for tumors with a relatively slow doubling time, such as colorectal cancers.[3,4] It has been suggested that the mechanisms of resistance to 5-FU depend on the modality of its administration. Bolus administration of 5-FU inhibits RNA synthesis, whereas continuous infusion (CI) may be more cytotoxic via inhibition of thymidilate synthase.[5] Delivering 5-FU by CI rather than by bolus intravenous infusion permits the delivery of more drug and changes the limiting toxicity from myelosuppression to stomatitis and hand-foot syndrome. This shift of the toxicity profile is due to a much higher concentration of 5-FU in the bone marrow after bolus infusion than after CI.[4] It is well known that CI allows higher doses of 5-FU than rapid bolus infusion.[6]

Early nonrandomized studies with 5-FU CI reported response rates of 30% to 40%.[7-9] Subsequently, seven phase III trials that compared bolus intravenous 5-FU versus 5-FU CI have been undertaken.[10-16] Overall, more than 1,200 patients have been included in these trials. Most of the studies confirmed that CI increased the chance of tumor response to 5-FU when compared with bolus infusion. However, the exact magnitude of this tumor response benefit and its impact on survival are still debatable. We addressed these questions in a meta-analysis based on individual patient data of all trials that compared 5-FU bolus versus 5-FU CI chemotherapy. The two main end points of interest were tumor response and overall survival. The main toxicities were also studied.

See Appendix for Writing Committee and Collaborators.

Submitted January 15, 1997; accepted July 23, 1997.

Supported in part by the Association Europenne de Recherche en Oncologie, Creteil, France.

Address reprint requests to Pascal Piedbois, MD, Department of Oncology, Henri Mondor Hospital, Creteil, France; Email pascal.piedbois@hmn.ap-hop-paris.fr.

0732-183X/98/1601-0009$3.00/0

DESIGN

Selection of Trials

The search of all randomized clinical trials was initiated in January 1994 by consulting MEDLINE and the proceedings of major congresses over the last 10 years, and thereafter through personal contacts with the investigators. Seven trials were identified.[10-16] One of the trials (70 patients)[10] could not be included in the meta-analysis, because original patient data could not be retrieved. Moreover, the randomization procedure adopted in this old trial was based on hospital record numbers, a procedure that can lead to serious biases.[17,18]

Trials included in the meta-analysis are listed in Table 1, along with a brief description of treatment schedules. All trials had started to accrue patients between 1984 and 1989. In all trials, treatment was maintained until disease progression or severe toxicity.

The Eastern Cooperative Oncology Group (ECOG) study[11] was a three-arm trial. The patient arm that received 5-FU CI plus cisplatin was not considered in the meta-analysis, because it could not be directly compared with any other treatment arm. For the same reason, three of the seven arms of the Southwest Oncology Group (SWOG) trial[13] were not considered in the present study: the 5-FU CI plus N-(phosphonacetyl)-L-aspartic acid (PALA) arm, the high-dose weekly CI 5-FU arm, and the 5-FU bolus plus high-dose weekly LV arm. The four arms of the SWOG trial that were kept in the meta-analysis were compared two by two. The first comparison, which will be called the SWOG 1 comparison in this report, compared 5-FU CI 300 mg/m^2 from day 1 to day 28 every 35 days versus 5-FU bolus 500 mg/m^2 from day 1 to day 5 every 35 days. The second comparison, which will be called the SWOG 2 comparison here, compared 5-FU CI 200 mg/m^2 from day 1 to day 28 every 35 days plus LV 20 mg/m^2 intravenously every 7 days versus 5-FU bolus 425 mg/m^2 plus LV 20 mg/m^2 intravenously from day 1 to day 5 every 28 days for two courses then every 35 days (Table 1).

In the SWOG 2 comparison,[13] and in the trial performed in Jerusalem,[16] 5-FU was modulated by LV in the 5-FU bolus arms and in the 5-FU CI arms.

We expressed the duration of CI as a percentage of time. In the ECOG trial[11] and the Mid-Atlantic Oncology Program (MAOP) trial,[14] CI 5-FU was administered without a rest period, ie, for 100% of the time. In the SWOG trial,[13] 5-FU infusion was maintained over more than 80% of the time, whereas in the National Cancer Institute of Canada (NCIC) trial[12] and in the French trial,[15] the duration of 5-FU infusion was between 33% and 50% of the time.

Predicted cumulative dose of 5-FU is listed in Table 2 for each trial. In all trials except the Jerusalem trial,[16] the predicted cumulative dose of 5-FU was much higher in the 5-FU CI arm than in the 5-FU bolus arm. Actually received doses of 5-FU were not available.

Table 2. Predicted Cumulative Doses of 5-FU in 5-FU Bolus Arm and in 5-FU CI Arm

Trial	Treatment Arm	After Week No. 1	4	8	12
ECOG[11]	5-FU CI	2,100	8,400	16,800	25,200
	5-FU bolus	2,500	3,700	6,100	8,500
NCIC[12]	5-FU CI	2,450	4,900	9,800	14,700
	5-FU bolus	2,250	2,250	4,500	6,750
SWOG 1[13]	5-FU CI	2,100	8,400	14,700	21,000
	5-FU bolus	2,500	2,500	5,000	7,500
MAOP[14]	5-FU CI	2,100	8,400	16,800	25,200
	5-FU bolus	2,500	2,500	5,000	7,500
France[15]	5-FU CI	5,250	10,500	15,750	21,000
	5-FU bolus	2,500	2,500	5,000	7,500
SWOG 2[13]	5-FU CI	1,400	5,600	9,800	14,000
	5-FU bolus	2,125	2,125	4,250	6,375
Jerusalem[16]	5-FU CI	3,000	6,000	9,000	12,000
	5-FU bolus	3,000	6,000	9,000	12,000

NOTE. Doses are expressed in mg/m^2.

Protocol for the Meta-Analysis

A protocol was sent in September 1994 to all principal investigators, who were asked to provide individual patient data. Information requested for every randomized patient included identification number, date of randomization, eligibility, treatment assigned by randomization, age at randomization, sex, performance status according to the ECOG scale, primary tumor site (colon or rectum), prior treatment (chemotherapy or radiotherapy in metastatic areas), localization of metastases, overall response status with the first assigned treatment, crossover to another treatment arm, second treatment arm in case of crossover, date of death or last visit, survival status, and cause of death if applicable. In contrast with previous meta-analyses performed by the Meta-analysis Group in Cancer, investigators were also asked to provide individual patient data on the main toxicities: hematologic toxicity, hand-foot syndrome, and other nonhematologic toxicities (diarrhea, nausea/vomiting, and mucositis).

Table 1. Randomized Clinical Trials Comparing 5-FU CI Versus 5-FU Bolus in Patients With Advanced Colorectal Cancer

Trial	5-FU CI	5-FU Bolus	No. of Patients
ECOG[11]	5-FU 300 mg/m^2/d without interruption	5-FU 500 mg/m^2 d1-d5, then 5-FU 600 mg/m^2 d, q 7 d	324
NCIC[12]	5-FU 350 mg/m^2 d1-d15, q 28 d	5-FU 400-450 mg/m^2 d1-d5 q 28 d	185
SWOG 1[13]	5-FU 300 mg/m^2 d1-d28, q 35 d	5-FU 500 mg/m^2 d1-d5, q 35 d	181
MAOP[14]	5-FU 300 mg/m^2/d without interruption	5-FU 500 mg/m^2 d1-d5, q 35 d	173
France[15]	5-FU 750 mg/m^2 d1-d7, q 21 d	5-FU 500 mg/m^2 d1-d5, q 28 d	155
SWOG 2[13]	5-FU 200 mg/m^2 d1-d28, q 35 d, + folinic acid 20 mg/m^2 IV q 7 d	5-FU 425 mg/m^2 + folinic acid 20 mg/m^2 IV d1-d5, q 28 d $\times$2, then q 35 d	175
Jerusalem[16]	5-FU 600 mg/m^2 + folinic acid 15 mg/6 h orally d1-d5, q 21 d	5-FU 600 mg/m^2 + folinic acid 15 mg/6 h orally d1-d5, q 21 d	26

NOTE. The ECOG trial was a 3-arm trial. The 5-FU CI plus cisplatin arm is not considered in the meta-analysis (see text). The SWOG trial was a 7-arm trial. Three treatment arms are not considered in the meta-analysis, because they cannot be directly compared with any other treatment arm (see text).

Abbreviations: d, days; q, every; IV, intravenous; h, hours.

Data Collection

All data were provided by the investigators of individual trials and were received by April 1996 with the exception of some toxicity data, which were completed by December 1996. Data were extensively checked and discussed with all collaborators at a plenary meeting of the group.

Patient Characteristics

A total of 1,219 patients were considered in the meta-analysis. The median patient age was 63 years. Sixty-one percent of patients were male. At the time of analysis, 91% of patients had died. Main patient characteristics are listed in Table 3. There were no apparent differences in patient characteristics among trials. In all trials except the SWOG trial,[13] inclusion criteria specified that the patient must have measurable disease. In the SWOG trial,[13] 116 patients (33%) had nonmeasurable disease. These patients were included in the survival analysis, but not in the tumor response analysis.

Tumor Response and Survival

Complete response (CR) and partial response (PR) criteria adopted in individual trials followed the classic World Health Organization (WHO) recommendations[19] and were identical in all trials. Patients with minimal response, stable disease, or tumor progression were considered to have had no response for the purpose of the meta-analysis. Duration of survival was calculated from the date of randomization to the date of death, whatever the cause of death.

Toxicity

Toxicity reported in individual trials followed the WHO toxicity scale or another toxicity scale easily transposable into the WHO grading system. Only grade 3 or 4 hematologic or nonhematologic toxicities were considered in the analyses. The hand-foot syndrome was considered as a binary parameter (yes or no) and there was no attempt to adopt any grading system for this particular toxicity.

Statistical Analysis

Statistical methods for meta-analyses based on individual patient data have been described in previous publications by our group.[1,2,20] All analyses were based on an intention-to-treat basis, without any patient exclusion.

Response data were analyzed through a Mantel-Haenszel test[21] and through a logistic regression model.[22] Survival data were analyzed through a stratified log-rank test[23] and through a proportional hazards regression model.[24] The median survival time and its 95% confidence interval (95% CI) were estimated using reflected intervals.[25] All P values resulted from the use of two-sided statistical tests.

The SWOG 2 comparison[13] and the Jerusalem trial,[16] in which 5-FU was modulated by LV, were included in the main analysis. This analysis was stratified into two groups of trials according to the modulation of 5-FU by LV (the SWOG 2 comparison and the Jerusalem trial *v* the other trials).

RESULTS

Tumor Response

A total of 1,103 patients have been included in the tumor response analysis, since 116 patients in the SWOG trial[13] had nonmeasurable disease. Tumor response rate was 22% for patients assigned to 5-FU CI (CR, 3%; PR, 19%) and 14% for patients assigned to 5-FU bolus (CR, 2%; PR, 12%). The response odds ratios (ORs) are presented in Fig 1. The overall response OR was 0.55 (95% CI, 0.41 to 0.75), which indicates a highly significant advantage for 5-FU CI (P = .0002). This is equivalent to a risk reduction of 45% with a standard error of 12%. Interestingly, although there was a general trend in favor of 5-FU CI, the advantage of 5-FU CI over 5-FU bolus was statistically significant in only

Table 3. Patient Characteristics

Trial	Accrual Period	Treatment Arm	No. of Patients	Primary Colon (%)	PS < 2 (%)	Metastases (%)	
						Liver Only	Lung Only
ECOG[11]	1987-90	5-FU CI	162	81	94	23	8
		5-FU bolus	162	80	89	23	7
NCIC[12]	1986-89	5-FU CI	95	68	85	49	5
		5-FU bolus	90	78	89	49	4
SWOG 1[13] *	1989-92	5-FU CI	88	85	88	NA	NA
		5-FU bolus	93	72	89	NA	NA
MAOP[14]	1984-86	5-FU CI	88	76	90	34	5
		5-FU bolus	85	74	91	34	8
France[15]	1987-90	5-FU CI	77	66	92	44	12
		5-FU bolus	78	64	90	51	12
SWOG 2[13] *	1989-92	5-FU CI	86	70	92	NA	NA
		5-FU bolus	89	72	88	NA	NA
Jerusalem[16]	1984-86	5-FU CI	11	38	82	45	18
		5-FU bolus	15	80	93	33	13
Total	1984-92	5-FU CI	607	75	91	35	7
		5-FU bolus	612	75	90	36	7

Abbreviations: PS, performance status; NA, not available.

*SWOG 1 and SWOG 2 refer to 2 different arms of 1 SWOG trial (see Table 1).

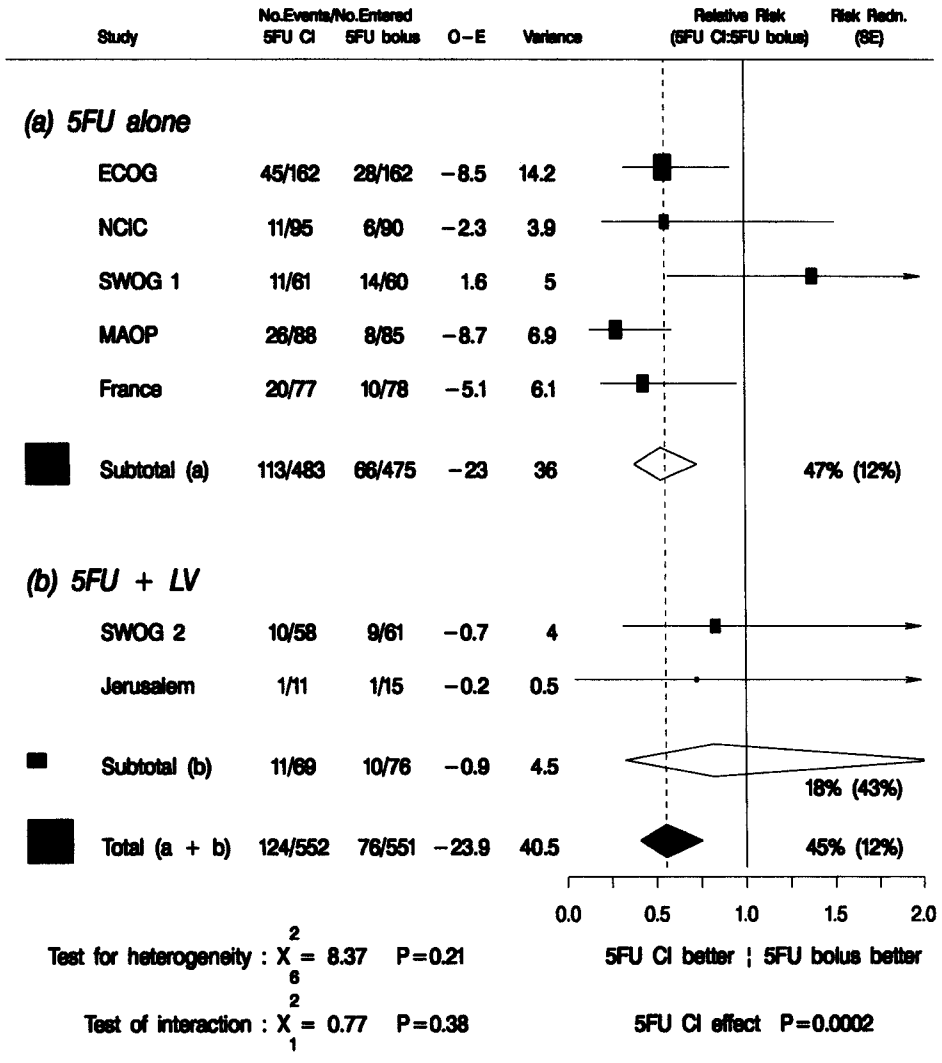

Fig 1. Tumor response OR in individual trials and overall. O, observed; E, expected; Risk Redn, reduction in the odds of not achieving a tumor response. (Test for treatment effect, $P = .0002$.)

three individual trials (the ECOG trial, the MAOP trial, and the French trial).

In a logistic regression model, treatment and performance status were the only independent prognostic factors. There was no interaction between the two.

Median duration of tumor response was 7.1 months in the 5-FU CI arm (95% CI, 5.7 to 8.5 months) and 6.7 months in the 5-FU bolus arm (95% CI, 5.7 to 8.5 months).

In the group of trials that used a biochemical modulation of 5-FU by LV (SWOG 2 comparison and Jerusalem trial), the difference between continuous 5-FU + LV and bolus 5-FU + LV failed to reach statistical significance (tumor response OR, 0.82; 95% CI, 0.33 to 2.07). However, the statistical tests have low power given that only 145 patients were included in this group.

The duration of the 5-FU infusion in the 5-FU CI group did not appear to have an impact on the benefit of CI (data not shown). The tumor response OR was 0.55 (95%CI, 0.37 to 0. 81) when the duration of 5-FU infusion was greater than 80% of the time (ECOG trial, MAOP trial, and SWOG 1 comparison), compared with 0.48 (95%CI, 0.26 to 0.89) when the duration of 5-FU infusion was between 33% and 50% of the time (χ^2 for interaction, 0.14; $P = .70$).

Survival

Survival hazards ratios (HRs) are presented in Fig 2. Although no individual trial showed a benefit of 5-FU CI, their combination led to a small but statistically significant advantage of 5-FU CI over 5-FU bolus (HR, 0.88; 95% CI, 0.78 to 0.99; $P = .04$). The median survival duration was

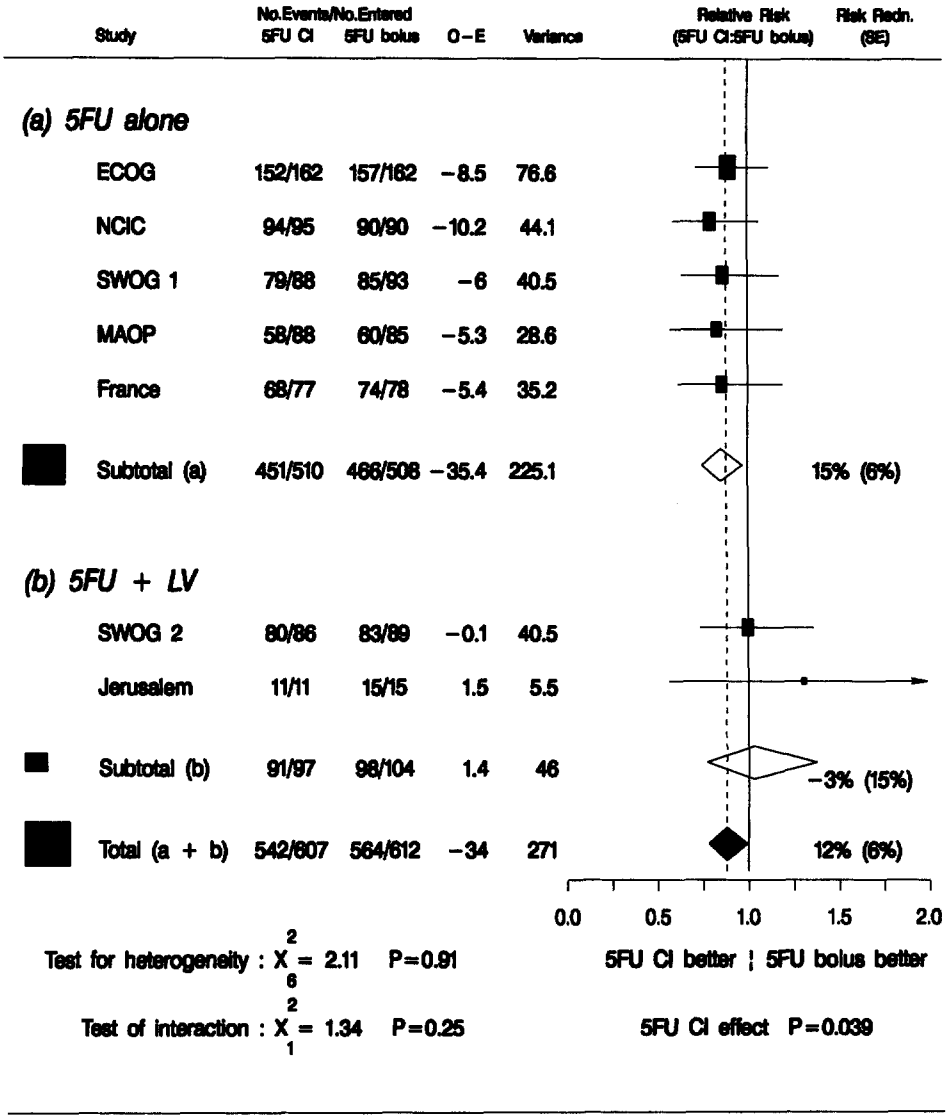

Fig 2. Survival HR in individual trials and overall. (Test for treatment effect, $P = .039$.)

12.1 months (95% CI, 11 to 13.1) in the 5-FU CI group versus 11.3 months (95% CI, 10.5 to 12) in the 5-FU bolus group. Survival curves are shown in Fig 3. The number of patients still alive in the 5-FU CI group versus the 5-FU bolus group were, respectively, 99 versus 102 at 2 years, 39 versus 23 at 3 years, and 16 versus six at 4 years.

When 5-FU was modulated by LV (SWOG 2 comparison and Jerusalem trial), overall survival did not appear to be better for patients assigned to 5-FU CI compared with patients assigned to 5-FU bolus (HR, 1.03; 95% CI, 0.77 to 1.38; $P = .84$), but as for tumor response, this result was based on too few patients to be informative (Fig 2).

A Cox regression model[24] stratified for trial showed that treatment, performance status, and primary tumor site were independent prognostic factors for survival (Table 4). There was no interaction between the effect of treatment and any prognostic factors.

Toxicity

A grade 3 or 4 hematologic toxicity was reported in 31% of patients allocated to 5-FU bolus (191 of 612) compared with 4% of patients assigned to 5-FU CI (23 of 607). This difference is highly significant ($P < 10^{-16}$). There were few cases of grade 3 or 4 anemia or thrombocytopenia, and most of the hematologic toxicity consisted of leucopenia.

Thirteen percent of patients assigned to 5-FU bolus (77 of 612) experienced hand-foot syndrome, compared with 34% of patients assigned to 5-FU CI (206 of 607)($P < 10^{-7}$).

The proportions of other nonhematologic toxicities were identical in the two treatment groups (14% and 13% for

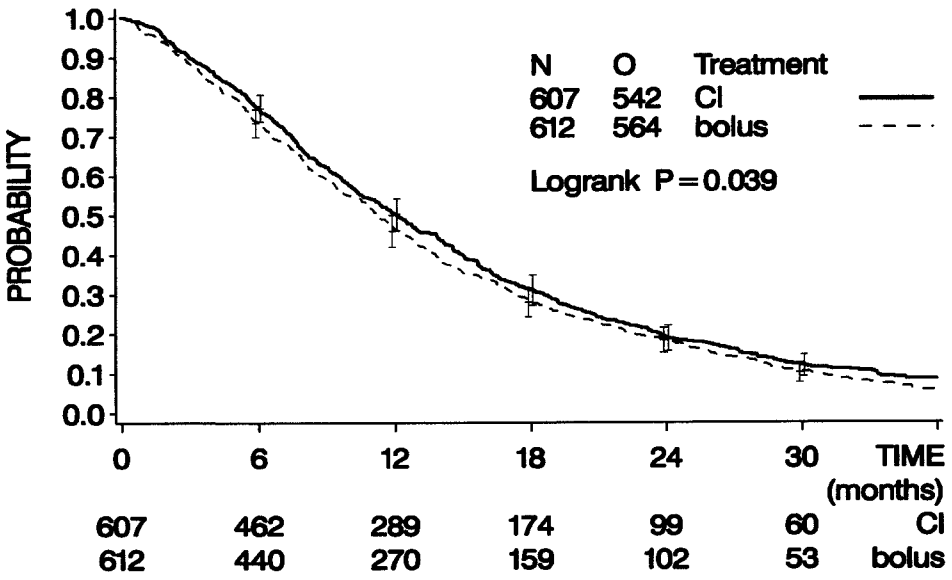

Fig 3. Overall survival curves.

5-FU bolus and 5-FU CI arms, respectively). The incidences of diarrhea, nausea/vomiting, and mucositis did not differ between the two treatment groups.

DISCUSSION

Meta-analyses previously performed by our group in the field of advanced colorectal cancer addressed the question of the modulation of 5-FU by LV[1] or by MTX,[2] and the question of hepatic arterial infusion of fluoropyrimidines.[20] All of these questions were addressed through meta-analyses based on individual patient data.[26] These meta-analyses showed that 5-FU alone given as a bolus intravenous injection yields a tumor response rates between 10% and 14%, and a median survival duration of approximately 1 year. Biochemical modulation of 5-FU by LV[1] or by MTX[2] doubles tumor response rate, without a substantial improvement of survival. Administration of fluoropyrimidines by hepatic artery yields much higher tumor response rates than intravenous 5-FU (41% *v* 14%),[20] with an increase of 3.8 months in median survival, which failed to reach statistical significance. Moreover, hepatic artery infusion is limited to patients with metastases confined to the liver.

Table 4. Independent Prognostic Factors for Tumor Response and Survival

Parameter	Tumor Response		Survival	
	χ^2	*P*	χ^2	*P*
Treatment (5-FU CI *v* 5-FU bolus)	13.96	.0002	5.02	.025
PS (0 *v* 1 *v* 2+)	28.01	<.0001	92.06	<.0001
Primary tumor site (rectum *v* colon)	NS	NS	9.09	.003

Abbreviation: NS, not significant.

The present meta-analysis confirmed the limitations of bolus intravenous 5-FU. In this group of patients, the tumor response rate was 14% and the median survival duration was 11.3 months. Tumor response rate was significantly higher in the group of patients assigned to 5-FU CI (22% *v* 14%, $P = .0002$). Interestingly, the tumor response rate obtained with 5-FU CI is close to those observed in previously performed meta-analyses with 5-FU/LV[1] or with 5-FU/MTX[2] regimens (23% and 19%, respectively). However, an indirect comparison between 5-FU CI and 5-FU–modulated regimens may be misleading because of possible differences between patient conditions in these three sets of trials. Nevertheless, it appears that the best tumor response rates with the most widely used chemotherapy regimens (5-FU CI, 5-FU/LV, or 5-FU/MTX) are approximately 20% to 25%. It is also interesting to note that these regimens do not result in an increase of CR rates when they are compared with intravenous bolus 5-FU. In the present study, the CR rate was 3% in patients assigned to 5-FU CI and 2% in patients assigned to 5-FU bolus. Direct comparisons of 5-FU CI and 5-FU/LV failed to show a significant difference in favor of either treatment approach. Such comparisons were performed in the SWOG trial,[13] which had, among others, two 5-FU intravenous push plus LV arms (high-dose or low-dose LV). In this trial, tumor response rates were 27% for 5-FU IV push plus low-dose LV and 21% for 5-FU IV push plus high-dose LV, compared with 29% for 5-FU CI. Median survival times were 14 months, 13 months, and 15 months for 5-FU IV push plus low-dose LV, 5-FU IV push plus high-dose LV, and 5-FU CI, respectively. A direct comparison of 5-FU CI and 5-FU/LV was also performed in

a trial conducted in France by Conroy et al.[27] In this trial, 150 patients were randomized to receive 5-FU CI 300 mg/m^2/d (plus allopurinol) or 5-FU 370 mg/m^2 (escalated to 400 mg/m^2) plus LV 200 mg/m^2 intravenously from day 1 to day 5 every 28 days. Tumor response rates were 20% and 16% for the 5-FU CI and 5-FU bolus groups, respectively. The median survival duration was 9 months in both treatment groups.

In the present meta-analysis, the administration of 5-FU by CI rather than as a bolus also permitted a statistically significant increase of survival duration ($P = .04$). However, the magnitude of the benefit in terms of survival was small. The median survival time was 12.1 months in the 5-FU CI group compared with 11.3 months in the 5-FU bolus group. The contrast between a large benefit in tumor response rate and a small benefit in survival had also been observed in other meta-analyses conducted in advanced colorectal cancer.[1,2,20] The relationship between response and survival in advanced disease is complex and is currently being investigated by our group.[28] In patients with resected rectal cancer, O'Connell et al[29] showed a statistically significant survival benefit of 5-FU CI over 5-FU bolus.

In the present study, multivariate analyses showed that randomized treatment and performance status were the only two independent prognostic factors for response. These, plus the primary tumor site, were independent prognostic factors for survival. Once again, performance status was the most important prognostic factor for both tumor response and survival. The following figures illustrate the influence of performance status. Tumor response rate was 25% in patients with grade 0 performance status (ECOG scale), 14% in patients with grade 1 performance status, and 8% in patients with performance status $\geq$ grade 2. The median survival time was 15.1 months in patients with grade 0 performance status, 9.6 months in patients with grade 1 performance status, and 5.6 months in patients with $\geq$ grade 2 performance status. In previously performed meta-analyses,[1,2,20] primary tumor site was not found to be a prognostic factor for survival. No plausible explanation was found in the currently available data to explain the fact that in the present study patients with rectal cancer had a better survival than patients with a colon cancer (median survival times, 12.9 months and 11.3 months, respectively).

Subgroup analyses must be regarded with extreme caution. When 5-FU was modulated by LV,[13,16] there seemed to be no difference between 5-FU CI and 5-FU bolus in terms of either tumor response or survival (Figs 1 and 2). However, tests of interaction indicated that this apparent difference between trials according to biochemical modulation of 5-FU was not statistically significant. The same statistical approach showed no striking difference between trials according to the duration of 5-FU infusion.

In most of the trials, the cumulative dose of 5-FU achieved by CI was two to three times higher than with bolus administration (Table 2). Such an increase in 5-FU dose plus the prolonged exposure of tumor cells to the drug may explain the better results of CI over bolus administration.

Toxicity profiles were quite different between the two treatment modalities. Hand-foot syndrome was much more frequent in patients who received 5-FU CI than in patients who received 5-FU bolus, whereas grade 3 to 4 hematologic toxicity was much more frequent in the 5-FU bolus group. No significant difference was observed between the two groups in terms of diarrhea, nausea/vomiting, or mucositis incidence.

We conclude that 5-FU CI is superior to 5-FU bolus in terms of tumor response and survival, even though the magnitude of the benefit in survival is small. The advantage of 5-FU CI over 5-FU bolus is reinforced by the fact that severe hematologic toxicity is less frequent in patients who receive 5-FU CI. The advantage of 5-FU CI over 5-FU bolus observed in patients with advanced colorectal cancer provides a rationale to study this approach in the surgical adjuvant setting.

APPENDIX

Meta-analysis Group In Cancer

Writing Committee: Pascal Piedbois, Philippe Rougier, Marc Buyse, Jean-Pierre Pignon, Louise Ryan, Richard Hansen, Benny Zee, Brian Weinerman, Joseph Pater, Cynthia Leichman, John Macdonald, Jacqueline Benedetti, Jacob Lokich, John Fryer, George Brufman, Rut Isacson, Agnès Laplanche, and Eric Levy

Collaborators: L. Ryan, R. Hansen, D. Harrington, E. McFadden, A. Ribble, R. Jacobson (Eastern Cooperative Oncology Group), B. Zee, B. Weinerman, J. Pater, (National Cancer Institute Canada), C. Leichman, J. Macdonald, J. Benedetti, (Southwest Oncology Group), J. Lokich, J. Fryer (Mid-Atlantic Oncology Program Study), P. Rougier, J.P. Pignon, A. Laplanche, M. Luboinski, (Gustave Roussy Institute, Villejuif, France), George Brufman, Rut Isacson (Hadassah University Hospital, Jerusalem, Israel), V. Vaitkevicius (Michigan Cancer Foundation, Detroit, MI, USA), P. Piedbois, J.P. Le Bourgeois, Y. Piedbois, E. Gauthier, E. Lévy, I. Durand-Zaleski (Henri Mondor Hospital, Creteil, France), and M. Buyse (International Institute for Drug Development, Brussels, Belgium)

Board of the Meta-analysis Group in Cancer: N. Wolmark (Allegheny Hospital, Pittsburgh, PA), P. Piedbois (Henri Mondor Hospital, Creteil, France), M. Buyse (International Institute for Drug Development, Brussels, Belgium), R. Carlson (Stanford University, Stanford, CA), Y. Rustum (Roswell Park Cancer Institute, Buffalo, NY), and C. Erlichman (Mayo Clinic, Rochester, MN)

REFERENCES

1. Advanced Colorectal Cancer Meta-analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. J Clin Oncol 10:896-903, 1992

2. Advanced Colorectal Cancer Meta-analysis Project: Meta-analysis of randomized trials testing the biochemical modulation of 5-fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol 12:960-969, 1994

3. Myers CE, Diasio R, Eliot HM, et al: Pharmacokinetics of the fluoropyrimides: Implications for their clinical use. Cancer Treat Rev 3:175-183, 1975

4. Fraile RJ, Baker LH, Buroker TR, et al: Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. Cancer Res 40:2223-2228, 1980

5. Aschele C, Sobrero A, Faderan MA, et al: Novel mechanism(s) of resistance to 5-fluorouracil in human colon cancer (HCT-8) sublines following exposure to two different clinically relevant dose schedules. Cancer Res 52:1855-1864, 1992

6. Carlson R: Continuous intravenous infusion chemotherapy, in Perry MC (ed): The Chemotherapy Source Book. Baltimore, MD, Williams & Wilkins, 1996, pp 225-251

7. Lokich JJ, Bothe A, Fine N, et al: Phase I study of protracted venous infusion of 5-fluorouracil. Cancer 48:2565-2568, 1981

8. Leichman L, Leichman CG, Kinzie J, et al: Long-term low dose 5-fluorouracil in advanced measurable colon cancer: No correlation between toxicity and efficacy. Proc Am Soc Clin Oncol 4:333, 1985 (abstr)

9. Belt RJ, Davidner ML, Myron MC, et al: Continuous low dose 5-fluorouracil for adenocarcinoma: Confirmation of activity. Proc Am Soc Clin Oncol 4:349, 1985 (abstr)

10. Seifert P, Baker LH, Reed ML, et al: Comparison of continuously infused 5-fluorouracil with bolus injection in treatment of patients with colorectal adenocarcinoma. Cancer 36:123-128, 1975

11. Hansen RM, Ryan L, Anderson T, et al: Phase III study of bolus versus infusion fluorouracil with or without cisplatin in advanced colorectal cancer. J Natl Cancer Inst 88:668-674, 1996

12. Weinerman B, Shah A, Fields A, et al: Systemic infusion versus bolus chemotherapy in measurable colorectal cancer. Am J Clin Oncol 15:518-523, 1992

13. Leichman CG, Fleming TR, Muggia FM, et al: Phase II study of fluorouracil and its modulation in advanced colorectal cancer: A Southwest Oncology Group study. J Clin Oncol 13:1303-1311, 1995

14. Lokich JJ, Ahlgren JD, Gullo JJ, et al: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program study. J Clin Oncol 7:425-432, 1989

15. Rougier P, Paillot B, Laplanche A, et al: End results of a multicenter randomized trial comparing 5-FU in continuous systemic infusion to bolus administration in measurable metastatic colorectal cancer. Proc Am Soc Clin Oncol 11:465, 1992 (abstr)

16. Isacson S: 5-fluorouracil and folinic acid in the treatment of colorectal carcinoma: A randomized trial of two different schedules of administration. Second International Conference on Gastro-Intestinal Cancer, Jerusalem, Israel, 1989

17. DerSimonian R, Charette LJ, McPeek B, et al: Reporting on methods in clinical trials. N Engl J Med 306:1332-1337, 1982

18. Chalmers TC, Celano P, Sacks HS, et al: Bias in treatment assignment in controlled clinical trials. N Engl J Med 309:1358-1361, 1983

19. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47:207-214, 1981

20. Meta-analysis Group in Cancer: Reappraisal of hepatic arterial infusion in the treatment of non resectable liver metastases from colorectal cancer. J Natl Cancer Inst 88:252-258, 1996

21. Mantel H, Haenzel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719-748, 1959

22. Cox DR: The Analysis of Binary Data. London, United Kingdom, Methuen, 1970

23. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient (II. analysis and examples). Br J Cancer 35:1-39, 1977

24. Cox DR: Regression models and life tables (with discussion). J R Stat Soc B 34:187-220, 1972

25. Slud EV: Confidence limits for median survival time of censored and uncensored data. Biometrics 40:587-600, 1984

26. Buyse M, Piedbois P: Meta-analyses, use and misuse. J Clin Oncol 11:382, 1993 (letter)

27. Conroy T, Adenis A, Brucker P, et al: A prospective randomized trial of protracted infusional 5 FU with allopurinol versus bolus 5 FU and high-dose leucovorin in metastatic colorectal cancers. Proc Am Soc Clin Oncol 11:462, 1992 (abstr)

28. Buyse M, Piedbois P: On the relationship between response to treatment and survival time. Stat Med 15:2797-2812, 1996

29. O'Connell M, Martenson JA, Wieand HS, et al: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331:502-507, 1994