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ORIGINAL REPORT

Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Rectal Cancer: Surgical End Points From National Surgical Adjuvant Breast and Bowel Project Trial R-04

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ABSTRACT

Purpose
The optimal chemotherapy regimen administered concurrently with preoperative radiation therapy (RT) for patients with rectal cancer is unknown. National Surgical Adjuvant Breast and Bowel Project trial R-04 compared four chemotherapy regimens administered concomitantly with RT.

Patients and Methods
Patients with clinical stage II or III rectal cancer who were undergoing preoperative RT (45 Gy in 25 fractions over 5 weeks plus a boost of 5.4 Gy to 10.8 Gy in three to six daily fractions) were randomly assigned to one of the following chemotherapy regimens: continuous intravenous infusional fluorouracil (CVI FU; 225 mg/m^2, 5 days per week), with or without intravenous oxaliplatin (50 mg/m^2 once per week for 5 weeks) or oral capecitabine (825 mg/m^2 twice per day, 5 days per week), with or without oxaliplatin (50 mg/m^2 once per week for 5 weeks). Before random assignment, the surgeon indicated whether the patient was eligible for sphincter-sparing surgery based on clinical staging. The surgical end points were complete pathologic response (pCR), sphincter-sparing surgery, and surgical downstaging (conversion to sphincter-sparing surgery).

Results
From September 2004 to August 2010, 1,608 patients were randomly assigned. No significant differences in the rates of pCR, sphincter-sparing surgery, or surgical downstaging were identified between the CVI FU and capecitabine regimens or between the two regimens with or without oxaliplatin. Patients treated with oxaliplatin experienced significantly more grade 3 or 4 diarrhea ($P < .001$).

Conclusion
Administering capecitabine with preoperative RT achieved similar rates of pCR, sphincter-sparing surgery, and surgical downstaging compared with CVI FU. Adding oxaliplatin did not improve surgical outcomes but added significant toxicity. The definitive analysis of local tumor control, disease-free survival, and overall survival will be performed when the protocol-specified number of events has occurred.

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INTRODUCTION

The propensity of rectal carcinoma to relapse in local as well as distant sites after potentially curative surgery has long been known.[1,2] In the absence of a curative systemic therapy, this dual pattern of relapse has led to the development of a combined-modality therapy of operable rectal cancer—surgical resection, regional radiation therapy, and chemotherapy. Early randomized clinical trials in the United States demonstrated improved outcomes with postoperative combined radiation and fluorouracil (FU) chemotherapy.[3-5] In 1994, a national intergroup trial[6] demonstrated further improvement in outcomes when FU was given continuously during postoperative radiation therapy with the use of ambulatory infusion pumps, and thus established a standard of care in clinical practice.

Subsequently, the oral fluorinated pyrimidine prodrug capecitabine (Xeloda, Roche, Basel, Switzerland) was shown to have antitumor activity in metastatic colorectal cancer[7,8] and was administered concomitantly with radiation therapy as a radiation sensitizer.[9] The selective activation of capecitabine to its active metabolite within tumor cells in preclinical models[10] provided a rationale that the use of this agent might be associated with an improved therapeutic index in patients with cancer when administered with radiation therapy. If it was tolerable and at least as active as FU in the adjuvant therapy of rectal cancer, it would be possible to eliminate the need for cumbersome ambulatory infusion pumps.

Oxaliplatin (Eloxatin, sanofi-aventis, Paris, France) was approved by the US Food and Drug Administration in 2004 for use in combination with a fluorinated pyrimidine for the treatment of advanced metastatic colorectal cancer,[11] and was subsequently shown to be of value in the postoperative adjuvant therapy of colon cancer.[12,13] This platinum analog also had in vitro radiation-sensitizing properties,[14] and therefore was a good test as a component of combined-modality adjuvant therapy of rectal cancer.

Many European investigators have favored the preoperative (versus postoperative) use of radiation and chemotherapy to treat operable rectal cancer over the past several decades.[15,16] A landmark randomized controlled trial of preoperative versus postoperative rectal cancer adjuvant radiation and chemotherapy was conducted in Germany, which clearly established the superiority of the preoperative sequence of radiation and chemotherapy before surgery,[17] and changed the treatment paradigm in the United States.

With this background, the National Surgical Adjuvant Breast and Bowel Project (NSABP) led a national randomized intergroup clinical trial to test the value of capecitabine and oxaliplatin as components of preoperative (neoadjuvant) combined-modality therapy in patients with clinical stage II and III rectal cancer. Our article details the impact of treatment on the surgical outcomes of pathologic complete response (pCR), sphincter-sparing surgery, and surgical downstaging.

PATIENTS AND METHODS

Patient Eligibility

NSABP R-04 was approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the US Department of Health and Human Services. Written informed consent was required.

Patients were required to be at least 18 years old with an Eastern Cooperative Oncology Group performance score of 0 to 1 and a life expectancy of 5 years (Fig 1). Adenocarcinoma of the rectum diagnosis had to have been established via a biopsy technique, which left the major portion of the tumor intact within 42 days before random assignment. The distal border of the tumor was required to be less than 12 cm from the anal verge, and the tumor had to be palpable by digital rectal exam or accessible via proctoscope or sigmoidoscope. The tumor had to be confirmed clinically (by transrectal ultrasonography and computed tomography [CT] scan or magnetic resonance imaging [MRI]) to be stage II (T3-4N0) or stage III (T1-4N1-2, with a positive node defined as at least 1.0 cm in diameter on imaging). There must have been no evidence of metastatic disease on physical examination, chest x-ray, or CT scan of the abdomen and pelvis. If technically feasible, a complete colonoscopic examination was performed; otherwise, a proctoscopic or sigmoidoscopic examination was performed. Satisfactory hematologic parameters, liver function tests and renal function tests were required. Patients with nonmalignant systemic disease, which would preclude safe administration of therapy or prescribed follow-up, were excluded. The tumor had to be considered amenable to curative resection by the surgeon, and there could be no evidence of pelvic sidewall involvement on imaging studies. Before random assignment, the investigator had to specify whether a sphincter-sparing operation was feasible or whether nonsphincter-sparing surgery would be required.

Random Assignment and Treatment

Patients were stratified by institution, sex, intended operative procedure (sphincter-saving surgery or non–sphincter-saving surgery), and clinical tumor stage (stage II [T3-4N0] or stage III [T1-4N1-2]). Patients were randomly assigned to treatment groups using the NSABP biased-coin minimization algorithm.[18]

Radiation Therapy

Radiation therapy was delivered at 1.8 Gy per day, five days per week, for a total of 25 fractions over 5 weeks, for a total dose of 45 Gy to the large pelvic

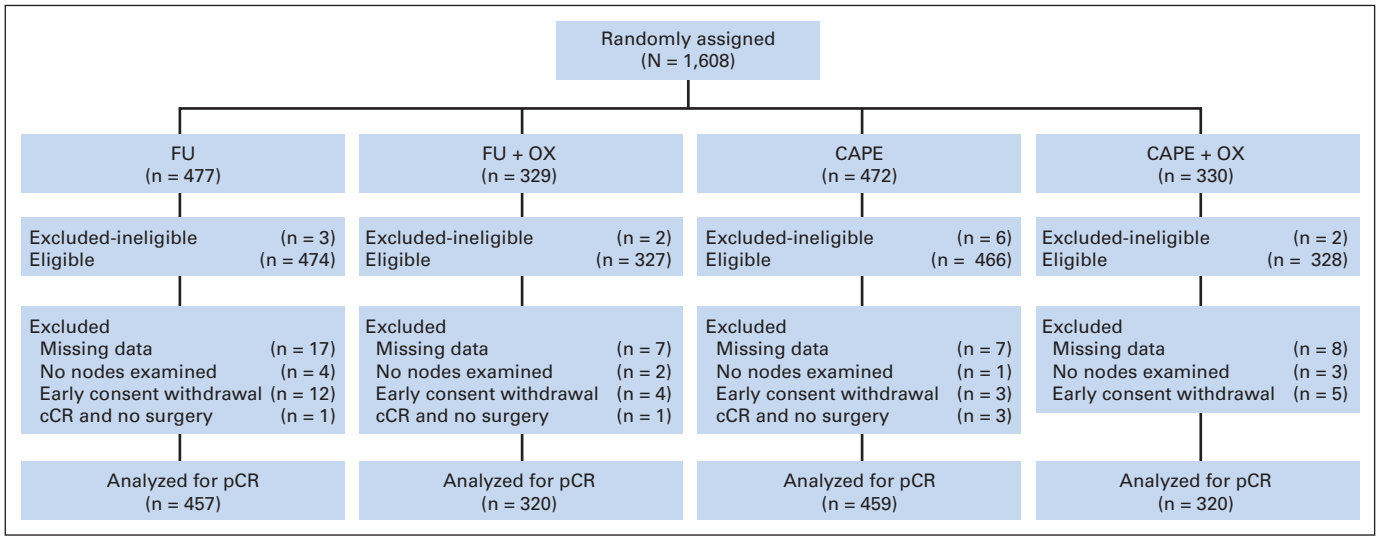

Fig 1. CONSORT diagram for NSABP (National Surgical Adjuvant Breast and Bowel Project) R-04. CAPE, capecitabine; cCR, complete clinical response; FU, fluorouracil; OX, oxaliplatin; pCR, pathologic complete response.

field. A minimum boost of 5.4 Gy (administered over 3 days in 1.8 Gy fractions) was required for patients with T3 nonfixed cancer and nondistal tumors (total cumulative dose of 50.4 Gy, including large pelvic fields). For patients with T4 fixed cancer and/or distal rectal tumors, a boost dose of 10.8 Gy (given over 3 days in 3.6 Gy fractions) was required (total cumulative dose of 55.8 Gy, including large pelvic fields).

Chemotherapy

NSABP R-04 began in July 2004, and patients were randomly assigned to receive either radiation therapy plus FU (group 1) or radiation therapy plus capecitabine (group 2). For group 1, 225 mg/m^2/day FU was delivered by continuous intravenous infusion (CVI), 7 days per week beginning the day of the start of radiation therapy and ending the evening of the last dose of radiation therapy. For group 2, oral capecitabine 825 mg/m^2 was administered twice per day throughout the course of radiation therapy, 7 days per week beginning the day of the start of radiation therapy and ending with the last dose of radiation therapy.

Protocol Amendment

In October 2005, the protocol was amended to add oxaliplatin (50 mg/m^2 intravenous [IV] once per week for 5 weeks during radiation therapy), creating a 2×2 factorial design with four treatment groups: radiation therapy plus FU (group 3), radiation therapy plus FU plus oxaliplatin (group 4), radiation therapy plus capecitabine (group 5), and radiation therapy plus capecitabine plus oxaliplatin (group 6). The daily dose of chemotherapy remained the same, but the number of days of capecitabine and FU treatment was reduced from 7 days per week to five, with administration of chemotherapy only on days of planned radiation therapy to reduce the incidence of severe diarrhea.

The protocol required surgery to be performed within 6 to 8 weeks after the completion of radiation therapy.

End Points

The primary end point of NSABP R-04 is time from random assignment to first locoregional failure. This will be presented in a future article.

The secondary end points of pCR, sphincter-sparing surgery, surgical downstaging, and toxicity are the focus of this article. pCR was determined by gross and microscopic examination of tissue removed at surgery. pCR was defined as no histologic evidence of invasive tumor cells in the surgical specimen at the site of the primary tumor or in the lymph nodes (or in tissue in the area where the tumor had been if there was a complete clinical response). The intended operative procedure was specified before random assignment (non–sphincter-sparing surgery or sphincter-sparing surgery). Surgical downstaging was defined as conversion from intended non–sphincter-sparing surgery at random assignment to sphincter-sparing surgery following chemoradiotherapy. Sphincter-sparing surgery as an end point is the rate of sphincter-sparing surgery regardless of intended surgery.

Toxicity

Toxicity data was graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. All grade 2 and higher adverse events from random assignment up until but not including the day of surgery are included in the toxicity analysis. If surgery was not performed, all grade 2 and higher adverse events from random assignment up until 60 days after completing chemoradiotherapy were included.

Statistical Methods

Toxicity analyses included all postamendment patients, and Fisher's exact test was used to test for differences in toxicity. All other analyses were conducted using eligible patients only, as specified in the protocol.

A patient was considered an early consent withdrawal if they withdrew consent less than 56 days after the end of protocol therapy or within 91 days of random assignment if the patient had not begun protocol therapy. These patients would not be expected to report surgical outcomes.

Patients for whom no surgery form was submitted or whose surgery form reported the patient did not have a resection are included in the surgical outcomes analysis as failures. The only exceptions to this are patients who had a complete clinical response and no surgery or patients who were early consent withdrawals. These patients were excluded from the surgical outcome analyses.

Fisher's exact test was used to test the difference between proportions. Cochran-Mantel-Haenszel tests were used to test for treatment differences controlling for the other treatment not being tested. The Breslow-Day test of homogeneity of the odds ratio was used to test for an oxaliplatin-fluoropyrimidine interaction. P values were two-sided and $P < .05$ is considered significant. Exact fiducial CIs were calculated for proportions.[19]

Table 1. Patient Entry and Characteristics: NSABP R-04

	Before Amendment				After Amendment							
	FU (2 Arm)		CAPE (2 Arm)		FU (4 Arm)		FU + OX (4 Arm)		CAPE (4 Arm)		CAPE + OX (4 Arm)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Among all patients												
Randomly assigned	147		146		330		329		326		330	
Ineligible	1		5		2		2		1		2	
Average months on study*	89.0		89.1		54.0		54.1		54.3		54.1	
Age, years												
≤ 59		59.2		52.7		56.1		61.4		57.1		61.2
≥ 60		40.8		47.3		43.9		38.6		42.9		38.8
Sex												
Male		68.0		67.8		67.0		68.1		67.8		67.6
Female		32.0		32.2		33.0		31.9		32.2		32.4
Clinical stage†												
II		49.7		46.6		61.5		61.7		62.3		61.5
III		50.3		53.4		38.5		38.3		37.7		38.5
Surgical intent†												
Sphincter sparing		74.8		71.9		73.6		73.6		74.2		73.3
Not sphincter sparing		25.2		28.1		26.4		26.4		25.8		26.7

Abbreviations: CAPE, capecitabine; FU, flourouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin.
*As of December 31, 2012.
†As reported at the time of random assignment.

Table 2. Comparison of FU With CAPE: NSABP R-04

End Point	FU (± OX)			CAPE (± OX)			P
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	
pCR	138 of 777	17.8	15.1 to 20.6	161 of 779	20.7	17.9 to 23.7	.14
SSS	463 of 780	59.4	55.8 to 62.8	462 of 779	59.3	55.8 to 62.8	.98
SD	43 of 202	21.3	15.9 to 27.6	44 of 209	21.1	15.7 to 27.2	.95
Grade 3-5 diarrhea*	75 of 639	11.7	9.3 to 14.5	75 of 641	11.7†	9.3 to 14.4	1.0

Abbreviations: CAPE, capecitabine; FU, flourouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin; pCR, pathologic complete response; SSS, sphincter-sparing surgery; SD, surgical downstaging.
*Restricted to the postamendment population, groups 3-6.
†Two patients in the CAPE + OX arm died as a result of diarrhea.

Comparisons between FU and capecitabine were performed using both pre- and postamendment populations, except for toxicity. Because patients were not assigned to oxaliplatin/no oxaliplatin groups before the amendment, comparisons between oxaliplatin and no-oxaliplatin effects were conducted only on the postamendment population.

RESULTS

Accrual

The first patient was randomly assigned to the original two-arm study September 14, 2004. There were 293 patients who were accrued to the original two-arm study (FU, n = 147; capecitabine, n = 146). After the protocol was amended to include oxaliplatin, 1,315 patients were randomly assigned to the four-arm study: 330 patients to radiation therapy plus FU, 329 patients to radiation therapy plus FU plus oxaliplatin, 326 patients to radiation therapy plus capecitabine, and 330 patients to radiation therapy plus capecitabine plus oxaliplatin. On August 16, 2010, accrual was successfully completed with 1,608 patients. This slightly exceeded our target accrual of 1,606 patients.

Patient Characteristics

Table 1 lists the distribution of patient characteristics by treatment group. Thirteen patients (< 1%) were determined to be ineligible. Patient characteristics are similar across treatments both before and after the amendment. Clinical stage was roughly evenly balanced between stage II and III, both before and after the amendment. However, the proportion of stage II patients increased subsequent to the amendment. Overall, 96.5% of patients had a staging MRI or ultrasound. Among the 3.5% of patients whose primary tumor was staged only with CT or positron emission tomography/CT were those found to be T4 or to have enlarged regional lymph nodes consistent with metastatic disease and were not required to undergo ultrasound or MRI.

Outcomes for FU Compared With Capecitabine

Outcomes for patients receiving FU or capecitabine (with or without oxaliplatin) are listed in Table 2. Of the patients receiving FU, 17.8% had a pCR compared with 20.7% of those receiving capecitabine ($P = .14$). The proportion of patients who underwent sphincter-sparing surgery was 59.4% in the FU group and 59.3% in the capecitabine group ($P = .98$). Surgical downstaging was also similar (FU, 21.3%; *v* capecitabine, 21.1%; $P = .95$). Of patients receiving both FU and capecitabine, 11.7% of patients experienced grade 3+ diarrhea.

Outcomes for Oxaliplatin Versus No Oxaliplatin

Outcomes for patients receiving either oxaliplatin or no oxaliplatin (with FU or capecitabine) are listed in Table 3. Of the patients receiving oxaliplatin, 19.5% had a pCR compared with 17.8% among patients not receiving oxaliplatin ($P = .42$). Patients not receiving oxaliplatin had higher proportions of sphincter-sparing surgery and surgical downstaging than did patients who did receive oxaliplatin (sphincter-sparing surgery: no oxaliplatin, 61.0% *v* oxaliplatin, 57.8%; $P = .24$; surgical downstaging: no oxaliplatin, 23.5% *v* oxaliplatin, 17.9%; $P = .20$), although these differences were not statistically significant. Patients receiving oxaliplatin had significantly more grade 3+ diarrhea (oxaliplatin, 16.5% *v* no oxaliplatin, 6.9%; $P < .001$).

Fluoropyrimidine-Oxaliplatin Interaction

There were no significant interactions between FU/capecitabine and oxaliplatin for pCR ($P = .99$), sphincter-sparing surgery

Table 3. OX Versus No OX: NSABP R-04*

End Point	No OX (FU or CAPE)			OX (FU or CAPE)			P
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	
pCR	113 of 636	17.8	14.9 to 21.0	125 of 640	19.5	16.5 to 22.8	.42
SSS	388 of 636	61.0	57.1 to 64.8	372 of 644	57.8	53.8 to 61.6	.24
SD	39 of 166	23.5	17.2 to 30.7	30 of 168	17.9	12.4 to 24.5	.20
Grade 3-5 diarrhea	44 of 636	6.9	5.1 to 9.2	106 of 644	16.5†	13.7 to 19.6	<.001

Abbreviations: CAPE, capecitabine; FU, fluorouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin; pCR, pathologic complete response; SSS, sphincter-saving surgery; SD, surgical downstaging.
*Restricted to a postamendment population, groups 3-6.
†Two patients in the CAPE + OX arm died as a result of diarrhea.

Table 4. NSABP R-04 Postoperative Complications of Eligible Patients With Resection (% of patients)

Complication	Before Amendment*		After Amendment*			
	FU (n = 140)	CAPE (n = 131)	FU (n = 308)	FU + OX (n = 309)	CAPE (n = 304)	CAPE + OX (n = 309)
Any complication*	30.7	37.4	37.3	37.5	36.2	40.5
Death	0.7	0.0	0.3	0.7	0.7	0.0
Second operation was necessary	5.0	9.2	6.5	6.2	5.9	5.2
Abdominal wound infection	2.1	3.1	3.6	4.9	3.3	4.2
Perineal wound infection	3.6	3.1	5.5	5.5	4.0	5.2
Wound dehiscence/fistula	2.1	6.1	3.9	3.2	3.0	4.9
Intra-abdominal abscess	2.1	2.3	3.3	4.2	4.3	3.6
Bowel obstruction/ileus	8.6	6.9	7.5	7.8	8.2	9.4
Cardiopulmonary complication	2.1	4.6	2.9	1.6	2.3	3.2
Urinary complication	10.0	13.7	10.4	10.7	7.2	7.8
Anastomotic leak	2.1	3.1	1.3	3.6	3.0	1.6
Other complication	9.3	17.6	16.9	15.5	12.8	17.8

Abbreviations: CAPE, capecitabine; FU, flourouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin.
*There were no significant differences in the proportion of patients reporting any postoperative complications. Testing was completed separately for groups before and after amendment.

($P = .52$), or surgical downstaging ($P = .33$), suggesting the effect of oxaliplatin was independent of the fluoropyrimidine chemotherapy.

Postoperative Complications

Complications occurring from surgery through 30 days after surgery were included in the analysis and are listed in Table 4. Surgical complication data was available for 1,501 patients. The rate of postoperative complications varied from a low of 30.7% for preamendment FU arm to a high of 40.5% for the postamendment capecitabine plus oxaliplatin arm.

Toxicity

Toxicity is listed in Table 5. Diarrhea was the most frequently reported grade 3+ toxicity. The incidence of grade 3+ diarrhea decreased from approximately 16% in the preamendment study arms to 7% in postamendment CVI FU and capecitabine arms when chemotherapy was reduced to only being administered on days radiation therapy was delivered. Significantly more grade 3+ diarrhea occurred in patients receiving oxaliplatin (oxaliplatin, 16.5% *v* no oxaliplatin, 6.9%; $P < .001$). The treatment-related mortality rate was 0.9% for patients receiving oxaliplatin (six of 644 patients), and approximately 41% of patients receiving oxaliplatin with radiation therapy had at least one grade 3 to 5 toxicity.

Chemotherapy Administered

The percentage of eligible patients who started at least one protocol agent was at least 95% on each arm (Table 6). The dose of single-agent FU delivered to postamendment FU patients was significantly higher ($P < .05$), as was the FU dose-intensity ($P < .05$) compared with the dose and dose-intensity of FU received by

Table 5. NSABP R-04: Toxicity as of December 31, 2012 (% of patients)

Toxicity	Before Amendment		After Amendment			
	FU (n = 141)	CAPE (n = 146)	FU (n = 317)	FU + OX (n = 322)	CAPE (n = 319)	CAPE + OX (n = 322)
Greatest toxicity						
Grade 3	28.4	35.6	25.6	37.0	26.6	36.6
Grade 4	2.8	2.7	0.6	2.8	2.2	3.7
Grade 5	0.7	0.7	0.3	0.3	1.3	1.6
Grades 3-5	31.9	39.0	26.5	40.1	30.1	41.9
Toxicity, greatest grade observed						
Diarrhea, grades 3-5	15.6	17.1	6.9	16.5	6.9	16.5
Nausea, grade 3	1.4	2.7	0.3	0.6	1.3	2.2
Vomiting, grade 3	0	3.4	0.3	1.6	0	1.2
Fatigue, grade 3	3.5	6.8	1.3	4.0	2.2	5.9
Abdominal pain, grade 3	2.1	3.4	1.6	2.8	0.3	1.9
Anal pain, grade 3	1.4	5.5	3.2	4.0	3.4	3.1
Radiation dermatitis, grades 3-4	2.1	7.5	2.5	2.2	2.5	1.2
Dehydration, grade 3	5.0	8.2	0.3	2.8	2.2	4.0
Hand-foot syndrome, grade 3	1.4	3.4	0.3	0	0.3	0.3
Peripheral sensory neuropathy, grades 2-4	2.1	2.1	0.6	5.6	2.2	6.5

Abbreviations: CAPE, capecitabine; FU, flourouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin.

Table 6. Dose Administered for Eligible Patients Who Started at Least One Protocol Agent: NSABP R-04

	Before Amendment				After Amendment							
	FU (n = 139)		CAPE (n = 141)		FU (n = 315)		FU + OX (n = 319)		CAPE (n = 319)		CAPE + OX (n = 322)	
Dose	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Percent of eligible patients who started at least one protocol agent	95.2		100.0		96.0		97.6		98.2		98.2	
FU												
Dose delivered, mg/m^2	8,463	8,311 to 8,710			6,057	5,826 to 6,239	5,611	5,476 to 5,745				
Dose-intensity, mg/m^2/wk	1,467	1,411 to 1,509			1,078	1,050 to 1,102	1,018	981 to 1,039				
CAPE												
Dose delivered, mg/m^2			61,414	59,553 to 62,432					44,868	43,982 to 45,593	43,027	42,108 to 44,158
Dose-intensity, mg/m^2/wk			10,576	10,167 to 10,876					7,834	7,658 to 7,971	7,777	7,597 to 7,873
OX												
Dose delivered, mg/m^2							238.1	233.0 to 242.1			237.4	232.4 to 240.4
Dose-intensity, mg/m^2/wk							56.7	55.6 to 57.8			57.5	56.1 to 58.4

Abbreviations: CAPE, capecitabine; FU, flourouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OX, oxaliplatin.

FU-plus-oxaliplatin patients. The dose of single-agent capecitabine delivered to postamendment capecitabine patients was significantly higher ($P < .05$) compared with the dose received by capecitabine-plus-oxaliplatin patients. No other relevant treatment comparisons were statistically significant.

DISCUSSION

This prospective randomized clinical trial of 1,608 patients suggests that there is no significant detrimental effect on pCR, sphincter-sparing surgery, or surgical downstaging when radiation therapy is combined with capecitabine instead of CVI FU for the neoadjuvant treatment of stage II and III rectal cancer among patients eligible for this clinical trial. The similarity in pathologic complete response rates we observed is consistent with previously reported nonrandomized retrospective comparisons of capecitabine and FU combined with preoperative radiation therapy for rectal cancer in which no statistically significant differences in pCR were observed.[20,21]

Toxicity from either single-agent fluoropyrimidine chemotherapy regimen was tolerable. Treatment-related mortality was less than 1% (seven of 923 patients) for patients receiving capecitabine or CVI FU without oxaliplatin. As expected, the most frequent toxicity was diarrhea. The incidence of grade 3 to 5 diarrhea decreased from approximately 16% to 7% when the protocol was amended to administer capecitabine or CVI FU only on the days radiation therapy was delivered (5 days per week), rather than continuously during neoadjuvant treatment. Grade 3 hand-foot syndrome was observed in only 0.3% of patients receiving either capecitabine or CVI FU 5 days per week combined with radiation therapy.

Capecitabine has the advantage of oral administration, without FU's cumbersome continuous intravenous infusion and its attendant risks of infection, bleeding, and thrombosis associated with central venous catheters, and it is clinically tolerable combined with pelvic radiation in the dosage schedule used in patients eligible for this clinical trial.

In contrast, there was no improvement in surgical outcomes when oxaliplatin was added to the fluorinated pyrimidine chemotherapy regimens in our study. Significantly increased grade 3 to 5 diarrhea was observed when oxaliplatin was administered (6.9% *v* 16.5%; $P < .001$). The treatment-related mortality rate was 0.9% for patients receiving oxaliplatin (six of 644 patients), and approximately 41% of patients receiving oxaliplatin with radiation therapy had at least one grade 3 to 5 toxicity. These results are consistent with results of the STAR-01 (Studio Terapia Adiuvante Retto) clinical trial,[22] the ACCORD 12 (Actions Concertées dans les Cancers Colorectaux et Digestifs)/0405 PRODIGE 2 (Routage de Produits Intelligents) clinical trial,[23,24] and the PETACC 6 (Pan European Trial Adjuvant Colon Cancer) clinical trial.[25] Each of these studies evaluated adding oxaliplatin to fluoropyrimidine chemotherapy combined with radiation therapy in the rectal cancer neoadjuvant setting. None of those studies reported improved pCR rates or other measures of surgical outcome, and all of them observed increased toxicity with the addition of oxaliplatin.

The database associated with the NSABP R-04 clinical trial will serve as a rich resource for additional investigations of rectal cancer biology, prognosis, treatment, and survivorship. For example, more than 900 preoperative formalin-fixed paraffin-embedded tumor specimens or unstained slides, more than 100 preoperative tumor specimens preserved in RNA Later, and more than 400 post-treatment surgical specimens are stored in microarrays in the NSABP tissue bank. Genomic studies of these specimens will be of particular interest given the recent characterization of colorectal cancer by the Cancer Genome Atlas network.[26] In addition, a comparative effectiveness study of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer and a quality of life study are underway.[27,28]

Additional follow-up will be required to assess the primary study end point of the NSABP R-04 clinical trial: locoregional tumor relapse at 3 years. It will be of interest to correlate the pCR rate with the locoregional tumor relapse rate, a more clinically relevant parameter of local tumor control. Disease-free and overall survival will also be reported. This additional information should provide a definitive evaluation of the role of capecitabine and oxaliplatin in the preoperative combined-modality therapy of rectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: A pooled analysis. J Clin Oncol 22:1785-1796, 2004

2. Gunderson LL, Jessup JM, Sargent DJ, et al: Revised tumor and node categorization for rectal cancer based on Surveillance, Epidemiology, and End Results and rectal pooled analysis outcomes. J Clin Oncol 28:256-263, 2010

3. Gastrointestinal Tumor Study Group: Prolongation of the disease-free interval in surgically treated rectal carcinoma: Gastrointestinal Tumor

Study Group. N Engl J Med 312:1465-1472, 1985

4. Krook JE, Moertel CG, Gunderson LL, et al: Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 324:709-715, 1991

5. Wolmark N, Wieand HS, Hyams DM, et al: Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 92:388-396, 2000

6. O'Connell MJ, Martenson JA, Wieand HS, et al: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331:502-507, 1994

7. Van Cutsem E, Twelves C, Cassidy J, et al: Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol 19:4097-4106, 2001

8. Mayer RJ: Should capecitabine replace infusional fluorouracil and leucovorin when combined with oxaliplatin in metastatic colorectal cancer? J Clin Oncol 25:4165-4167, 2007

9. Dunst J, Reese T, Sutter T, et al: Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. J Clin Oncol 20:3983-3991, 2002

10. Miwa M, Ura M, Nishida M, et al: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectivity in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274-1281, 1998

11. Rothenberg ML, Oza AM, Bigelow RH, et al: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol 21:2059-2069, 2003

12. André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-2351, 2004

13. Kuebler JP, Wieand HS, O'Connell MJ, et al: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. J Clin Oncol 25:2198-2204, 2007

14. Cividalli A, Ceciarelli F, Livdi E, et al: Radiosensitization by oxaliplatin in a mouse adenocarcinoma: Influence of treatment schedule. Int J Radiat Oncol Biol Phys 52:1092-1098, 2002

15. Frykholm GJ, Glimelius B, Påhlman L: Preoperative or postoperative irradiation in adenocarcinoma of the rectum: Final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 36:564-572, 1993

16. Gerard JP: The use of radiotherapy for patients with low rectal cancer: An overview of the Lyon experience. Aust N Z J Surg 64:457-463, 1994

17. Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731-1740, 2004

18. White SJ, Freedman LS: Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 37:849-857, 1978

19. Wang YH: Fiduciary intervals: What are they? Am Stat 54:105-111, 2000

20. Das P, Lin EH, Bhatia S, et al: Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: A matched-pair analysis. Int J Radiat Oncol Biol Phys 66:1378-1383, 2006

21. Ramani VS, Sun Myint A, Montazeri A, et al: Preoperative chemoradiotherapy for rectal cancer: A comparison between intravenous 5-fluorouracil and oral capecitabine. Colorectal Dis 12:37-46, 2010 (suppl 2)

22. Aschele C, Cionini L, Lonardi S, et al: Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: Pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 29:2773-2780, 2011

23. Gérard JP, Azria D, Gourgou-Bourgade S, et al: Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: Results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 28:1638-1644, 2010

24. Gérard JP, Azria D, Gourgou-Bourgade S, et al: Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 30:4558-4565, 2012

25. Schmoll H-J, Haustermans K, Price TJ, et al: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial. J Clin Oncol 31:212s, 2013 (suppl; abstr 3531)

26. Cancer Genome Atlas Network: Comprehensive molecular characterization of human colon and rectal cancer. Nature 487:330-337, 2012

27. Ganz PA, Lopa SH, Yothers G, et al: Comparative effectiveness of sphincter-sparing surgery (SSS) vs. abdomino-perineal resection (APR) in rectal cancer: Patient reported outcomes (PROs) from NSABP R-04. J Clin Oncol 30:214s, 2012 (suppl 15s; abstr 3545)

28. Yothers G, Ganz PA, Lopa SH, et al: Patient reported outcomes (PROs) comparison of 5-FU and capecitabine (cape) with concurrent radiotherapy (RT) for neoadjuvant treatment of rectal cancer: Results of NSABP R-04. J Clin Oncol 30, 2012 (suppl 9; abstr 391)

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