ORIGINAL ARTICLE

Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

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ABSTRACT

BACKGROUND

The standard adjuvant treatment of colon cancer is fluorouracil plus leucovorin (FL). Oxaliplatin improves the efficacy of this combination in patients with metastatic colorectal cancer. We evaluated the efficacy of treatment with FL plus oxaliplatin in the postoperative adjuvant setting.

METHODS

We randomly assigned 2246 patients who had undergone curative resection for stage II or III colon cancer to receive FL alone or with oxaliplatin for six months. The primary end point was disease-free survival.

RESULTS

A total of 1123 patients were randomly assigned to each group. After a median follow-up of 37.9 months, 237 patients in the group given FL plus oxaliplatin had had a cancer-related event, as compared with 293 patients in the FL group (21.1 percent vs. 26.1 percent; hazard ratio for recurrence, 0.77; P=0.002). The rate of disease-free survival at three years was 78.2 percent (95 percent confidence interval, 75.6 to 80.7) in the group given FL plus oxaliplatin and 72.9 percent (95 percent confidence interval, 70.2 to 75.7) in the FL group (P=0.002 by the stratified log-rank test). In the group given FL plus oxaliplatin, the incidence of febrile neutropenia was 1.8 percent, the incidence of gastrointestinal adverse effects was low, and the incidence of grade 3 sensory neuropathy was 12.4 percent during treatment, decreasing to 1.1 percent at one year of follow-up. Six patients in each group died during treatment (death rate, 0.5 percent).

CONCLUSIONS

Adding oxaliplatin to a regimen of fluorouracil and leucovorin improves the adjuvant treatment of colon cancer.

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COLORECTAL CANCER IS THE SECOND leading cause of death from cancer in Western countries[1]; 40 to 50 percent of patients who undergo potentially curative surgery alone ultimately relapse and die of metastatic disease.[2] The most important prognostic indicator of survival in early colon cancer is the stage of the tumor (T, according to the tumor–node–metastasis [TNM] classification), determined by the depth of penetration through the bowel wall, and the number of involved lymph nodes.[3]

The demonstration that postoperative adjuvant treatment with fluorouracil and levamisole reduced the mortality rate by 33 percent among patients with stage III colon cancer[4] prompted several trials, which established six months of treatment with fluorouracil plus leucovorin (FL) as the standard adjuvant chemotherapy for stage III colon cancer.[5-11] Oxaliplatin is a third-generation platinum derivative, which, when combined with fluorouracil and leucovorin, is among the most effective chemotherapies for metastatic colorectal cancer.[12-15] To determine whether oxaliplatin can also benefit patients with disease in an earlier stage, we conducted an international phase 3 clinical trial in patients with stage II or III colon cancer — the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC).

METHODS

PATIENTS

Patients were eligible if they had undergone complete resection of histologically proven stage II (T3 or T4,N0,M0) or stage III (any T,N1 or N2,M0) colon cancer, as defined by the presence of the inferior pole of the tumor above the peritoneal reflection — that is, at least 15 cm from the anal margin. Treatment had to be started within seven weeks after surgery. Other eligibility criteria included an age of 18 to 75 years; a Karnofsky performance-status score of at least 60; a carcinoembryonic antigen level of less than 10 ng per milliliter; the absence of prior chemotherapy, immunotherapy, or radiotherapy; and adequate blood counts and liver and kidney function. Written informed consent was required from all patients, and the study was approved by the ethics committees of the participating centers.

TREATMENT

Eligible patients were randomly assigned to receive FL alone or with oxaliplatin. In the FL group, each cycle comprised a 2-hour infusion of 200 mg of leucovorin per square meter of body-surface area followed by a bolus of 400 mg of fluorouracil per square meter and then a 22-hour infusion of 600 mg of fluorouracil per square meter given on 2 consecutive days every 14 days, for 12 cycles. In the group given FL plus oxaliplatin, the same FL regimen was used, plus a two-hour infusion of 85 mg of oxaliplatin (Eloxatin, Sanofi-Synthelabo) per square meter on day 1, given simultaneously with leucovorin, with the use of a Y infusion device. The use of disposable pumps (LV5 infusors, Baxter Healthcare) allowed outpatients to receive a continuous infusion of fluorouracil.

Adverse effects were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 1. According to these criteria, a score of 1 indicates mild adverse effects, a score of 2 moderate adverse effects, a score of 3 severe adverse effects, and a score of 4 life-threatening adverse effects. Dose reductions were based on the worst adverse effects observed during the previous cycle. The dose of oxaliplatin was to be reduced to 75 mg per square meter in the event of persistent (at least 14 days) paresthesias, temporary painful paresthesias, or functional impairment. Oxaliplatin was discontinued in cases of persistent painful paresthesias or functional impairment. Together with reductions in the dose of oxaliplatin, the bolus dose of fluorouracil was reduced to 300 mg per square meter and the infusion to 500 mg per square meter in the event of grade 3 or 4 neutropenia or thrombocytopenia (or both), diarrhea, stomatitis, or other drug-related adverse effects of grade 3. Only the dose of fluorouracil was scheduled to be reduced in the event of skin-related adverse effects of grade 3 or 4. Treatment was delayed by up to three weeks until the patient recovered from various adverse effects, the neutrophil count exceeded 1500 per cubic millimeter, and the platelet count exceeded 100,000 per cubic millimeter. Chemotherapy was stopped in the event of cardiac or neurocerebellar adverse effects or grade 3 or 4 allergic reactions.

FOLLOW-UP

Patients were assessed before randomization, every two weeks during treatment, and then every six

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months for five years. The baseline assessment involved a medical history taking, physical examination, biologic tests, measurement of the carcinoembryonic antigen level, chest radiography, and abdominal ultrasonography or computed tomography. Patients were monitored for adverse effects throughout the treatment period and until 28 days after the last cycle of chemotherapy, unless treatment-related adverse effects required additional follow-up.

The diagnosis of recurrence was made on the basis of imaging and, if necessary, cytologic analysis or biopsy. An elevated carcinoembryonic antigen level as a solitary finding was not accepted as evidence of relapse. Neurologic adverse effects were to be reported at each visit during follow-up and were assessed with the use of the neurosensory section of the Common Toxicity Criteria of the National Cancer Institute, version 1.

STATISTICAL ANALYSIS

Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to the TNM stage (T2 or T3 vs. T4 and N0, N1, or N2), the presence or absence of bowel obstruction or tumor perforation, and the medical center. The sample size of 2200 patients was calculated under the assumptions of a three-year disease-free survival rate of 73 percent in the control group and 79 percent in the group given FL plus oxaliplatin, with a ratio of stage II disease to stage III disease of 0.4:0.6, an enrollment period and a follow-up period of three years, a decrease in the risk of relapse after three years, a statistical power of 90 percent, and an alpha value of 0.05 and two-sided P values derived with the use of the log-rank test. The primary efficacy variable was disease-free survival, defined as the time from randomization to relapse or death, whichever occurred first. Second colorectal cancers were considered relapses, whereas noncolorectal tumors were disregarded in the analyses.

The primary statistical analysis of efficacy was the comparison, after three years of follow-up, of disease-free survival between groups according to the intention-to-treat principle, with the use of a two-sided log-rank test stratified according to baseline disease stage. Hazard ratios and 95 percent confidence intervals were calculated with the use of the Cox proportional-hazards model. Survival curves were drawn according to Kaplan–Meier methods.

To assess the consistency of the effect of treatment on disease-free survival across prognostic subgroups, we calculated hazard ratios and 95 percent confidence limits for subgroups defined according to the following variables: sex, age, disease stage (II vs. III), baseline serum carcinoembryonic antigen level, number of involved lymph nodes (≤4 vs. >4), T classification (T4 vs. T1, T2, or T3), degree of cellular differentiation (well vs. poorly differentiated), and the presence or absence of perforation, obstruction, and venous invasion.

The cutoff date of the analysis was April 22, 2003. The duration of follow-up was defined as the number of months from randomization to the cutoff date.

Secondary end points were safety, including long-term adverse effects, and overall survival, measured from the time of randomization to death from any cause. With a median follow-up of three years, it is too early to compare the two treatment groups statistically in terms of survival, and only descriptive analyses of overall survival are presented. Safety analyses included patients who had received at least one cycle of treatment.

ORGANIZATION OF THE TRIAL

The concept underlying this study was developed by Dr. de Gramont, and the investigation was designed by the investigators and Sanofi-Synthelabo. Data were collected, managed, and analyzed by the sponsor. The article was written by the investigators, on the basis of data and statistical analyses provided by Sanofi-Synthelabo.

A data and safety monitoring board of independent experts reviewed safety data every six months during the treatment period to provide the sponsor with independent advice on the progress of the study and on safety. No interim analysis was planned or performed.

RESULTS

STUDY POPULATION

Between October 1998 and January 2001, 2246 patients were enrolled at 146 centers in 20 countries: 1123 patients were randomly assigned to receive FL plus oxaliplatin and 1123 to receive FL without oxaliplatin. Of these patients, 1108 received at least one cycle of FL plus oxaliplatin and 1111 received at least one cycle of FL. The patients' characteristics were well matched in the two groups (Table 1). In both groups, 60 percent of the patients had stage III disease and 40 percent had stage II disease. The

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Table 1. Baseline Characteristics of the Patients in the Group Given Fluorouracil and Leucovorin (FL) plus Oxaliplatin and the FL Group.

Characteristic	FL plus Oxaliplatin (N=1123)	FL (N=1123)
All patients		
Age — yr		
Median	61	60
Range	19–75	20–75
Age <65 yr — no. (%)	723 (64.4)	743 (66.2)
Sex — no. (%)		
Male	630 (56.1)	588 (52.4)
Female	493 (43.9)	535 (47.6)
Karnofsky performance-status score — no. (%)		
<60	5 (0.4)	5 (0.4)
60–70	150 (13.4)	134 (11.9)
80–100	968 (86.2)	984 (87.6)
Disease stage — no. (%)		
II	451 (40.2)	448 (39.9)
III	672 (59.8)	675 (60.1)
Depth of invasion — no. (%)		
T2	51 (4.5)	54 (4.8)
T3	853 (76.0)	852 (75.9)
T4	213 (19.0)	208 (18.5)
Unknown	6 (0.5)	9 (0.8)
Bowel obstruction — no. (%)	201 (17.9)	217 (19.3)
Perforation — no. (%)	78 (6.9)	78 (6.9)
Histologic appearance — no. (%)		
Well differentiated	934 (83.2)	914 (81.4)
Poorly differentiated	142 (12.6)	148 (13.2)
Unknown	47 (4.2)	61 (5.4)
Patients with stage III disease — no. (%)		
No. of nodes involved		
1–4	499 (44.4)	513 (45.7)
>4	170 (15.1)	160 (14.2)
Unknown	2 (0.2)	2 (0.2)
Patients with stage II disease — no. (%)		
T4	84 (18.6)	87 (19.4)
No. of lymph nodes examined		
<10	152 (33.7)	149 (33.3)
≥10	295 (65.4)	294 (65.6)
Bowel obstruction	71 (15.7)	87 (19.4)
Perforation	38 (8.4)	43 (9.6)
Histologic appearance		
Well differentiated	385 (85.4)	378 (84.4)
Poorly differentiated	47 (10.4)	42 (9.4)
Unknown	19 (4.2)	28 (6.3)

overall median time between surgery and the start of chemotherapy was 5.7 weeks (range, 1.1 to 17.0).

A total of 41 patients (1.8 percent) did not strictly meet eligibility criteria related to baseline disease. In one patient in each group, the resection of primary tumor was incomplete. Four patients in the group given FL plus oxaliplatin and six in the FL group had a history of cancer, including colorectal cancer. Thirteen patients (four in the group given FL plus oxaliplatin and nine in the FL group) had stage IV cancer, and three patients (two in the group given FL plus oxaliplatin and one in the FL group) had cancer of the middle or lower rectum. Four patients in the group given FL plus oxaliplatin and nine in the FL group had various other eligibility-criteria violations.

CHEMOTHERAPY

The median number of cycles of chemotherapy received was 12 in both groups; 74.7 percent of patients in the group given FL plus oxaliplatin and 86.5 percent in the FL group received the planned 12 cycles. In the group that received FL plus oxaliplatin, the median dosage of oxaliplatin was 34.2 mg per square meter per week across all cycles received and 36.5 mg per square meter per week across cycles including oxaliplatin. In both cases, more than 80 percent of the planned dose was actually given (80.5 percent and 85.9 percent, respectively). The dose of fluorouracil received was 84.4 percent of the planned dose in the group given FL plus oxaliplatin and 97.7 percent of the planned dose in the FL group.

SAFETY

Neutropenia, diarrhea, and vomiting were the most frequent grade 3 or 4 adverse effects in the group given FL plus oxaliplatin (Table 2). Grade 3 or 4 neutropenia was much commoner with FL plus oxaliplatin than with FL (41.1 percent vs. 4.7 percent, P<0.001) but was complicated by fever or infection in only 1.8 percent of cases (20 patients) in the group given FL plus oxaliplatin and in 0.2 percent of cases (2 patients) in the FL group (P<0.001). The incidence of thromboembolic events among patients who received at least one cycle of the assigned regimen was similar in the two groups (63 of 1108 patients [5.7 percent] and 72 of 1111 patients [6.5 percent], respectively).

Although 92.1 percent of patients treated with FL plus oxaliplatin had peripheral neuropathy during treatment, half of these episodes were of grade 1

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Table 2. Adverse Events in the Group Given Fluorouracil and Leucovorin (FL) plus Oxaliplatin and the FL Group.*

Adverse Event	FL plus Oxaliplatin (N=1108)			FL (N=1111)			P Value	
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grades 3 and 4
	percent							
Paresthesia†	92.0	12.4	NA	15.6	0.2	NA	<0.001	0.001
Neutropenia	78.9	28.8	12.3	39.9	3.7	1.0	<0.001	<0.001
Thrombocytopenia	77.4	1.5	0.2	19.0	0.2	0.2	<0.001	0.001
Anemia	75.6	0.7	0.1	66.9	0.3	0.0	<0.001	0.09
Nausea	73.7	4.8	0.3	61.1	1.5	0.3	<0.001	<0.001
Diarrhea	56.3	8.3	2.5	48.4	5.1	1.5	<0.001	<0.001
Vomiting	47.2	5.3	0.5	24.0	0.9	0.5	<0.001	<0.001
Stomatitis	41.6	2.7	0.0	39.6	2.0	0.2	0.34	0.41
Skin‡	31.5	1.4	0.6	35.5	1.7	0.7	0.05	0.67
Alopecia§	30.2	NA	NA	28.1	NA	NA	0.28	NA
Allergic reaction	10.3	2.3	0.6	1.9	0.1	0.1	<0.001	<0.001
Thrombosis or phlebitis	5.7	1.0	0.2	6.5	1.7	0.1	0.48	0.29
Neutropenia with fever or infection	1.8	1.4	0.4	0.2	0.1	0.1	<0.001	<0.001

* Fisher's exact test was used to calculate P values. NA denotes not applicable.
† There are only three grades of paresthesia in version 1 of the Common Toxicity Criteria of the National Cancer Institute.
‡ This category included the hand–foot syndrome.
§ There are only two grades of alopecia in version 1 of the Common Toxicity Criteria of the National Cancer Institute. The incidence of grade 2 alopecia was 5.0 percent in each group.

(Table 3). Of the 137 patients (12.4 percent) who had grade 3 peripheral neuropathy during treatment, grade 3 symptoms were still present in 8 patients at the six-month follow-up visit and in 5 patients at the one-year visit. In 12 patients, grade 3 peripheral neurosensory symptoms appeared after the end of treatment, and 6 of these patients had persistent grade 3 symptoms after one year. In total, 11 of 1018 patients (1.1 percent) who were assessed one year after the end of treatment continued to have grade 3 peripheral neurosensory symptoms. This number dropped to five (0.5 percent) after 18 months (Table 3).

Twelve patients — six in each group (0.5 percent) — died within 1 month after the end of treatment; these included three deaths in each group during the first 60 days of treatment. In the group given FL plus oxaliplatin, four patients died of infection or sepsis (two with neutropenia) and two of intracranial hemorrhage. In the FL group, one patient each died of sepsis, Stevens–Johnson syndrome in the context of severe diarrhea and fluconazole treatment, and anoxic cerebral infarction; one patient committed suicide; and two died suddenly from cardiac causes.

FOLLOW-UP

There was good compliance with follow-up visits. The mean time between visits was 5.97 months in the group given FL plus oxaliplatin and 5.98 months in the FL group. The median interval was 6.01 months in both groups.

Table 3. Incidence of Neurosensory Symptoms during Treatment and Follow-up in the Group Given Fluorouracil, Leucovorin, and Oxaliplatin.*

Grade	During Treatment (N=1106)	1 Mo Follow-up (N=1092)	6 Mo Follow-up (N=1058)	12 Mo Follow-up (N=1018)	18 Mo Follow-up (N=967)
	number (percent)				
0	87 (7.9)	424 (38.8)	624 (59.0)	718 (70.5)	738 (76.3)
1	533 (48.2)	439 (40.2)	338 (31.9)	240 (23.6)	191 (19.8)
2	349 (31.6)	174 (15.9)	82 (7.8)	49 (4.8)	33 (3.4)
3	137 (12.4)	55 (5.0)	14 (1.3)	11 (1.1)	5 (0.5)

* Only patients who actually received treatment were included in the analysis. A grade of 0 indicates no change or no symptoms, a grade of 1 mild paresthesia and loss of deep tendon reflexes, a grade of 2 mild or moderate objective sensory loss and moderate paresthesia, and a grade of 3 severe objective sensory loss or paresthesias that interfere with function.

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DISEASE-FREE SURVIVAL

At the time of analysis (median follow-up, 37.9 months), 237 patients in the group given FL plus oxaliplatin (21.1 percent) had relapsed or died, as compared with 293 (26.1 percent) in the FL group. The hazard ratio for recurrence in the group given FL plus oxaliplatin, as compared with the FL group, was 0.77 (P=0.002), corresponding to a 23 percent reduction in the risk of relapse. The probability of disease-free survival at three years was 78.2 percent (95 percent confidence interval, 75.6 to 80.7 percent) in the group given FL plus oxaliplatin and 72.9 percent (95 percent confidence interval, 70.2 to 75.7 percent) in the FL group (P=0.002 by the stratified log-rank test) (Table 4 and Fig. 1).

Among patients with stage III disease, the hazard ratio for relapse was 0.76 (95 percent confidence interval, 0.62 to 0.92) in the group given FL plus oxaliplatin, as compared with the FL group, and the three-year disease-free survival rate was 72.2 percent and 65.3 percent, respectively (Fig. 2). Among patients with stage II disease, the hazard ratio for relapse was 0.80 (95 percent confidence interval, 0.56 to 1.15) in the group given FL plus oxaliplatin, as compared with the FL group, and the three-year disease-free survival rates were 87.0 percent and 84.3 percent, respectively (Fig. 2).

A Cox-model analysis showed that the reduced risk of recurrence with FL plus oxaliplatin was similar in patients with stage II and those with stage III disease (P=0.77). Calculation of hazard ratios and 95 percent confidence intervals (Fig. 3) showed that the reduced risk of relapse was consistent in all subgroups defined on the basis of prognostic factors at baseline.

Table 4. Analysis of Disease-free Survival According to the Intention-to-Treat Principle.*

Variable	FL plus Oxaliplatin (N=1123)	FL (N=1123)
Follow-up — mo		
Median	37.9	37.8
Range	27–54	27–54
Probability of disease-free survival at 3 yr — % (95% CI)†	78.2 (75.6–80.7)	72.9 (70.2–75.7)
Event — no. (%)	237 (21.1)	293 (26.1)
Relapse‡	208 (18.5)	279 (24.8)
Metastasis	169 (15.0)	229 (20.4)
Second colorectal carcinoma	6 (0.5)	9 (0.8)
Local relapse	38 (3.4)	51 (4.5)
Death without relapse	29 (2.6)	14 (1.2)

* FL denotes fluorouracil and leucovorin, and CI confidence interval.
† P=0.002 by the stratified log-rank test for the comparison between groups.
‡ The same patient could have been counted in more than one relapse category if several types of relapses were reported at the same follow-up visit.

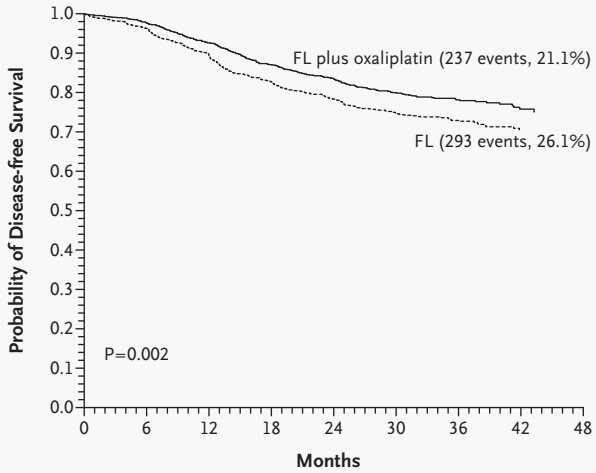


Figure 1. Kaplan–Meier Estimates of Disease-free Survival in the Group Given Fluorouracil and Leucovorin (FL) and the Group Given FL plus Oxaliplatin, According to the Intention to Treat.

The hazard ratio for recurrence in the group given FL plus oxaliplatin, as compared with the FL group, was 0.77 (95 percent confidence interval, 0.65 to 0.91; P=0.002).

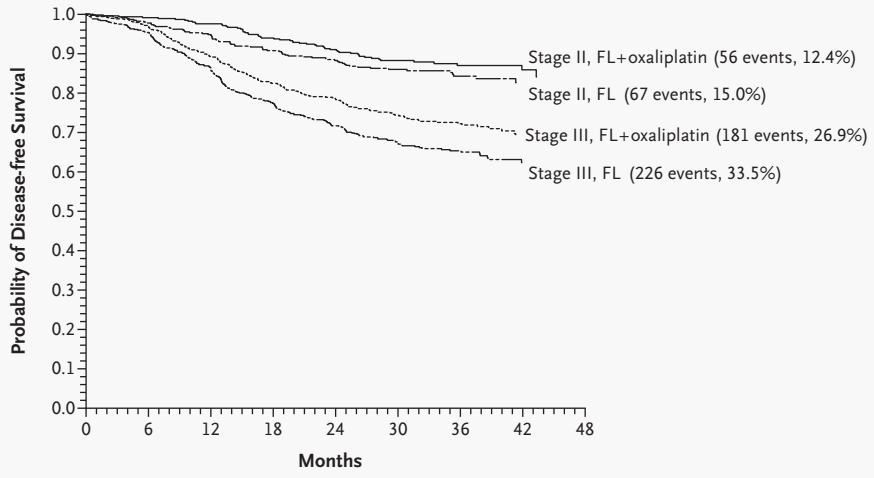
OVERALL SURVIVAL

At the time of the cutoff date of the primary analysis, 133 patients had died in the group given FL plus oxaliplatin, as compared with 146 patients in the FL group (hazard ratio for death, 0.90; 95 percent confidence interval, 0.71 to 1.13), and the probability of survival at three years was 87.7 percent and 86.6 percent, respectively. Most of the patients who died had stage III disease (104 in the group given FL plus oxaliplatin and 119 in the FL group); the hazard ratio for death in this subgroup was 0.86 (95 percent confidence interval, 0.66 to 1.11).

DISCUSSION

In previous trials, the addition of oxaliplatin to fluorouracil and leucovorin doubled the response rate and prolonged progression-free survival among patients with metastatic colorectal cancer.[14] The efficacy and safety of this regimen were recently confirmed in a large, randomized, phase 3 trial,

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No. at Risk							
Stage II, FL+oxaliplatin	451	445	435	417	387	295	170
Stage II, FL	448	435	418	400	369	274	162
Stage III, FL+oxaliplatin	672	641	588	542	501	368	225
Stage III, FL	675	631	563	503	448	345	194

Figure 2. Kaplan–Meier Estimates of Disease-free Survival in the Group Given Fluorouracil and Leucovorin (FL) and the Group Given FL plus Oxaliplatin, According to the Stage of Disease and the Intention to Treat.

which found that this approach was superior (with respect to all efficacy variables, including overall survival) to the combination of irinotecan, fluorouracil (given as a bolus), and leucovorin.[15] Our trial was designed to test the efficacy of adjuvant treatment with the regimen of FL plus oxaliplatin. We chose disease-free survival as the primary end point of the study because, like others,[16] we believe that the absence of relapse is the best indicator of efficacy, since it relates directly to the effect of the treatment under investigation. By allowing early appraisal of the results, the use of three-year disease-free survival as the primary end point for adjuvant trials of patients with colon cancer should permit rapid evaluation of new treatments. Whether disease-free survival should be a primary end point is still under discussion, but a recent analysis of several studies supports the appropriateness of the use of three-year disease-free survival as a good predictor of five-year overall survival in trials of adjuvant treatment of colon cancer.[17]

Disease-free survival in the FL group in our study falls within the highest range reported in most studies of adjuvant treatment of colon cancer with FL.[6-8,18,19] The improvement in disease-free survival among patients who were treated with FL plus oxaliplatin corresponds to a relative reduction in the risk of recurrence of 23 percent. Since most relapses after curative surgery occur within the first three years, we consider our results in this respect to be complete.

Although it is agreed that patients with stage III disease benefit from adjuvant treatment, whether all patients with stage II disease should receive such treatment remains debatable. This controversy was sustained for years by the contradictory conclusions of two large groups of investigators. The National Surgical Adjuvant Breast and Bowel Project concluded that the relative benefits of treatment were largely the same for stage II and stage III tumors,[20] whereas the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) failed to demonstrate a statistically significant benefit for stage II tumors.[21]

A recent meta-analysis from the Mayo Clinic,[22] which evaluated individual data on 3300 patients who were enrolled in five randomized trials, including those analyzed in IMPACT B2, concluded that patients with stage II disease could benefit from adjuvant chemotherapy, but to a lesser extent than patients with stage III tumors. Indeed, the absolute benefit among patients with stage II disease is only half as great as that among patients with stage III disease, and twice as many patients with stage II tumors are required in such studies in order to detect a difference.

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A test for interaction is an appropriate statistical approach to the question of whether the benefit of adjuvant treatment differs between stage II and stage III colorectal cancer.[23] In our study, this test showed no significant interaction between the stage of disease and the treatment, indicating that FL plus oxaliplatin benefited both stage II and stage III colorectal cancer. From a clinical standpoint, stage II colon cancer occurs in a heterogeneous, node-negative population in which clinical and biologic prognostic factors other than the status of lymph-node involvement need to be taken into account. Tools are being developed to help physicians assess the risk–benefit ratio of adjuvant chemotherapies for individual patients.[22]

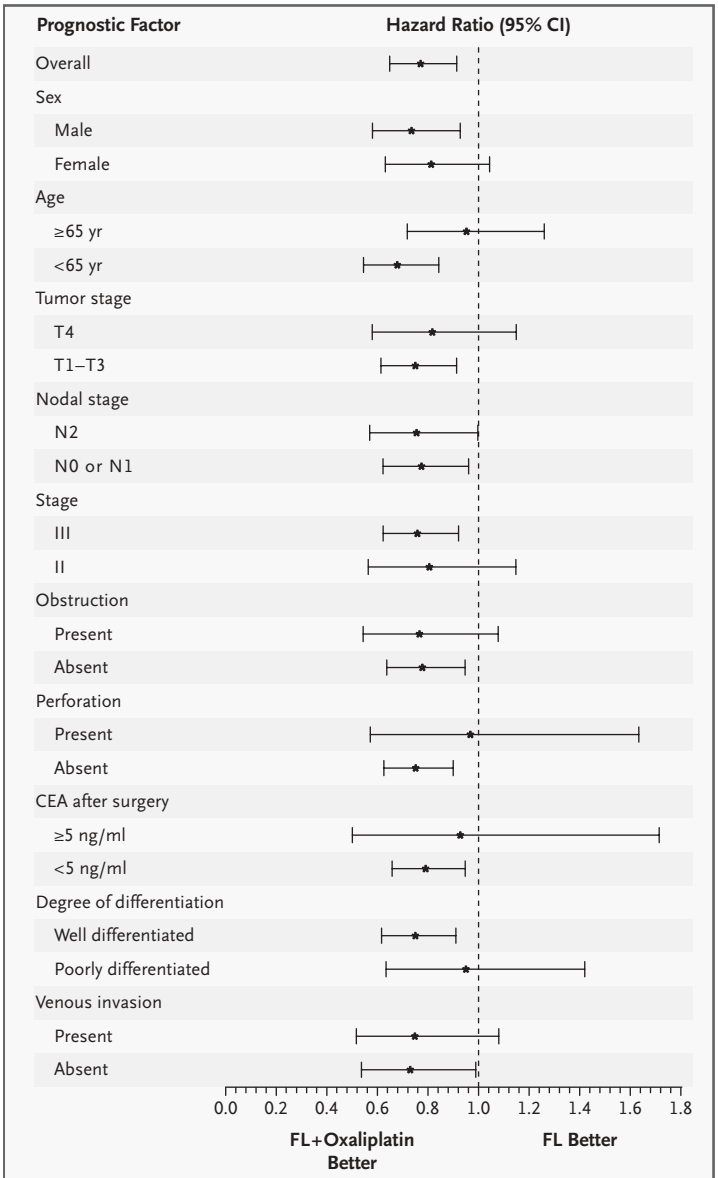


Figure 3. Hazard Ratios and 95 Percent Confidence Intervals for Recurrence in the Group Given Fluorouracil and Leucovorin (FL) plus Oxaliplatin, as Compared with the FL Group, According to Baseline Prognostic Factors and the Intention to Treat.

CEA denotes carcinoembryonic antigen.

With no clear consensus on the most effective FL regimen to be used for adjuvant treatment, we chose a twice-monthly regimen because of its efficacy and low rates of adverse effects in patients with advanced colorectal cancer, alone and in combination with oxaliplatin.[12,14,24] Supporting our decision are recent results demonstrating that this approach to adjuvant therapy is less toxic than monthly bolus injections of FL and is just as effective.[18] This approach led to a straightforward study design, since the treatment in both groups was similar except for the addition of oxaliplatin in the group given FL plus oxaliplatin. The improved disease-free survival in the FL-plus-oxaliplatin group is thus directly linked to oxaliplatin.

The main safety concern regarding the use of oxaliplatin is peripheral neuropathy. Oxaliplatin induces frequent, transient, distal paresthesias during or shortly after the first minutes of infusion. In some cases these neurosensory symptoms increase in intensity with cumulative doses, persist between cycles, and interfere with function (in the case of grade 3 effects).[12,14,25] We observed grade 3 peripheral neuropathy in 12.4 percent of patients who were receiving oxaliplatin. At one year, 11 patients (1.1 percent) had grade 3 neuropathy. Among them, two were found to have underlying disease that could have caused these symptoms (diabetes and hemiplegia, respectively). Although more frequent among patients receiving FL plus oxaliplatin than among those treated with FL alone, grade 3 or 4 neutropenia led to fever or infection in only 1.8 percent of patients in the former group. Similar findings have been reported among patients with metastatic colorectal cancer.[14] From a safety standpoint, the rate of death from any cause was similarly low during treatment in both groups and, at 0.5 percent, is among the lowest figures reported in trials of adjuvant chemotherapy.[5,18,26,27]

Figures for overall survival at this stage of the study are preliminary, and no conclusion can be drawn about differences in survival between the treatment groups. Since the median overall survival from the time of diagnosis of metastatic colorec-

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tal cancer is approximately 20 months,[13-15,28] we expect that the effect of oxaliplatin on survival will become apparent within the next 2 years.

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