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Pre-operative bevacizumab, capecitabine, oxaliplatin and radiation among patients with locally advanced or low rectal cancer: A phase II trial

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ABSTRACT

Background: To evaluate the safety and efficacy of pre-operative chemoradiation, using capecitabine, oxaliplatin and bevacizumab with standard doses of radiation, in patients with high-risk rectal cancer.

Methods: Patients with locally advanced or low rectal cancer were treated with capecitabine 825 mg/m^2 twice daily on days 1–14 and 22–35, oxaliplatin 50 mg/m^2 on days 1, 8, 22 and 29, bevacizumab 5 mg/kg on days 14, 1, 15 and 29, and radiation 50.4 Gy in 28 fractions including boost. Total mesorectal excision was performed 7–9 weeks after chemoradiation. The primary end-point was complete tumour regression (ypT0NX) by central review.

Findings: Forty-two evaluable patients were enrolled, and 38 proceeded to definitive surgery. Eighteen patients (43%) had clinical T4 tumours and/or N2 tumours. Mean relative dose intensity was >90% for all systemic agents, and 97% for radiation. Grade 3/4 diarrhoea occurred in 10 patients (24%) and pain in 4 patients (10%) pre-operatively, while grade 3/4 pain, fatigue and infection were each reported among 5 patients (13%) post-operatively. Re-operation due to complications occurred in 4 patients (11%). Complete tumour regression (ypT0) was seen in 9 patients (23.7%) of which two had N1 disease and the pathological complete response (pCR) rate (ypT0N0) was 18.4%. Central review changed pathologic stage in six cases (16%).

Interpretation: In this study, pre-operative bevacizumab added to oxaliplatin, capecitabine and radiation was safe and resulted in a promising tumour regression rate. Surgical complications were closely monitored and occurred with the expected frequency. Central pathology review should be considered for trials with pathologic response as the primary end-point.

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1. Introduction

Colorectal cancer remains the second most frequent cause of cancer-related death in North America,[1] and one-third of colorectal cancer deaths are due to rectal cancer. Rectal cancer is characterised by locoregional and distant relapse; modern trials report locoregional relapse rates of 6–8% and 5-year disease-free survival (DFS) rates of 54–74% in patients with stage II/III disease.[2–4] Patients generally receive trimodality therapy consisting of pre-operative radiation with or without fluoropyrimidine chemotherapy, followed by surgery and post-operative chemotherapy. Although phase III trials evaluating post-operative oxaliplatin in rectal cancer have not yet been reported, adjuvant combination chemotherapy with oxaliplatin plus a fluoropyrimidine is commonly recommended for stage II/III rectal cancer based on benefits reported in stage II/III colon cancer.[5,6]

Patients with low or locally-advanced rectal tumours are at greater risk of locoregional and – among patients with advanced tumours – distant relapse.[7,8] These patients are generally treated with combined-modality therapy with 5-fluorouracil (5-FU) or capecitabine plus radiation to maximise downstaging, decrease the risk of locoregional relapse, increase the rate of sphincter-sparing surgery and provide early exposure to systemic therapy in order to decrease the risk of distant relapse.

Numerous phase II trials have demonstrated safety and high pathological complete response (pCR) rates with oxaliplatin, 5-FU or capecitabine, and radiation.[9,10] Preoperative chemoradiation with daily capecitabine 825 mg/m^2 twice daily plus weekly oxaliplatin 50 mg/m^2 in weeks 1, 2, 4 and 5 led to a 16% pCR rate and grade 3/4 diarrhoea in 12% of 103 patients with stage II/III rectal cancer.[9] Two recent phase III studies, STAR-01 and ACCORD 12, failed to demonstrate an improvement in pCR rates when oxaliplatin was added to radiation and a fluoropyrimidine.[11,12] Distant relapse and overall survival, the primary end-point of the STAR-01 study,[12] have not yet been reported.

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor. Bevacizumab plus 5-FU-based chemotherapy improves overall survival in patients with metastatic colorectal cancer;[13] however, in two recent trials of adjuvant bevacizumab plus oxaliplatin-based chemotherapy in stage II/III colon cancer, chemotherapy plus bevacizumab did not demonstrate any benefit over chemotherapy alone.[14,15] In an early trial of bevacizumab plus infusional 5-FU and radiation in stage II/III rectal cancer, bevacizumab administered as a single agent 14 d prior to chemoradiation induced normalisation of tumour vasculature and reduced interstitial fluid pressure.[16] A high rate of tumour regression, 100% 5-year local control and overall survival were observed.[17] A number of phase II and randomised phase II trials are currently underway to explore the benefit of neoadjuvant bevacizumab in rectal cancer.

This is the final safety and efficacy report from a phase II trial of bevacizumab plus capecitabine and oxaliplatin, administered concurrently with standard doses of radiation to patients with stage II–IV low or locally-advanced rectal cancer. The primary end-point of this study is pCR, as defined by complete tumour regression on central review (ypT0).

2. Patients and methods

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients in the study. Approval of the protocol was obtained from the local Research Ethics Board at each site.

2.1. *Eligibility criteria and pre-treatment evaluation*

Patients had locally-advanced or low rectal adenocarcinoma, clinical stage II–IV (American Joint Committee on Cancer version 6). The rectum was defined as the segment of large bowel <15 cm from the anal verge. Locally advanced tumours were defined as potentially resectable T4 lesions, fixed or partially-fixed T3 lesions, or any T-stage with N2 lymphadenopathy or demonstrating pelvic adenopathy adjacent to or invading the mesorectum. Low rectal tumours were defined as tumours <6 cm from the anal verge and at least T3 or T4. Endorectal ultrasound or pelvic MRI was used to define T category and N category. MX and M1 disease were permitted provided definitive primary tumour resection was planned. Adequate organ function (absolute neutrophil count $\geqslant 1.5 \times 10^9$, platelets $\geqslant 100 \times 10^9$, creatinine $\leqslant 1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase $\leqslant 2.5 \times$ ULN, bilirubin $\leqslant 1.5 \times$ ULN, albumin $\geqslant 25$ g/L) and normal coagulation parameters were required. Patients were $\geqslant 18$ years of age and had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Patients with uncontrolled hypertension, clinically significant cardiac disease, CNS metastasis or having undergone major surgery within 28 d of trial therapy were excluded. Abdominal and pelvic computed tomographic (CT) scans and chest imaging were required within 30 d of enrollment.

2.2. *Treatment*

2.2.1. *Systemic therapy*

Bevacizumab 5 mg/kg was administered over 90 min 2 weeks [day 14] prior to the start of radiation (Fig. 1). Subsequent bevacizumab (5 mg/kg) infusions were given on days 1, 15 and 29 over 30–60 min. Oxaliplatin 50 mg/m^2 was administered over 1 h on days 1, 8, 22 and 29. Capecitabine 825 mg/m^2 was taken orally twice daily on days 1–14 and 22–35. The first dose was to be taken 2 h prior to radiation in the morning and the second dose 12 h later.

Adverse events were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Unless otherwise noted, for non-haematologic toxicity grade $\geqslant 3$, treatment with all three drugs was withheld until resolution of toxicity to grade $\leqslant 1$. In the case of grade 3 stomatitis, hand–foot syndrome and diarrhoea, the capecitabine dose was reduced 1 dose level; for grade 4 events it was reduced 2 dose levels. If chemotherapy was discontinued due to toxicity then bevacizumab could be continued.

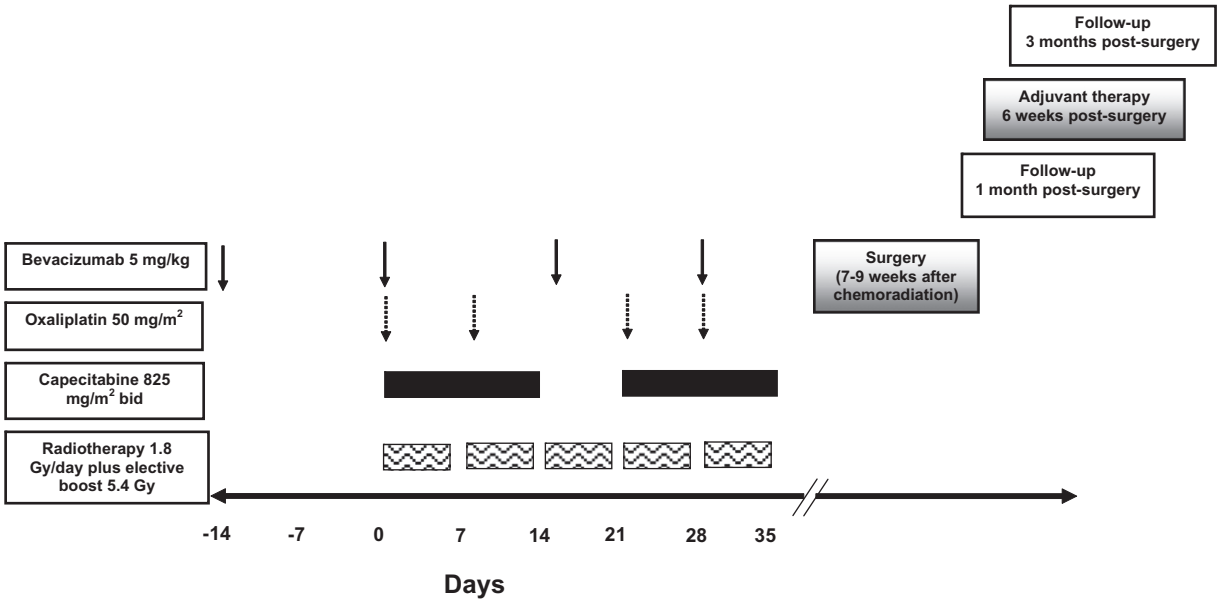

Fig. 1 – Schematic diagram of study treatment.

Patients were seen on day (–)14 and weekly during radiation therapy. The post-operative adjuvant chemotherapy regimen was selected by the investigator. Adjuvant therapy could commence no earlier than 6 weeks post-operatively; the cumulative dose of oxaliplatin (pre- and post-operative) was limited to 1,020 mg/m^2.

2.2.2. *Radiation therapy*

On days 1–35, 45 Gy of pelvic radiation was delivered from Monday to Friday, followed by an elective boost of 5·4 Gy to all identifiable disease, with a margin of $\geqslant$2 cm. The total dose could not exceed 50.4 Gy (daily fraction size 1.8 Gy). If chemotherapy was interrupted due to toxicity, consideration was given to holding radiation until toxicity resolved to grade $\leqslant$1.

2.2.3. *Surgery*

Total mesorectal excision (TME) was performed no earlier than 7 weeks after completion of radiation (8 weeks after last dose of bevacizumab) and no later than 9 weeks after completion of radiation. Surgery was required for all patients irrespective of the extent of clinical response. Post-operative visits were planned at 1 and 3 months.

2.3. *Pathology*

Surgical specimens were processed and reviewed at the local institution and centrally reviewed for response. Once the mesorectal excision was evaluated, the specimen was opened and tumourous and fibrotic areas described. For obvious residual tumour, a minimum of four tissue blocks were processed and an additional large area of tumour was embedded. When no tumour was visible, the whole area was sliced and embedded. Presence of tumour, fibrosis and other chemoradiation-related changes were semi-quantitatively described at central review by the trial pathologist (Dr. Zhou). Regression was graded 0–4 on the scale established by Dworak et al.[18] and validated by Rödel et al.[9] pCR was defined as the complete absence of any viable tumour in the rectal specimen (ypT0).

2.4. *Study design and statistical methods*

Based on previous trials, a conservative estimate of pCR rate for patients with T3/4 or node-positive rectal cancer treated with a fluoropyrimidine, oxaliplatin and radiation is approximately 15%.[9,11] If a pCR rate of $\geqslant$25% was seen with the addition of bevacizumab to capecitabine and oxaliplatin, this would be an acceptable rate to justify a subsequent phase III trial. A one-stage phase II design[19] was used to test the null hypothesis that the pCR rate of evaluable patients was $\leqslant$15%; the alternate hypothesis was a pCR rate of $\geqslant$30%. Setting alpha at 0·1 and beta at 0·2, the study needed to enrol a minimum of 37 patients. The null hypothesis would be rejected if 9 or more patients experienced a pCR. Sample size calculations assumed that a 1-sided test of proportions would use the normal approximation approach.

The primary end-point, pCR rate, was calculated and the 90% confidence bounds were estimated using normal approximation. Secondary end-points were safety, rate of sphincter-sparing surgery in patients deemed to require an abdominoperineal resection prior to neoadjuvant therapy, post-surgical complication rate and complete resection rate; 95% confidence intervals (CI) were calculated for all secondary end-points based on the normal approximation. Rate of re-operation was ascertained from operative notes, discharge summaries and during protocol-specified 1- and 3-month post-operative visits.

The safety analysis was conducted on an intention-to-treat basis and included all patients who initiated trial ther-

apy. The efficacy analysis included all patients who proceeded to surgery.

2.5. Role of the funding source

The sponsors of the study were Hoffmann-La Roche, Canada and Sanofi Aventis, Canada. The sponsors had no role in study design, data collection, analysis or writing of the paper and decision to submit to publication.

3. Results

Between January 2007 and May 2009, 43 patients were accrued from six Canadian institutions. One patient chose not to commence therapy and was excluded. Forty-two evaluable patients initiated therapy; of these, 38 proceeded to surgery and were evaluable for tumour regression. Patient baseline characteristics are summarised in Table 1.

3.1. Treatment and dose modifications

Among 42 patients commencing therapy, dose reductions, interruptions or discontinuations occurred in 16 patients (38%). The mean relative dose intensity (RDI) ratio, defined as delivered/planned dose, was high for bevacizumab (0.95), oxaliplatin (0.97) and capecitabine (0.91). The median radiation dose was 5,040 cGy and the mean RDI was 0.97. Thirty-five patients received the full dose of radiation, four had a dose reduction due to adverse events, two did not receive the elective boost and one did not receive an elective boost due to equipment malfunction. Thirty-eight patients proceeded to surgery; four did not proceed to surgery for clinical reasons ($n = 3$) or due to a complete clinical response ($n = 1$).

Table 1 – Baseline characteristics of 42 evaluable patients with locally advanced or low adenocarcinoma of the rectum.

Characteristic		(N = 42)
Gender, *n*	Male:Female	33:9
Age, years	Median (range)	61.0 (37.7–83.7)
ECOG performance status, *n*	0:1	31:11
Body surface area, m^2	Median (range)	2.00 (1.43–2.50)
T stage, *n*	T2	1
	T3	32
	T4	9
N stage, *n*	Nx	3
	N0	8
	N1	19
	N2	12
M stage, *n*	Mx	7
	M0	29
	M1	6
Distance from anal verge, cm	Median	5
	Range	0.4–13.5
	Lower third (⩽6)	25
	Middle third (6–12)	12
	Upper third (>12)	2
	Unknown	3

ECOG, Eastern Cooperative Oncology Group.

3.2. Safety

Adverse events were grouped by occurrence pre-operatively, post-operatively or, for patients not undergoing surgery, during follow-up. The most common grade 3/4 pre-operative toxicities were diarrhoea (24%), pelvic pain (10%) and fatigue (10%) (Table 2). The most common grade 3/4 post-operative toxicities were pain, fatigue and infection (all 13%).

In Table 3, pre- and post-operative toxicities of interest are listed, including related adverse events and serious adverse events. Pre-operatively, 7 patients (17%) experienced bleeding, with no reported grade 3/4 events. Pelvic infection was observed in 3 patients (7%), of which 1 (2%) was grade 3/4. No fistulae or perforations were observed. Post-operative complications were documented among 24 of 38 patients

Table 2 – Most common adverse events among 42 patients receiving pre-operative bevacizumab, capecitabine and oxaliplatin in combination with radiation and 38 patients who proceeded to surgical resection.

Adverse events[a]	No. of patients (%)	
	All events	Grade 3/4 events
Pre-operative events, N = 42		
Pain	37 (81)	4 (10)
Diarrhoea	32 (76)	10 (24)
Fatigue	27(64)	4 (10)
Neuropathy, sensory	26 (62)	0 (0)
Nausea	21 (50)	0 (0)
Haemorrhage, gastrointestinal	19 (45)	0 (0)
Constipation	17 (41)	1 (2)
Insomnia	16 (38)	0 (0)
Weight loss	13 (31)	0 (0)
Hypertension	12 (29)	2 (5)
Anorexia	12 (29)	0 (0)
Proctitis	11(26)	0 (0)
Rash, hand-foot syndrome	11 (26)	3 (7)
Urinary frequency/urgency	10 (24)	0 (0)
Mood alteration	9 (21)	0 (0)
Post-operative events, N = 38		
Pain	32 (84)	5 (13)
Fatigue	28 (74)	5 (13)
Weight loss	21 (55)	2 (5)
Neuropathy, sensory	14 (37)	0 (0)
Infection	13 (34)	5 (13)
Nausea	13 (34)	0 (0)
Hypertension	11 (29)	2 (5)
Mood alteration	11 (29)	0 (0)
Insomnia	10 (26)	0 (0)
Anorexia	8 (21)	0 (0)
Constipation	8 (21)	0 (0)
Diarrhoea	8 (21)	0 (0)
Anaemia	7 (18)	1 (3)
Vomiting	7 (18)	0 (0)
Leak (including anastomotic)	6 (16)	2 (5)

Note: One patient with post-operative grade 2 sensory neuropathy developed grade 3/4 sensory and motor neuropathy of the lower extremities reported by SAE at month 5.

[a] An adverse event was considered attributable to bevacizumab, capecitabine, oxaliplatin, radiation or surgery if it was deemed possibly, probably or definitely related.

Table 3 – Frequency of pre-defined toxicities of interest, including related adverse events and all reported serious adverse events (SAEs) in the pre- and post-operative periods. Events that were possibly, probably or definitely attributed to bevacizumab were considered bevacizumab related.

Event, *n* (%)	Pre-operative (*N* = 42)				Post-operative (*N* = 38)			
	Related toxicities (All)		Bevacizumab related		Related toxicities (All)		Bevacizumab related	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Bleeding	7 (17)	0	6 (14)	0	4 (11)	1 (3)	2 (5)	1 (3)
Fistulae	0	0	0	0	3 (8)	0	2 (5)	0
Pelvic infection	3 (7)	1 (2)	1 (2)	1 (2)	11 (29)	6 (16)	4 (11)	2 (5)
Perforation	0	0	0	0	0	0	0	0
Delayed healing	–	–	–	–	7 (18)	3 (8)	6 (16)	3 (8)
Anastomotic leak	–	–	–	–	6 (16)	2 (5)	4 (11)	1 (3)
Re-operation	–	–	–	–	4 (11)	–	2 (5)	–

(63%) including pelvic infection in 11 patients (29%). Delayed healing was observed in 7 patients (18%), and was grade 3/4 in 3 patients (8%). Six patients had an anastomotic leak (16%), two (5%) of whom were grade 3/4. Grade 1 or 2 fistulae was observed in 3 patients (8%). There were no perforations. A total of four patients (11%) required a second surgery, three to drain pelvic infections or abscesses and one for drain placement for an anastomotic leak.

3.3. *Efficacy*

R0 resection was possible in 92% of patients; the remainder underwent R1 surgery (Table 4). Among 24 patients with low rectal tumours, seven (29.2%; 95% CI: 11.0%, 47.4%) had sphincter-sparing surgery. A pCR, as defined by complete regression of the tumour (ypT0), was documented in 9 patients (23.7%; 1-sided 90% lower CI bound = 14.8%; *p*-value for test of *H*0 = 0.104). A pCR defined as ypT0N0 was observed in seven cases (18.4%; 95% CI: 6.1%, 30.7%). Two patients with complete tumour regression (Dworak grade 4) had nodal metastases.

Table 4 – Surgical parameters and tumour response of 38 patients treated with neoadjuvant capecitabine, oxaliplatin, bevacizumab and standard doses of radiation.

Parameter	Patients (%)
Surgery type	
Anterior resection	19 (50%)
Abdominoperineal resection	18 (47%)
Other (protocolectomy)	1 (3)
Sphincter preservation among patients with low tumours	7/24 (29.2)
Resection status	
R0	35 (92.1)
R1	3 (7.9)
R2	0
Pathologic complete response (pCR)	
pT0	9/38 (23.7)
pT0N0	7/38 (18.4)
Dworak's tumour regression grade	
4 (complete regression)	9 (23.7)
3 (>50% of tumour mass)	12 (31.6)
2 (⩾25–50% of tumour mass)	15 (39.5)
1 (<25% of tumour mass)	2 (5.3)
0 (no regression)	0

Table 5 – Changes to pathological stage on central pathology review of specimen slides.

Institution stage	Central stage	Impact of review
T1N1	T2N1	Upstaged
T0N0	T3N0	Upstaged
T3N0	T2N0	Downstaged
T2N0	T0N0	Downstaged
TisN1	T0N1	Downstaged
T3N2	T3N1	Downstaged

Central review of tumour slides resulted in a higher pathologic stage in two cases and a lower stage in four cases (see Table 5). Central pathology review was mandated by the study protocol and resulted in a change in pathological diagnosis in 6 of 38 cases (16%), three of which affected the primary end-point. In one case a tumour defined as ypT0N0 by the local institution was classified ypT3N0 centrally. Two others were downstaged from ypT2N0 to ypT0N0 and from ypTisN1 to ypT0N1, respectively.

4. Discussion

In this multicenter phase II trial, a high mean RDI was achieved for bevacizumab plus capecitabine, oxaliplatin and standard doses of pre-operative radiation. A high pCR rate was achieved, but did not meet the predefined efficacy end-point. Pre-operative toxicity was similar to that reported in phase II/III trials of chemoradiation using 5-FU and oxaliplatin. Analysis of expected post-operative events revealed a high rate of infection, while other complications occurred at expected rates.

The primary end-point of this study was pCR, as defined by complete tumour regression, ypT0. The prognostic value of pCR has been described in a recent meta-analysis of 3,105 patients treated with pre-operative chemoradiation,[20] where 5-year crude DFS rates were 83.3% and 65.6% for patients with and without pCR tumours, respectively ($p < 0.0001$). The prognostic value of pCR defined by complete tumour regression, the primary end-point in this trial, was further established

Table 6 – Summary of reported post-operative complications and pathologic response rate in select phase II/III trials among patients treated with pre-operative chemoradiotherapy. Radiation dose was 5040 Gy in fractions of 180 cGy/day unless otherwise noted.

Study	Phase	N	Therapy	Post-operative complications						pCR (%)
				All (%)	Delayed healing (%)	Anas leak (%)	Re-operation (%)	Fistula (%)	Pelvic infx[a] (%)	
Bujko et al.[28]	III	157	Bolus 5FU/LV × 5d/w 1, 5	22	21[b]	9	11	0	21[b]	16
Sauer et al.[4]	III	421	Infusion 5FU × 5 x5d/w 1, 5	36	10	11	–	–	–	8
Gérard et al.[22,c]	III	375	Bolus 5FU/LV × 5d/w 1, 5	21	–	–	–	7	–	12
Gérard et al.[11]	III	287	Capecitabine × 5d/w 1–5	33[d]	–	–	13	–	–	14
Gérard et al.[11]	III	287	Capecitabine x5d/w 1–5 Oxaliplatin ×1/w 1–5	31[d]	–	–	13	–	–	19
Rödel et al.[9]	II	103	Capecitabine w 1, 2, 4, 5 Oxaliplatin × 1/w1, 2, 4, 5	43	18	12	6	6	5	16
Willett et al.[17]	II	32	Infusion 5FU w 2, 3, 4 Bevacizumab × 1/w 1, 2, 3, 4	–	6	3	–	–	16	–
Crane et al.[27]	II	25	Capecitabine × 5d/w 1–5 Bevacizumab × 1/w 1, 3, 5	32	25	8	12	–	4	32
Current study	II	38	Capecitabine w 1, 2, 4, 5 Oxaliplatin × 1/w 1, 2, 4, 5 Bevacizumab × 1/w 2, 1, 3, 5	63	18	16	11	8	29	18 (24 pT0)

5FU, 5-fluorouracil; anas, anastomotic; d, day; infx, infection; LV, leucovorin; pCR, pathological complete response; w, week.

[a] Including abscess.

[b] Combined healing delay and/or wound infection.

[c] Radiotherapy 45 GY/25 fractions.

[d] Medical postoperative toxicity and second surgery.

in a review of patients in a phase III trial[21] of pre-operative 5-FU chemoradiation. Five-year DFS was 86% for patients with tumours classified as tumour regression grade (TRG) 4 (ypT0), 75% for patients with grouped TRG 2 + 3 tumours and 63% for patients with grouped TRG 0 + 1 tumours ($p = .006$). Among patients classified as TRG 4, 10% had N+ disease. pCR defined as complete tumour regression (ypT0) has also been used as the primary end-point in previous phase III trials.[22–24] In the European Organization of Cancer 22921 study,[23,24] nodal involvement was found in 9 of 90 (10%) patients with ypT0 tumours. In the current study, 2 of 9 patients with ypT0 tumours had N1 disease, leading to the discordance between the protocol-defined pCR rate (23.7%) and pCR defined as ypT0N0 (18.4%). This may suggest that some nodes removed at surgery were outside the radiation field.[25]

Central pathology review was mandated by the study protocol and resulted in a change in pathological diagnosis in 6 of 38 cases (16%), three of which affected the primary end-point. While the frequency of change in pathological diagnosis as a result of central review has been reported in other tumour sites,[26] there is little published information about the impact of central review in clinical trials where pathological downstaging is the primary end-point. Results of the current study suggest that, for single-arm phase II trials where pCR is the primary end-point, central review should be considered.

A relevant end-point of this trial is the rate of peri-operative complications. While previous phase II trials have described the safety of radiation with fluoropyrimidines and bevacizumab,[17,27] this is the first reported phase II study of bevacizumab combined with capecitabine, oxaliplatin and radiation. Bleeding, fistulae, pelvic infection and perforation were monitored throughout the study. With the exception of one patient with a grade 3/4 pelvic infection, no such grade 3/4 events occurred in the pre-operative period.

In Table 6, post-operative complication rates from selected phase II/III trials are compared with rates observed in the current study. Studies included patients with rectal cancer treated pre-operatively with standard doses of radiation plus either fluoropyrimidines alone or in combination with oxaliplatin and/or bevacizumab, and were required to provide sufficient information about post-operative complications. Rates of anastomotic leak and pelvic infections were numerically higher in the current study but delayed healing and fistulae occurred with similar frequency compared to other studies. The rate of re-operation due to post-operative complications were similar to that identified previously (11% vs. 11–13%).

A general trend of increased post-operative complications is observed as more systemic agents are added to pre-operative chemoradiation (Table 6). Compared to two phase II studies of 5-FU/capecitabine plus bevacizumab, toxicity was higher in the current study, in which therapy included oxaliplatin. When compared to phase II/III trials of capecitabine and oxaliplatin, post-operative toxicity reported in this trial was also higher. This may be partially due to more comprehensive reporting of toxicity in phase II versus phase III trials, and highlights the importance of collecting this information. Increased pre-operative toxicity was reported with oxaliplatin in the ACCORD 12 and STAR trials,[11,12] but post-operative toxicity was similar between the arms. As surgery often takes place at locations or institutions different from the site of chemoradiation administration, not all information may be captured or is only reported retrospectively.

A trend to higher pCR rates as more systemic agents are added to standard chemoradiation is also observed (Table 6). Phase III trials of capecitabine/5-FU-based chemoradiation reported pCR rates of 8–16%, while the experimental arms of phase III trials with similar patients reported non-significantly higher rates of 16–19% when oxaliplatin was added. In the ACCORD 12 trial, pCR was the primary end-point whereas in the STAR trial pCR was the secondary end-point (the primary end-point was overall survival).[11,12] The observed pCR of 23.7% in the current trial is promising with a p-value of 0.104 for rejecting the null hypothesis. The results of the current study may be affected by the high proportion of node-positive (73%) or locally advanced patients (43%) who had either T4 and/or N2 tumours.

While modern rectal cancer trials with trimodality therapy have reported locoregional recurrence rates of only 4–8%, 5-year DFS rates remain low at 59–77%,[4,22,23] highlighting the importance of both locoregional and distant disease control. More recent trials have set out to evaluate the feasibility of 'induction' pre-operative chemotherapy prior to or instead of chemoradiation.[29,30] Given the survival benefit of oxaliplatin in stage III colon cancer,[5,6] oxaliplatin will remain a relevant agent in the pre- or post-operative management of high-risk rectal cancer, unless subsequent trials provide evidence to the contrary.

The role of bevacizumab is as yet undefined. In the adjuvant treatment of colon cancer, two trials have now reported no benefit from the addition of bevacizumab to standard oxaliplatin-based chemotherapy.[14,15] The benefit of neoadjuvant bevacizumab is likely to be evaluated separately from the adjuvant setting, as pre-operative downstaging and improvement in locoregional therapy are relevant considerations for patients with rectal cancer. While results of this study do not justify a phase III trial of this regimen, the results of numerous other studies of neoadjuvant bevacizumab are awaited.

Contributions of authors

Hagen Kennecke was responsible for study design, protocol development, patient enrollment, data analysis and writing of the manuscript. John Hay, Scott Berry, Keith Tankel, Jacob Easaw and Sanjay Rao contributed to study design and enrolled patients into the study. Chen Zhou was the study pathologist and centrally reviewed all pathology specimen slides. Jacqueline Post was the chief study monitor at Ozmosis Research Inc. The manuscript was reviewed by all co-authors.

Conflict of interest statement

Hagen Kennecke has received grant research funding, honoraria and travel grant from Sanofi Aventis Canada and Hoffmann-La Roche Canada within the past 3 years. He does not have any relevant stock ownership, employment, paid testimony or patent applications.

Scott Berry has consultant/advisory relationships with Sanofi Aventis and Hoffmann-La Roche, and has received honoraria from Sanofi Aventis and Hoffmann-La Roche. He has no employment or leadership position, stock ownership, research funding, expert testimony or other remuneration disclosures.

Ralph Wong has consultant/advisory relationships with Sanofi Aventis and Hoffmann-La Roche, and has received honoraria from Sanofi Aventis and Hoffmann-La Roche. He has no employment or leadership position, stock ownership, research funding, expert testimony or other remuneration disclosures.

Chen Zhou has no disclosures.

Keith Tankel has no disclosures.

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Jacqueline Post has no disclosures.

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