Randomized Trial Comparing Monthly Low-Dose Leucovorin and Fluorouracil Bolus With Bimonthly High-Dose Leucovorin and Fluorouracil Bolus Plus Continuous Infusion For Advanced Colorectal Cancer: A French Intergroup Study

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Purpose: **This multicenter study compared the therapeutic ratio of a monthly schedule of low-dose leucovorin (LV) and fluorouracil (5-FU) bolus with a bimonthly schedule of high-dose LV and 5-FU bolus plus continuous infusion in patients with advanced colorectal cancer.**

Patients and Methods: **Of the 448 patients randomly assigned to treatment, 433 were assessable. Treatment A was a monthly regimen of intravenous (IV) LV 20 mg/m^2 plus bolus 5-FU 425 mg/m^2 for 5 days every 4 weeks. Treatment B was a bimonthly regimen of IV LV 200 mg/m^2 as a 2-hour infusion followed by bolus 5-FU 400 mg/m^2 and 22-hour infusion 5-FU 600 mg/m^2 for 2 consecutive days every 2 weeks. Therapy was continued until disease progression. Second-line chemotherapy, which included 5-FU continuous infusion, was allowed in both arms.**

Results: **The response rates in 348 patients with measurable lesions were 14.4% (monthly regimen) and 32.6% (bimonthly regimen) (P = .0004). The median progression-free survival times were 22 weeks (monthly regimen) and 27.6 weeks (bimonthly regimen) (P = .0012). The median survival times were 56.8 weeks (monthly regimen) and 62 weeks (bimonthly regimen) (P = .067). Grade 3-4 toxicities occurred in 23.9% of patients in the monthly arm compared with 11.1% of those in the bimonthly arm (P = .0004). Patients in arm A more frequently experienced severe granulocytopenia (7.3% *v* 1.9%), diarrhea (7.3% *v* 2.9%), and mucositis (7.3% *v* 1.9%) than patients in arm B.**

Conclusion: **The bimonthly regimen was more effective and less toxic than the monthly regimen and definitely increased the therapeutic ratio. However, there was no evidence of increased survival.**

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FLUOROURACIL (5-FU) is the standard cytostatic agent in colorectal cancer. Its mechanisms of action are inhibition of thymidylate synthetase (TS) by its metabolite FdUMP and incorporation of its other metabolites into nucleic acids (FUTP into RNA and FdUTP into DNA).[1,2] Used clinically since 1957, alone and in a bolus dose, 5-FU produces a 10% to 15% response rate and a median survival time of 6 to 9 months in metastatic cancers.

5-FU is modulated by leucovorin (LV). LV is metabolized into 5-10 methylene tetrahydrofolate, which, with the FdUMP substrate from the metabolism of 5-FU and TS, forms a stable ternary complex that inhibits the enzyme that is essential to the synthesis of thymidine.

Clinically, the first protocols used high-dose LV and 5-FU bolus, either monthly for 5 consecutive days (LV 200 mg/m^2, 5-FU 370 mg/m^2) or weekly for 1 day (LV 500 mg/m^2, 5-FU 600 mg/m^2).[3,4] Meta-analysis of the results of randomized trials showed an increase in the response rate compared with the use of 5-FU alone, but there was no survival benefit.[5] The optimal dose of LV in vivo has not yet been determined. With the monthly schedule, low-dose LV (20 mg/m^2) gives similar or better results than high-dose LV, but the opposite has been shown with the weekly schedule.[6,7]

The monthly low-dose LV schedule (North Central Cancer Treatment Group [NCCTG]—Mayo Clinic regimen) was shown by Poon et al[7] to increase patient survival (in those with nonmeasurable disease), interval to progression, and tumor response, and to enhance quality of life more than the use of 5-FU alone.[7] A further study showed that the monthly low-dose LV regimen was associated with superior survival compared with a regimen of 5-FU plus high-dose methotrexate and was associated, after covariate adjustment, with improved survival over the monthly regimen with high-dose LV.[8] In another study, the monthly low-dose LV regimen showed a superior therapeutic index to that of the weekly high-dose LV schedule (in this study 500 mg/m^2) in terms of toxicity and cost.[9]

Continuous intravenous (IV) administration increases

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the time that tumor cells are exposed to 5-FU and also allows an increase in the total tolerated dose compared with bolus administration. Continuous infusion results in different toxicities from bolus injection: a higher incidence of hand-foot syndrome but fewer cases of neutropenia.[10] Randomized studies that have compared bolus 5-FU with continuous 5-FU have shown a higher response rate for continuous infusion, which generally is considered symptomatically beneficial, but no improvement in survival time.[10,11] LV also can potentiate continuous 5-FU. However, there is no evidence that LV enhances the therapeutic effect of either a 4-day infusion of 5-FU or a protracted infusion of 5-FU.[12,13] Optimal dosing schedules for 5-FU and LV, as well as the optimal dose and duration of continuous infusion of 5-FU, remain controversial.

The combination of 5-FU bolus and continuous infusion with high-dose LV allows for the administration of higher doses of 5-FU. A bimonthly 48-hour regimen that combines LV and 5-FU bolus and continuous infusion permits the doses of 5-FU to be double those of the LV 5-FU bolus regimen.[14] This bimonthly regimen has been found to be well tolerated and effective in several phase II studies.[14-16] Also, in vitro synergism between 5-FU bolus and 5-FU continuous infusion has been shown: the human colon adenocarcinoma cell line HCT-8, resistant to short-term 5-FU exposure, retains sensitivity to continuous exposure.[17]

The present study was undertaken to compare the therapeutic ratio, efficacy, and toxicity of the monthly schedule of 5-FU bolus plus low-dose LV for 5 consecutive days with the fortnightly schedule of 5-FU bolus plus continuous infusion with high-dose LV.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility criteria were histologically proven adenocarcinoma of the colon or rectum, progressive or histologically proven nonresectable metastases at presentation, no central nervous system metastasis, no exclusive bone metastases, no second malignancy (except adequately treated in situ carcinoma of the cervix or nonmelanomic skin cancer), life expectancy over 2 months, age between 18 and 75 years old, World Health Organization (WHO) performance status 0 to 2, no previous therapy for metastatic disease, no previous adjuvant therapy if completed less than 6 months before inclusion or, if it included LV, metastases outside the radiation field in patients who had previously had radiation therapy, initial evaluation 2 weeks or less before inclusion, neutrophils greater than 1,500/mm^3, platelets greater than 100,000/mm^3, serum creatinine less than 300 μmol/L, and partial thrombin time (PTT) greater than 50%. Human investigations were performed after approval by the local Human Investigations Committee. Written informed consent was obtained from each patient or from his or her guardian.

Randomization

Patients were stratified according to performance status (0 *v* 1-2), measurable disease (present *v* absent), synchronous versus metachronous metastases, and institution. Patients then were randomly assigned to receive either the NCCTG-Mayo Clinic regimen (monthly regimen: arm A) or the high-dose LV with 5-FU bolus and continuous infusion regimen (bimonthly regimen: arm B).

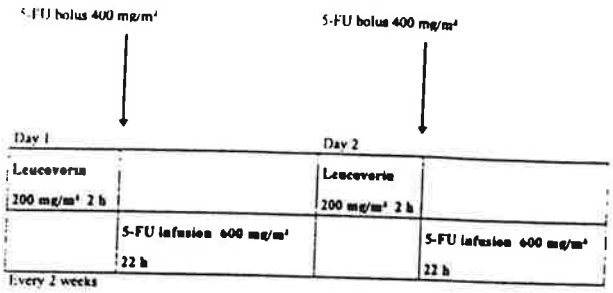

Fig 1. Infusion schedule. Bimonthly LV and 5-FU bolus plus continuous infusion.

Chemotherapy

Arm A. Patients received monthly 5-FU bolus, low-dose LV for 5 consecutive days. LV was given by IV bolus at 20 mg/m^2/d and immediately was followed by 5-FU IV bolus at 425 mg/m^2/d, repeated for 5 consecutive days. Cycles were administered every 4 weeks.

Arm B. Patients received bimonthly high-dose LV with 5-FU bolus and continuous infusion for 2 consecutive days. LV was given at 200 mg/m^2/d as a 2-hour infusion followed by IV bolus 5-FU at 400 mg/m^2/d and 22-hour infusion 5-FU 600 mg/m^2/d, all repeated for 2 consecutive days. Cycles were administered at 2-week intervals (Fig 1).

The full regimen was administered until disease progression, that is, while neutrophils were more than 1,500/mm^3, platelet count was more than 100,000/mm^3, and toxicity remained tolerable (WHO grade 0-2). In the presence of disease progression, the study regimen was stopped and second-line chemotherapy, which included 5-FU continuous infusion, could be administered in both arms.

Study Parameters

Physical examination and full blood counts were performed every cycle. Measurement of carcinoembryonic antigen (CEA) was repeated every 12 weeks. Chest roentgenograms and computed tomographic (CT) scans or sonograms also were obtained every 12 weeks.

Complete response was defined as the complete disappearance of all clinically assessable disease for at least 4 weeks, and partial response was defined as a decrease of at least 50% in the sum of the products of the diameters of measurable lesions. Stable disease was defined as a decrease of less than 50% or an increase less than 25% in tumor size. Progressive disease was defined as an increase of at least 25% in tumor size or the appearance of a new neoplastic lesion. Responses were evaluated only in patients with measurable lesions. Serosal effusions and CEA levels were not considered measurable. In rectal cancers, measurable metastases were outside the pelvis. Toxicity was recorded according to WHO criteria.

Disease progression was defined as progressive disease in patients with measurable lesions, the appearance of new lesions, or evident progression of lesions in patients with nonmeasurable lesions. In patients who were not evaluated before death, the date of progression

was defined as the date of the last evaluation without progression. Patients who died more than 6 months after an evaluation without progression were considered nonprogressive from the date of the last evaluation.

Normalization of CEA levels or more than a 50% decrease in CEA levels was considered a biologic effect in patients whose CEA levels were increased at baseline. Disappearance of, or improvement in, tumor-related symptoms (eg, pain, jaundice, fever) was considered relief from symptoms in patients who had baseline tumor-related symptoms. The definition of weight gain that was used was an increase in baseline weight greater than 5%.

Statistical Considerations

The protocol was designed to ensure that the study would have a power to detect a 15% difference in survival between the two arms at 18 months using a two-sided log-rank test. The Mantel-Haenszel test, with stratification criteria adjusted, was used for population, response rate, and toxicity comparisons.[18]

Response duration, progression-free survival, and survival were calculated using the Kaplan-Meier method from the date of randomization; the end point was March 1, 1996.[19] The follow-up time of the whole cohort was 43.5 months. The stratified log-rank test and Cox proportional hazard model were used for testing the association between treatment and outcome.[20] Statistical analyses were performed using BMDP procedures (BMDP Statistical Software, Inc., Berkeley, CA).[21]

RESULTS

Patients' Characteristics

From February 13, 1991 to April 8, 1994, 448 patients were randomly assigned to treatment in 70 institutions. Eight institutions enrolled 56% of the patients. Four centers that randomly assigned seven patients to treatment but did not submit any data were excluded. Eight patients were ineligible, four in arm A and four in arm B; one patient had adenocarcinoma of the lung, one had a nondocumented disease, one had no metastases, and five had received chemotherapy less than 6 months before randomization. The other 433 patients were included in the analysis: 216 in arm A and 217 in arm B. There were six protocol violations, one in the monthly arm and five in the bimonthly arm; four patients did not receive the chemotherapy, one received levamisole in addition to the regimen, and one received the monthly regimen in place of the bimonthly. Fifteen crossovers were recorded after tumor progression, eight from arm A to arm B and seven from arm B to arm A.

Pretreatment characteristics of the patients according to treatment arm are listed in Table 1. The population was well balanced between both arms.

Objective Tumor Responses

Measurable disease was observed in 348 patients, 173 in arm A and 175 in arm B. The monthly regimen produced a 2.3% complete response rate and a 12.1% partial response rate, for an overall objective response rate of 14.5%. The bimonthly regimen produced a 5.7% complete response rate and a 26.9% partial response rate, for an overall objective response rate of 32.6% (Table 2).

The difference was significant ($P = .0004$). In arm A, the response rate in patients with liver metastases only was 14.6%; in patients with metastases to the liver and

Table 1. Patients' Characteristics

Characteristics	Arm A* Monthly Low-Dose LV, 5-FU Bolus, 5 Days		Arm B† Bimonthly High-Dose LV, 5-FU Bolus & Continuous, 2 Days	
	No.	%	No.	%
Male	145	67.1	135	62.2
Female	71	32.9	82	37.8
Age, mean years (SD)	61.7 (SD 9.6)		60.9 (SD 9.5)	
WHO performance status 0	98	45.4	97	44.7
WHO performance status 1-2	118	54.6	120	55.3
Synchronous metastases	144	66.7	147	67.7
Metachronous metastases	72	33.3	70	32.3
Measurable disease	173	80.1	175	80.6
Nonmeasurable disease	43	19.9	42	19.4
Primary site colon	142	65.7	139	64.1
Primary site rectum	68	31.5	73	33.6
Primary multiple or nonspecified	6	2.8	5	2.3
Liver metastases	172	80.7	176	81.5
Lung metastases	34	16.0	34	15.7
Other sites of metastasis	40	18.8	40	18.5
Number of sites: 1	182	85.0	182	84.3
Number of sites: ≥ 2	32	15.0	34	15.7
Number of sites nonspecified	2		1	
CEA normal	40	19.2	46	22.3
CEA 1-100 × normal	136	65.4	128	62.1
CEA >100 × normal	32	15.4	32	15.5
CEA unknown	8		11	

*Total number of patients in arm A = 216.
†Total number of patients in arm B = 217.

Table 2. Objective Tumor Responses

Response	Number of Patients: Arm A* Monthly Low-Dose LV 5-FU Bolus, 5 Days	Number of Patients: Arm B† Bimonthly High Dose LV 5-FU Bolus & Continuous, 2 Days
Complete response (CR)	4, 2.3%	10, 5.7%
Partial response (PR)	21, 12.1%	47, 26.9%
Stable	68, 39.3%	62, 35.4%
Progression	80, 46.2%	56, 32%
Objective response (CR + PR)	25, 14.45%‡	57, 32.57%‡

*N = 173.
†N = 175.
‡P = .0004

other sites, 16.7%; and in patients with lung metastases only, 28.6%. In arm B, the response rate in patients with liver metastases only was 28.6%; in patients with metastases to the liver and other sites, 37.5%; and in patients with lung metastases only, 45.5%. The response rate was significantly higher in arm B for the patients with liver metastases only (P = .005). The median duration of responses was 48.5 weeks in arm A and 47 weeks in arm B (P = .78).

Carcinologic surgery was performed in six patients in arm A (2.8% [liver resection, four patients; lung and liver, one patient; and lymph node, one patient; two were responders to chemotherapy]) and 14 in arm B (6.5% [liver resection, 12 patients; lung and liver, one patient; and lung, one patient; five were responders]) (P = .064) The median survival in these patients was 3.1 years.

After progression, second-line chemotherapy was recorded for 119 patients. Twenty-seven patients (13%) who were randomly assigned to the monthly arm (5-FU bolus) received second-line chemotherapy with 5-FU continuous infusion.

Palliative and Biologic Effects

Symptoms regressed or disappeared in 29 of 58 assessable patients in arm A (50%) and 31 of 60 in arm B (51.7%) (P = .80). A weight increase of 5% or more was observed in 32 of 192 patients in arm A (16.7%) and 44 of 196 in arm B (22.4%) (P = .12). Performance status improved in 31 of 105 assessable patients in arm A (29.5%) and 34 of 109 in arm B (31.2%) (P = .40). CEA levels normalized or decreased greater than 50% in 30 of 147 assessable patients in arm A (20.4%) and in 55 of 147 in arm B (37.4%) (P = .002).

Survival

Patients who received the bimonthly regimen had significantly longer median progression-free survival than patients who received the monthly regimen (27.6 weeks *v* 22 weeks; P = .0010; odds ratio (OR) = .72). The progression-free survival curves are shown in Fig 2.

Median survival also was longer with the bimonthly regimen than with the monthly regimen (62.0 *v* 56.8 weeks). However, this difference was not statistically significant (P = .067). The survival curves are shown in Fig 3.

Patients with measurable disease had a median survival of 63 versus 46 weeks in patients with nonmeasurable disease (P = .0186). Interaction test between treatment arms and measurable or nonmeasurable disease showed a borderline significance (P = .07). OR was significant only for patients with measurable disease treated with the bimonthly regimen compared with the monthly regimen (OR = .75; P = .015). The median survival in patients with measurable disease was 72 weeks in the bimonthly treatment arm and 58.4 weeks in the monthly treatment arm. Fig 4 shows the survival in patients with measurable disease.

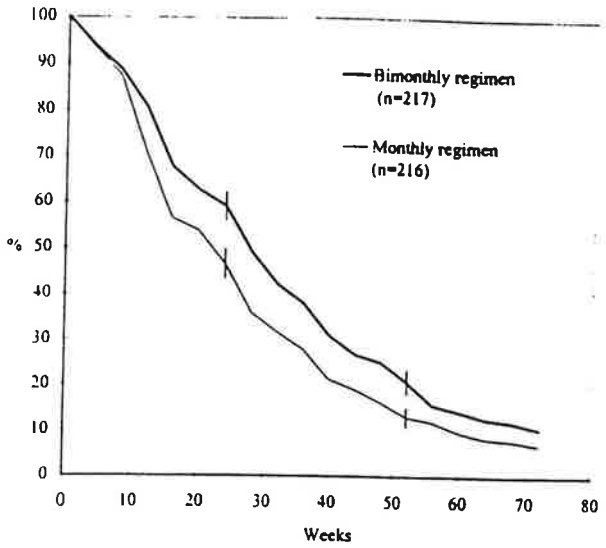

Fig 2. Progression-free survival.

Toxicity

In the monthly arm, toxicity was recorded in 205 patients, who received a median of five cycles (range, 1 to

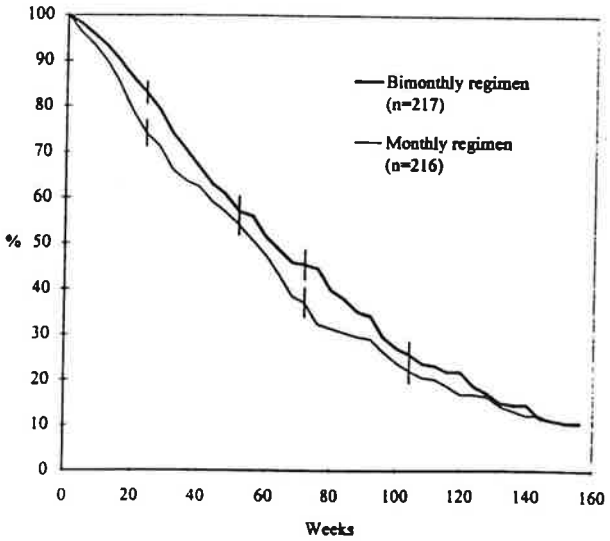

Fig 3. Survival.

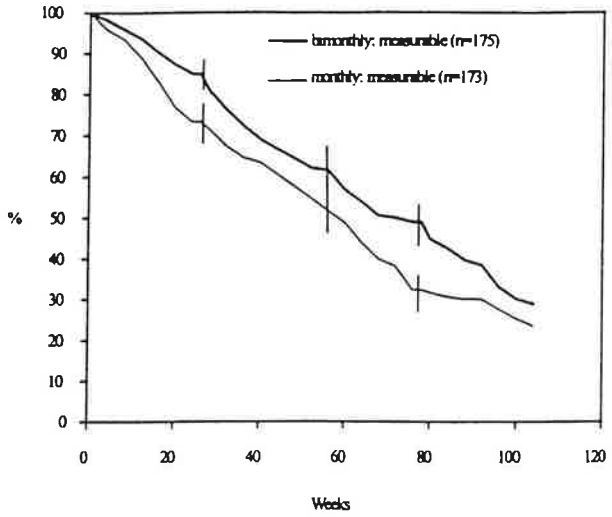

Fig 4. Overall survival in patients with measurable disease.

21; 1,172 cycles were analyzed). In the bimonthly arm, toxicity was recorded in 208 patients, who received a median of 12 cycles (range, 1 to 42; 2,714 were analyzed). In the monthly arm, 23.9% of the patients experienced grade 3-4 toxicities, which included the only therapy-related death in the study. In the bimonthly arm, 11.1% of the patients experienced grade 3-4 toxicities. The difference was highly significant ($P = .0004$).

Grade 3-4 neutropenia, diarrhea, and mucositis occurred significantly more frequently in the monthly arm than in the bimonthly arm. However, more instances of epistaxis and conjunctivitis occurred in the bimonthly arm, although none of these events were severe enough to cause any patients to withdraw from treatment. Table 3 lists the toxicities.

Interaction between sex, age, and toxicity has been studied. The best therapeutic ratio in favor of the bimonthly arm was observed in the female patients under 65 years of age (Table 4).

Table 4. Grade 3-4 Toxicity According to Sex and Age

	Arm A Low-Dose LV, 5-FU Bolus, 5 Days/4 Weeks %	Arm B High-Dose LV, 5-FU Bolus & Continuous, 2 Days/2 Weeks %	Ratio Arm B/Arm A
Male < 65 years	14.1	8.6	0.61
Male ≥ 65 years	21.2	10.0	0.47
Female < 65 years	39.5	12.0	0.30
Female ≥ 65 years	32.0	17.9	0.56

DISCUSSION

In the first NCCTG-Mayo Clinic study, the monthly 5-day regimen with low-dose LV and 5-FU bolus produced a 43% response rate, a 7.5-month median progression-free survival, and a 12.7-month median survival.[8] In the second study, in which the monthly regimen was compared with the weekly regimen, the figures for the monthly arm were 35%, 5 months, and 9.3 months, respectively.[9] Since 1991, this regimen has been evaluated in five other randomized studies, which include three with fewer than 100 patients.[13,22-25] All of these studies have

Table 3. Toxicity per Patient

	Arm A* Low-Dose LV, 5-FU Bolus, 5 Days/4 Weeks		Arm B† High-Dose LV, 5-FU Bolus & Continuous, 2 Days/2 Weeks		Comparison Grade 3-4 (Grade 1-2)
	Grade 1-2, %	Grade 3-4, %	Grade 1-2, %	Grade 3-4, %	
Neutrophils	14, 6.8	15, 7.3	20, 9.6	4, 1.9	0.0052
Platelets	1, 0.5	1, 0.5	1, 0.48	2, 1.0	1.00
Infection	14, 6.8	8, 3.9	11, 5.3	2, 1.0	0.095
Nausea	72, 35.1	7, 3.4	80, 38.5	8, 3.9	0.95
Diarrhea	54, 26.3	15, 7.3	59, 28.4	6, 2.9	0.039
Mucositis	38, 18.5	26, 12.7	42, 20.2	4, 1.9	0.0001
Angina pectoris	2, 1.0	0	8, 3.8	0	(0.14)
Cutaneous	25, 12.2	0	31, 14.9	2, 1.0	(0.59)
Alopecia	26, 12.7	3, 1.5	25, 12.0	1, 0.5	0.37
Epistaxis	7, 3.4	0	19, 9.1	0	(0.019)
Conjunctivitis	10, 4.9	0	29, 13.9	0	(0.003)
Neurologic	3, 1.5	0	7, 3.4	1, 0.5	1.00
Maximal	90, 43.9	49, 23.9	119, 57.2	23, 11.1	0.0004

*N = 205
†N = 208

Table 5. Results of the Monthly 5-Day Low-Dose LV and 5-FU Bolus in Randomized Trials

Study	No	No Measurable	Overall Response Rate (%)	Median Progression-Free Survival Months	Median Survival, Months
Poon, 1989-1991 (NCCTG, Mayo Clinic)	153	81	43	7.5	12.7
Borner, 1992 (Switzerland)	30	29	28	NS	13.1
Buroker, 1994 (NCCTG, Mayo Clinic)	183	102	35	5	9.3
Scheithauer, 1994 (Austria)	68	68	19	5.2	12.6
Leichman, 1995 (SWOG)	85	61	27	6	14
Valsecchi, 1995 (GISCAD, Italy)*	NS	184	11.4	6	10
Seitz, 1996 (Europe)	212	NS	16.5	3.6	10.5
Present study	205	173	14.4	4.9	12.6

*1-LV and 5-FU 370 mg/m².

Abbreviation: NS, not specified.

shown a lower response rate (11% to 28%) than the earlier studies, a median progression-free survival of between 5 and 6 months, and a median survival of between 10 and 14 months (Table 5). The discrepancy in response rate can be attributed to the method of evaluation and to patient selection: a higher proportion of patients in the later studies had measurable lesions. In our study, the response rate in the monthly arm was 15%. The large number of participating centers did not allow systematic extramural review of CT scans or sonograms to evaluate the collected data. However, no causes of underevaluation of the number of responses were found. We cannot attribute this low response rate to a lower administered dose of 5-FU. The dose intensity in this study was even higher than in the original one with strictly monthly cycles. The interval between cycles was 5 weeks after the third cycle in the NCCTG-Mayo Clinic studies. However, we noted better tolerance (only 24% of the patients had grade 3-4 toxicities, which included 12.7% with mucositis, and only one therapy-related death) than in the previous studies, which reported severe stomatitis rates of 24% and 28% (percentage of patients with grade 3-4 toxicity not specified) and one and five toxic deaths, respectively.[8,9]

Even if the monthly regimen could be considered standard, there is no evidence that it is superior to 5-FU continuous infusion.[13,26] Likewise, the optimum duration of infusion is not known. If infusion is protracted, the patient's comfort is reduced by the permanent presence of the administration system.

The bimonthly regimen with high-dose LV and 5-FU bolus and infusion achieved better control of advanced colorectal cancer with a higher response rate and longer progression-free survival than the monthly regimen. However, as with most trials, overall survival was not significantly different, even if a trend was observed in patients with measurable disease. It is possible that the 18% difference in response rate may not have been high enough to translate into a survival benefit in a population of 433 patients. The time from disease progression to death may have been longer in arm A (the monthly arm) because of second-line therapies. However, there were only a few crossover patients in this study and 5-FU infusion, known to achieve about a 10% response in patients who progress on 5-FU bolus,[27] was administered after progression to only 13% of the patients in the monthly arm. The bimonthly 5-FU bolus and continuous infusion regimen has been used in only one other randomized study, which was conducted by the Medical Research Council in the United Kingdom. In that study, the bimonthly regimen achieved a 27% response rate and a 10-month median survival in 260 patients.[28] The low toxicity of the bimonthly regimen also has been shown by the low percentage of grade 3 or 4 toxicities (11.1%) in the present study, which includes asymptomatic grade 3 neutropenia or alopecia, and the far lower incidence of life-threatening side effects. This regimen can be used in combination with other drugs.[29,30] The constraints of continuous infusion are in part resolved by electronic or disposable pumps and implantable venous access sites, which permit outpatient treatment. The results achieved with the bimonthly regimen of high-dose LV and 5-FU bolus and infusion are encouraging, although the overall therapeutic benefit remains limited.

Ongoing trials are comparing this regimen with low-dose LV, plus oxaliplatin, raltitrexed, a weekly 5-FU 24-hour infusion, or 5-FU protracted infusion (French, British, and European trials). The bimonthly regimen will also be compared with the monthly regimen with high-dose LV in the adjuvant setting (French trial).

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APPENDIX

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