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Effect of Celecoxib vs Placebo Added to Standard Adjuvant Therapy on Disease-Free Survival Among Patients With Stage III Colon Cancer
The CALGB/SWOG 80702 (Alliance) Randomized Clinical Trial

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IMPORTANCE Aspirin and cyclooxygenase 2 (COX-2) inhibitors have been associated with a reduced risk of colorectal polyps and cancer in observational and randomized studies. The effect of celecoxib, a COX-2 inhibitor, as treatment for nonmetastatic colon cancer is unknown.

OBJECTIVE To determine if the addition of celecoxib to adjuvant chemotherapy with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) improves disease-free survival in patients with stage III colon cancer.

DESIGN, SETTING, AND PARTICIPANTS Cancer and Leukemia Group B (Alliance)/Southwest Oncology Group 80702 was a 2 × 2 factorial design, phase 3 trial conducted at 654 community and academic centers throughout the United States and Canada. A total of 2526 patients with stage III colon cancer were enrolled between June 2010 and November 2015 and were followed up through August 10, 2020.

INTERVENTIONS Patients were randomized to receive adjuvant FOLFOX (every 2 weeks) for 3 vs 6 months with or without 3 years of celecoxib (400 mg orally daily; n = 1263) vs placebo (n = 1261). This report focuses on the results of the celecoxib randomization.

MAIN OUTCOMES AND MEASURES The primary end point was disease-free survival, measured from the time of randomization until documented recurrence or death from any cause. Secondary end points included overall survival, adverse events, and cardiovascular-specific events.

RESULTS Of the 2526 patients who were randomized (mean [SD] age, 61.0 years [11 years]; 1134 women [44.9%]), 2524 were included in the primary analysis. Adherence with protocol treatment, defined as receiving celecoxib or placebo for more than 2.75 years or continuing treatment until recurrence, death, or unacceptable adverse events, was 70.8% for patients treated with celecoxib and 69.9% for patients treated with placebo. A total of 337 patients randomized to celecoxib and 363 to placebo experienced disease recurrence or died, and with 6 years' median follow-up, the 3-year disease-free survival was 76.3% for celecoxib-treated patients vs 73.4% for placebo-treated patients (hazard ratio [HR] for disease recurrence or death, 0.89; 95% CI, 0.76-1.03; P = .12). The effect of celecoxib treatment on disease-free survival did not vary significantly according to assigned duration of adjuvant chemotherapy (P for interaction = .61). Five-year overall survival was 84.3% for celecoxib vs 81.6% for placebo (HR for death, 0.86; 95% CI, 0.72-1.04; P = .13). Hypertension (any grade) occurred while treated with FOLFOX in 14.6% of patients in the celecoxib group vs 10.9% of patients in the placebo group, and a grade 2 or higher increase in creatinine levels occurred after completion of FOLFOX in 1.7% vs 0.5% of patients, respectively.

CONCLUSIONS AND RELEVANCE Among patients with stage III colon cancer, the addition of celecoxib for 3 years, compared with placebo, to standard adjuvant chemotherapy did not significantly improve disease-free survival.

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Visual Abstract

Editorial page 1257

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1323

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Although colorectal cancer is considered both preventable and curable, an estimated 52 980 individuals will die of colorectal cancer in the United States in 2021,[1] along with more than 915 880 projected worldwide.[2] Eighty percent of patients diagnosed with colorectal cancer did not initially have evidence of metastatic disease. However, about 50% of patients with regional lymph node-positive disease (stage III) recurred within the first 5 years when treated with surgery alone. Randomized trials in the 1980s and 1990s demonstrated the benefit of adjuvant chemotherapy to reduce the risk of recurrence and improve survival for stage III patients.[3] For the next 20 years, duration of therapy and optimal regimens were defined (using a fluoropyrimidine-oxaliplatin combination),[4,5] resulting in absolute 25% improvement in disease-free survival compared with no adjuvant treatment. However, there remains significant variability in individual patient outcomes based on multiple prognostic factors. Additional strategies are therefore needed to maximize the cure rate for colon cancer survivors.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have long been studied as agents that may influence cancer development and progression.[6,7] Aspirin and selective cyclooxygenase 2 (COX-2) inhibitors were associated with lower risk of colorectal adenomas, cancer, or both in observational studies and randomized trials.[8-10] Hypotheses for the mechanism of action of these agents include inhibiting the COX family of enzymes (mediating apoptosis and altering prostaglandin production to angiogenic factors), inhibiting activation of nuclear factor-κB, and interfering with the binding of the peroxisome proliferator-activated receptor to DNA.[7] Furthermore, observational studies have shown that usage of aspirin and the COX-2 inhibitor either before or after colorectal cancer diagnosis was associated with a lower risk of recurrent disease than with nonusers.[11-13]

This trial was conducted to determine whether the addition of a COX-2 inhibitor, celecoxib, reduced the risk of recurrence and improved survival in patients with stage III colon cancer receiving standard adjuvant chemotherapy.

Key Points

Question Does the cyclooxygenase 2 inhibitor celecoxib, when added to standard adjuvant chemotherapy, improve disease-free survival among patients with stage III colon cancer?

Findings In this randomized clinical trial that involved 2526 patients, the addition of celecoxib for 3 years, compared with placebo, to standard adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) did not significantly improve disease-free survival (76.3% vs 73.4% at 3 years; hazard ratio for disease recurrence or death, 0.89).

Meaning Among patients with stage III colon cancer, the addition of celecoxib, compared with placebo, to standard adjuvant chemotherapy did not significantly improve disease-free survival.

Methods

The Cancer and Leukemia Group B (now part of the Alliance for Clinical Trials in Oncology) and Southwest Oncology Group (SWOG) 80702 trial was designed in collaboration with the National Cancer Institute (NCI), activated in June 2010, and enrolled patients until November 2015. The trial used a 2 × 2 factorial design to test the primary hypothesis of superiority of celecoxib vs placebo with adjuvant chemotherapy for stage III colon cancer. The secondary hypothesis of noninferiority of 3 months compared with standard 6 months of adjuvant chemotherapy. To increase the precision with which the noninferiority margin for the secondary hypothesis could be estimated, the study was prospectively part of the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration of 6 trials pooling individual patient data from trial initiation. The IDEA results did not demonstrate statistically significant noninferiority for 3 months of chemotherapy compared with 6 months in the overall population[14]; however, 3 months was noninferior to 6 months among patients treated with capecitabine and oxaliplatin, particularly in the lower-risk subgroups of stage III disease. This report focuses on the results of the celecoxib vs placebo comparison. Institutional review board approval was obtained at all participating centers, and patients provided written informed consent. The trial protocol with the statistical analysis plan is available in Supplement 1.

Patient Eligibility

Patients were enrolled at centers across the National Cancer Trials Network in the United States and Canada. Eligible patients had margin-negative resected, histologically documented colon adenocarcinoma, entirely lying above the peritoneal reflection. Tumors had either at least one pathologically confirmed positive lymph node or N1c designation (defined as tumor deposit[s] in the subserosa, mesentery, or nonperitonealized pericolic tissues without regional lymph node metastases). Patients were 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 to 2 and normal hepatic, renal, and hematologic laboratory values.

Low-dose aspirin not exceeding 100 mg/d was permitted, but average use of NSAIDs at any dose greater than 2 times per week or 325 mg of aspirin more than 3 times per week was not allowed. Other ineligibility criteria included previous or concurrent malignancy, except treated basal or squamous cell skin cancer, treated in situ cervical or breast cancer, or any other cancer for which the patient was disease-free for at least 5 years; baseline grade 2 or greater neuropathy; prior allergic reaction or hypersensitivity to platinum compounds, sulfonamides, celecoxib, or NSAIDs; history of upper gastrointestinal ulceration, bleeding, or perforation within the past 3 years; uncontrolled high blood pressure; unstable angina; history of documented myocardial infarction or cerebrovascular accident; New York Heart Association class III or IV heart failure; or pregnant or nursing at time of enrollment.

Race and ethnicity were collected as mandated by the National Institute of Health and based on self-report, per each institution's standard for collection of these data.

Treatment and Other Study Procedures

Therapy was recommended to start between 21 and 56 days after surgical resection of the primary tumor. Patients were

randomized 1:1 to celecoxib or placebo (ignoring FOLFOX duration assignments), and independently 1:1 to 6 treatments (3 months) vs 12 treatments (6 months) of FOLFOX (ignoring oral agent assignments), with 2 different sets of stratification factors. Randomization for celecoxib was stratified by number of positive lymph nodes and concurrent low-dose aspirin usage (yes vs no). Randomization for the duration of chemotherapy was stratified by number of positive lymph nodes (1-3 or N1c vs ≥4). Patient randomization was based on fixed-size permutated block method with block size of 6 and the blocks were permutated according to computer generated pseudorandom number sequence.

The FOLFOX regimen consisted of 2-hour infusions of oxaliplatin at 85 mg/m^2 and leucovorin at 400 mg/m^2, followed by a 400-mg/m^2 bolus infusion of fluorouracil, then a 46- to 48-hour continuous infusion of 2400 mg/m^2 of fluorouracil, repeated every 2 weeks.

Patients and clinicians were blinded to the treatment administration of celecoxib or placebo. Oral celecoxib was dosed at 400 mg daily, starting by the first day of the second treatment of FOLFOX. The study drugs were administered daily for 3 years after the initiation of the first dose until recurrence of disease or until unacceptable adverse events occurred. Patients recorded their usage of the study medication in a daily diary.

Standard-dose adjustment criteria were used. Adverse events were first assessed using the NCI Common Toxicity Criteria version 4.0 through March 31, 2018, and then were assessed using version 5.0 thereafter.

Once patients completed the FOLFOX course, they were assessed by history, physical examination, and carcinoembryonic antigen measures every 3 months for 3 years following commencement of therapy and subsequently every 6 months for 6 years after randomization or until disease recurrence, whichever came first. Patients randomized to 6 treatments of FOLFOX had their first posttreatment carcinoembryonic antigen testing and surveillance imaging (chest imaging with either chest x-ray or computed tomography and abdominal and pelvis imaging with either computed tomography, magnetic resonance imaging, or positron emission tomography) within 4 months after completion of chemotherapy; those randomized to 12 treatments had carcinoembryonic antigen testing and imaging within 6 weeks following therapy completion. Thereafter, all patients had surveillance imaging every 6 months from their last scan for at least 3 years after initiation of celecoxib or placebo and then yearly for 3 years, or until disease recurrence.

Clinical Outcomes

The primary study end point was disease-free survival, defined as the time from randomization until documented disease recurrence or death from any cause. Patients without an event were censored at their last disease evaluation date. Secondary end points included overall survival (measured from randomization until death from any cause), adverse events from celecoxib vs placebo, and risk of cardiovascular-specific events. In addition, the contribution of disease-free and overall survival data that compared 6 months vs 3 months of adjuvant FOLFOX was a secondary end point in this article. However, these data were compared with the IDEA collaboration in a previously published article.[14]

Statistical Considerations

The superiority hypothesis of celecoxib use was tested for disease-free survival. The trial was designed to enroll 2500 patients over 3.125 years with a follow-up period of 3 years. The 775 expected disease-free survival events at the conclusion of the trial was estimated using the method proposed by Schoenfeld.[15] A hazard ratio (HR) for disease recurrence or death of 0.79 in favor of celecoxib was assumed with power of 0.91 and 2-sided α of .05, corresponding to an increase in the probability of being disease-free at 3 years from 0.72 to 0.77. This improvement was considered to be clinically meaningful because it was consistent with the HR for disease recurrence or death detected when adding oxaliplatin to fluoropyrimidine as adjuvant therapy.[4,5]

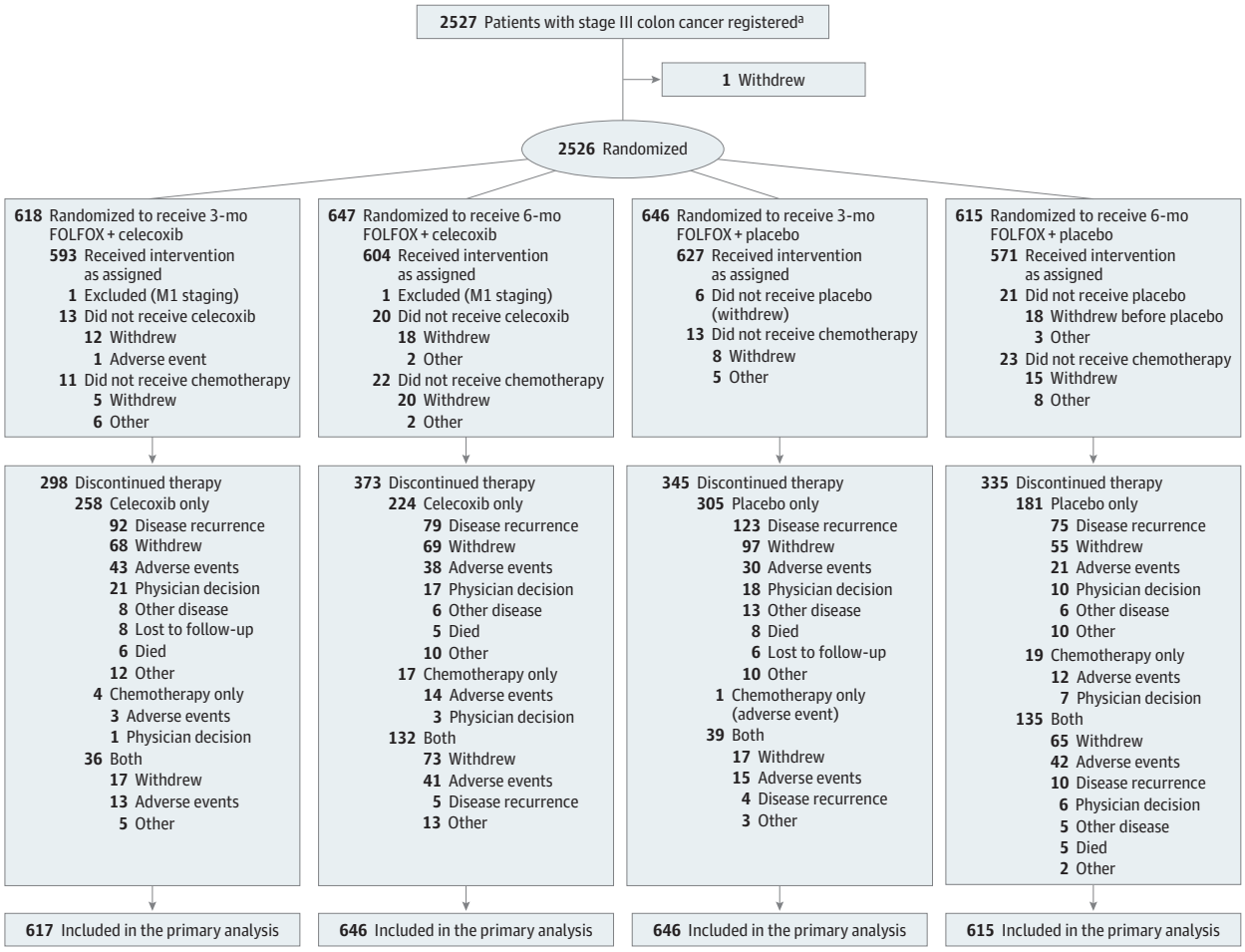
After our trial had fully accrued, a 2020 study using the ACCENT database comparing 1998-2003 with 2004-2009 treatment results demonstrated that patients with stage III colon cancer treated with FOLFOX had improved outcomes (3-year disease-free survival of 74.7 %-76%).[16] These findings required that we recalibrate our power assumptions. Because our trial enrolled fewer patients with T4 tumors (14.7%) than did the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial[4] upon which we relied for our initial effect size assumptions (≈ 19%), the observed disease recurrence and mortality rates were lower than expected such that the originally planned number of events required would not be achievable unless we extended follow-up by several years. To report our trial results in a timely fashion without substantially compromising power, the power calculation was updated in September 2019 by an independent statistician who was blinded to the trial data (Supplement 1). A reduced number of disease-free survival events, 696, was required to provide 85% power to detect an HR for disease recurrence or death of 0.79 in favor of celecoxib (3-year disease-free survival rate from 0.75 to 0.796). The calculation accounted for the 9 previously conducted interim analyses by setting a 2-sided α of .038; neither the efficacy nor futility boundary was crossed in any of these interim analyses. In February 2020, the Alliance Data and Safety Monitoring Board released the results with 689 disease-free survival events because simulations showed that analyses including the remaining 7 events would not affect the conclusions.

Analyses in this current report are based on updated clinical data and patient follow-up as of August 10, 2020, pertaining to 700 disease-free survival events. Post hoc conditional power of a significant result, which might have been reached if the study had continued to observe the original targeted number of events of 775, was conducted according to methods by Proschan et al.[17]

Statistical Analyses

The primary analysis was based on all patients who were randomized and confirmed with stage III colon cancer,

Figure 1. Study Enrollment and Flow Through CALGB/SWOG 80702 (Alliance) Randomized Clinical Trial



[a] Sites were not required to provide screening logs during the recruitment phase. Thus, the number of patients assessed for eligibility is not available.

according to the treatment assignment at randomization (**Figure 1**). Log-rank test stratified with the stratification factors used to compare disease-free survival and overall survival between oral treatment groups (celecoxib vs placebo). The proportional hazards assumption for the Cox model was examined with the use of scaled Schoenfeld residuals. Additional post hoc sensitivity analyses were conducted based on patients who started any treatment and patients who received at least 6 months of celecoxib or placebo, as well as using a mixed-effects model that included enrolling centers as a random effect factor.[18] Post hoc subgroup analyses were conducted according to duration of adjuvant FOLFOX treatment and baseline patient characteristics. Interaction between oral agent treatment and these variables were tested, with Bonferroni correction,[19] and χ^2 tests were used to compare adverse event rates (measured by the maximum grade of events) between treatment groups. Two-sided *P* values of less than .05 were considered to be significant for secondary end point analyses. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Treatment with celecoxib or placebo was intended to be for a total of 3 years from the initial dose and was discontinued if patients experienced disease recurrence, death, or potentially significant celecoxib-related adverse events. Adherence with protocol treatment was defined post hoc as receiving 2.75 or more years of celecoxib or placebo or continuing treatment until recurrence, death, or unacceptable adverse events.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SAS version 9.4M6, SAS Institute Inc). Data quality was reviewed and audited by the Alliance Statistics and Data Center and by the study chairs (J.A.M and A.F.S) following Alliance policies.

Results

From June 2010 to November 2015, 2527 patients were enrolled and 2526 were randomized in this 2 × 2 factorial design study with randomization to treatment with celecoxib vs placebo and were randomized to receive 3 vs 6 months of chemotherapy (Figure 1). Patient and tumor characteristics

are presented in **Table 1**. The treatment groups were well-balanced for age, sex, race, ethnicity, performance status, extent of invasion through the bowel wall, nodal stage, tumor location, usage of low-dose aspirin, and body mass index. These characteristics were also balanced when considering duration of therapy randomization and by 4 treatment groups (eTable in Supplement 2).

Treatment Adherence

Figure 2 illustrates the percentage of patients that completed 1, 2, and 3 (approximated by ≥2.75) years of celecoxib or placebo and the initial reasons patients stopped therapy; patients may have discontinued the study medication for another reason and had a recurrence at a later time, explaining the reason that fewer recurrences are noted in Figure 2 than occurred in the study.

Adherence with protocol celecoxib treatment was 70.8% for patients treated with celecoxib and 69.9% for patients treated with placebo (P = .69). For those receiving at least 1 dose of celecoxib or placebo, 547 patients (45.7%) treated with celecoxib and 538 (44.9%) treated with placebo completed 3 years of study medication. Overall, 165 patients (13.8%) treated with celecoxib and 193 patients (16.1%) treated with placebo discontinued due to disease recurrence; and 135 (11.3%) treated with celecoxib and 107 (8.9%) treated with placebo due to adverse events. In addition, 350 patients (29.2%) treated with celecoxib and 360 (30.1%) treated with placebo discontinued study medication for other reasons; the vast majority withdrew consent (20% between both groups) with 3% due to physician discretion, 2% due to other complicating comorbidities, and the rest for a variety of other reasons.

Patient Outcome

The median follow-up for surviving patients was 6.0 years, with 700 patients experiencing disease recurrence or death, and 448 died (**Figure 3**). Three-year disease-free survival was 76.3% (95% CI, 73.8%-78.8%) for celecoxib and 73.4% (95% CI, 70.8%-76.0%) for placebo (HR for disease recurrence or death, 0.89; 95% CI, 0.76-1.03), with a P value of .13 frozen on February 17, 2020, and a P value of .12 for the data and safety management board reporting and this current article on August 10, 2020. Similarly, at 5 years, there was no significant difference in overall survival with 84.3% (95% CI, 82.2%-86.5%) alive for celecoxib and 81.6% (95% CI, 79.4%-83.9%) for placebo (HR for death, 0.86; 95% CI, 0.72-1.04; P = .12). No violation of the proportional-hazards assumption was detected for either the disease-free survival (P = .35) or overall survival (P = .47) end points.

The effect of celecoxib treatment did not significantly differ according to assigned duration of adjuvant chemotherapy. We considered an interaction between duration of adjuvant FOLFOX and celecoxib. When considering 4 treatment groups (eFigure 1A and 1B in Supplement 2), we did not detect significant differences in disease-free survival (P for interaction = .61) or overall survival (P for interaction = .79). Similarly, age, nodal status, extent of bowel invasion, concurrent low-dose aspirin usage, sex, race, ethnicity, baseline Eastern Cooperative Oncology Group performance status, body mass index, and tumor location did not significantly affect the effect of celecoxib treatment on disease-free survival (eFigures 2A and 2B in Supplement), after adjustment for Bonferroni multiple comparisons (10 comparisons with α correction .05/10, defining significance as P < .005).

Table 1. Baseline Patient Characteristics in Primary Analysis Population

	No. (%) of patients	
	Celecoxib (n = 1263)	Placebo (n = 1261)
Age, y		
Mean (SD)	61.0 (11)	60.9 (11)
Median (range)	61.7 (21.8-88.7)	61.0 (19.3-86.5)
Sex		
Women	573 (45.4)	561 (44.5)
Men	690 (54.6)	700 (55.5)
Race		
White	988 (78.2)	1009 (80.0)
Black or African American	161 (12.7)	158 (12.5)
Asian	64 (5.1)	43 (3.4)
All others or not reported	50 (4.0)	51 (4.0)
Hispanic or Latino, No./total (%)	94/1232 (7.6)	97/1227 (7.9)
Low dose aspirin usage	272 (21.5)	270 (21.4)
BMI		
Mean (SD)	30.0 (19)	29.5 (11)
Median	27.8	28.1
ECOG performance status[a]		
0	904 (71.6)	891 (70.7)
1-2	359 (28.4)	370 (29.3)
Extent of invasion through bowel wall, No./total (%)[b]		
T1 or T2	231/1242 (18.6)	217/1253 (17.3)
T3	823/1242 (66.3)	849/1253 (67.8)
T4	188/1242 (15.1)	187/1253 (14.9)
Nodal stage[c]		
N1	925 (73.2)	926 (73.4)
N2	338 (26.8)	335 (26.6)
Tumor location, No./total. (%)		
Left-sided	574/1250 (45.9)	598/1246 (48.0)
Right-sided	670/1250 (53.6)	643/1246 (51.6)
Multiple	6/1250 (0.5)	5/1246 (0.4)

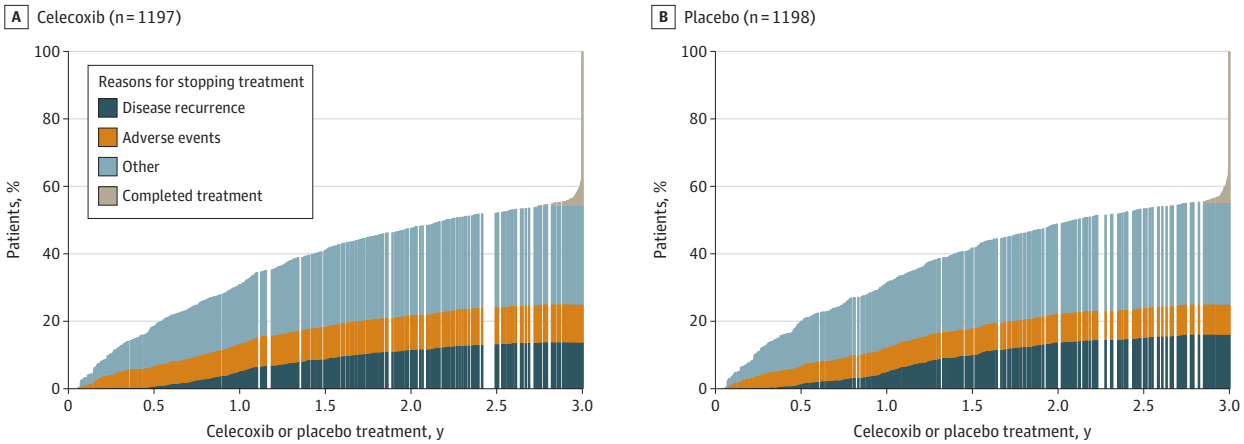
Abbreviations: BMI, body mass index, calculated as in weight in kilograms divided by height in meters squared ; ECOG, Eastern Cooperative Oncology Group.

[a] Performance status: 0 indicates, fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; and 2, ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

[b] T1 indicates tumor has grown into the submucosa; T2, growth into the muscularis propria; T3, grown through the muscularis propria and into the subserosa; and T4, grown into the surface of the visceral peritoneum or into or has attached to other organs or structures.

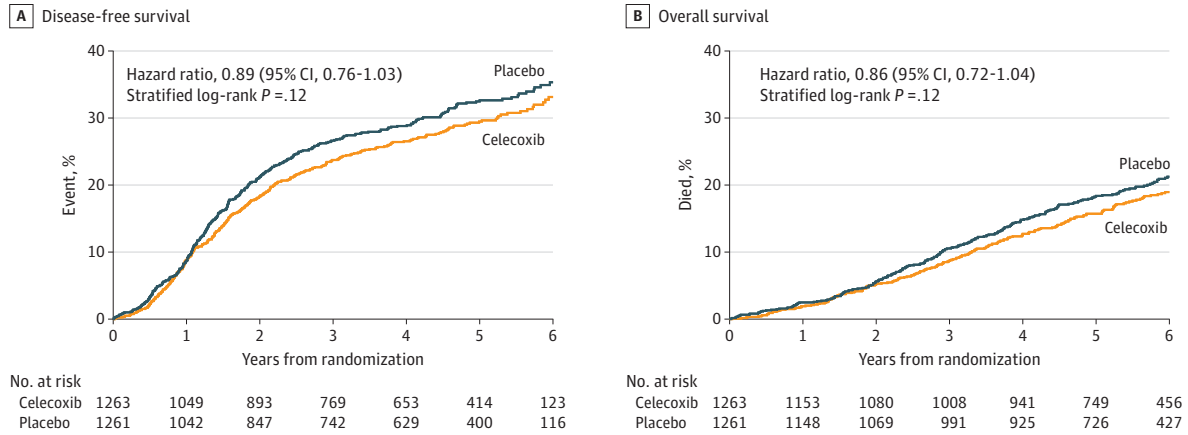
[c] N1 indicates 1 to 3 lymph nodes tested positive for cancer (or for this table, N1c: tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional lymph node metastases); N2, 4 or more positive lymph nodes.

Figure 2. Patient Adherence With Celecoxib or Placebo



Sixty-six patients in the celecoxib and 63 patients in the placebo plus fluorouracil, leucovorin, and oxaliplatin (FOLFOX) groups dropped out of the study before they received either celecoxib or placebo.

Figure 3. Disease-Free and Overall Survival by Celecoxib vs Placebo



A, Disease-free survival (cancer recurrence or death from any cause); 337 events were observed in the celecoxib group and 363 events in the placebo group. Median observation time for celecoxib was 4.1 years (interquartile range [IQR], 1.6-5.3 years) and for placebo was 4.0 years (IQR, 1.4-5.2 years). The 3-year disease-free survival rate was 76.3% (95% CI, 73.8%-78.8%) in the celecoxib group and 73.4% (95% CI, 70.8%-76.0%) in the placebo group. Median disease-free survival was not reached.

B, Overall survival (death from any cause); 212 deaths occurred in the celecoxib group and 236 in the placebo group. Median observation time for celecoxib was 5.5 years (IQR, 4.0-6.1 years) and for placebo was 5.5 years (IQR, 3.8-6.0 years). The 5-year overall survival rate was 84.3% (95% CI, 82.2%-86.5%) in the celecoxib group and 81.6% (95% CI, 79.4%-83.9%) in the placebo group. Median overall survival was not reached.

Two post hoc sensitivity analyses were conducted. First, restricting analyses to the 2455 patients who started any treatment (97% of those randomized), there were no significant differences in 3-year disease-free survival rates (celecoxib, 81.3% vs placebo, 81.7%; HR for disease recurrence or death, 0.95; 95% CI, 0.86-1.04) or 5-year overall survival rates (71.6% vs 71.6%; HR for death, 0.96; 95% CI, 0.88-1.05). Second, including only the 1935 patients who received at least 6 months of celecoxib or placebo, there were no significant differences in 3-year disease-free survival rates (86.8% vs 86.0%; HR for disease recurrence or death, 0.96; 95% CI, 0.86-1.06) or 5-year overall survival rates (74.3% vs 74.6%; HR for death, 0.95; 95% CI, 0.86-1.05). The post hoc mixed-effects model analysis using the enrolling center as a random effect of the primary end point yielded results almost identical to those of the primary analysis (disease-free survival HR, 0.89; 95% CI, 0.77-1.03; $P = .13$; overall survival HR, 0.87; 95% CI, 0.72-1.05; $P = .15$). Post hoc conditional power of a significant result that might have been reached if the study was continued to observe the original targeted number of events of 775 is 14.23% under the current trend and 25.98% under the alternative hypothesis.

Adverse Events

During receipt of FOLFOX, 2394 patients (94.8%) reported at least 1 adverse event possibly related to 1 or more agents in the treatment (FOLFOX, celecoxib, or placebo); 653 patients (51.7%)

assigned to FOLFOX with celecoxib and 640 (50.8%) assigned to FOLFOX with placebo experienced grade 3 or higher adverse events. When considering potential celecoxib-related adverse events (**Table 2**), patients receiving celecoxib had a higher risk of any grade hypertension both while receiving FOLFOX (14.6% vs 10.9% treated with placebo, $P = .01$) and following completion of FOLFOX treatment (13.0% vs 10.0%, $P = .04$). Following completion of FOLFOX treatment and while receiving celecoxib or placebo, a grade 2 or greater creatinine increase was more frequently observed with celecoxib (1.7%) vs placebo (0.5%; $P = .01$).

Table 2. Potential Clinically Significant Adverse Events of Celecoxib and Placebo When Given During and After FOLFOX Therapy[a,b]

	No./Total (%)	
Adverse effects	Celecoxib	Placebo
During FOLFOX therapy		
Neutrophils decrease (≥grade 3)	380/1215 (31.3)	389/1214 (32.0)
Nausea (≥grade 2)	221/1215 (18.2)	216/1213 (17.8)
Platelets decrease (≥grade 2)	215/1219 (17.6)	188/1214 (15.5)
Hypertension (any grade)	163/1119 (14.6)	122/1122 (10.9)
Peripheral neuropathy (grade 3 or 4)	124/1206 (10.3)	108/1188 (9.1)
Diarrhea (grade 3 or 4)	78/1206 (6.5)	80/1195 (6.7)
Fatigue (grade 3 or 4)	54/1220 (4.4)	50/1209 (4.1)
Gastritis (any grade)	49/1178 (4.2)	53/1171 (4.5)
Creatinine increase (≥grade 2)	22/1200 (1.8)	18/1209 (1.5)
Gastric ulcer (any grade)	10/1151 (0.9)	7/1143 (0.6)
Myocardial ischemia (any grade)	10/1145 (0.9)	10/1133 (0.9)
Cerebral ischemia (any grade)	4/1140 (0.4)	6/1133 (0.5)
After FOLFOX therapy		
Hypertension (any grade)	127/976 (13.0)	98/976 (10.0)
Peripheral neuropathy (grade 3 or 4)	50/1025 (4.9)	42/1023 (4.1)
Gastritis (any grade)	31/1020 (3.0)	20/1008 (2.0)
Creatinine increase (≥grade 2)	18/1034 (1.7)	5/1029 (0.5)
Gastric ulcer (any grade)	9/1003 (0.9)	5/998 (0.5)
Myocardial ischemia (any grade)	9/989 (0.9)	3/981 (0.3)
Cerebral ischemia (any grade)	3/986 (0.3)	6/985 (0.6)
Diarrhea (grade 3 or 4)	3/1028 (0.3)	3/1019 (0.3)

[a] At least possibly related to protocol therapy; adverse events during fluorouracil, leucovorin, and oxaliplatin (FOLFOX) treatment also at least possibly attributed to chemotherapy. Maximum grade of adverse events for patients are included.

[b] Based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, each adverse event is graded from 1 to 5 (1, mild; 2, moderate; 3, severe; 4, life-threatening or disabling; and 5, death related to the adverse event).

Discussion

In this randomized clinical trial of celecoxib vs placebo added to 3 or 6 months of FOLFOX adjuvant chemotherapy, celecoxib did not significantly improve disease-free or overall survival compared with placebo. Celecoxib did significantly increase the risk of hypertension and creatinine elevation.

Primary prevention of colorectal cancer with aspirin and secondary prevention of recurrent polyps with aspirin and COX-2 inhibitor has been established in numerous observational and interventional trials.[11-13,20-25] Several observational studies have indicated that patients with colorectal cancer who take these drugs had a lower risk of recurrent disease and death from cancer. In the Seattle Colon Cancer Family Registry, NSAID usage preceding a colorectal cancer diagnosis was associated with a 21% lower rate of colorectal cancer mortality following diagnosis compared with never use.[13] In a National Cancer Institute-led colon cancer adjuvant therapy trial, Ng and colleagues[12] observed that consistent users of aspirin had significant improvement in recurrence-free survival (83.1% at 5 years for users vs 74.9% for nonusers (HR for recurrence, 0.51; 95% CI, 0.28-0.95). Chan et al[11] found that regular usage of aspirin after colorectal cancer diagnosis was associated with a 35% lower risk in colorectal cancer-specific mortality for women in the Nurses' Health Study.

The VICTOR (Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regimen) trial[26] planned to accrue 7000 patients with stage II and III colon cancer to be randomized after surgery and adjuvant therapy to either 2 or 5 years of rofecoxib or placebo, but the trial prematurely terminated after 2.5 years due to the worldwide withdrawal of rofecoxib from the market due to cardiovascular risks.[27] With 2434 patients enrolled, median treatment duration of 7.8 months, and median follow-up of 4.8 years, there was no significant difference in disease-free survival or overall survival for rofecoxib or placebo.[26] Of note, the HR for disease recurrence or death was 0.89 (95% CI, 0.77-1.04), which are the same as this current trial, and the 3-year disease-free survival landmarks were 75.6% for rofecoxib and 73.4% for placebo, which are similar to this current trial of 76.3 and 73.4%, respectively.

The reasons for discordance between the observational studies and the results of this trial are unclear. In this trial, a selective COX-2 inhibitor was used. Although COX-2-dependent pathways are associated with antineoplastic effects of NSAIDs, it is plausible that COX-2-independent pathways are critical and affected by aspirin more effectively than by celecoxib. There are multiple ongoing adjuvant colon cancer trials with aspirin that will define the role of aspirin in this setting.[28-31] In addition, the trial did not incorporate biomarker-directed patient selection. Molecular pathological epidemiology studies report a differential benefit of aspirin and/or NSAIDs related to *BRAF*[32] or *PIK3CA* mutation status[33,34] and tumoral prostaglandin-endoperoxide synthase 2 (PTGS2)[11] or major histocompatibility complex class I antigen expression.[35] Almost 1600 tumor samples and 1900 baseline blood samples have been collected from consenting patients in this trial and will be used to explore the potential predictive value of specific molecular alterations or signatures with a COX inhibitor. Currently, there are at least 3 adjuvant therapy trials underway with enrollment restricted to *PIK3CA* variant colon cancer (ClinicalTrials.gov IDs NCT02467582, NCT02945033, and NCT02647099).

Strengths of this trial include the large sample size, inclusion of patients treated at community and academic practices, and inclusion of a racially diverse population (12.6% Black or African American and 21% minority).

Limitations

The study has several limitations. First, 29.6% of patients discontinued celecoxib or placebo prior to recurrence, adverse event, or completion of 3 years of therapy. The choice of 3 years was based on observations that longer duration of COX inhibitors is associated with a reduced risk of developing colorectal cancer. However, these data reflect that exposures prior to initiation of cancer and that there may be different pathways by which aspirin, NSAIDs, or COX-2 inhibitors influence cancer recurrence or metastases but not initiation.[20,22] In sensitivity analyses, receiving at least 6 months of celecoxib or placebo did not alter results, and at least for chemotherapy, most patients will achieve a benefit from adjuvant cytotoxic chemotherapy with fewer than 6 months of treatment. Second, the original statistical assumptions of the trial assumed faster enrollment and more events than were achieved. This required adjustment to power, which could increase the potential for a false-negative result. Third, the population was limited to stage III disease, already receiving adjuvant chemotherapy. It is unknown if a benefit in an earlier stage of disease, including those not receiving chemotherapy (stage II), would have accrued.

Conclusions

Among patients with stage III colon cancer, the addition of celecoxib for 3 years, compared with placebo, to standard adjuvant chemotherapy did not significantly improve disease-free survival.

ARTICLE INFORMATION

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