Leucovorin and Fluorouracil With or Without Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer

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Purpose: **In a previous study of treatment for advanced colorectal cancer, the LV5FU2 regimen, comprising leucovorin (LV) plus bolus and infusional fluorouracil (5FU) every 2 weeks, was superior to the standard North Central Cancer Treatment Group/Mayo Clinic 5-day bolus 5FU/LV regimen. This phase III study investigated the effect of combining oxaliplatin with LV5FU2, with progression-free survival as the primary end point.**

Patients and Methods: **Four hundred twenty previously untreated patients with measurable disease were randomized to receive a 2-hour infusion of LV (200 mg/m²/d) followed by a 5FU bolus (400 mg/m²/d) and 22-hour infusion (600 mg/m²/d) for 2 consecutive days every 2 weeks, either alone or together with oxaliplatin 85 mg/m² as a 2-hour infusion on day 1.**

Results: **Patients allocated to oxaliplatin plus LV5FU2 had significantly longer progression-free survival (median, 9.0 *v* 6.2 months; *P* = .0003) and better response rate (50.7% *v* 22.3%; *P* = .0001) when compared with the control arm. The improvement in overall survival did not reach significance (median, 16.2 *v* 14.7 months; *P* = .12). LV5FU2 plus oxaliplatin gave higher frequencies of National Cancer Institute common toxicity criteria grade 3/4 neutropenia (41.7% *v* 5.3% of patients), grade 3/4 diarrhea (11.9% *v* 5.3%), and grade 3 neurosensory toxicity (18.2% *v* 0%), but this did not result in impairment of quality of life (QoL). Survival without disease progression or deterioration in global health status was longer in patients allocated to oxaliplatin treatment (*P* = .004).**

Conclusion: **The LV5FU2-oxaliplatin combination seems beneficial as first-line therapy in advanced colorectal cancer, demonstrating a prolonged progression-free survival with acceptable tolerability and maintenance of QoL.**

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COLORECTAL CANCER accounts for 10% to 15% of all cancers and is the second leading cause of cancer deaths in Western countries. Approximately one half of all patients develop metastatic disease.[1] The prognosis for these patients is poor, although palliative chemotherapy has been shown to be able to prolong survival and to improve the quality of life (QoL) over best supportive care.[2] To date, no other single agent has been shown to be more effective as first-line therapy than the antimetabolite fluorouracil (5FU), which has been available for more than 40 years. Leucovorin (LV) modulation of 5FU increases the response rate (RR) but has no major impact on survival.[3]

Although there is no internationally accepted gold-standard 5FU/LV regimen, the monthly 5-day bolus North Central Cancer Treatment Group/Mayo Clinic regimen[4] is commonly used as a reference treatment in phase III trials. In a previous trial, this regimen was compared with LV5FU2, a bimonthly schedule of LV and bolus-plus-infusion 5FU. LV5FU2 proved superior in terms of RR (32.6% *v* 14.5%), progression-free survival (PFS; 27.6 *v* 22.0 weeks), and toxicity (grade 3 or 4 in 11.1% *v* 22.9% patients), but not overall survival (OS).[5]

Oxaliplatin, a new cytotoxic agent from the diaminocyclohexane platinum family, has a mechanism of action similar to that of other platinum derivatives, but its spectrum of antitumor activity against tumor models differs from those of cisplatin and carboplatin. Activity against cisplatin-resistant colon carcinoma cell lines has been demonstrated.[6] In addition, experimental data showed synergistic activity of the oxaliplatin/5FU combination.[6] Oxaliplatin clinical toxicity is also distinct from other platinum drugs: it has no renal toxicity and minimal hematotoxicity; it causes both a reversible acute, cold-related dysesthesia and a dose-limit-

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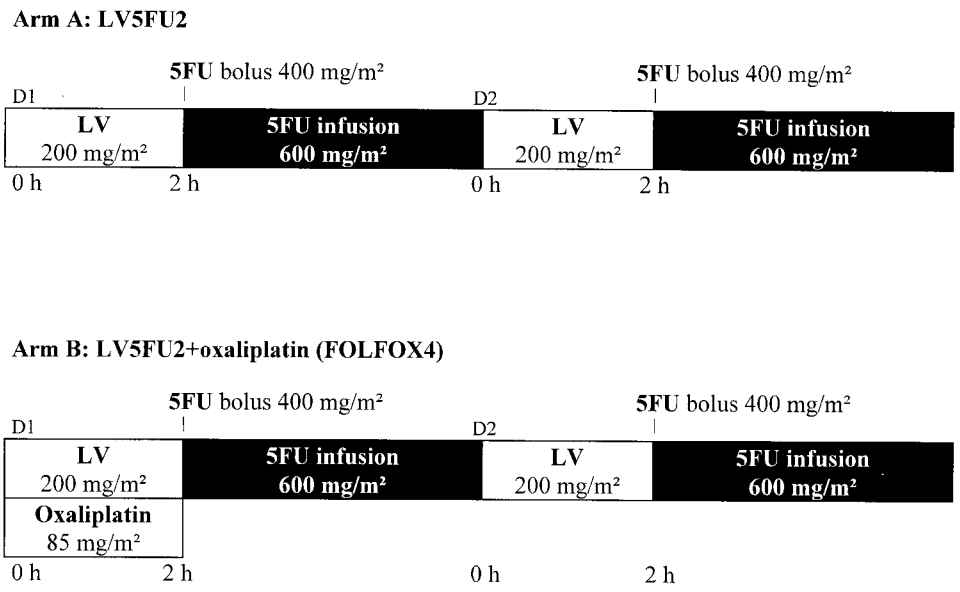


Fig 1. Chemotherapy regimens.

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ing cumulative peripheral sensory neuropathy that usually rapidly regresses after treatment withdrawal. Activity as a single agent in metastatic colorectal cancer patients either previously untreated or treated with 5FU was demonstrated in phase II trials with RRs ranging between 10% and 24%.[7-10] Consistent with laboratory evidence of oxaliplatin/5FU synergy, there is evidence for the clinical activity of 5FU/LV/oxaliplatin combinations, with RRs of 20% to more than 50% reported for the three-drug combination in phase II trials.[11-13]

To further investigate the value of oxaliplatin to the treatment of previously untreated metastatic colorectal cancer, a randomized study was designed to assess the impact of combining oxaliplatin to the bimonthly LV5FU2 schedule. The primary objective was to demonstrate whether adding oxaliplatin would prolong PFS. The secondary objectives were to compare the two treatments in terms of RR, OS, tolerability, and QoL.

PATIENTS AND METHODS

Patient Eligibility

The eligibility criteria were adenocarcinoma of the colon or rectum; unresectable metastases; at least one bidimensionally measurable lesion of ≥ 2 cm; adequate bone marrow, liver, and renal function; World Health Organization (WHO) performance status of 0 to 2; age 18 to 75 years; and ability to complete QoL questionnaires. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients with CNS metastases, second malignancies, or disease confined to previous radiation fields were excluded. Written informed consent was required and the study was approved by the ethics committees of all of the participating centers.

Chemotherapy

Arm A (LV5FU2; Fig 1) consisted of LV 200 mg/m^2/d as a 2-hour infusion followed by bolus 5FU 400 mg/m^2/d and a 22-hour infusion of 5FU 600 mg/m^2/d, repeated for 2 consecutive days every 2 weeks.[5] Arm B (FOLFOX4) consisted of the same bimonthly regimen, with the addition of oxaliplatin 85 mg/m^2 on day 1 only, given as a 2-hour infusion in 250 mL of dextrose 5%, concurrent with LV. Oxaliplatin must not be mixed with normal saline; therefore, when LV and oxaliplatin were given concurrently via a Y-connector, both drugs were administered in 5% dextrose. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3–receptor antagonist was used for FOLFOX4 but was not necessary for LV5FU2. The use of implantable ports and disposable or electronic pumps allowed chemotherapy to be administered on an outpatient basis. Treatment was continued until disease progression or unacceptable toxicity occurred or until a patient chose to discontinue treatment.

Patients were assessed before starting each 2-week cycle using the National Cancer Institute common toxicity criteria. Chemotherapy was delayed until recovery if neutrophils decreased to less than 1.5×10^9/L or platelets decreased to less than 100×10^9/L or for significant persisting nonhematologic toxicity. The 5FU dose was reduced after National Cancer Institute common toxicity criteria grade ≥ 3 diarrhea, stomatitis, or dermatitis occurred. Oxaliplatin was reduced for grade 3/4 neutropenia, and in cases of persistent (≥ 14 days) paresthesia or temporary (7 to 14 days) painful paresthesia or functional impairment. In cases of persistent (≥ 14 days) painful paraesthesia or functional impairment, oxaliplatin was omitted from the regimen until recovery.

Study Parameters

Physical examinations and blood counts were performed every cycle. Hepatic and renal function tests, carcinoembryonic antigen (CEA), and computed tomography (CT) scans or magnetic resonance imaging (MRI) of measurable lesions were assessed at baseline and repeated every four 2-week cycles. Completion of the European Organization

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for Research and Treatment of Cancer QoL questionnaire QLQ-C30 (version 2.0)[14] was also required every fourth treatment cycle.

WHO criteria were used to assess tumor response. 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% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. CT or MRI scans were performed 4 weeks later to confirm a response. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% of measurable lesions, and progressive disease was defined as an increase of at least 25% of measurable lesions or the appearance of new malignant lesion(s). All CT and MRI scans were subjected to external review by at least two radiologists who were blinded to the patients' treatment to confirm responses and the date of progression.

PFS was defined as the time interval from the randomization date to the date of disease progression or, if the patient died without evidence of progression, to the date of death. When CT scans were not available or were not performed, or if there was a discrepancy between investigators and radiologists, a clinical expert blinded to the treatment received was asked to make the final decision.

Poststudy second-line chemotherapy was allowed for both arms at the discretion of the investigators and prospectively monitored for exploratory survival analysis. Cross-over from arm A to arm B was allowed, provided that disease progression under LV5FU2 was documented.

Statistical Considerations

Randomization was performed using a minimization technique,[15] stratifying patients by performance status, number of metastatic sites, and institution. The study was designed to have the power to detect a 3-month prolongation of PFS using a two-sided log-rank test with an alpha risk of 0.05 and a beta risk of 0.20.[16]

Two interim analyses were scheduled for stopping rules[17,18]: (1) after inclusion of 41 patients on arm B with fewer than eight responses, and (2) after 100 patients had been enrolled per arm and when RR differed by at least 26% between arms.

The Mantel-Haenszel test was used for population, RR, and toxicity comparisons.[19] Response duration, PFS, and OS were calculated from the date of randomization using the Kaplan-Meier method.[20] Stepwise analyses were undertaken to identify subsets of factors associated with response, PFS, and OS using the Cox proportional hazards model.[21] Variables for inclusion in the model were assigned treatment, sex, age, performance status, primary site of disease, synchronous/metachronous metastases, number of metastatic sites, liver metastases, adjuvant chemotherapy, prior radiotherapy, baseline alkaline phosphatase, CEA, lactate dehydrogenase (LDH), serum creatinine, serum ALT, serum AST, institution, and poststudy chemotherapy.

RESULTS

Patient Characteristics

From August 1995 to July 1997, 420 patients were randomized at 35 institutions and nine countries, 210 in each arm (Table 1). No significant imbalances in major prognostic variables occurred in the randomization; minor differences in performance status, CEA, and alkaline phosphatases would, if anything, favor the control arm. Seven patients were unassessable for treatment efficacy, four on arm A (one patient was ineligible, two were not treated, and one withdrew early) and three on arm B (one patient was not treated and two experienced early disease-related death). These patients were retained for the intent-to-treat analysis. At the cutoff date (December 1, 1998), the median potential follow-up time for the entire cohort was 27.7 months.

Objective Tumor Responses

The investigators' assessments of objective response were recorded as follows: the RRs for arms A and B were 28.6% (60 of 210 patients) and 49.5% (104 of 210 patients), respectively. The external panel of radiologists was able to review CT scans of 380 patients (90.5%), confirming 46 and 105 responses on arms A and B, respectively. The RRs obtained in the population of assessable patients are, therefore, 22.3% and 50.7%, respectively. The intent-to-treat RRs are 21.9% (95% confidence interval, 17.9% to 25.9%) and 50.0% (95% confidence interval, 46.1% to 54.9%; $P = .0001$), respectively. The RRs are reported as a function of various patient characteristics in Table 2.

For arm A and arm B, the median times to response were 12 weeks and 9 weeks, respectively, and the median durations of the responses were 46.1 and 45.1 weeks. Secondary surgery to remove metastases could be performed in seven patients (3.3%) on arm A and 14 (6.7%) on arm B.

Only two independent prognostic factors were found to be significant for response in the multivariate analysis: treatment allocation to oxaliplatin and synchronous metastases (Tables 3 and 4). CEA levels normalized or decreased more than 50% in 57 (34.5%) of 165 patients with elevated CEA level at baseline on arm A versus 107 (62.6%) of 171 patients on arm B ($P = .0001$).

PFS

According to the investigators' assessments, median PFS was significantly shorter for arm A than for arm B (with oxaliplatin): 6.2 months (26.9 weeks) versus 9.0 months (39.0 weeks), respectively ($P = .0001$). According to the external review, these values were 6.0 months (26.1 weeks) and 8.2 months (35.6 weeks), respectively ($P = .0003$; Fig 2). In the multivariate analysis, there were three independent prognostic factors for improved PFS: treatment allocation to oxaliplatin, low LDH level, and good performance status (Tables 3 and 4).

Survival

Although median OS was shorter for arm A than arm B (14.7 months [63.9 weeks] *v* 16.2 months [70.6 weeks], respectively), this difference was not statistically significant (log-rank test $P = .12$; Wilcoxon $P = .05$; Fig 3). Sixty-nine

Table 1. Patient Characteristics

Parameter	Arm A: LV5FU2		Arm B: LV5FU2 + Oxaliplatin	
	No. of Patients	%	No. of Patients	%
Demographic characteristics				
No. of patients	210	100	210	100
Male	122	58.1	127	60.5
Female	88	41.9	83	39.5
Age, years				
Median	63		63	
Range	22-76		20-76	
WHO performance status				
0	102	48.6	91	43.3
1	88	41.9	97	46.2
2	20	9.5	22	10.5
Primary site				
Colon	147	70.0	151	71.9
Rectum	61	29.0	59	28.1
Multiple or not specified	2	1.0	0	0
Metastases				
Synchronous	139	66.2	135	64.3
Metachronous	70	33.3	70	33.3
Unknown	1	0.5	5	2.4
Metastatic site(s)				
Liver	173	82.4	182	86.7
Lung	63	30.0	50	23.4
Other	25	11.4	26	12.4
No. of sites				
1	84	40.0	90	42.9
≥ 2	126	60.0	120	57.1
CEA				
Normal	37	17.6	31	14.8
1-20 $\times$ normal	92	43.8	95	45.2
$> 20 \times$ normal	73	34.8	76	36.2
Unknown	8	3.8	8	3.8
Alkaline phosphatase				
Normal	112	53.3	102	48.6
Increased	95	45.2	106	50.5
Unknown	3	1.4	2	1.0
LDH				
Normal	88	41.9	80	38.1
Increased	94	44.8	97	46.2
Unknown	28	13.3	33	15.7
Adjuvant chemotherapy				
Yes	43	20.5	42	20.0
No	167	79.5	168	80.0

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percent of the patients receiving the LV5FU2-oxaliplatin combination (arm B; FOLFOX4) were alive at 1 year compared with 61% of the patients in the control arm. Poststudy chemotherapy was administered to 127 patients on arm A (60.5%) and 122 patients on arm B (58.1%). Among those, 78 patients on arm A and 62 patients on arm B received poststudy chemotherapy with oxaliplatin (arm A, 58 patients, 27.6%) and/or irinotecan (arm A, 42 patients, 20%; arm B, 62 patients, 29.5%). For the patients in this study who did not receive second-line poststudy oxaliplatin or irinotecan, the median OS was 12.2 months (52.9 weeks) for arm A (132 patients) and 14.8 months (64.1 weeks) for arm B (148 patients) ($P = .04$). The median time from progression to death was 8.2 months (35.7 weeks) for arm A and 7.2 months (31.1 weeks) for arm B.

In the multivariate analysis, independent prognostic factors for improved OS were treatment allocation to oxaliplatin, low LDH level, good performance status, low alkaline phosphatase level, and a limited number of involved sites (Tables 3 and 4).

Table 2. Objective Tumor Response Rates After External Review

Event Rate	Arm A: LV5FU2			Arm B: LV5FU2 + Oxaliplatin		
	No. of Patients	No. of Responses	%	No. of Patients	No. of Responses	%
Overall						
Intent to treat	210	46	21.9	210	105	50.0
Assessable	206	46	22.3	207	105	50.7
CR	210	1	0.5	210	3	1.4
PR	210	45	21.4	210	102	48.6
Stable disease	210	107	51.0	210	67	31.9
Disease progression	210	34	16.2	210	21	10.0
Not reviewed/not assessable	210	23	10.9	210	17	8.1
Response (CR/PR) by age						
≤ 65 years	126	28	22.2	134	67	50.0
> 65 years	84	18	21.4	76	38	50.0
Response (CR/PR) by disease						
Synchronous	139	32	23.0	135	76	56.3
Metachronous	70	14	20.0	70	29	41.4
Liver only	68	16	23.6	79	43	54.4
Liver + other sites	105	23	21.9	103	54	52.4
Other sites	37	7	18.9	28	8	28.6
Response (CR/PR) by prior adjuvant chemotherapy						
Yes	43	6	14.0	42	16	38.1
No	167	40	23.9	168	89	53.0

Abbreviations: CR, complete response; PR, partial response.

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Toxicity

Arm A patients received on study a median of 11 cycles; those on arm B received a median of 12 cycles. There was one therapy-related death on arm B that resulted from gastrointestinal and hematologic toxicities. Grade 3/4 neutropenia, diarrhea, mucositis, and neuropathy were more frequent on arm B than on arm A (Table 5). Grade 3/4 neutropenia was the only toxicity that occurred more frequently in women than in men (52% *v* 35%; $P = .015$). Grade 1/2 alopecia was similar in both treatment groups. Cardiac events occurred in three patients on arm A and two patients on arm B. Four patients (1.9%) on arm B had severe allergic reactions.

Although grade 3/4 neutropenia was common on arm B, patients responded well to dose modification and few

Table 3. Prognostic Factors in Univariate Analysis

Variable	Response		PFS		OS	
	P	Odds Ratio	*P*	Risk Ratio	*P*	Risk Ratio
WHO performance status, continuous	.5938		.0049	1.24	.0001	1.52
Synchronous/metachronous metastases	.0423	1.58	.2458		.1548	
No. of metastatic sites, continuous	.1040		.0008	1.21	.0001	1.34
Alkaline phosphatase, NCI grade	.5887		.0031	1.25	.0001	1.59
LDH, ≤ upper limit versus > upper limit	.4944		.0001	1.57	.0001	2.17
Assigned oxaliplatin	.0001	3.43	.0001	0.81	.1171	
Treatment center	.0504		.6637		.0079	—
Sex	.8903		.0793		.4079	
Age, continuous	.7390		.3976		.5753	
Liver involved, yes versus no	.2439		.2773		.8469	
Prior chemotherapy	.0400	0.57	.5632		.2163	
Prior radiotherapy	.5958		.2253		.0374	0.65
Primary site, colon versus rectum	.3026		.6282		.3798	
ALT, NCI grade	.6829		.1070		.0012	1.38
AST, NCI grade	.8721		.6455		.5086	
Creatinine, NCI grade	.5684		.5019		.5960	
CEA, ≤ 5 ng/mL, 5-50 ng/mL, > 50 ng/mL	.5406		.0015	1.251	.0001	1.48

Abbreviation: NCI, National Cancer Institute (common toxicity criteria).

Table 4. Prognostic Factors in Multivariate Analysis

Variable	Response		PFS		OS	
	Odds Ratio	*P*	Risk Ratio	*P*	Risk Ratio	*P*
WHO performance status	—	NS	1.30	.0023	1.50	.0001
Synchronous/metachronous metastases	1.57	.0306	—	NS	—	NS
No. of metastatic sites	—	NS	—	NS	1.17	.0029
Alkaline phosphatase	—	NS	—	NS	1.34	.0062
LDH	—	NS	1.60	.0001	1.94	.0001
Assigned oxaliplatin	1.84	.0001	1.71	.0001	0.80	.0001

Abbreviations: NS, not significant.

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complications were seen. Only 22 patients (10.5%) had more than one episode, and only two patients (1%) experienced febrile neutropenia. Neurosensory toxicity was observed in 68% of the arm B patients and reached grade 3 in 18%. Cold-related dysesthesia was reported in 141 patients (67.5%). Paresthesia without pain was observed in 136 patients (65.1%). Paresthesia with pain occurred in 22 patients (10.5%). Cumulative paresthesia interfering with function occurred in 34 patients (16.3%). Investigators also reported pharyngolaryngeal dysesthesia in 47 patients (22.5%), but only two patients (1%) had a laryngospasm-like syndrome. Cramps were experienced in 12 patients (5.7%), loss of deep tendon reflexes in 24 patients (11.5%), and a Lhermitte's sign in seven patients (3.3%). The estimated incidences of grade 2 and 3 neuropathies, respectively, calculated for patients exposed to oxaliplatin, reached 10% after three and nine cycles, 25% after eight and 12 cycles, and 50% after 10 and 14 cycles. Reversibility of grade 3 sensory neurotoxicity was observed in 25 (74%) of 34 patients. The median time to recovery from grade 3 neurotoxicity was 13 weeks (Fig 4).

Seven patients (3.4%) were withdrawn from the study because of toxicity on arm A and 22 (10.6%) were withdrawn because of toxicity on arm B, including eight patients with sensory neuropathy (3.8%). The elderly patients (> 65 years; n = 160) did not experience increased toxicity as compared with the younger patients, except for grade 3/4 diarrhea (18% *v* 8%; *P* = .034).

Dose-Intensity

For arm A, the 5FU dose-intensity was 92% of the scheduled dose for the first four cycles and 89% for all cycles. For arm B, the 5FU dose-intensity was 84% and the oxaliplatin dose-intensity was 86% during the first four cycles, with 76% for 5FU and 73% for oxaliplatin during all cycles.

QoL

Three hundred fifty-one patients (83.6%) participated in the QoL assessment. Age and sex influenced the baseline QoL scores. At cycle 4, emotional functioning improved and insomnia was attenuated on both arms, general condi-

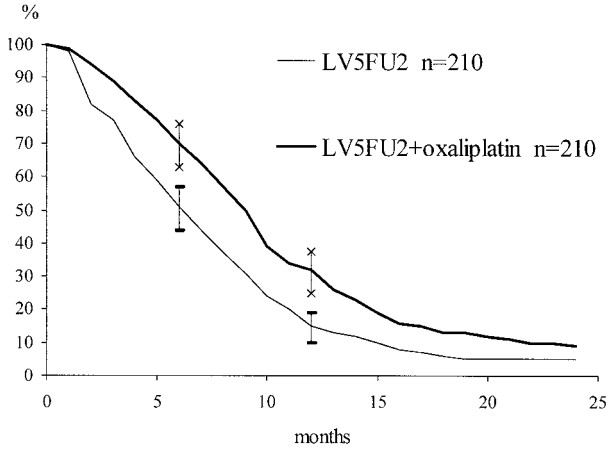


Fig 2. PFS curves.

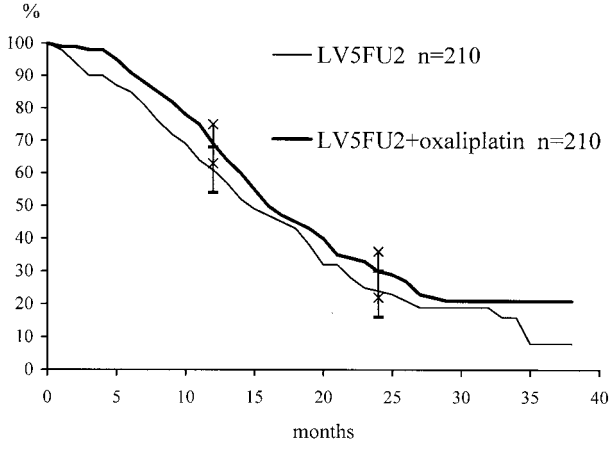


Fig 3. OS curves.

Table 5. Maximum Toxicity* per Patient (%)

	Arm A: LV5FU2				Arm B: LV5FU2 + Oxaliplatin (n = 209)				
	1	2	3	4	1	2	3	4	*P* (grade 3/4)
Neutropenia	16.3	8.6	3.8	1.5	14.3	14.3	29.7	12.0	<.001
Thrombocytopenia	26.5	2.4	0.5	0.0	62.2	11.5	2.0	0.5	NS
Anemia	57.7	21.2	1.5	1.0	59.8	23.5	3.3	0.0	NS
Infection	15.9	5.8	1.0	0.5	17.7	6.7	1.5	0.0	NS
Nausea	40.4	11.1	2.0	NA	44.0	22.5	5.7	NA	.043
Vomiting	18.3	9.1	1.5	0.5	24.0	24.4	4.3	1.5	.043
Diarrhea	27.9	10.6	3.8	1.5	30.6	16.3	8.6	3.3	.015
Mucositis	25.0	9.1	1.5	0.0	24.9	12.9	5.3	0.5	.019
Cutaneous	20.2	10.6	0.0	0.5	19.6	9.1	0.0	0.0	NS
Alopecia	15.4	3.4	NA	NA	15.8	1.9	NA	NA	NA
Neurologic toxicity	9.1	2.9	0.0	NA	20.6	29.2	18.2	NA	< .001

Abbreviation: NA, not applicable.
*According to NCI grade.

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tion improved and pain decreased on arm A, and nausea and vomiting were worse and appetite returned on arm B. At cycle 8, emotional functioning improved on both arms; role functioning and general condition improved and insomnia diminished on arm A; nausea or vomiting worsened on arm B. Overall, the median QoL scores for the two treatment arms were comparable. Neither response to treatment nor occurrence of side effects significantly influenced the changes in patients' QoL. Furthermore, the time to deterioration of the global health status of 20% or 40% was significantly prolonged on arm B ($P = .0039$ and $P = .0004$, respectively; Fig 5).

Weight increase of at least 5% was recorded for 83 patients (39.5%) on arm A and in 90 (42.9%) on arm B. Performance status improved in 59 (54.6%) of 108 patients on arm A and in 71 (59.7%) of 119 patients on arm B.

DISCUSSION

The results of this study demonstrate that the addition of oxaliplatin to the LV5FU2 bimonthly regimen significantly extends the PFS of patients with metastatic colorectal cancer. The results we obtained with the control arm, ie, the LV5FU2 bimonthly regimen alone, were consistent with those observed in prior phase III studies: the median PFS of 6.2 months and RR of 29% in the present study (as assessed by the investigators) are comparable to the median PFS of 6.4 months and RR of 32.6% in the previous French Intergroup study and the RR of 27% in the study conducted by the Medical Research Council.[5,22] The present study also confirmed the good tolerability of this regimen, which makes it a reasonable option for combination with other drugs.

The median PFS as assessed by investigators was improved by 45% or 12.1 weeks (2.8 months). Multivariate analyses identified only three factors that contributed to prolonged PFS: assignment to oxaliplatin, baseline LDH level, and performance status.

The median OS in both arms was well in excess of 1 year, in contrast to most of the studies performed before the era of second-line therapies.[22-26] The prolonged survival cannot be attributed to a selected patient population with a good prognosis; 58% of the patients in the study had more than

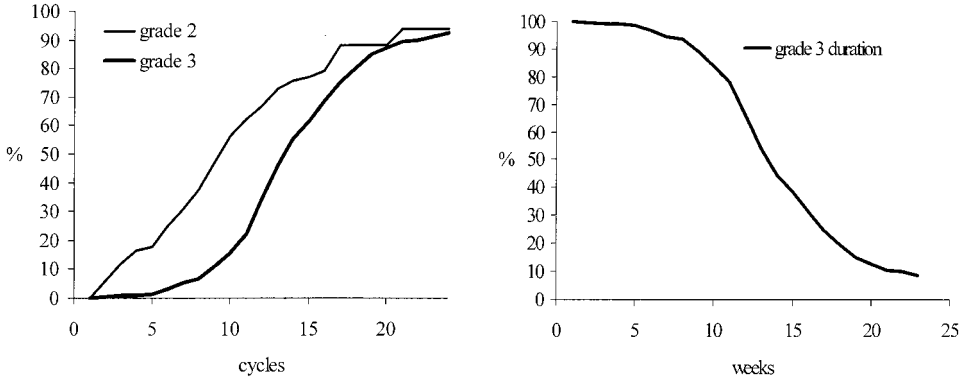


Fig 4. Cumulative incidence (left) and recovery (right) from sensory neurotoxicity.

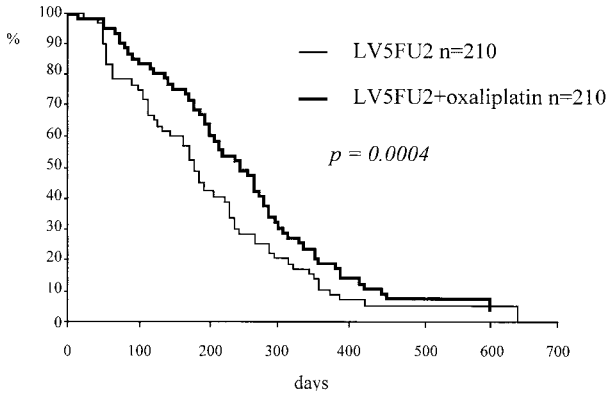


Fig 5. Time to global health status deterioration of 40%.

one metastatic site. Among nine other randomized studies[5,13,23-30] that specified the number of metastatic sites, only two had enrolled more than 50% of the patients with more than one metastatic site.[29,30]

There was a nonsignificant survival advantage on arm B, with 10.4% or 6.7 weeks median survival improvement (1.5 month). This raises the question of why a higher RR and an extended PFS were not translated into extended OS. In the meta-analysis of 5FU plus LV in advanced colorectal cancer, where no difference in survival was observed between 5FU and 5FU plus LV, the authors proposed four hypotheses to answer this question: first, duration of tumor responses may have been too short; second, the RR could be too small; third, the complete RR may be too low; fourth, cross-over may have obscured a small impact on survival.[3] In our study, we can retain only the two latter hypotheses. As of today, no study, including ours, has ever reported a high complete RR. Therefore, only cross-over or active poststudy chemotherapy are relevant in our purpose.

As a matter of fact, we observed an unusually good survival among patients on the control arm in which 37% (78 patients) received poststudy chemotherapy with oxaliplatin and/or irinotecan. The efficacy of these two new agents as second-line therapies has already been demonstrated.[7,8,11,31,32] The impact on survival of the second-line therapies suggests that PFS rather than OS should be the end point of first-line studies in metastatic colorectal cancer or that therapeutic strategy studies that include two lines of therapy in the study design should be initiated.

The RR was more than two times higher in the LV5FU2 plus oxaliplatin arm (FOLFOX4) compared with LV5FU2 alone. This high RR in patients with oxaliplatin may have contributed to the early divergence in the survival curves observed in this study. This suggests that patients with bulky or rapidly progressive disease might particularly benefit from the early use of oxaliplatin, as these patients might not otherwise survive to receive subsequent therapy. Furthermore, the high RR (54%) obtained in patients with isolated liver metastases, which might improve the possibility of curative liver resection, supports the use of oxaliplatin as first-line therapy in this population. Another phase III trial evaluating the contribution of oxaliplatin to a chronomodulated LV5FU regimen also found a significantly higher RR with the addition of oxaliplatin.[33]

Median QoL scores were similar for the two arms in the study, despite the increased incidence of 5FU-related side effects and the specific peripheral neurotoxicity recorded for patients who received the oxaliplatin-containing regimen. Furthermore, the time to deterioration in global health status was prolonged in the oxaliplatin-containing arm.

Among patients who were assigned to receive oxaliplatin, neutropenia grade 3/4 occurred in 41.7% of patients but was febrile in only 1.0%, whereas grade 3/4 vomiting and mucositis affected only 5.8% of patients and diarrhea affected 11.9%. On the other hand, the incidences and severities of 5FU skin toxicity and alopecia remained particularly low.

The cumulative dose-limiting toxicity of the oxaliplatin arm was sensory neuropathy. Reversible paresthesia interfering with function was observed in 16.3% of the patients and led to oxaliplatin withdrawal for 3.8% after they had received a minimum of nine cycles (or at least 4 months) of chemotherapy. This time to onset should be put into perspective with the median time to response of 2.1 months, allowing the maximum effect of the treatment to be obtained before cumulative toxicity appeared and thus not negatively affecting patients who did not benefit from treatment in terms of an objective response.

The reversibility of the significant sensory neuropathy is important for future adjuvant studies. Because the elderly group performed quite similarly to the other patients, we concluded that the oxaliplatin-LV5FU2 combination may be safely administered to patients older than 65 years.

This study also demonstrates that oxaliplatin-5FU/LV combination provides a significant improvement of disease control versus 5FU/LV alone. In this setting, raltitrexed, a pure thymidylate synthase inhibitor, and antimetabolites such as capecitabine, uracil and tegafur, and trimetrexate, given alone, did not generate superior results over the monthly 5-day LV5FU bolus regimen.[34-39] However, irinotecan in combination with 5FU/LV was associated with an improved PFS and a prolonged survival.[40,41] These results and those achieved in phase III studies using oxaliplatin provide clear evidence that the addition of an active anticancer drug to 5FU/LV improves the disease outcome as compared with 5FU/LV alone.

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The LV5FU2 plus oxaliplatin combination, which seems beneficial as first-line therapy of metastatic colorectal cancer, will be further examined as adjuvant therapy for colon cancer (Multicenter International Study of Oxaliplatin 5FU-LV in the Adjuvant Treatment of Colon Cancer) to verify whether it can improve survival in this setting. A higher oxaliplatin dose, which induced a high RR in second-line therapy in combination with a simplified bimonthly regimen,[42,43] is also to be studied as first-line therapy.

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