Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online April 29, 2015

DOI: 10.1634/theoncologist.2015-0106

Title: Phase II Trial of Preoperative Radiation With Concurrent Capecitabine, Oxaliplatin, and Bevacizumab Followed by Surgery and Postoperative 5-Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX), and Bevacizumab in Patients With Locally Advanced Rectal Cancer: 5-Year Clinical Outcomes ECOG-ACRIN Cancer Research Group E3204

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ClinicalTrials.gov Identifier: NCT00321685

Sponsor(s): ECOG-ACRIN

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IRB Approved: Yes

Disclosures

Al Bowen Benson: Sanofi, Genentech/Roche (C/A), Genentech (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Lessons Learned

- The 5-year oncologic outcomes from the trial regimen were excellent. However, the neoadjuvant and surgical toxicity of this regimen was significant and was the primary reason for the low compliance with adjuvant systemic therapy.
- Due to the lack of an improvement in the pathologic complete response rate, the substantial associated toxicity, and the negative phase III trials of adjuvant bevacizumab in colon cancer, this regimen will not be pursued for further study.

Author Summary: Abstract and Brief Discussion

Background

The addition of bevacizumab to chemotherapy improves overall survival for metastatic colorectal cancer. We initiated a phase II trial to evaluate preoperative capecitabine, oxaliplatin, and bevacizumab with radiation therapy (RT) followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab for locally advanced rectal cancer. The purpose of this report is to describe the 5-year oncologic outcomes of this regimen.

Methods

In a phase II Simon two-stage design study, we evaluated preoperative treatment with capecitabine (825 mg/m^2 b.i.d. Monday–Friday), oxaliplatin (50 mg/m^2 weekly), bevacizumab (5 mg/kg on days 1, 15, and 29), and RT (50.4 Gy). Surgery was performed by 8 weeks after RT. Beginning 8–12 weeks after surgery, patients received FOLFOX plus bevacizumab (5 mg/kg)

every 2 weeks for 12 cycles (oxaliplatin stopped after 9 cycles). The primary endpoint was a pathologic complete response (path-CR) rate of 30%. Fifty-seven patients with resectable T3/T4 rectal adenocarcinoma were enrolled between 2006 and 2010.

Results

Of 57 enrolled patients, 53 were eligible and included in the analysis. Forty-eight (91%) patients completed preoperative therapy, all of whom underwent curative surgical resection. Nine patients (17%) achieved path-CR. There were 29 worst grade 3 events, 8 worst grade 4 events, and 2 patient deaths, 1 of which was attributed to study therapy. Twenty-six patients (54%) began adjuvant chemotherapy. After a median follow-up period of 41 months, the 5-year overall survival (OS) rate for all patients was 80%. Only 2 patients experienced cancer recurrence: 1 distant (liver) and 1 loco-regional (pelvic lymph nodes), respectively. Both of these patients are still alive. The 5-year relapse-free survival rate was 81%.

Conclusion

Despite the path-CR primary endpoint of this trial not being reached, the 5-year OS and recurrence-free survival rates were excellent. However, the neoadjuvant and surgical toxicity of this regimen was significant and was the primary reason for the low compliance with adjuvant systemic therapy. Because of the lack of an improvement in the path-CR rate, the substantial associated toxicity, and the negative phase III trials of adjuvant bevacizumab in colon cancer, this regimen will not be pursued for further study.

Discussion

This multi-institutional phase II trial of preoperative radiation therapy (RT) with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab did not meet its primary endpoint of an expected 30% pathologic complete response (path-CR) rate and was associated with significant acute toxicity and surgical complications, primarily wound infection, and wound/fascial dehiscence [1]. However, these initial results are only based on the intensified neoadjuvant component of the treatment regimen and do not reflect any potential gain in tumor control of the study adjuvant systemic therapy.

Despite no increase in path-CR, this phase II trial demonstrated a very low rate of distant recurrence compared with historical controls and trials that incorporated either oxaliplatin or bevacizumab in the neoadjuvant phase but used either no adjuvant therapy or standard adjuvant chemotherapy. This trial continued bevacizumab in the adjuvant phase in addition to standard chemotherapy. Although the role of adjuvant chemotherapy after neoadjuvant chemoradiation therapy (CRT) for patients with locally advanced rectal cancer (LARC) is somewhat controversial [14], there may be a suggestion from these data that intensified adjuvant therapy may have some efficacy in reducing the occurrence of distant relapse. However, this is only hypothesis generating because this trial was not intention-to-treat analyzed and is single-armed with a relatively small patient population (Fig. 1). Also, only 26 of 48 patients (54%) who underwent curative resection started adjuvant chemotherapy, with only 18 (38%) completing all adjuvant cycles per protocol. The elevated rates of acute toxicity during neoadjuvant CRT and surgical complications were the primary cause of not initiating adjuvant chemotherapy. In addition, multiple trials investigating the use of adjuvant bevacizumab in addition to fluoropyrimidine-based chemotherapy for stage II–III resected colon cancer have been negative, thereby calling into question the efficacy of bevacizumab in the adjuvant setting [15, 16]. Finally, although the pilot study of neoadjuvant chemotherapy without RT followed by surgery for selected patients with stage II–III rectal cancer did incorporate bevacizumab, the ongoing PROSPECT trial (N1048, available at http://www.ctsu.org) does not use an antiangiogenic agent for reasons similar to those discussed above [17].

In conclusion, distant recurrence rates with this regimen compared favorably with historical controls and trials that incorporated either oxaliplatin or bevacizumab in the neoadjuvant phase but used either no adjuvant therapy or standard adjuvant chemotherapy. However, the acute CRT and surgical toxicity of this regimen was significant and was the primary reason for the low compliance with adjuvant systemic therapy. Because of the lack of an improvement in the path-CR rate, the substantial associated toxicity, and negative phase III trials of adjuvant bevacizumab in colon cancer, this regimen cannot be recommended for further study.

Trial Information

Disease	Rectal cancer
Stage of disease / treatment	Neoadjuvant
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Complete Response Rate
Secondary Endpoint	Toxicity

Secondary Endpoint	Overall Survival
Additional Details of Endpoints or Study Design	The primary endpoint of this study was pathologic complete response. Fifty-five eligible patients were planned to be accrued in this trial. To allow for 5% ineligibility, 58 patients were planned to be entered. If the treatment was indicative of a true path-CR rate of 30%, we would consider it a promising regimen for further study. A true path-CR rate of less than 15% was considered unpromising. To limit accrual if the treatment was not effective, a two-stage design was used, allowing early stopping if the true path-CR rate was less than 15%. If at least 4 pathologic complete responses were observed among the first 23 eligible patients, 34 additional patients (assuming 32 eligible) would be entered in the second stage. Five of the first 15 patients (33%) who completed preoperative therapy and surgery demonstrated a path-CR after the first stage of accrual, and the decision was made to continue to the second stage. If 12 or more pathologic complete responses are seen in the 55 eligible patients, the treatment will be considered promising.
Investigator's Analysis	Active but too toxic as administered in this study

Drug Information

Drug 1 **Generic/Working name**	Capecitabine
Trade name	Xeloda
Company name	Genentech
Drug class	Antimetabolite
Dose	825 mg/m^2
Route	Oral (PO)
Schedule of Administration	825 mg/m^2 every 12 hours, by mouth, 5 days per week during RT
Drug 2 **Generic/Working name**	Oxaliplatin
Drug class	Platinum compound
Dose	50 mg/m^2
Route	IV
Schedule of Administration	50 mg/m^2, IV over 2 hours, once per week, days 1, 8, 15, 22, 29 of RT
Drug 3 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Genentech
Drug type	Biological
Drug class	Vascular endothelial growth factor (VEGF)
Dose	5 mg/kg
Route	IV
Schedule of Administration	5 mg/kg, IV over 30–90 minutes, once every other week, days 1, 15, and 29 of RT
Drug 4 **Generic/Working name**	Leucovorin
Dose	400 mg/m^2
Route	IV
Schedule of Administration	Adjuvant chemotherapy: 400 mg/m^2, IV over 2 hours, day 1. Cycles were repeated every 2 weeks for a total of 12 (2-week) cycles.
Drug 5 **Generic/Working name**	5-Fluorouracil
Drug class	Antimetabolite
Dose	400 mg/m^2

Route	IV, per push
Schedule of Administration	Adjuvant chemotherapy: 400 mg/m^2, IV bolus, day 1 followed by 2,400 mg/m^2, continuous IV infusion over 46 hours, days 1–2. Cycles were repeated every 2 weeks for a total of 12 (2-week) cycles.
Drug 6 **Generic/Working name**	Oxaliplatin
Drug class	Platinum compound
Dose	85 mg/m^2
Route	IV
Schedule of Administration	Adjuvant chemotherapy: 85 mg/m^2, IV infusion over 2 hours, day 1. Cycles were repeated every 2 weeks for a total of 12 (2-week) cycles, except for oxaliplatin, which was administered for 9 cycles only.
Drug 7 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Genentech
Drug type	Biological
Drug class	VEGF
Dose	5 mg/kg
Route	IV
Schedule of Administration	Adjuvant chemotherapy: 5 mg/kg, IV infusion over 90 minutes, day 1. Cycles were repeated every 2 weeks for a total of 12 (2-week) cycles.

Patient Characteristics

Number of patients, male	36		
Number of patients, female	17		
Stage, *n* (%)			
	Clinical T stage		
	3	49	(92)
	4	4	(8)
	Clinical N stage		
	0	17	(32)
	1	29	(55)
	2	5	(9)
	X	2	(4)
Age	Median (range): 54 (25–83)		
Number of prior systemic therapies	Median (range): 0		
Performance Status: ECOG	• 0 — 41 • 1 — 12 • 2 — • 3 — • unknown —		
Other	**Surgical procedure**	*n*	%
	Curative surgery	48	91
	TME	37	77[a]
	APR	11	
	LAR	15	
	[a]Percentage of 48 patients who underwent curative resection. Abbreviations: APR, abdominoperineal resection; LAR, coloanal anastomosis 22; TME, total mesorectal excision.		
Cancer Types or Histologic Subtypes	Rectal adenocarcinoma 53		

Primary Assessment Method

Control Arm: Rectal Adenocarcinoma

Number of patients enrolled	57
Number of patients evaluable for toxicity	55
Number of patients evaluated for efficacy	53
Evaluation method	Pathologic complete response
Response assessment CR	$n = 9$ 17%

Adverse Events at All Dose Levels

Name	1	2	3	4	5	*Grades 3–5
Neutrophils/granulocytes (ANC/AGC)			16%	2%	0%	18%
Leukocytes (total WBC)			13%	2%	0%	15%
Lymphopenia			13%	2%	0%	15%
Fatigue (asthenia, lethargy, malaise)			13%	2%	0%	15%
Diarrhea			11%	2%	0%	13%
Thrombosis/thrombus/embolism			0%	4%	0%	4%
Weight loss			4%	0%	0%	4%
Dehydration			9%	0%	0%	9%
Aspiration			0%	0%	2%	2%
Nausea			4%	2%	0%	6%
Proctitis			2%	0%	0%	2%
Vomiting			5%	0%	0%	5%
Hemorrhage, CNS			0%	2%	0%	2%
Pain			18%	5%	0%	23%
Death not associated with CTCAE term			0%	0%	2%	2%

Adverse Events Legend
*Only grade 3 and above toxicities were reported.
Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NC, not counted; WBC, white blood cells.

Serious Adverse Events

Name	Grade	Attribution
Death not otherwise specified	5	Unrelated
Death caused by aspiration	5	Probable

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Active but too toxic as administered in this study

Discussion

This multi-institutional phase II trial of preoperative RT with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative FOLFOX and bevacizumab did not meet its primary endpoint of an expected 30% pathologic CR rate and was associated with significant acute toxicity and surgical complications, primarily wound infection, and wound/fascial dehiscence [1]. However, these initial results are only based on the intensified neoadjuvant component of the treatment regimen and do not reflect any potential gain in tumor control of the study adjuvant systemic therapy.

Pathologic CR as a dichotomous assessment is a known robust prognostic factor for both locoregional recurrence and distant metastases after neoadjuvant therapy for LARC [2]. Current guidelines define the optimal interval to surgery after neoadjuvant CRT to maximize the potential for pathologic CR [3]. Pathologic CR has become a surrogate endpoint for long-term oncologic outcome and has been the primary endpoint of recent phase III randomized trials [4]. However, whether pathologic CR leads to improved oncologic outcomes in itself or whether it acts primarily as a marker of more favorable inherent cancer biology is yet unknown. This relates to the heart of the question asked by many neoadjuvant therapy intensification trials for LARC: does increasing the pathologic CR rate lead to improved cancer outcomes?

This same question has been asked in other cancer sites. There have been numerous trials of neoadjuvant chemotherapy in breast cancer in which the primary goal was an increase in the pathologic CR rate. The Food and Drug Administration recently approved a drug in breast cancer based on increases in pathologic CR as a surrogate marker of long term outcome [5]. Despite these efforts and the accrual of thousands of patients, the answer to this fundamental question is still unknown, but evidence is mounting. Two recent meta-analyses of patients with breast cancer who received neoadjuvant chemotherapy confirmed the strong prognostic effect of pathologic CR versus less than CR for event-free survival and OS but were unable to demonstrate that increases in pathologic CR rates led to improvement of these outcomes [6, 7]. In a similar vein, the neoadjuvant combination of lapatinib and trastuzamab with taxane-based chemotherapy led to significantly higher rates of pathologic CR than either biologic agent individually with paclitaxel in a phase III trial for early stage breast cancer [8]. However, when these regimens were tested in the adjuvant setting with the primary endpoint of disease-free survival (DFS) in more than 8,000 randomized patients, there were no statistically significant differences in outcomes between randomized arms [9]. These data call into question whether pathologic CR, and relatedly increases in pathologic CR rate, can be used as a true surrogate for long term outcomes, at least in the breast cancer setting.

The disease control outcomes demonstrated here compare favorably with other trials of neoadjuvant therapy intensification using either bevacizumab or oxaliplatin. Willett et al. [10] conducted a phase II trial in which 32 patients with LARC were treated with neoadjuvant bevazicumab in addition to standard continuous infusion 5-fluorouracil and RT. Surgery was followed by physician choice standard chemotherapy. The pathologic CR rate was 16% (5 of 32 patients), and the 5-year local control and OS rates were both 100%. The 5-year DFS rate was 75% because of 5 patients developing metastases postsurgery. Crane et al. [11] conducted a similar phase II trial in which patients with LARC were treated with neoadjuvant bevacizumab, capecitabine, and RT, followed by surgery and physician choice standard adjuvant chemotherapy. Of 25 patients, 8 (32%) experienced pathologic CR. With a median follow-up period of 22.7 months, the 2-year estimated local recurrence rate was 6% (1 event). Three additional patients developed distant recurrence for a 2-year estimated DFS of 77%. The only phase III trial to publish clinical outcomes of intensified neoadjuvant CRT incorporating oxaliplatin is the ACCORD 12/0405 PRODIGE 2 trial [12]. This trial compared neoadjuvant capecitabine and 45-Gy RT (Cape45) with a regimen of oxaliplatin, capecitabine, and RT to 50 Gy (CapeOx50). Approximately 42% of patients received fluoropyrimidine-based adjuvant chemotherapy. There were no significant differences in any oncologic outcomes (Cape45 vs. CapeOx50): 3-year cumulative incidence of local recurrence, 6.1% versus 4.4%; overall survival, 87.6% versus 88.3%; disease-free survival, 67.9% versus 72.7%. Of 598 total patients, 30 (5%) experienced local recurrence, whereas 139 patients (23%) experienced distant recurrence during a median follow-up period of 36.8 months. The only other trial we are aware of that investigated the combined use of neoadjuvant oxaliplatin and bevacizumab in addition to fluoropyrimidine-based CRT has not reported clinical outcomes [13].

Despite no increase in pathologic CR, this phase II trial demonstrated a very low rate of distant recurrence compared with historical controls and trials that incorporated either oxaliplatin or bevacizumab in the neoadjuvant phase but used either no adjuvant therapy or standard adjuvant chemotherapy. This trial continued bevacizumab in the adjuvant phase in addition to standard chemotherapy. Although the role of adjuvant chemotherapy after neoadjuvant CRT for patients with LARC is somewhat controversial [14], there may be a suggestion from these data that intensified adjuvant therapy may have some efficacy in reducing the occurrence of distant relapse. However, this is only hypothesis generating because this trial was not intention-to-treat analyzed and is single-armed with a relatively small patient population. Also, only 26 of 48 patients (54%) who underwent curative resection started adjuvant chemotherapy, with only 18 (38%) completing all adjuvant cycles per protocol. The elevated rates of acute toxicity during neoadjuvant CRT and surgical complications were the primary cause of not initiating adjuvant chemotherapy. In addition, multiple trials investigating the use of adjuvant bevacizumab in addition to fluoropyrimidine-based chemotherapy for stage II–III resected colon cancer have been negative, thereby calling into question the efficacy of bevacizumab in the adjuvant setting [15, 16]. Finally, although the pilot study of neoadjuvant chemotherapy without RT followed by surgery for selected patients with stage II–III rectal cancer did incorporate bevacizumab, the ongoing PROSPECT trial (N1048, available at http://www.ctsu.org) does not use an antiangiogenic agent for reasons similar to those discussed above [17].

Acknowledgments

This study was conducted by the ECOG-ACRIN Cancer Research Group (Robert L. Comis and Mitchell D. Schnall, Group Co-Chairs) and supported in part by Public Health Service Grants CA180820, CA180794, CA180864, and CA180870 and by the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

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Figure

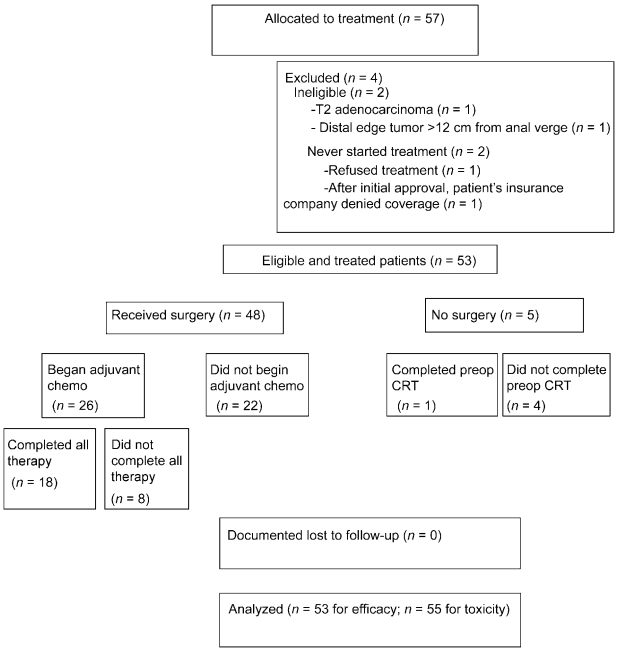

Figure 1. CONSORT diagram with patient flow.
Abbreviations: chemo, chemotherapy; CRT, chemoradiation; preop, preoperative.