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Phase I Study of Preoperative Radiation Therapy with Concurrent Infusional 5-Fluorouracil and Oxaliplatin followed by Surgery and Postoperative 5-Fluorouracil plus Leucovorin for T3/4 Rectal Adenocarcinoma: ECOG E1297

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Abstract

Purpose—Oxaliplatin is a platinum analog and radiosensitizer active in colorectal cancer. We performed a phase I trial to test the safety and preliminary efficacy of adding oxaliplatin to standard preoperative chemoradiation therapy for rectal cancer.

Patients and Methods—Eligible patients had T3-4 rectal adenocarcinoma. Patients received standard-dose radiation (50.4 Gy/5.5 weeks) with concurrent infused 5-fluorouracil (5-FU) at 200 mg/m² per day, 7 days/week. Oxaliplatin was given three times at 14-day intervals at 55, 70, or 85

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Statements: In this phase I trial, we found that the radiosensitizer oxaliplatin could safely be added to standard preoperative chemoradiation for rectal cancer without compromising the ability to deliver the full systemic dose and that this treatment led to impressive rates of sphincter preservation and pathologic response.

Preliminary results of this trial were presented at the 2003 meeting of the American Society of Clinical Oncology in Chicago, IL.

Conflicts of Interest: yes

David I. Rosenthal, MD - Honararia and advisory board for Sanofi-Aventis

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mg/m² during the 5.5-week radiation period, before resection. Adjuvant therapy consisted of four cycles of 5-FU (500 mg/m² per week) with leucovorin (500 mg/m² per week) given every 6 weeks. The main goals were to identify the maximum tolerated dose (MTD) of oxaliplatin and the dose-limiting toxicities (DLTs) when given with 5-FU and RT. Secondary goals were to determine resectability, pathologic response, sphincter preservation, and overall survival rates.

Results—Twenty-one patients were enrolled, 5 at the 55 mg/m² oxaliplatin dose level, 5 at 70 mg/m², and 11 at 85 mg/m². All patients were able to complete the preoperative chemoradiation regimen with no dose adjustments. No DLTs or differences in the type or extent of toxicity were noted among the groups. Nineteen patients underwent surgery (3 abdominopelvic resections and 16 low anterior resections), for an 84% sphincter preservation rate. The pathologic complete response rate was 26% (5 patients) and minimal microscopic residual tumor was found in another 4 patients (21%).

Conclusion—Oxaliplatin was well tolerated at 85 mg/m² given every 2 weeks in combination with standard preoperative chemoradiation for rectal cancer. The rates of major pathologic response and sphincter preservation are promising.

Keywords

rectal cancer; radiation therapy; chemoradiation; oxaliplatin; phase I; dose-escalation study; Eastern Cooperative Oncology Group

Introduction

The historic incidence of pelvic disease failure after surgical resection alone for transmural (T3-4) or node-positive rectal cancer has ranged from 35% to 60%.¹ Postoperative adjuvant treatment consisting of radiation therapy (RT), 5-fluorouracil (5-FU) and leucovorin has been the standard of care in the United States for transmural or node-positive rectal cancer since publication of a National Cancer Institute consensus conference recommendation in 1990 based on trials demonstrating improved cancer control and survival.² Although total mesorectal excision can reduce local pelvic failure rates to 10% or less,^{3, 4} a recent Dutch trial showed that preoperative RT followed by total mesorectal excision significantly reduced local recurrence in locally advanced rectal cancer.⁵ The German CAO/ARO/AIO-94 trial, the only prospective evaluation of pre- versus postoperative chemoradiation for rectal cancer completed to date, confirmed the many theoretical advantages of preoperative chemoradiation by demonstrating improved pelvic control, sphincter preservation for those with distal tumors, and decreased toxicity.⁶

Oxaliplatin, a third-generation platinum derivative, is the only platinum analog with clinical activity, both directly and as a radiosensitizer, in colorectal cancer⁷; it also has significant additive or synergistic activity with 5-FU.⁸ Single-agent oxaliplatin has produced consistent response rates of about 10% for patients with metastatic colorectal cancer refractory to multiple previous treatments.^{9–11} Oxaliplatin combined with 5-FU or leucovorin has led to objective response rates of 25% in patients with 5-FU-refractory disease and 54% when given as first-line therapy.^{12,13} On the basis of these findings, we performed a phase I trial to evaluate the feasibility of adding oxaliplatin to a standard preoperative chemoradiation

regimen for rectal cancer. Our short-term goals were to determine the maximum tolerated dose (MTD) and assess the dose-limiting toxicity (DLT) of this regimen. The ultimate goals were to improve resectability, pathologic response rates, sphincter preservation, and survival for patients with T3-4 rectal cancer.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients had histologically confirmed, locally advanced, nonmetastatic T3 or T4 primary adenocarcinoma of the rectum, with the distal border of the tumor at or below the peritoneal reflection (defined as within 12 centimeters of the anal verge by endoscopy). Evidence of transmural extension was required, as demonstrated by magnetic resonance imaging (MRI) or by computed tomography (CT) complemented by endoscopic sonography. Tumors could be either resectable or unresectable. Unresectable tumors were defined as those fixed to the sidewall or sacrum. Other inclusion criteria included having an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, white blood cell count >4,000/ml, platelet count of 150,000 cells/ml, creatinine level 1.5 mg/dl, and serum bilirubin level less than 2.0 mg/dl. Patients could not be pregnant or lactating or have neuropathy, metastatic disease, active inflammatory bowel disease, high-grade large bowel obstruction (unless they had had a diverting colostomy), prior chemotherapy or pelvic RT, or previous or concurrent malignancy (except for non-melanoma skin cancer, in situ cervical cancer, or treated non-pelvic cancer from which the patient had been continuously disease-free more than 5 years). All patients had to be able to evaluate and sign an informed consent form that was approved by the institutional review boards at the participating institutions.

Patient Evaluation

Patients were evaluated with medical history and physical examination, electrocardiography, and laboratory studies (complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, bilirubin, alanine aminotransferase, alkaline phosphatase, and carcinoembryonic antigen). Disease was staged before chemoradiation therapy was begun by digital rectal examination, chest x-ray, abdominopelvic imaging by MRI or CT, colonoscopy, and endorectal sonography or MRI.

Treatment Sites

Treatment sites for this ECOG trial (E1297) were limited to the H. Lee Moffitt Cancer Center and Research Institute and the hospitals of the University of Pennsylvania, Emory University, and Northwestern University.

Radiation Therapy

All patients were to receive 50.4 Gy external megavoltage RT with a minimum energy of 4 MV at 1.8 Gy per fraction per day over 5 1/2 weeks. The entire pelvis was treated to a dose of 45 Gy followed by a boost of an additional 5.4 Gy to encompass the tumor volume, as defined by pretreatment imaging and physical evaluation, with a 2-cm margin in all directions. Multiple field techniques, either 3 fields with a posterior and 2 lateral wedged

fields, or 4 fields with anterior, posterior, and 2 lateral wedged fields, were mandatory. All fields were to be treated daily. Intensity-modulated RT was not used.

Chemotherapy

All patients received preoperative and postoperative chemotherapy via an implanted central or peripheral venous access line and an external infusion device. . All patients were treated during the 5 1/2-week RT period with a continuous infusion of 5-FU at a dose of 200 mg/m² per day, beginning on the first day of RT and continuing until the RT was completed. Oxaliplatin was given as a 2-hour intravenous infusion on weeks 1, 3, and 5. Patients received four additional cycles of adjuvant chemotherapy, starting 21 to 42 days after surgery, consisting of weekly 5-FU 500 mg/m² per day with leucovorin 500 mg/m² per day; each cycle lasted 6 weeks.

Surgery

Resectability and the type of resection required at the time of diagnosis were planned to be confirmed by the operating surgeon before the preoperative therapy was to begin; Resectable disease was treated by abdominopelvic resection, low anterior resection, or low anterior resection with coloanal anastomosis between 28 and 42 days after completion of the preoperative therapy. Disease restaging was to be done in all cases before surgery with a CT scan of the abdomen and pelvis and a chest x-ray. Even if no clinical evidence of tumor regression was present at restaging, patients were to undergo exploratory surgery, and the type of resection to be performed was to be based on intraoperative assessment.

Pathology

The extent of viable residual tumor in the resected surgical specimen was classified as gross disease, minimal microscopic residual disease, or complete response with no residual viable cells. Pathologic results were reviewed by each participating institution; no central pathology review was done.

Study Design

The primary endpoint of this phase I dose-escalation study was to identify the MTD and DLT of preoperative oxaliplatin given with concurrent RT and 5-FU, the latter by protracted venous infusion. Additional endpoints included the resection rate for T4 rectal cancers, the pathologic response rate for T3 and T4 rectal cancers, and the type of resection performed.

The oxaliplatin dose was to be 55 mg/m² per day for patients in the first dose cohort (to consist of 5 patients) and then escalated according to a modified Fibonacci series, in which another 5 patients would receive 70 mg/m² per day and then another 10 patients would receive 85 mg/m² per day. Since 85 mg/m² per day is considered the standard full systemic dose given without RT, we had no plans to escalate further. Subsequent patients after those in the first dose level were treated at the next highest dose level if no more than 1 patient experienced a DLT. The MTD was defined as having been exceeded and dose escalation was to be ceased if any 2 patients in a cohort experienced a DLT. The maximum dose level at which no more than 1 patient experienced a DLT was defined as the MTD. The initial design included the addition of postoperative adjuvant oxaliplatin to 5-FU/leucovorin, but

this plan was later modified to 5-FU/leucovorin alone to focus on the question of the effect of the phase I preoperative therapy.

DLT was defined in terms of the National Cancer Institute Common Toxicity Criteria (V2.0) as follows: grade 4 decrease in absolute neutrophil count; grade 3 nonhematologic toxicity; diarrhea that does not respond to a low-fiber diet or antidiarrheal medication (e.g., Lomotil or Imodium) and requires an interruption in treatment of > 14 days; anastomotic breakdown in > 2 patients at any dose level; or grade > 3 neuropathy that does not resolve before the next oxaliplatin cycle is begun.

Patient registration and clinical data capture were managed by Theradex (Princeton, NJ) for the ECOG Statistical Center. Analyses were conducted with descriptive statistics for most variables; Kaplan-Meier analysis was used to compute overall survival.

RESULTS

A total of 21 patients were enrolled (Table 1), all of whom were assessable for toxicity (Table 2). Five patients completed the 55 mg/m² dose level and another 5 patients completed the 70 mg/m² dose level without anyone experiencing a DLT. One patient in the 55 mg/m² dose group developed lung metastasis and did not undergo surgery. Ten patients were treated at the 85 mg/m² dose level. An eleventh patient was added to the final dose-level group to replace one who had died pre-operatively from an unrelated but documented upper gastrointestinal bleed. Dose escalation was ceased at the 85 mg/m²/d dose level according to the study design.

No unanticipated toxic effects were noted (Table 2). Moreover, no differences were found in the type or extent of toxic effects among dose levels, and no patient experienced DLT according to the protocol definition. All 19 patients who underwent surgery had complete (R0) resections. Three patients underwent abdominopelvic resection, 9 had low anterior resection with coloanal anastomosis, and 7 had low anterior resection, for an 84% sphincter preservation rate. Pathology review of the surgical specimens revealed gross residual tumor in 10, complete response in 5 (26%), and minimal microscopic residual in 4, for a pathologic complete response rate + microscopic-residual rate of 47%. As of this analysis 5 of the 21 patients had died. The overall 1-year and 2-year survival rates were 90% and 80%.

DISCUSSION

This ECOG study demonstrated that oxaliplatin given in an every-other-week dose schedule at its established full systemic dose, in combination with infusional 5-FU, was well tolerated when added to preoperative pelvic RT for rectal cancer. There was no febrile neutropenia or high-grade neurotoxicity. Four transient cases of grade 3 diarrhea (which did not constitute a DLT according to our prospectively defined criteria) were experienced, one in the 70-mg/m² group and three in the 85-mg/m² group. Furthermore, no dose-response relationship was apparent for any specific toxic effect monitored, and no DLTs were encountered. We thus recommend for phase II study an oxaliplatin dose of 85 mg/m², given every 2 weeks, in combination with 50.4 Gy pelvic RT and continuous-infusion 5-FU at 200 mg/m² per day

During the trial design, we selected this oxaliplatin dose schedule on the basis of the standard systemic regimens typically used at that time, i.e., either every 2 weeks or every 3 weeks. Our use of an every-2-weeks schedule allowed us to deliver the oxaliplatin three times during RT to maximize the opportunity for radiosensitization. Other subsequent studies have used weekly dose schedules, such as the Cancer and Leukemia Group B trial, reported by Ryan et al,¹⁴ that deliver as many as 6 doses of oxaliplatin; the dose recommended for that schedule was 60 mg/m².^{14–16} However, that dose schedule delivers a cumulative potential dose as high as 360 mg/m² as opposed to the maximum 255 mg/m² in our study and in a similar trial reported by Loi et al.¹⁷ The cumulative maximum oxaliplatin dose reported in published chemoradiation trials varies between 200 and 360 mg/m² (Table 3). In the weekly-dose schedule trial reported by Ryan et al, however, only 72% of patients were able to tolerate 4 cycles, in which the actual delivered cumulative dose was 240 mg/m², similar to the total 255 mg/m² dose delivered in our study. We believe that a regimen that does not compromise the ability to deliver the full systemic dose of oxaliplatin may offer benefit for the patient with respect to direct drug effect on the local tumor and nodes as well as distant micro-metastases.

The main DLT for oxaliplatin in combination with 5-FU and RT for rectal cancer is high-grade diarrhea. Rates of grade 3 diarrhea in our study and in that of Loi et al., both of which used the 85 mg/m² every-2-weeks dose schedule, were 19% and 12%. These rates are similar to the 16% and 18% reported with the weekly 60 mg/m² dose schedule reported by Aschele et al.¹⁶ and Francois et al.,¹⁵ respectively, but lower than the 32% reported by Ryan et al.,¹⁴ in which only 56% of patients were able to complete all 6 cycles.

The addition of newer and more active chemotherapy agents and targeted agents to treat disseminated colorectal cancer may further improve treatment results for patients with newly diagnosed rectal cancer undergoing curative therapy. Bevacizumab, irinotecan, and cetuximab have been shown to improve results of systemic therapy for colorectal cancer¹⁸ and so are being introduced into adjuvant or neoadjuvant therapy for rectal cancer, as was done with oxaliplatin in this ECOG trial.

Potential advantages of preoperative chemoradiation over postoperative chemoradiation are lesser toxicity, the chance for tumor downstaging resulting in higher rates of sphincter preservation, especially for patients with distal tumors, and improved pelvic control and disease-free survival rates. The German trial⁶ demonstrated that preoperative chemoradiation for rectal cancer was associated with less acute and chronic toxicity, fewer pelvic failures (13% vs. 6%), a pathologic complete response rate of 8% in the preoperative group, and a higher rate of sphincter preservation for distal tumors (39% vs. 19%) as compared with postoperative chemoradiation.⁶ Additional analysis of those data suggests that higher rates of pathologic response in the resected specimens may correlate with improved 5-year disease-free survival.¹⁹ Bouzourene et al.²⁰ also showed that tumor regression in the resected specimen correlated with disease-free survival in patients treated with preoperative RT alone.²⁰ Wheeler et al.²² and Dworak et al.²¹ have proposed methods of grading pathologic response to preoperative chemoradiation for rectal cancer, but at this time neither has been prospectively validated or uniformly accepted.^{21, 22}

Our findings from the present study showed that the addition of oxaliplatin to preoperative chemoradiation for rectal cancer was well tolerated and produced a favorable pathologic complete response rate. The results shown in Table 3 from published oxaliplatin chemoradiation trials indicate that the complete pathologic response rates range from 7% and 28%. This ECOG study resulted in a 26% pathologic complete response rate and a 47% partial response rate (either pathologic complete response or microscopic residual disease). These numbers compare very favorably to the 10% complete response rate reported in the German trial⁶ of RT and 5-FU. Shortcomings of our multi-institutional study are the inconsistent information on the surgeons' preoperative assessment of resectability and the type of resection thought to be required before chemoradiation.

In summary, the addition of every-other-week oxaliplatin to 50.4 Gy pelvic irradiation and infusional 5-FU was feasible and was well tolerated without the need to reduce the full systemic dose oxaliplatin; moreover, this regimen did not seem to increase the toxicity of the chemoradiation. The rates of sphincter preservation and pathologic response in our study are comparable to those in other published series, leading us to propose that this regimen may well translate to improved rates of disease-free and overall survival and sphincter preservation.

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Table 1

Patient Characteristics

	Oxaliplatin Dose Level		
	55 mg/m ²	70 mg/m ²	85 mg/m ²
Sex	5 M, 0 F	3 M, 2 F	8 M, 3 F
Age, years			
Mean (range)	53.8 (37–69)	57.6 (40–65)	55.6 (44–68)
Race			
White	3	4	9
Black	2	1	2
Weight, kg			
Mean (range)	88.94 (69–105)	81.44 (54.5–97.5)	83.45 (51–121.4)
Disease Classification or Stage *			
T3N0	1	4	2
T3N1	3	1	4
T3N2	0	0	1
T4	1	0	2
II	0	0	1
III	0	0	1
III/IV	0	0	1
ECOG Performance Score			
0	3	5	10
1	1	0	0
2	0	0	1
Baseline CEA Level, µg/L			
Mean (range)	13.76 (1.9–50.4)	7.16 (0.7–28.9)	9.63 (3.6–21.4)

* Disease stage was assessed before chemoradiation therapy.

Table 2

Observed Toxicity	Oxaliplatin Dose Level and Toxicity Grade											
	55 mg/m ²			70 mg/m ²			85 mg/m ²					
	1	2	3	1	2	3	1	2	3	1	2	3
Numbers of Patients Experiencing Toxicity												
Cytopenias												
Thrombocytopenia	2	0	0	2	0	0	1	0	0	1	0	0
Anemia	4	1	0	1	0	0	3	0	0	3	0	0
Leukopenia	1	3	1	0	1	0	2	1	0	2	1	0
Lymphocytopenia	0	0	0	0	0	2	0	0	1	0	0	1
Neutropenia	2	0	1	0	0	1	0	0	0	0	0	0
Fever	1	0	0	0	0	0	5	0	0	0	0	0
Gastrointestinal												
Nausea	2	3	0	2	1	0	6	0	0	0	0	0
Diarrhea	2	2	0	0	2	1	1	4	3	0	0	0
Flatus	0	0	0	1	0	0	1	0	0	0	0	0
Vomiting	1	2	0	0	0	0	1	0	0	0	0	0
Decreased appetite	3	1	0	1	0	0	1	0	0	0	0	0
Rectal pain	0	0	1	0	1	1	0	1	0	0	1	0
Weight loss	1	0	0	0	1	0	3	2	0	0	0	0
Abdominal bloating	1	0	0	1	1	0	1	0	0	0	0	0
Rectal bleeding	0	0	0	1	0	0	0	0	0	0	0	0
Genitourinary												
Pelvic pain	2	1	0	0	1	0	0	0	0	0	0	0
Urinary retention	0	1	0	1	0	0	0	0	0	0	0	0
Urinary frequency	0	0	0	0	0	0	1	0	0	0	0	0
Urinary tract infection	0	1	0	0	0	0	0	0	0	0	0	0
Dysuria	1	0	0	0	1	0	1	0	0	0	0	0
Hematuria	0	0	0	0	0	0	0	0	0	0	2	0

Table 3

Oxaliplatin-Radiation Therapy Trials in Rectal Cancer

Reference	Oxaliplatin Dose and Schedule	Cumulative Oxaliplatin Dose	Incidence of Grade 3-4 Diarrhea	Oxaliplatin Compliance	pCR + Near-CR Rates
Sauer et al.6	None	NA	12%	NA	10% + NS
ECOG 1297	85 mg/m ² × 3	255 mg/m ²	4 of 21	100%	26% + 21%
Rodel et al.19	50 or 60 mg/m ² × 4	200-240 mg/m ²	2 of 6 and 2 of 26	89%	10% + 52%
Ryan et al.14 (CALGB)	60 mg/m ² × 6	360 mg/m ²	32%	56	25% + NS
Carraro et al.23	25 mg/m ² × 4d × 2	200 mg/m ²	6 of 22	--	25% + 2/12
Machiels et al.24	50 mg/m ² × 5	250 mg/m ²	30%	85%	14% + 18% *
Francois et al.15	60 mg/m ² × 5	300 mg/m ²	8 of 43	--	13% + 13% **
Sebag-Montefiore et al.25	130 mg/m ² × 2	260 mg/m ²	11 of 32	100%	7% + 11%
Aschele et al.16	60 mg/m ² × 6	360 mg/m ²	16%	--	28% + 48%
Loi et al.17	85 mg/m ² × 3	255 mg/m ²	2 of 16	--	2 **
Gerard et al.26	130 mg/m ² × 2	260 mg/m ²	3 of 40	100%	15% + 30%

* included T2 tumors

** included < T3 tumors

pCR, pathologic complete response (no residual viable cells in the surgical specimen); near-CR, minimal microscopic residual tumor in the surgical specimen; NA, not applicable; NS, not stated.