Phase I/II Study of Preoperative Oxaliplatin, Fluorouracil, and External-Beam Radiation Therapy in Patients With Locally Advanced Rectal Cancer: Cancer and Leukemia Group B 89901

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ABSTRACT

Purpose
The addition of oxaliplatin to fluorouracil in patients with advanced colorectal cancer improves survival. This phase I/II study evaluated the addition of weekly oxaliplatin to preoperative continuous infusion fluorouracil (FU) and external-beam radiation therapy (RT) in patients with locally advanced rectal adenocarcinoma.

Patients and Methods
Patients with clinical T3/T4 rectal adenocarcinoma and no evidence of metastases were treated with weekly oxaliplatin, continuous infusion FU 200 mg/m² intravenously, and RT. A total of 6 weekly doses of oxaliplatin were planned. RT dose was 1.8 Gy/fraction to a total dose of 50.4 Gy. In the phase I portion, oxaliplatin was escalated from 30 to 60 mg/m².

Results
Forty-four patients were entered onto the study, 18 on the phase I portion and 26 on the phase II portion. The maximum-tolerated dose (MTD) for oxaliplatin was determined to be 60 mg/m². At the MTD, 12 patients experienced grade 3 or 4 diarrhea, two patients experienced grade 3 neutropenia, and one patient experienced grade 3 thrombocytopenia. Fifty-six percent of patients entered at the MTD completed all 6 weeks of oxaliplatin. Eight (25%) of 32 patients enrolled at the phase II dose experienced a pathologic complete response.

Conclusion
In this multicenter study, the addition of oxaliplatin to intravenous continuous infusion FU and RT for patients with locally advanced rectal cancer was associated with a high pathologic complete response rate but more toxicity than when FU is used alone. A regimen of weekly oxaliplatin, continuous infusion FU, and radiation therapy is now being evaluated by the National Surgical Adjuvant Breast and Bowel Project.

J Clin Oncol 24:2557-2562. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Surgery is the foundation of treatment for localized adenocarcinoma of the rectum. The standard surgical approach has changed over the last 20 years and sharp dissection of the total mesorectum (TME) is now the standard of care. Despite excellent local control with this technique, the Dutch Colorectal Cancer Group recently demonstrated that preoperative radiation improved local control for patients compared with the use of TME alone.¹

For patients with pathologic T3 or T4 tumors, the use of adjuvant therapy with both chemoradiotherapy and chemotherapy has been associated with improved survival. Several centers have demonstrated that preoperative chemoradiotherapy can result in excellent rates of local control, better tolerability, and a higher likelihood of sphincter preservation.²⁻⁵ Recently, the German Rectal Cancer Study Group demonstrated in a randomized controlled trial that preoperative chemoradiotherapy was associated with improved local control and less toxicity when compared with postoperative chemoradiotherapy.⁶

Fluorouracil (FU) administered as a continuous infusion throughout the entire course of external-beam radiation is generally accepted in the United States as the standard chemoradiotherapy regimen for patients with T3, T4, or node-positive rectal cancer.⁷ When combined with FU, oxaliplatin...
improves the overall survival for patients with metastatic colorectal cancer and the rate of progression-free survival for patients with completely resected stage II and III colon cancer. In addition to improving the efficacy of systemic therapy for patients with colorectal cancer, oxaliplatin has radiation sensitization properties. In this study conducted by the Cancer and Leukemia Group B (CALGB), we combined oxaliplatin and continuous infusion FU in patients with clinically staged T3 or T4 rectal cancers. Our aims were to assess the safety of this combination in a phase I trial and to assess the efficacy and tolerability of this combination in a multi-institutional phase II trial, with the long-term goal of developing a treatment plan that would improve local control and sphincter preservation while managing systemic disease.

**Eligibility Criteria**

Patients entering the study had histologically confirmed rectal adenocarcinoma beginning within 12 cm of the anal verge, as determined by endoscopy. The tumor had to be fixed on physical examination or have evidence of T3 or T4 disease by endoscopic ultrasound or magnetic resonance imaging. In addition, patients could have no evidence of metastatic disease by abdominal computed tomography scan and could have no history of neurotoxicity. We included patients with granulocytes ≥ 1500/μL, platelets ≥ 150,000/μL, bilirubin ≤ the upper limit of normal, AST or ALT ≤ 2.5× the upper limit of normal, and creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min/1.73 m². All patients signed written informed consent approved by the participating institution’s institutional review board.

**Evaluation**

All patients underwent a medical history, physical examination, laboratory studies, (complete blood count with differential, electrolytes, creatinine, blood urea nitrogen, calcium, magnesium, AST, alkaline phosphatase, bilirubin, glucose, phosphate, total protein, albumin, and carcinoembryonic antigen) and ECG. Staging studies (chest x-ray, abdominal-pelvis computed tomography scan, colonoscopy or sigmoidoscopy, and endorectal magnetic resonance imaging or ultrasound) were completed within 28 days of study registration. All patients were assessed for toxicity weekly and underwent weekly complete blood counts and serum electrolytes, creatinine, and blood urea nitrogen determination.

**Treatment**

**Radiotherapy.** All patients received pelvic radiation therapy with concurrent chemotherapy. Treatments were given with a linear accelerator with a minimum energy of 4 MeV through three fields (posteroanterior and two lateral fields) or four fields (anteroposterior, posteroanterior, right and left laterals) to the primary tumor bed and surrounding soft tissue, internal iliac, and presacral nodes. The large fields were treated at 1.8 Gy per fraction to a total dose of 45 Gy in approximately 5 weeks. A booster dose of 5.4 Gy in three fractions was given to a reduced field that encompassed, as a minimum, the tumor bed and adjacent lymph nodes with a margin of 2 cm. Before therapy, all treatment plans were reviewed by a radiation oncologist (J.E.T.). Radiation was delivered at least 2 hours after each dose of oxaliplatin to try to maximize radiation sensitization.

**Chemotherapy.** All patients received central venous access for chemotherapy, FU was administered by an infusion pump over a period of 24 hours each day of each treatment week and the dose was fixed at 200 mg/m²/d. FU was started simultaneously with oxaliplatin each week. Oxaliplatin was administered on day 1 of each 7-day treatment cycle as a 1-hour infusion. Patients were not allowed to receive more than six cycles of therapy. All patients were premedicated to minimize nausea and vomiting and the use of anti-5-HT3 medications was encouraged. Adjuvant treatment with FU and leucovorin was recommended for all patients following surgery.

**Phase II Segment of the Study**

During the phase II segment of the study, chemoradiotherapy was held for toxicities ≥ grade 3 or for grade 2 toxicities at the discretion of the investigator. If a treatment was held for more than 7 days, oxaliplatin was discontinued from the regimen.

**Surgery.** It was recommended that patients undergo surgery after a 4-to-6 week rest period after completion of chemoradiotherapy. A total mesorectal excision was recommended.

**Pathology.** The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer (AJCC/Union Against Cancer (AJCC/UICC)) using the prescript “y” to indicate that the tumor has been treated before surgical resection. Only histologically viable tumors were staged according to the residual tumor classification. A pathologic complete response was defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ic, ypT0, ypN0).

**Study Design**

**Phase I.** This study had a phase I/II study design. Dose-limiting toxicities (DLT) were defined in the phase I portion of the study as any grade 4 neutropenia, any grade 3 thrombocytopenia, any nonhematologic toxicity ≥ grade 3 that resulted in more than 7 days’ interruption in therapy, or any neuropathy greater than grade 3, or neuropathy that was not resolved by the time the next cycle of therapy was to be administered. Cohorts of three to six patients were treated. If no DLTs were experienced, subsequent patients were treated at the next highest dose level. If one patient experienced a DLT, the dose level was expanded to a minimum of six patients. A minimum of six patients was treated at the DLT. If two of these six patients experienced a DLT, it was determined that the preceding dose level was the maximum-tolerated dose (MTD). The dose of oxaliplatin was specified not to exceed 60 mg/m²/cycle.

**Phase II.** In addition to the six patients studied at the MTD in the phase I portion of the trial, 19 patients were to be enrolled at the MTD during phase II in order to estimate the true toxicity rate more accurately. With radiation therapy and concurrent FU, the pathologic complete response rate has typically been reported to be in the range of 10% to 15%. The trial was designed to detect the difference between a pathologic complete response rate of 0.10 and 0.30 with 91% power (Exact test one-sample binomial proportion, 1-sided α = .1). The new regimen was to be considered worthy of further investigation if five or more pathologic complete responses were observed in the 25-patient cohort treated at the MTD.

Patient registration and clinical data capture were managed by the CALGB Statistical Center. All statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC) and S-Plus 7.0 (Insightful Corporation, Seattle, WA).

**RESULTS**

**Patient Characteristics**

Between December 2000 and November 2003, 44 patients were enrolled onto the study; 18 during the phase I portion and 26 during the phase II portion. Patient characteristics are listed in Table 1.

**Phase I Trial**

The phase I portion of the study enrolled 18 patients at four different dose levels (Table 2). No DLTs were observed at the first three oxaliplatin dose levels of 30, 40, and 50 mg/m², although two patients had to be replaced because of an allergic reaction in one patient and obstruction after a barium enema in another. Seven patients were treated at the 60 mg/m² dose level. One patient experienced grade 3 diarrhea that caused a more than 7-day interruption in therapy. An additional patient at this dose level was replaced for the phase I evaluation because of a disease-related bowel perforation, but is included in the phase II analyses. The 60 mg/m² dose was determined to be the MTD for oxaliplatin.
**Phase II Trial**

**Toxicity.** Twenty-six patients were enrolled onto the phase II portion of the study. The six patients treated at the MTD during phase I were also included in this toxicity analysis (n = 32). Diarrhea was the most common severe toxicity as 12 patients (38%) experienced grade 3 or 4 diarrhea (Table 3). Grade 3 nausea occurred in three patients and grade 3 vomiting occurred in one patient. Severe neurotoxicity was not observed, but 21 patients (66%) experienced grade 1 or 2 sensory neuropathy. Grade 3 fatigue occurred in six patients (19%). Myelosuppression was mild and grade 3 neutropenia and thrombocytopenia occurred in two patients and one patient, respectively.

Since dose reductions were not allowed, the oxaliplatin dose was discontinued if a delay in treatment of more than 7 days occurred due to toxicity, or oxaliplatin was discontinued at the investigator’s discretion if moderate-to-severe toxicity was experienced. Of the 32 patients enrolled at the phase II dose, 18 patients (56%) completed six cycles of oxaliplatin. Twenty-three patients (72%) completed at least four cycles of therapy.

In the phase II portion of the study, 19 patients underwent a low anterior resection and 11 patients underwent an abdominoperineal resection. Surgical morbidity is listed in Table 5. Two patients had...
colostomy/ileostomy ischemia. One patient had a wound infection and one patient had an anastomotic leak.

**Efficacy.** Eight (25%) of 32 patients (95% CI, 11% to 43%) enrolled at the phase II dose experienced pathologic complete responses, including two of five patients who had clinical T4 disease at study entry (Table 4). In addition, six patients had ypT2 disease and 23 patients (72%) were node negative after chemoradiotherapy. Of the eight pathologically complete responders, there has been one relapse in the pelvis and rectum at 9.1 months. Relapse-free times range from 9.9 to 26.1 months, with a median of 18 months in the remaining seven patients with complete responses. In all 32 patients enrolled at the phase II dose, there have been two additional relapses in the lung and liver, at 10.7 and 12.4 months, respectively. Two patients died at 15.5 and 20.5 months, and the current median follow-up time was 18.5 months.

<table>
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<th>Complications</th>
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<tr>
<td>Intra-abdominal infection</td>
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<td>Wound infection</td>
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<td>Colostomy/ileostomy ischemia</td>
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<td>Urinary outlet obstruction</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
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<td>retrorectal abscess; mild confusion; <em>Pseudomonas</em> urinary tract infection, ileus; ileus; urinary retention; occasional bleeding from rectum; stomal bleeding; vaginal fistula; left femoral neuropathy</td>
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**DISCUSSION**

Preoperative chemoradiotherapy with continuous infusional FU and external-beam radiation therapy has become the standard practice for patients with clinical T3, T4, and node-positive rectal adenocarcinoma in the United States. Preoperative therapy is associated with better local control and an improved toxicity profile when compared with postoperative chemoradiotherapy. Despite progress in surgical technique, and the use of adjuvant FU chemotherapy, many patients will experience a local and/or systemic recurrence. Integration of new agents such as oxaliplatin and irinotecan, which are associated with improved survival for patients with metastatic colorectal cancer, may improve local and systemic control for patients with stage II and II rectal cancer. Phase II studies have evaluated weekly administration schedules of oxaliplatin and FU and have demonstrated similar efficacy compared with once-every-2-weeks schedules. In preclinical studies, oxaliplatin has been associated with radiation sensitization. We evaluated weekly oxaliplatin with continuous infusion FU and external-beam radiation therapy in an attempt to maximize exposure to oxaliplatin.

In this multi-institutional CALGB phase I/II study, we have demonstrated that the addition of oxaliplatin to continuous infusion FU is feasible and associated with moderate toxicity. Despite lowering the dose of continuous infusion FU from the standard 225 mg/m² to 200 mg/m², 32% of patients experienced grade 3 or 4 diarrhea when weekly oxaliplatin 60 mg/m² was administered. Only 56% of patients were able to complete all six cycles of oxaliplatin. With dose reductions, it is possible that more patients could have completed six cycles of therapy. However, we did not want to compromise potentially curative therapy by having prolonged treatment delays and thus required investigators to discontinue oxaliplatin if there was a more than 7-day delay in therapy because of toxicity. It should also be noted that two patients experienced bowel obstruction during the phase I portion of the study. While these obstructions were related to a barium enema and metastases, respectively, it should also be noted that this regimen might have contributed to these events.

This rate of toxicity is higher than that which other investigators have reported utilizing FU and radiation in multi-institutional settings. Administering FU 1,000 mg/m² over 120 hours via continuous infusion during the first and fifth weeks of radiation therapy preoperatively, the German Rectal Cancer Study Group reported that 12% of 399 patients experienced grade 3 or 4 diarrhea. Using 5 days of bolus FU and leucovorin on the first and fifth week of radiation, the European Organisation for Research and Treatment of Cancer enrolled patients in a randomized trial of preoperative chemoradiotherapy versus preoperative radiation. They reported that 34% of patients experienced grade 2 or higher diarrhea in the chemoradiotherapy group but only 52 (13%) of 400 patients experienced a temporary suspension of chemoradiotherapy because of toxicity.

Single-center or limited institutional studies evaluating the combination of oxaliplatin and a fluoropyrimidine with radiation therapy for patients with rectal cancer have not reported high toxicity rates. Gerard et al. evaluated FU, leucovorin, and oxaliplatin 130 mg/m² during weeks 1 and 5 of radiation therapy and reported grade 3 or 4 diarrhea in three of 40 patients. In another study that used a weekly oxaliplatin regimen, Rodel et al. combined capcitabine (825 mg/m² bid days 1 through 14 and days 22 to 35) and oxaliplatin (50 or 60 mg/m² on days 1, 8, 22, and 29). Radiation therapy was delivered at 1.8 Gy/fraction up to a total dose of 50.4 Gy. Although two of six patients treated with 60 mg/m² of oxaliplatin experienced grade 3 diarrhea, only two of 26 patients experienced grade 3 diarrhea at the 50 mg/m² dose level. In the Rodel et al study, 89% of patients completed the full course of therapy compared with 56% patients in our study. However, the total dose of oxaliplatin over a period of 6 weeks was only 200 mg/m² in the Rodel study compared with 360 mg/m² in our trial.

Despite the increased toxicity, 25% of patients experienced a pathologic complete response. Single-institution series of preoperative FU and radiation therapy have demonstrated pathologic complete responses of 5% to 29%, but may have been subject to selection bias of patients in earlier stages. Of these studies, only Grann et al. used rectal ultrasound staging, and their pathologic complete response rate was 13%. Similarly, the German Rectal Cancer Study Group employed endorectal ultrasound for staging patients and reported a pathologic complete response of 8% in 415 patients undergoing preoperative chemoradiotherapy. In a preliminary report from a single-institution study, Aschele et al demonstrated a pathologic complete response in 29% of patients treated with preoperative continuous infusion FU, weekly oxaliplatin, and
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In summary, the addition of weekly oxaliplatin to continuous infusion FU and external-beam radiation therapy as preoperative therapy of clinical T3 and T4 rectal cancer is feasible, but associated with more toxicity than when FU is used alone as a radiation sensitizer. Nevertheless, most patients completed therapy as planned and 72% of patients completed at least four cycles of weekly oxaliplatin for a total oxaliplatin dose of at least 240 mg/m² over 6 weeks. The addition of oxaliplatin to standard chemoradiotherapy seems to be associated with a high pathologic complete response rate. A weekly regimen of oxaliplatin, continuous infusion of FU, and radiation therapy is now being evaluated by the National Surgical Adjuvant Breast and Bowel Project as one of the experimental arms in their protocol NSABP R-04.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for those authors indicating "No disclosures".

**REFERENCES**


Dollar Amount Codes

- (A) < $10,000
- (B) $10,000-99,999
- (C) ≥ $100,000
- (N/R) Not Required
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