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Randomized Multicenter Phase II Trial of a Biweekly Regimen of Fluorouracil and Leucovorin (LV5FU2), LV5FU2 Plus Cisplatin, or LV5FU2 Plus Irinotecan in Patients With Previously Untreated Metastatic Gastric Cancer: A Fédération Francophone de Cancérologie Digestive Group Study—FFCD 9803

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ABSTRACT

Purpose

To determine the efficacy and safety of a biweekly regimen of leucovorin (LV) plus fluorouracil (FU) alone or in combination with cisplatin or irinotecan in patients with previously untreated metastatic gastric adenocarcinoma and to select the best arm for a phase III study.

Patients and Methods

One hundred thirty-six patients (two were ineligible) were enrolled onto the randomized multicenter phase II trial. Patients received LV 200 mg/m^2 (2-hour infusion) followed by FU 400 mg/m^2 (bolus) and FU 600 mg/m^2 (22-hour continuous infusion) on days 1 and 2 every 14 days (LV5FU2; arm A), LV5FU2 plus cisplatin 50 mg/m^2 (1-hour infusion) on day 1 or 2 (arm B), or LV5FU2 plus irinotecan 180 mg/m^2 (2-hour infusion) on day 1 (arm C).

Results

The overall response rates, which were confirmed by an independent expert panel, were 13% (95% CI, 3.4% to 23.3%), 27% (95% CI, 14.1% to 40.4%), and 40% (95% CI, 25.7% to 54.3%) for arms A, B, and C, respectively. Median progression-free survival and overall survival times were 3.2 months (95% CI, 1.8 to 4.6 months) and 6.8 months (95% CI, 2.6 to 11.1 months) with LV5FU2, respectively; 4.9 months (95% CI, 3.5 to 6.3 months) and 9.5 months (95% CI, 6.9 to 12.2 months) with LV5FU2-cisplatin, respectively; and 6.9 months (95% CI, 5.5 to 8.3 months) and 11.3 months (95% CI, 9.3 to 13.3 months) with LV5FU2-irinotecan, respectively.

Conclusion

Of the three regimens tested, the combination of LV5FU2-irinotecan is the most promising and will be assessed in a phase III trial.

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INTRODUCTION

Although the incidence of gastric cancer has decreased in most western countries, it remains a significant problem in global health terms and is the second most common cause of cancer mortality worldwide.[1] Surgery is the only potentially curative treatment for localized gastric cancer, but most cases present at an advanced stage. The prognosis for the disease is extremely poor, with overall 5-year survival rates ranging from 10% to 15% in the United States and most developed countries.[2]

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The efficacy of chemotherapy with palliative intent compared with supportive care alone is now widely accepted.[3] Studies showed the benefit of combination regimens, such as fluorouracil (FU), doxorubicin, and methotrexate (FAMTX)[4,5] or etoposide, leucovorin (LV), and FU (ELF),[6] over best supportive care.[7-9] Other combination regimens investigated include epirubicin, cisplatin, and infusional FU (ECF) and 5-day infusional FU plus cisplatin (FUP).[4,6] The survival advantage is small, however, and no internationally accepted standard regimen has emerged.[10]

ECF is one standard regimen and is associated with median survival times of around 9 months.[11,12] Infusional FU plus cisplatin is another standard treatment that is active, but it failed to demonstrate its superiority over FU monotherapy or other combination regimens in three randomized studies.[6,13-15] Although the current regimens yield overall response rates (ORR) of up to 51%,[15] the median survival time in patients with advanced disease remains consistently below 10 months.[6,11,12]

An important issue in patients with gastric cancer is toxicity. The elderly patient population cannot tolerate aggressive combination chemotherapy. The anthracycline-containing regimens can be particularly toxic.[16]

FU is one of the most effective and widely used drugs in the treatment of advanced gastric cancer, and it forms part of all the current reference regimens. FU monotherapy, a standard treatment in Japan, is associated with a response rate of approximately 20%, manageable toxicity,[17] and overall survival (OS) times of between 5 and approximately 7 months in phase III randomized studies.[14,15,18] The modulation of FU by LV has generally enhanced antitumor efficacy (ORR, 22% to 48%) and produced some complete responses (5% to 9%).[19-22] The biweekly FU and LV regimen (LV5FU2), which is popular in Europe,[20,23] combined with low-dose cisplatin was less toxic than FUP in a retrospective study,[24] and therefore, LV5FU2 was chosen as the reference FU regimen in this study.

There is a clear need for more convenient and active new agents and regimens. Irinotecan is a new cytotoxic agent with promising activity in combination with FU in gastrointestinal cancers.[25-27] Irinotecan monotherapy is active in patients with gastric cancer, with response rates in phase II trials of 14% to 23%.[28-31] The drug is also active when administered with FU-LV, a combination that yields response rates of 21% to 29% and OS times of 6.4 to 7.6 months.[27,32,33] Irinotecan plus cisplatin is another active combination with response rates of 27% to 58% and an OS time of 9.0 months.[34-36]

Therefore, a multicenter randomized phase II study was conducted to compare LV5FU2 administered alone or in combination with cisplatin or irinotecan in patients with previously untreated metastatic gastric or cardial adenocarcinoma. The aim of the study was to select the best regimen for comparison with a reference treatment in a future phase III trial. The end points were ORR, progression-free survival (PFS), OS, safety, duration of hospital stay, and quality of life (QOL).

PATIENTS AND METHODS

Patients

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed and approved by the Ethics Review Committee of Champagne Ardennes (Reims, France). All patients provided written informed consent before inclusion in the trial. Eligible patients had histologically proven metastatic gastric or cardial adenocarcinoma without linitis, at least one measurable metastatic lesion located outside a previously irradiated area and measuring more than 15 mm in diameter, no symptomatic brain metastases, an age between 18 and 75 years, and a WHO performance status ≤ 2 with a life expectancy of more than 2 months. Adjuvant chemotherapy without cisplatin or irinotecan was allowed if completed at least 6 months before randomization. Prior radiotherapy was allowed if completed more than 4 weeks before randomization. All patients had adequate hematologic (neutrophils $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L), hepatic (bilirubin ≤ 25 μmol/L and AST and ALT $\leq 5 \times$ the upper normal limit), renal (creatinine ≤ 135 μmol/L and no contraindication to hyperhydration), and cardiac function. The main exclusion criteria were chronic diarrhea, prior enteropathy, or extensive intestinal resection.

Study Design and Randomization

The study was an open-label, multicenter, phase II, randomized trial with three treatment arms. After obtaining informed consent, eligible patients were registered at the Fédération Francophone de Cancérologie Digestive center and randomized with stratification by institution, tumor site (cardia *v* other localization), prior adjuvant chemotherapy (yes *v* no), and WHO performance status (0-1 *v* 2).

Chemotherapy Administration and Dose Adjustments

Patients assigned to the LV5FU2 arm (arm A) received LV 200 mg/m^2 intravenous (IV) over 2 hours followed by FU 400 mg/m^2 IV bolus then FU 600 mg/m^2 continuous infusion over 22 hours on days 1 and 2, repeated every 14 days (one cycle = 15 days). No systematic prophylactic premedication was administered. Patients assigned to the LV5FU2-cisplatin arm (arm B) received cisplatin 50 mg/m^2 IV over 1 hour on day 1 or 2 with LV5FU2 (one cycle = 15 days). Prophylactic medication consisted of IV antiemetics (setrons) and methylprednisolone 120 mg 10 minutes before cisplatin administration, hydration (1 L over 3 hours before and after cisplatin), oral antiemetics, and corticosteroids from days 2 to 5. Patients assigned to the LV5FU2-irinotecan arm (arm C) received irinotecan 180 mg/m^2 IV over 90 minutes on day 1 with LV5FU2 and no systematic prophylactic premedication (one cycle = 15 days).

Treatment was continued for at least four cycles or until disease progression, unacceptable toxicity, patient refusal, or physician decision. In the event of toxicity (WHO), the following dose reductions and treatment delays were planned. In cases of insufficient hematologic function (neutrophil count $< 1.5 \times 10^9$/L and platelet count $< 100 \times 10^9$/L) on day 14 of any cycle, treatment was delayed for up to 14 days. If recovery did not occur at this point, the treatment was discontinued. Any FU dose

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reductions were only applied to the continuous infusion. For grade 3 to 4 gastrointestinal toxicities, thrombocytopenia, and neutropenia, there were 25% FU, cisplatin, and irinotecan dose reductions. For grade 2 or greater cardiotoxicity, FU treatment was discontinued. Cisplatin administration was delayed if creatinine levels were more than 135 μmol/L, and irinotecan administration was delayed if bilirubin levels were more than 25 μmol/L. Patients showing a complete response received treatment for up to 1 year.

Study Evaluations

In the 4 weeks preceding treatment, patients underwent a chest x-ray and a computed tomography scan of the abdomen and of all measurable and assessable sites. In the week preceding treatment, patients underwent a complete medical history evaluation, a physical examination, a QOL evaluation, and an ECG. Baseline biologic analyses (blood cell count, serum creatinine, bilirubin, AST, ALT, lactate dehydrogenase, and alkaline phosphatase) were measured at baseline and before each cycle of chemotherapy. QOL evaluations were carried out every 2 months.

All adverse events were graded using the WHO toxicity criteria.[37] Planned tumor evaluations were carried out every four cycles during therapy with the appropriate clinical and radiologic examinations and confirmation of responses by further radiologic examinations within 4 weeks. All objective tumor responses and cases of disease stabilization were reviewed retrospectively by an external expert committee. PFS was calculated from the date of randomization to either the date of first progression, the date of the last assessment in the absence of progression if the patient was alive, the date of death from any cause, or the date of last contact. In patients with subsequent complete surgical resection, PFS was measured from the time of randomization to the date of documentation of progression after surgery. OS was measured from the date of randomization until death from any cause.

QOL

Patients were requested to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) before randomization and every 2 months thereafter.[38] Completed questionnaires were scored according to guidelines provided by the European Organization for Research and Treatment of Cancer.[39] The questionnaire comprises a global QOL scale, five functional scales (physical, role, cognitive, emotional, and social), and nine symptom scales (fatigue, pain, nausea and vomiting, constipation, diarrhea, sleep, dyspnea, appetite, and financial). The functional and global scores range from 0 (worst) to 100 (best), and the symptom scores range from 0 (best) to 100 (worst). The reliability and validity of this measure has been reported elsewhere.[40,41]

Statistical Analysis

The primary end point was ORR. Secondary end points were PFS, OS, safety, duration of hospitalization, and QOL. The expected number of patients for this study was calculated according to an Ensign-Minimax optimal three-stage design.[42] The ORR according to WHO criteria was used with the following hypotheses and estimations for the stopping rules in each arm: stop if ORR is less than 20% or more than 40% with alpha and beta levels of 0.05 and 0.10, respectively. An interim analysis was carried out after the first nine assessable patients had been recruited in each arm. If at least one objective response was observed, 16 additional patients were included in the second stage (total = 25 patients). For the second interim analysis, if more than five objective responses and less than 14 objective responses were observed, 20 additional patients were included in the third and last stage (total = 45 patients). If at least 14 responses were observed in a treatment arm, a phase III study was to be considered against the reference treatment (ECF or simplified ECF regimen yet to be determined). A sample of 135 patients was necessary with 45 patients per arm. PFS and OS were updated until October 1, 2002. Statistical comparisons were not planned in this selection study, with small numbers of patients in each arm. The criterion for choosing the best arm for a phase III study was at least 14 objective responses according to the external expert committee.

The QLQ-C30 scores were described as a mean, standard deviation, median, and range at the start of the study and at each 2-month follow-up visit; the mean of available global health scores was graphically reported at each follow-up. The missing data were described as a percentage of the calculated score among patients with follow-up. Prestudy scores were compared between treatment arms using analysis of variance and a Bonferroni test to adjust for multiple comparisons. During the first three follow-ups, the longitudinal change of QLQ-C30 scores was analyzed using a mixed model analysis of variance for repeated measurements[43] to study a global time effect whatever the treatment and to calculate differences in mean QOL scores between treatment arms whatever the follow-up (contrast analysis).

RESULTS

Patient Characteristics

One hundred thirty-six patients were enrolled between January 1999 and October 2001 in 41 centers in France. Two patients were considered ineligible; one had a lymphoma and the other had no metastatic disease. No arm was closed after the two interim analyses. Thus, the analyses were carried out on an intent-to-treat (ITT) basis with the remaining 134 enrolled patients. All eligible patients received treatment allocated by randomization. The patient characteristics, which are listed in Table 1, were similar between the three arms except for the number of patients with weight loss more than 10%; this was higher in arm C than in the other two treatment arms ($P = .05$). The median age of all patients was 65 years (range, 37 to 76 years). The most frequent metastatic site was the liver (79% of all patients), and half of the patients had undergone prior curative or palliative surgery for their primary tumor.

Response Rate

All of the 134 eligible patients were assessed for response. The response rate data per independent review on ITT basis are listed in Table 2. Ten patients (7%) were not evaluated for response review by the external expert committee because of the loss of computed tomography images. Three additional patients (2%) received insufficient treatment (fewer than four cycles) because of early toxicity (n = 2) or toxic death (n = 1). Early deaths (6%) related to disease progression occurred in three, two, and three patients in arms A, B, and C, respectively. The expert-assessed per protocol ORRs (eligible patients receiving at least four

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Table 1. Patient Characteristics

Characteristic	% of Patients		
	LV5FU2 (n = 45)	LV5FU2-Cisplatin (n = 44)	LV5FU2-Irinotecan (n = 45)
Sex			
Male	82	80	84
Female	18	20	16
Age, years			
Median	64	64	65
Range	45-75	43-76	37-76
WHO performance status			
0 or 1	73	75	78
2	27	25	22
Primary tumor location			
Cardia	29	30	33
Gastric	71	70	67
Prior surgery	51	50	51
Curative	25	34	27
Palliative	25	16	22
Unknown	2	0	2
Prior radiotherapy	0	0	2
Prior chemotherapy	0	2	0
Histology of adenocarcinoma			
Well differentiated	69	61	69
Poorly differentiated	22	32	27
Signet-ring cell	2	2	0
Unknown	7	5	4
Metastatic sites			
Liver	78	84	76
Lymph nodes	58	52	62
Peritoneum	22	14	20
Lung	18	11	16
Bone	4	5	5
Others	9	14	9
No. of organs			
1	33	46	36
2	47	39	47
> 2	20	16	18
Symptom			
Weight loss			
No	20	27	29
≤ 10%	49	34	18
> 10%	27	32	51*
Anorexia			
No	53	50	67
Yes	47	50	33
Dysphagia			
No	76	82	84
Yes	24	18	16
Pain			
No	49	57	62
Yes	51	43	38

Abbreviation: LV5FU2, biweekly regimen of leucovorin plus fluorouracil.
*The number of patients with weight loss greater than 10% was higher in the LV5FU2-irinotecan arm compared with the other two arms ($P = .05$).

cycles of chemotherapy) were 14% (95% CI, 3.6% to 24.3%; six of 43 patients), 30% (95% CI, 15.8% to 44.2%; 12 of 40 patients), and 47% (95% CI, 31.5% to 63.2%; 18 of 38 patients) for arms A, B, and C, respectively. The investigator-assessed ITT ORRs were 24% (95% CI, 11.9% to 37.0%), 30% (95% CI, 16.1% to 43.0%), and 40% (95% CI, 25.7% to 54.3%), of which 0%, 2%, and 4% were complete responses, for arms A, B, and C, respectively. The rate of agreement between investigator and expert evaluation was 83%. Three patients in arm C underwent subsequent complementary locoregional treatment (one had a resection of liver metastases, one had a resection of pulmonary metastases, and one had radiofrequency ablation of liver metastases). The primary tumor was also resected in one patient.

Survival

The median follow-up time was 26 months (95% CI, 20 to 33 months). One hundred sixteen patients (87%) were dead at the cutoff date of October 1, 2002. The numbers of patients still alive were four, eight, and six for arms A, B, and C, respectively. Table 3 lists the survival data, and Figures 1 and 2 show the OS and PFS of the patients in the study. The median PFS times were 3.2 months (95% CI, 1.8 to 4.6 months), 4.9 months (95% CI, 3.5 to 6.3 months), and 6.9 months (95% CI, 5.5 to 8.3 months) for arms A, B, and C, respectively. The median OS times were 6.8 months (95% CI, 2.6 to 11.1 months), 9.5 months (95% CI, 6.9 to 12.2 months), and 11.3 months (95% CI, 9.3 to 13.3 months) for arms A, B, and C, respectively. Patients receiving LV5FU2-irinotecan seemed to have a longer PFS and OS.

Safety

The median number of cycles administered per patient, the number of cycles delayed, and the median relative dose-intensities for the three treatment arms are listed in Table 4. Patients received a median of seven cycles (range, one to 20 cycles), seven cycles (range, one to 18 cycles), and 10 cycles (range, one to 25 cycles) of treatment in arms A, B, and C, respectively. The main reason for stopping treatment in all arms was disease progression (37 patients, 82%; 24 patients, 55%; and 27 patients, 60% in arms A, B, and C, respectively). Treatment was discontinued as a result of toxicity in 4%, 16%, and 11% of patients in arms A, B, and C, respectively (Table 5).

The grade 3 and 4 toxicities experienced during treatment are listed in Table 5. The main toxicity was hematologic (neutropenia, febrile neutropenia, and anemia), which was highest in the arm B and lowest in arm A. Gastrointestinal toxicity was also common, with nausea and vomiting experienced by more patients in arm B and diarrhea experienced by more patients in arm C. Stomatitis was uncommon with any treatment. Two deaths occurred that were considered likely to be related to treatment (one each in arms A and B, neutropenic infections). The overall mean duration of hospitalization for toxicity was 1.2 days (range, 0 to 14 days).

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Table 2. Response Rates for ITT Population Per Independent Review and Further Therapy

Response	LV5FU2 (n = 45)		LV5FU2-Cisplatin (n = 44)		LV5FU2-Irinotecan (n = 45)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete response	0	0	0	0	0	0
Partial response	6	13	12	27	18	40
Overall response	6	13	12	27	18	40
95% CI, %	3.4 to 23.3		14.1 to 40.4		25.7 to 54.3	
Stable disease	16	36	17	39	9	20
PD	21	47	11	25	11	24
Early death caused by PD	3	7	2	5	3	7
Not evaluated	2	4	4	9	7	6
Images not available	2	4	2	5	6	13
Early toxicity	0	0	1	2	1	2
Toxic death	0	0	1	2	0	0
Further therapy	32	71	33	75	32	71
Surgical resection	0	0	0	0	3	7
Second-line chemotherapy	24	53	23	52	23	51
Third-line chemotherapy	8	18	10	23	6	13

Abbreviations: ITT, intent to treat; LV5FU2, biweekly regimen of leucovorin plus fluorouracil; PD, progressive disease.

Hospital Stay

The median duration of hospital stay was 53 days (range, 7 to 300 days), 59 days (range, 3 to 124 days), and 56 days (range, 13 to 139 days) for arms A, B, and C, respectively. When converted to days per month of life, the median duration was 8.2 days per months (range, 2.1 to 30.5 days), 6.3 days per month (range, 0.7 to 19.9 days), and 5.7 days per month (range, 1.1 to 30.5 days) for arms A, B, and C, respectively. The two main reasons for hospitalization were chemotherapy administration, with a median of 30 days (range, 3 to 148 days) or 4 days per month of life (range, 1 to 15 days), and palliative care, with a median of 12 days (range, 0 to 103 days) or 1.1 days per month of life (range, 0 to 30.4 days).

QOL

Global QOL data were available for 82%, 75%, and 84% of patients at the time of inclusion compared with 41% (n = 22 patients with follow-up), 38% (n = 21), and 48% (n = 29) of patients at the third evaluation in arms A, B, and C, respectively. Thereafter, the number of patients with follow-up was small (fewer than 10 patients in each arm), whereas the rate of missing scores was maintained. A similar pattern was observed for the other 14 QOL scales. There was no difference in pretreatment global QOL scores between the study arms. However, patients in arms B and C had less constipation than patients in arm A ($P < .01$), and patients in arm C slept better than patients in arm A ($P < .05$). The trend in global health score was graphically equivalent between arms (Fig 3); compared with pretreatment scores, there was an increase in the global health score at all three evaluations, although the third evaluation revealed a slightly lower value than the second evaluation. However,

Table 3. Survival Data

Survival	LV5FU2 (n = 45)	LV5FU2-Cisplatin (n = 44)	LV5FU2-Irinotecan (n = 45)
OS, months			
Median	6.8	9.5	11.3
95% CI	2.6 to 11.1	6.9 to 12.2	9.3 to 13.3
1-Year OS, %	31	43	43
PFS, months			
Median	3.2	4.9	6.9
95% CI	1.8 to 4.6	3.5 to 6.3	5.5 to 8.3
9-Month PFS, %	7	18	24

Abbreviations: LV5FU2, biweekly regimen of leucovorin plus fluorouracil; OS, overall survival; PFS, progression-free survival.

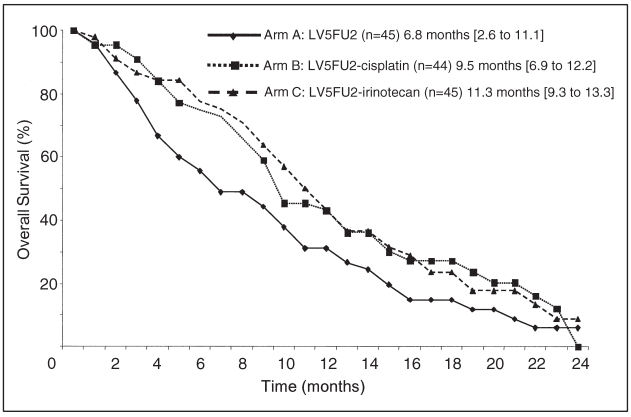

Fig 1. Overall survival according to treatment arm. The median survival times with 95% CIs are shown. LV5FU2, biweekly regimen of leucovorin plus fluorouracil.

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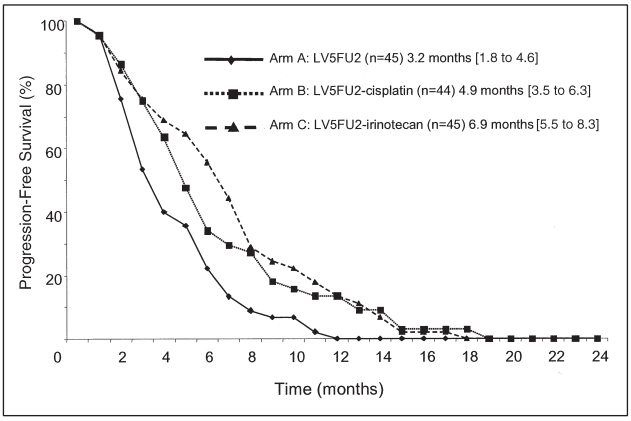

Fig 2. Progression-free survival according to treatment arm. The median progression-free survival times with 95% CIs are shown. LV5FU2, biweekly regimen of leucovorin plus fluorouracil.

longitudinal analysis showed that 14 mean scores were respectively higher in arm C than in arms A and B, regardless of the first three follow-ups (Table 6). The patients in all three arms had a significant improvement in QOL scores compared with pretreatment values (global QOL, $P < .0001$; role, $P < .01$; emotional, $P < .0001$; social, $P < .01$; pain, $P < .0001$; sleep, $P < .0001$; and appetite loss, $P < .01$; Table 6).

Comparison between arms during the third QOL assessment showed that six functional scores were higher in arm C compared with arm A (mean difference in scores: global, 2.2; physical, 2.4; role, 4.6; emotional, 4.1; cognitive, 8.3; and social, 4.7). In addition, with the exception of a worse financial score (2.1), all the symptom scores were improved (range, −1.1 for pain to −11.9 for constipation). Comparison of arms B and C showed that the irinotecan-based therapy was associated with higher global QOL (mean difference in score, 0.8) and functional scores (mean difference in scores ranging from 2.5 for social to 6.7 for emotional) and lower symptom scores (mean difference in scores ranging from −0.3 for constipation to −8.2 for sleep). The only exception was an improvement in dyspnea

Table 4. Treatment Delivery

Treatment	LV5FU2 (n = 45)	LV5FU2-Cisplatin (n = 44)	LV5FU2-Irinotecan (n = 45)
No. of cycles			
Median	7	7	10
Range	1-20	1-18	1-25
Cycles delayed for toxicity			
No.	12	45	28
%	3	13	6
RDI			
FU bolus			
Median	0.99	0.96	0.98
Range	0.82-1.07	0.24-1.18	0.63-1.17
FU CI			
Median	0.99	0.97	0.98
Range	0.84-2.00	0.72-1.92	0.73-1.18
Cisplatin			
Median	—	0.97	—
Range	—	0.73-1.04	—
Irinotecan			
Median	—	—	0.97
Range	—	—	0.69-1.01

Abbreviations: LV5FU2, biweekly regimen of leucovorin plus fluorouracil; RDI, relative dose-intensity; CI, continuous infusion; FU, fluorouracil.

Table 5. Grade 3/4 Toxicity by Patient According to WHO Grade

Toxicity	% of Patients		
	LV5FU2 (n = 45)	LV5FU2-Cisplatin (n = 44)	LV5FU2-Irinotecan (n = 45)
Hematologic toxicity	22	71	44
Neutropenia	11	61	40
Febrile neutropenia ± infection	9	18	11
Anemia	16	30	16
Thrombocytopenia	2	2	0
Gastrointestinal toxicity	18	25	33
Nausea and vomiting	11	23	9
Diarrhea	2	2	22
Stomatitis	4	0	7
Other toxicity			
Alopecia	0	0	13
Cutaneous	2	5	0
Neurosensory	0	5	0
Cardiac	0	0	2
Toxic deaths			
No.	1	1	0
%	2*	2*	0
Treatment stopped for toxicity	4	16	11

Abbreviation: LV5FU2, biweekly regimen of leucovorin plus fluorouracil.
*Neutropenic infection.

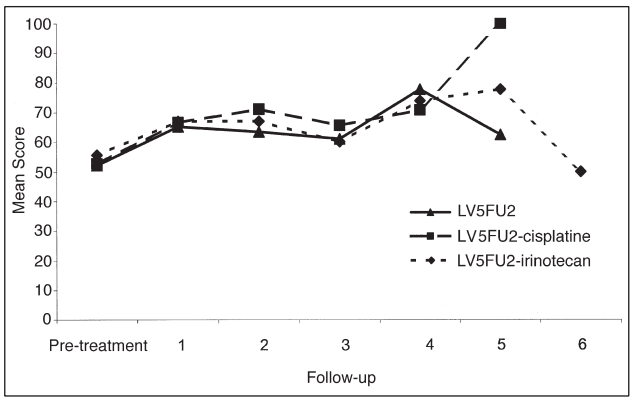

Fig 3. Quality of life global health score according to treatment arm. LV5FU2, biweekly regimen of leucovorin plus fluorouracil.

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Table 6. Main Results of the Logitudinal QLQ-C30 Analysis Using a Mixed Model Analysis of Variance for Repeated Measurement: Baseline and the First Three Follow-Ups

QLQ-C30 Scores	Time Effect,* *P*	Treatment Effect, *P*	Arm C *v* Arm A, Mean Difference in Scores	Arm C *v* Arm B, Mean Difference in Scores
Global health	< .0001	.89	+ 2.2	+ 0.8
Functional scales				
Physical	.45	.41	+ 2.4	+ 4.9
Role	< .01	.68	+ 4.6	+ 3.7
Emotional	< .0001	.29	+ 4.1	+ 6.7
Cognitive	.79	.15	+ 8.3	+ 2.6
Social	< .01	.71	+ 4.7	+ 2.5
Symptom scales				
Fatigue	.16	.12	− 10.2	− 4.4
Nausea	.99	.55	− 2.6	− 4.7
Pain	< .0001	.72	− 1.1	− 3.9
Dyspnea	.36	.17	− 3.5	+ 5.2
Insomnia	< .0001	.13	− 10.1	− 8.2
Appetite loss	< .01	.31	− 8.8	− 8.1
Constipation	.41	< .05	− 11.9	− 0.3
Diarrhea	.97	.27	− 4.7	− 5.9
Financial	.36	.72	+ 2.1	− 0.5

NOTE. $P < .05$ is significant.
Abbreviation: QLQ-C30, Quality of Life Questionnaire C30.
*Global change during the first three follow-ups. Scores vary from 0 (worst) to 100 (best) for functional and global health scales and from 0 (best) to 100 (worst) for symptom scales.

in patients receiving cisplatin-based therapy (mean difference in score for arm C *v* arm B, 5.2).

DISCUSSION

The externally reviewed ORRs reported here for the various regimens studied fall within the range (6% to 56%)[6,12-14,44-46] reported in phase II and III studies using FU, FU plus cisplatin, FAMTX, ELF, EAP (epirubicin, doxorubicin, cisplatin), and ECF and more recently in studies using taxane- or oxaliplatin-based regimens. For example, in the recent interim analysis of a randomized phase III trial, a response rate of 39% was reported for a docetaxel, cisplatin, and FU combination.[47] The 13% ORR (14% per protocol) obtained with the LV5FU2 regimen is similar to the 6% to 15% ORR found in two phase II studies using another infusional FU regimen.[13,48] The 27% ORR (30% as per protocol) for the LV5FU2-cisplatin regimen is similar to the response rates found in studies with other FU-cisplatin combination regimens (20%,[6] 23%,[47] 34%,[14] and 37%[13]). It is possible that the two patients considered inassessable may have achieved partial responses, and if this were the case, the number of responses would have been 14, and the ORR would have been 32%. The externally reviewed ORR of 40% (47% per protocol) for the LV5FU2-irinotecan regimen is similar to the 42% ORR reported in abstract form only for another randomized phase II study.[44] In that study, irinotecan 80 mg/m^2, LV 500 mg/m^2, and FU 2 g/m^2 over 22 hours were administered weekly for 6 weeks followed by a 1-week rest.[44] In both cases, the ORRs for irinotecan combined with infusional FU-LV were higher than the 22% ORR reported for irinotecan combined with bolus FU-LV.[27]

The median PFS and OS (6.9 and 11.3 months, respectively) for the LV5FU2-irinotecan combination were promising when compared with the PFS and OS reported in previously published randomized studies, and this suggests that this combination is one of the most active to date. The results are even more noteworthy in view of greater pretreatment weight loss in this group, indicating a potentially worse prognostic group, and the fact that all the patients had metastatic disease, in contrast with other studies that included patients with locally advanced gastric cancer. OS times of 8.7 and 6.1 months have been reported for ECF and FAMTX, respectively,[4,12] and OS times of 6.7, 7.2, and 7.2 months have been reported for FAMTX, ELF, and FUP, respectively.[6] The results have recently been published from a phase II study of oxaliplatin 100 mg/m^2, LV 400 mg/m^2 (2-hour infusion), and FU 400 mg/m^2 (bolus) followed by 3 g/m^2 (46-hour continuous infusion) every 14 days. Although a higher dose of FU was used, the combination resulted in a median time to progression and OS of only 6.2 months and 8.6 months, respectively.[49] Also, the interim analysis of a randomized phase III trial involving docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1, then FU 750

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mg/m^2/d repeated every 3 weeks showed a time to progression of 5.2 months and OS of 10.2 months.[47]

The LV5FU2-irinotecan regimen was not only active but also well tolerated. Indeed, treatment compliance for all the regimens studied was very good, with the median relative dose-intensity profile favoring the LV5FU2-irinotecan combination and with no study deaths in this arm. As expected, the LV5FU2 regimen was less toxic when delivered alone than when combined with cisplatin or irinotecan. The LV5FU2-cisplatin regimen was associated with the highest rate of nausea and vomiting and hematologic toxicity. As known from studies in patients with colorectal cancer, the LV5FU2-irinotecan regimen was associated with diarrhea.[26] Stomatitis was uncommon with any treatment, and the duration of hospital stay was similar for the three regimens. The irinotecan-containing regimen seemed to be less toxic than the regimens used in other studies involving patients with gastric carcinoma. In particular, severe nausea and vomiting occurred less frequently compared with cisplatin-based regimens.

Compared with pretreatment scores, chemotherapy seemed to improve social, emotional, and global QOL in the early first three follow-ups. The global QOL increased after the treatment induction and was maintained for 6 months. This finding is consistent with the QOL benefits reported with the ELF regimen.[7] The finding also suggests an advantage of the LV5FU2-irinotecan combination over the ECF regimen, which was associated with a maintained but not improved global QOL.[11,12] The reduction in the availability of QOL data during follow-up, together with the small number of patients, prevented an analysis of QOL after the third follow-up. This lack of data could have biased the longitudinal QOL analyses; patients with a shorter survival time and/or progression had a poor compliance in completing the QLQ-C30 assessment and probably a poor QOL. Therefore, it is likely that there is an overestimation in the mean scores, especially in the later follow-ups.

To further increase survival of patients with gastric cancer, future studies should investigate new strategies with novel drugs in different settings, including neoadjuvant, adjuvant, first line, and second line. Recent preliminary data have shown that neoadjuvant ECF significantly increases the curative resection rate from 69% to 79%.[50] Our observation that three patients in the LV5FU2-irinotecan arm were able to undergo surgery or radiofrequency ablation after their chemotherapy supports the evaluation of this regimen in the neoadjuvant setting. Although the role of chemotherapy in the adjuvant treatment of gastric cancer remains controversial, recent literature-based meta-analyses have suggested a small but statistically significant benefit.[51-55] Postoperative bolus FU-LV chemoradiotherapy is emerging as an internationally accepted standard,[56] but it is recognized that there is a need for large well-designed randomized trials in this area. The efficacy and tolerability of the LV5FU2-irinotecan regimen reported here support the evaluation of this combination in the adjuvant setting.

On the basis of ORR alone, the LV5FU2-cisplatin regimen might have warranted consideration for the phase III study. However, the decision regarding the phase III trial was based on the benefit to risk ratio and the high activity and better safety profile of the LV5FU2-irinotecan regimen makes it a more attractive treatment option. We are awaiting the results of a randomized phase III trial comparing irinotecan plus infusional FU-LV with FUP. A planned randomized French intergroup phase III study aims to compare first-line simplified LV5FU2 plus irinotecan (FOLFIRI) followed by second-line epirubicin, cisplatin, and capecitabine (ECC)[46] with ECC followed by FOLFIRI.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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