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Effect of Aflibercept Plus Modified FOLFOX6 Induction Chemotherapy Before Standard Chemoradiotherapy and Surgery in Patients With High-Risk Rectal Adenocarcinoma

The GEMCAD 1402 Randomized Clinical Trial

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IMPORTANCE Preclinical studies suggest that a vascular endothelial growth factor (VEGF) blockade may play a role in the preoperative treatment of rectal adenocarcinoma; however, how to combine anti-VEGF drugs with neoadjuvant chemotherapy (CT) and/or chemoradiotherapy (CRT) remains controversial.

OBJECTIVE To study the effect of aflibercept plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) induction CT prior to standard CRT and total mesorectal excision (TME) surgery in patients with high-risk rectal adenocarcinoma.

DESIGN, SETTING, AND PARTICIPANTS In the Grupo Español Multidisciplinar En Cancer Digestivo (GEMCAD) 1402 phase 2 randomized clinical trial, 180 patients aged 18 to 75 years, identified by centrally reviewed magnetic resonance imaging to have mrT3c-d/T4/N2 rectal adenocarcinoma, were enrolled from 20 treatment centers in Spain between January 2015 and March 2017. Patients were randomized in a 2:1 treatment to control arm ratio. The primary end point was evaluated at 2 interim and 1 final analyses. The study was designed to perform hypothesis testing at $\alpha = .2$ and $\beta = .2$. A 2-sided *P* value of <.1984 in the final analysis of the intention-to-treat population was the threshold for considering the experimental treatment to be more effective than the control.

INTERVENTIONS Patients received neoadjuvant mFOLFOX6 with (arm A; n = 115) or without (arm B; n = 65) aflibercept, 4 mg/kg (every 2 weeks, 6 cycles, and 3 months) prior to standard CRT and TME surgery.

MAIN OUTCOMES AND MEASURES The primary end point was a pathologic complete response (pCR) (ypTONO). Secondary end points included toxic effects, surgical morbidity, R0 resections, compliance, and 3-year disease-free survival.

RESULTS For the 115 patients who received treatment with mFOLFOX6 plus aflibercept, the median (range) age was 60 (32-75) years, 77 men (66.9%) and 38 women (33.0%). For the 65 patients who received induction CT treatment with only mFOLFOX6, the median (range) age was 65 (39-75) years, 39 men (60.0%) and 26 women (40.0%). The pCR rate in the intention-to-treat population was 22.6% (95% CI, 15.3%-31.3%) in arm A and 13.8% (95% CI, 6.5%-24.6%) in arm B (*P* = .15). The main differential toxic effect was grade 3/4 hypertension during the induction phase. Postoperative complications were similar in both arms (15.5% in arm A and 12.9% in arm B). A total of 106 patients (92.1%) in arm A and 63 (96.9%) in arm B received all treatment cycles.

CONCLUSIONS AND RELEVANCE The study met its primary end point. The findings suggest that adding aflibercept to an induction regimen using mFOLFOX6 plays a role in increasing the pCR rate in patients with high-risk rectal adenocarcinoma, without substantially increasing surgical complications. The GEMCAD 1402 trial provides a rationale for phase 3 trials.

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Supplemental content

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Preoperative induction chemotherapy (CT) followed by chemoradiotherapy (CRT) and total mesorectal excision (TME) surgery, together referred to as total neoadjuvant therapy, is an accepted treatment option for clinical stage high-risk rectal adenocarcinoma,[1] and results in fewer toxic effects and improved compliance than that obtained by the traditional approach of CRT followed by TME and adjuvant CT.[2-4] Building on this concept, the integration of new drugs that have demonstrated improved outcomes in advanced diseases, either during the induction period and/or the CRT, is a logical next step and an active area of research.[5]

Several preclinical studies have shown that vascular endothelial growth factor (VEGF) blockade reduces interstitial fluid pressure or edema, while transiently increasing perfusion, oxygenation, and drug delivery in human tumor xenografts. These changes in the tumor microenvironment, which were first proposed in 2001, are a result of vessel normalization.[6] Subsequently, Willet et al.[7] demonstrated that developing a VEGF blockade with bevacizumab led to similar changes in patients with rectal adenocarcinoma. Given that tumor oxygenation enhances the radiation response, the combination of anti-VEGF drugs with preoperative CRT has become an active area of investigation, where the optimal timing of VEGF administration in relation to radiotherapy and surgery requires elucidation. Several phase 2 studies have reported the use of bevacizumab in the preoperative treatment of locally advanced rectal adenocarcinoma, and a recent meta-analysis estimated a pathologic complete response (pCR) rate of 27.0% in neoadjuvant therapy regimens containing bevacizumab.[8] A single-arm phase 2 trial reported a pCR rate of 36.0% for an induction CT regimen comprising capecitabine plus oxaliplatin (CAPOX), and bevacizumab, followed by CRT combined with bevacizumab, for the treatment of CT3-T4 rectal adenocarcinoma. This study used the same radiologic criteria for patient selection as in our GCR-3 study,[2] in which we obtained a pCR rate of 14.0% in the induction arm by using a similar regimen but without bevacizumab.[2] However, consistent with other studies using bevacizumab during CRT, an unacceptable rate of postoperative morbidity was observed.[9]

Aflibercept (ziv-aflibercept in the United States), an antiangiogenic agent that acts as a soluble receptor, binds to human VEGF-A, VEGF-B, and the placental growth factor. It complexes with the VEGF and interferes with its biological actions, thus preventing its interaction with receptors on endothelial cells.[10] Aflibercept combined with fluorouracil, leucovorin, and irinotecan (FOLFIRI) achieved a statistically significant improvement in survival and response rates in the second-line treatment of advanced colorectal adenocarcinoma.[11]

These preclinical and clinical findings led us to hypothesize that the antiangiogenic properties of aflibercept may improve the pCR rate, and that by increasing the interval between CT and TME surgery, the postoperative morbidity would not become inferior. We therefore designed a randomized phase 2 trial of induction CT with mFOLFOX6 with or without aflibercept, followed by conventional CRT and TME surgery, for the treatment of high-risk rectal adenocarcinoma. This study presents the results for the primary end point (ie, pCR rate) and the early secondary end points (ie, toxic effects, compliance, surgical morbidity, R0 resection rate, circumferential margin-free, and tumor regression grades) of the trial.

Key Points

Question What is the effect of an induction chemotherapy treatment with aflibercept plus a modified schedule of fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) followed by standard chemoradiotherapy and total mesorectal excision surgery in patients with magnetic resonance imaging–defined high-risk, locally advanced rectal adenocarcinoma?

Findings In this phase 2 randomized clinical trial of 180 patients with rectal adenocarcinoma, the proportion achieving a pathologic complete response was 22.6% with aflibercept vs 13.8% without.

Meaning This study provides information on the design of larger trials with agents targeting the vascular endothelial growth factor for treating locally advanced rectal adenocarcinoma.

Methods

This study (GEMCAD 1402) was an investigator-initiated, open-label, randomized phase 2 trial performed at 20 treatment centers in Spain. The trial protocol is available in Supplement 1. The trial protocol was approved by the respective ethics committees of all participating institutions, and written informed consent was obtained from all patients prior to participation in the study. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligibility and Pretreatment Evaluation

The eligibility criteria included patients aged 18 to 75 years with histologically confirmed rectal adenocarcinoma, with an inferior margin distal border below the peritoneal reflection, and considered high-risk based on high-resolution, thin-slice (3 mm) magnetic resonance (mr) imaging. The mr criteria for high-risk rectal adenocarcinoma included an mrT3 low-lying tumor at or below the levators, mrT3 tumors in the middle-third position extending 5 mm or more into the perirectal fat, or the presence of extramural venous invasion (mrEMVI+) or mrT3 tumors or lymph node extending to within 1 mm of or beyond the mesorectal fascia (mrMRF+). In both the distal- and middle-third positions, any mrT4 (ie, tumor invading the surrounding structures or peritoneum) or mrN2 (ie, ≥4 nodes with mixed signal intensity or irregularly bordered nodes) tumors were considered high-risk. Two radiologists independently reviewed all pretreatment magnetic resonance imaging (MRI) scans. In the case of disagreement with the local radiologist, the final diagnosis was made by the central reviewer (for additional inclusion and exclusion criteria, see the eAppendix in Supplement 2).

Random Assignment, Stratification, and Treatment

The participants were randomly assigned in a 2:1 ratio to arm A (induction CT with aflibercept plus mFOLFOX6, n = 115) or arm B (induction CT with mFOLFOX6 alone, n = 65) using a permuted block design (block size, 3) and stratified by the mrT category,

mrEMVI status (positive vs negative), and treatment center. Randomization was performed by PIVOTAL in Madrid, Spain, using a computer-generated random allocation sequence by the ReRand randomization tool integrated in the remote data capture module of the eCRF Oracle, version 5.1 (Oracle Corporation).

All patients received mFOLFOX6 consisting of oxaliplatin (intravenous [IV] dose of 85 mg/m^2 over 2 hours) together with leucovorin (IV dose of 400 mg/m^2 over 2 hours), followed by fluorouracil (dose of 400 mg/m^2 as a bolus and 2400 mg/m^2 intravenously over 46 hours). Patients in arm A received aflibercept (4 mg/kg IV over 1 hour) before CT.

All drugs were administered on day 1 of a 14-day cycle for 6 cycles, followed 4 weeks later by CRT and TME surgery. Radiotherapy was performed by a linear accelerator with a minimum voltage of 6 mV by using a 3- or 4-field technique. The treatment volume included the primary tumor and the mesorectal, presacral, and internal iliac lymph nodes up to the level of the bottom part of the fifth lumbar vertebra. Patients received a total dose of 50.4 Gy (to convert to rad, multiply by 100), and daily fractions of 1.8 Gy were given on 5 days per week. During CRT, oral capecitabine was administered at a fixed dose of 825 mg/m^2 twice daily on days 1 through 5 for 5 weeks.

Surgery and Pathology

The TME surgery was performed at 6 to 8 weeks after CRT completion in both treatment arms. The final choice of surgical procedure (ie, abdominoperineal excision or low anterior resection) was at the surgeon's discretion. Standardized pathology examinations were performed according to the methodology of Quirke and Williams.[12] The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer,[13] with the prescript "y" used to indicate that the tumor had been treated before surgical resection. After preoperative CRT, residual tumor masses were semiquantitatively evaluated according to the 5-point regression grading scale established by Mandard et al.[14] The status of the surgical circumferential resection margin (CRM) (involvement defined as a tumor within 1 mm from the CRM) and the plane of surgery were assessed by pathologists using the classification proposed by Quirke et al.[15] A pCR was defined as the absence of viable tumor cells in the primary tumor and lymph nodes (ypT0N0).

Outcomes and Statistical Analysis

The primary end point of the study was the pCR rate. The secondary end points were other early efficacy end points (ie, proportion of patients with circumferential margin-free and R0 resections, and tumor regression grade), CT and CRT toxic effects, surgical morbidity, 3-year disease-free survival, and overall survival. The disease-free survival and overall survival are not reported in this manuscript because the required follow-up has not been reached yet.

We chose a randomized design to avoid comparison with historical cohorts and used a hypothesis testing design with a 2-sided α error of 20%, given the exploratory nature of a phase 2 trial. From our previous data,[2] we assumed a pCR rate of 15.0% in the control group and a target efficacy of 30.0% in the study group. Under these assumptions, using a power of 80.0% and the 2:1 randomization, the study required 162 patients. The sample size was increased to 180 to allow for a 10.0% dropout rate. We planned 2 interim analyses (ie, when 33.0% and 66.0% of the sample sizes had been recruited) of the treatment safety, futility, and efficacy. To account for these interim analyses, the threshold for significance at the final analysis was penalized using an O'Brien-Fleming alpha spending function. Consequently, the study would be considered positive at the prespecified 20.0% 2-sided α error if the *P* value comparing the pCR rates between the 2 arms was lower than .1984 (see eFigure 1, eFigure 2, and eFigure 3 in Supplement 2 for the thresholds of significance and results of the 2 interim analyses) using a *z* test for independent binomial proportions without continuity correction.

The intention-to-treat population was used for all efficacy analyses. The χ^2 test was used to evaluate the association between the treatment groups for qualitative parameters. Standard descriptive statistics were presented for all variables and outcomes. Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

Between January 2015 and March 2017, 243 patients were assessed for eligibility. Of these patients, 180 were randomized to arm A (n = 115) or arm B (n = 65) (**Figure**). The cutoff date for this report was December 2017. The demographic and tumor characteristics were well balanced between the 2 arms (**Table 1**). For the 115 patients who received treatment with mFOLFOX6 plus aflibercept, the median (range) age was 60 (32-75) years, 77 men (66.9%) and 38 women (33.0%). For the 65 patients who received induction treatment with only mFOLFOX6, the median (range) age was 65 (39-75) years, 39 men (60.0%) and 26 women (40.0%). Most patients had more than one high-risk factors. After random assignment, 33 patients (28.6%) in arm A and 19 (29.2%) in arm B were observed to have mrT4 lesions, 68 patients (59.1%, arm A) and 37 (56.9%, arm B) were mrMRF+, and 79 (68.7%, arm A) and 46 (70.7%, arm B) had mrN2. In arm A, 55 patients (47.8%) and in arm B, 31 (47.6%) were mrEMVI+.

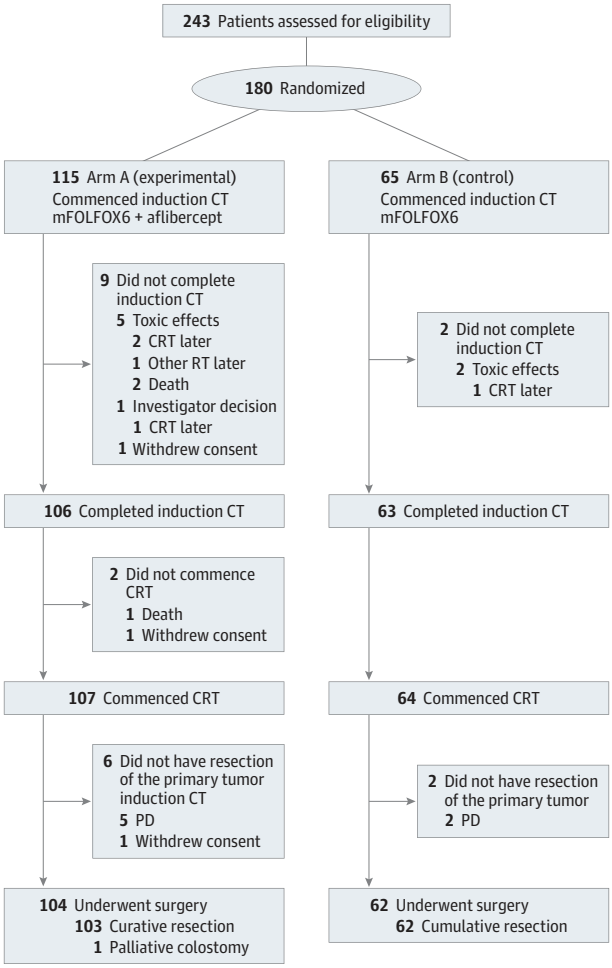
Compliance and Toxic Effects

Induction Treatment

A total of 106 patients (92.1%) in arm A and 63 (96.9%) in arm B completed the 6 cycles of induction CT, with or without dose reduction. During the induction period, in 59 patients (51.3%) treated with mFOLFOX6 plus aflibercept (arm A) and 15 (23.0%) treated with mFOLFOX6 alone (arm B) an adverse event (AE) of grade 3 or higher was recorded (**Table 2**); the most frequent AEs were hypertension (arm A, 28 [24.3%] vs arm B, 1 [1.5%]), neutropenia (arm A, 22 [19.1%] vs arm B, 11 [16.9%]), diarrhea (arm A, 5 [4.3%] vs arm B, 1 [1.5%]), and febrile neutropenia (arm A, 5 [4.3%] vs arm B, 0).

Two patients in arm A died within 30 days of their last treatment dose owing to AEs, 1 of whom died owing to an aortic dissection after receiving the full induction CT. For the second patient, who received 4 cycles, the cause of death was peritonitis, which developed because of a complication of an intestinal ob-

Figure. CONSORT Diagram



CT indicates chemotherapy; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; CRT, chemoradiotherapy; RT, radiotherapy; PD, progressive disease.

Table 1. Baseline Patient Demographics and Characteristics

Characteristic	Patients, No. (%)	
	Arm A (Induction mFOLFOX6 + Aflibercept [n = 115])	Arm B (Induction mFOLFOX6 [n = 65])
Age, median (range), y	60 (32-75)	65 (39-75)
Sex		
Male	77 (66.9)	39 (60.0)
Female	38 (33.0)	26 (40.0)
ECOG		
0	78 (67.8)	34 (52.3)
1	37 (32.1)	31 (47.6)
Clinical T stage		
Middle third		
mrT2	1 (0.8)	0
mrT3a	1 (0.8)	0
mrT3b	8 (6.9)	8 (12.3)
mrT3c	47 (40.8)	22 (33.8)
mrT3d	7 (6.0)	4 (6.1)
mrT4	21 (18.2)	13 (20.0)
Distal third		
mrT3	17 (14.7)	12 (18.4)
mrT4	12 (10.4)	6 (9.2)
Missing	1 (0.8)	0
MRF+	68 (59.1)	37 (56.9)
EMVI+ (score 3/4)	55 (47.8)	31 (47.6)
N2	79 (68.7)	46 (70.7)
Location		
Middle	84 (73.0)	46 (70.7)
Distal	30 (26.0)	18 (27.6)
Missing	1 (0.8)	1 (1.5)
Adenocarcinoma	115 (100.0)	65 (100.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EMVI, extramural venous invasion; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; MRF, mesorectal fascia.

struction that was operated on with a low anterior resection in the emergency department. Both deaths were judged by the investigators to be unrelated to the study treatment. No deaths were reported in arm B during the induction CT.

Preoperative Chemoradiotherapy

Of the 107 patients in arm A who began CRT, 97 (92.3%) received radiotherapy as prescribed (dose and technique) and 89 (84.7%) received the full capecitabine dose. Of the 64 patients in arm B who began CRT, 62 (96.8%) received radiotherapy as prescribed (dose and technique) and 58 (90.6%) received the full capecitabine dose. No differences in toxic effects were observed between the arms (Table 2).

Surgery

After CRT, 103 patients (89.5%) in arm A and 62 (95.3%) in arm B proceeded to undergo curative surgery. The proportion of postoperative complications of any grade was similar between both arms (Table 3) and no perioperative deaths were reported. For various reasons, 12 patients (10.4%) in arm A and 3 (4.6%) in arm B did not undergo surgery (Figure). Abdominoperineal excision was performed in 22 patients (21.3%) in arm A and 18 (29.0%) in arm B. The quality of surgery was considered good, with a pathologically confirmed mesorectal plane of surgery in 88 (85.4%) of the 103 resected patients in arm A and 47 (75.8%) of the 62 resected patients in arm B. Moderately good TME surgery was documented in 6 patients (5.8%) in arm A and 6 (9.6%) in arm B, and poor surgery was observed in 6 patients (5.8%) in arm A and 7 (11.2%) in arm B (**Table 3**).

Efficacy

In the intention-to-treat population, pCR (ypT0N0) was achieved in 26 of 115 patients in arm A (22.6%; 95% CI, 15.3%-31.3%) and 9 of 65 in arm B (13.8%; 95% CI, 6.5%-24.6%) (P = .15). In the patients who underwent curative surgery, pCR was achieved in 26 of 103 patients (25.2%; 95% CI, 17.2%-34.8%) in arm A and 9 of 62 (14.5%; 95% CI, 6.9%-25.8%) in arm B (P = .10). Complete remission of the primary tumor (Mandard 1) was achieved in 27 patients (26.2%) in arm A and 9 (14.5%) in arm B. The reported number of lymph nodes examined (13 in arm A and 13.5 in arm B) and the negative nodes were similar in both arms. Stage ypN2 (ie, ≥4

Table 2. Toxic Effects and Compliance

Characteristic	Patients, No. (%)	
	Arm A (Induction mFOLFOX6 + Aflibercept [n = 115])	Arm B (Induction mFOLFOX6 [n = 65])
Any grade 3/4 toxic effects during induction CT	59 (51.3)	15 (23.0)
Any grade 3/4 toxic effects during induction, excluding hypertension	36 (33.6)	13 (20.3)
Grade 3/4 nonhematologic toxic effects		
Diarrhea	5 (4.3)	1 (1.5)
Mucositis	3 (2.6)	0
Asthenia	2 (1.7)	0
Hypertension	28 (24.3)	1 (1.5)
Perforation	2 (1.7)	0
Acute coronary syndrome	1 (1.5)	1 (1.5)
Hematochezia	1 (0.8)	0
Dysphonia	1 (0.8)	0
Pulmonary embolism	1 (0.8)	0
Grade 3/4 hematologic toxic effects		
Neutropenia	22 (19.1)	11 (16.9)
Febrile neutropenia	5 (4.3)	0
Thrombocytopenia	0	2 (3.0)
Compliance induction CT, No. of cycles received per patient		
1	3 (2.6)	0
2	1 (0.8)	1 (1.5)
3	1 (0.8)	1 (1.5)
4	3 (2.6)	0
5	1 (0.8)	0
6	106 (92.1)	63 (96.9)
Any grade 3/4 toxic effects during CRT[a]	18 (17.1)	5 (7.8)
Grade 3/4 toxic effects		
Diarrhea	2 (1.7)	3 (4.6)
Palmar-plantar erythrodysesthesia	3 (2.6)	0
Proctitis	1 (0.8)	1 (1.5)
Hyponatremia	1 (0.8)	0
Neutropenia	2 (1.7)	0
Compliance CRT[a]		
Received total dose of RT	97 (92.3)	62 (96.8)
Received full dose of CT during RT	89 (84.7)	58 (90.6)

Abbreviations: CRT; chemoradiotherapy; CT, chemotherapy; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; RT, radiotherapy.

[a] Calculated among 105 (2 missing) and 64 patients receiving CRT.

positive nodes) was observed in 8 patients (7.7%) in arm A and 9 (14.5%) in arm B. Local complete R0 resections were performed in 101 patients (98.0%) in arm A and 60 (96.7%) in arm B, and clear CRMs (>1 mm) were observed in 96 patients (93.2%) in arm A and 56 (90.3%) in arm B (Table 3).

Discussion

Our results suggest that patients with high-risk T3 and T4 rectal adenocarcinoma may benefit from the use of combined aflibercept plus mFOLFOX6 induction CT prior to standard CRT and TME surgery. Although the patients in the aflibercept-containing arm had a higher pCR rate and higher acute toxic effects (mainly a class effect of VEGF inhibition) during the induction phase, these observations neither compromised the subsequent CRT or surgical resectability of the tumor nor resulted in additional surgical complications. The most frequent toxic effect was observed to be reversible hypertension, which was easily managed. The study results met the threshold for further investigation in the context of this phase 2 design. Hypothesis testing with a 2-sided α of .2 needs to be considered to interpret the results as being compatible with efficacy rather than as a definitive proof of it. The natural next step is to confirm the clinical benefit of this aflibercept-based induction strategy in a phase 3 trial.

Even with preoperative MRI, a major challenge in neoadjuvant trials of rectal adenocarcinoma is related to accurate tumor staging. Both overstaging and understaging are well-known issues that may contribute to outcome misinterpretation.[16] To minimize this in the GEMCAD 1402 trial, we performed a central review of the baseline MRI.

Our results should be interpreted in the context of other recently completed randomized trials of induction or consolidation CT and (chemo)radiation in a similar population. These include the GCR-3, EXPERT-C, and Polish trials (**Table 4**).[2,3,17] The pCR rate in the control group of our study (13.8%) was consistent with the results of these randomized trials. In the GCR-3 trial, the pCR rate after 12 weeks of induction treatment with CAPOX was 14.3%, but the proportion of patients with T4 tumors was higher in our GEMCAD 1402 study. In the control arm of the EXPERT-C trial, which used the same preoperative treatment strategy, the pCR rate was 15% and the proportions of patients with poor radiologic prognostic factors (mrT4, mrEMVI+, mrMRF+, and mrT3c-T3d) were similar to those of our trial. Both the GCR-3 and the EXPERT-C studies showed similar results in the experimental and control arms, in contrast to our results, which suggest an increased pCR in the experimental arm.

The Polish trial[17] compared standard preoperative long-course CRT with experimental preoperative short-term radiotherapy and consolidation with 3 cycles of FOLFOX4 and reported a pCR rate of 14% in the consolidation CT group. In this trial, 34% and 35% of the patients were staged by computed tomography and digital rectal examination, respectively, and approximately 60% had cT4 tumors.[17]

Our trial surgery was performed 6 to 8 weeks after CRT. In a nonrandomized phase 2 trial (cT2 tumors, 8%; cT3 tumors, 85%), higher rates of pCRs (38%) have been reported, extending until 19 weeks the interval to surgery and administering additional CT during the waiting (consolidation) period, suggesting that at least in part, lengthening the interval has a positive contribution in the outcome.[18] The phase 2R trial, evaluating induction vs consolidation CT, may provide a better estimate of this contribution.[19]

The results of the present study showed that aflibercept addition to the induction CT caused expected[9,20] higher acute toxic effects, mostly comprising easily managed hypertension. One patient with a baseline computed tomography scan showing aortic atheromatosis died after receiving the sixth cycle of mFOLFOX6 plus aflibercept, owing to spontaneous aortic rupture after surgery for an aortic Stanford type A dissection. Although judged by the investigators to be unrelated to the treatment, a recent population-based database study found

Table 3. Surgical Procedures, Toxic Effects, Grading of TME, and Pathologic Characteristics of Patients Who Underwent Curative Surgery

Characteristic	Patients, No. (%)	
	Arm A (mFOLFOX6 + Aflibercept [n = 103])	Arm B (mFOLFOX6 [n = 62])
Type of curative surgery		
Low anterior resection	76 (74.7)	42 (67.7)
Abdominoperineal resection	22 (21.3)	18 (29.0)
Others	5 (4.8)	2 (3.2)
Postoperative morbidity		
Overall AEs grade 3/4	16 (15.5)	8(12.9)
Anastomotic fistula	4 (3.8)	1 (1.6)
Wound-healing problems	4 (3.8)	5 (8.0)
Reoperation	9 (8.7)	5 (8.0)
Postoperative mortality	0	0
TME quality grading of operative specimen		
Mesorectal plane (good)	88 (85.4)	47 (75.8)
Intramesorectal plane (moderate)	6 (5.8)	6 (9.6)
Muscularis propia (poor)	6 (5.8)	7 (11.2)
Missing	3 (2.9)	2 (3.2)
Completeness of local tumor resection		
R0	101 (98.0)	60 (96.7)
R1	0	2 (3.2)
R2	1 (0.9)	0
Rx	1 (0.9)	0
Circumferential resection margin, mm		
≤1	3 (2.9)	3 (4.8)
>1	96 (93.2)	56 (90.3)
Missing data	4 (3.8)	3 (4.8)
Pathologic T category		
ypT0	27 (26.2)	9 (14.5)
ypTis	2 (1.9)	3 (4.8)
ypT1	4 (3.8)	6 (9.6)
ypT2	24 (23.3)	18 (29.0)
ypT3	44 (42.7)	24 (38.7)
ypT4	3 (2.9)	2 (3.2)
No. of lymph nodes examined (range)	13.0 (9.0-18.0)	13.5 (10.0-17.0)
Pathologic N category		
ypN0	78 (75.7)	48 (77.4)
ypN1	17 (16.5)	5 (8.0)
ypN2	8 (7.7)	9 (14.5)
Pathologic stage		
ypT0N0	26 (25.2)	9 (14.5)
ypTisN0	1 (0.9)	3 (4.8)
I	26 (25.2)	22 (35.4)
IIA	25 (24.2)	12 (19.3)
IIB	0	1 (1.6)
IIC	1 (0.9)	0
IIIA	3 (2.9)	1 (1.6)
IIIB	19 (18.4)	10 (16.1)
IIIC	2 (1.9)	2 (3.2)
IV	1 (0.9)	1 (1.6)
Missing data	0	1 (1.6)
Tumor regression grade (Mandard)		
TRG 1	27 (26.2)	9 (14.5)
TRG 2	33 (32.0)	21 (33.8)
TRG 3	28 (27.1)	23 (37.0)
TRG 4	12 (11.6)	8 (12.9)
TRG5	2 (1.9)	0
Missing data	1 (0.9)	1 (1.6)

Abbreviations: AEs, adverse events; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; TME, total mesorectal excision.

an increased risk of aortic dissection during systemic exposure to anti-VEGF inhibitors, suggesting a class effect for toxic effects.[21] This should be considered in the design of future studies. We did not observe differences in acute toxic effects or treatment compliance during CRT.

In studies of antiangiogenic agents, optimization of the dose and schedule for combination therapy is challenging. Based on the hypothesis that VEGF inhibition might normalize the tumor vasculature and thus improve the delivery of drugs and oxygen, we added aflibercept to the induction CT prior to performing standard CRT.[22] However, the length of the normalization window and whether it is sufficient to induce a sustained therapeutic benefit remain unknown, although some studies have demonstrated a prolonged maintenance of vascular normalization.[23] The prolongation of the interval between aflibercept administration and surgery may have been responsible for the low perioperative morbidity observed. Given that a prior randomized trial, which compared the use of mFOLFOX6 plus aflibercept with mFOLFOX6 alone for advanced colorectal adenocarcinoma, did not indicate any difference in the response rate between the 2 treatment groups, our results support the hypothesis that VEGF blockade prior to CRT is associated with the improvement in local efficacy via vascular normalization.

Limitations

A potential limitation of the trial is that statistically the chosen 2-sided α of 20% is high compared to that in contemporary randomized controlled trials. This α value could affect the results in that the experimental arm could be considered to have outperformed the control arm, when in fact it did not.

Conclusions

In summary, in a population with high-risk rectal adenocarcinoma treated with a total neoadjuvant therapy, our data support a possible role for VEGF inhibition combined with mFOLFOX6 during induction in increasing the pCR rate, without compromising the subsequent CRT or leading to a substantial increase in surgical complications. Further evaluation in a phase 3 trial is warranted.

Table 4. Randomized Trials With Induction or Consolidation Chemotherapy in cT3-T4 Rectal Adenocarcinoma

Trial Characteristics	GCR-3 (n = 108)	EXPERT-C (n = 165)	Polish (n = 541)	GEMCAD 1402 (n = 180)
Preoperative treatment	CRT: 50.4 Gy + capecitabine 825 mg/m^2 × 2, 5 d/wk for 5 wk + oxaliplatin 50 mg/m^2 weekly × 5	CAPOX and CRT: capecitabine 2000 mg/m^2 × 14 d, 1 week rest + oxaliplatin 130 mg/m^2 day 1 × 4 cycles, and 50.4 Gy + capecitabine 1650 mg/m^2/d + during RT	CRT: 50.4 Gy + bolus fluorouracil 325 mg/m^2/d and LV 20 mg/m^2/d ×5 d first and fifth week + weekly oxaliplatin 50 mg/m^2 × 5 wk	mFOLFOX6 and CRT: oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + bolus fluorouracil 400 mg/m^2 + 46 h CI 2400 mg/m^2 × 6 cycles and 50.4 Gy + capecitabine 825 mg/m^2, 5 d/wk for 5 wk
	CAPOX and CRT: capecitabine 2000 mg/m^2 × 14 d, 1 week rest + oxaliplatin 130 mg/m^2 day 1 × 4 cycles and 50.4 Gy + capecitabine 825 mg/m^2, 5 d/wk for 5 wk + oxaliplatin 50 mg/m^2 weekly × 5	CAPOX-C and CRT: capecitabine 2000 mg/m^2 × 14 d, 1 week rest + oxaliplatin 130 mg/m^2 day 1 + cetuximab 400 mg/m^2 on day 1 followed by 250 mg/m^2/wk × 4 cycles and 50.4 Gy + capecitabine 1650 mg/m^2 d + cetuximab 250 mg/m^2 weekly during RT	RT and FOLFOX4: 5 × 5 Gy + oxaliplatin 85 mg/m^2 day 1 + leucovorin 200 mg/m^2 + bolus fluorouracil 400 mg/m^2 + 22 h CI fluorouracil 600 mg/m^2 14 d × 3 cycles	mFOLFOX6 + Aflibercept and CRT: oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + bolus fluorouracil 400 mg/m^2 + 46 h CI 2400 mg/m^2 + aflibercept 4 mg/kg and 50.4 Gy + capecitabine 825 mg/m^2, 5 d/wk for 5 wk
cT3, %	CRT: 82.0% (n = 43 of 52)	CAPOX and CRT: 69.1% (n = 56 of 81)	CRT: 33.7% (n = 88 of 261)	mFOLFOX6 and CRT: 71.0% (n = 46 of 65)
	CAPOX and CRT: 87.5% (n = 49 of 56)	CAPOX-C and CRT: 56.6% (n = 47 of 83)	RT and FOLFOX4: 32.6% (n = 83 of 254)	mFOLFOX6-A and CRT: 69.5% (n = 80 of 115)
cT4, %	CRT: 5.7% (n = 3 of 52)	CAPOX and CRT: 23.4% (n = 19 of 81)	CRT: 63.2% (n = 165 of 261)	mFOLFOX6 and CRT: 29.2% (n = 19 of 65)
	CAPOX and CRT: 12.5% (n = 7 of 56)	CAPOX-C and CRT: 25.3% (n = 21 of 83)	RT and FOLFOX4: 64.1% (n = 163 of 254)	mFOLFOX6-A: 28.6% (n = 33 of 115)
Other poor MRI prognostic factors, %	CRT: T3c-T3d, NR; T4, 5.7% (n = 3 of 52); CRM-positive disease or at risk, 9.6% (n = 5 of 52); EMVI-positive disease, NR; N2, NR	CAPOX: T3c-T3d, 69.1% (n = 56 of 81; T4: 23.4% (n = 19 of 81); CRM-positive disease or at risk, 55.5% (n = 45 of 81); EMVI-positive disease, 74.0% (n = 60 of 81); N2, NR	NR	mFOLFOX6: T3c-T3d, 40.0% (n = 26 of 65); T4: 29.2% (n = 19 of 65); CRM-postive disease or at risk, 56.9% (n = 37 of 65); EMVI-positive disease, 47.6% (n = 31 of 65); N2, 70.7% (n = 46 of 65)
	CAPOX: T3c-T3d, NR; T4, 12.5% (n = 7 of 56); CRM-positive disease or at risk, 0% (n = 0); EMVI-positive disease, NR; N2, NR	CAPOX-C: T3c-T3d, 56.6% (n = 47 of 83); T4: 25.3% (n = 21 of 83); CRM-positive disease or at risk, 57.8% (n = 48 of 83); EMVI-postitive, 69.8% (n = 58 of 83); N2, NR		mFOLFOX6-A: T3c-T3d, 46.9% (n = 54 of 115); T4, 28.6% (n = 33 of 115); CRM-positive disease or at risk, 59.1% (n = 68 of 115); EMVI-positive disease, 47.8% (n = 55 of 115); N2, 68.7% (n = 79 of 115)
pCR[a]	13.4% (n = 7 of 52) vs 14.3% (n = 8 of 56)	9.0% (n = 4 of 44) vs 10.8% (n = 5 of 46)[b]	9.4% (n = 24 of 254) vs 13.7% (n = 36 of 261)	13.8% (n = 9 of 65) vs 22.6% (n = 26 of 115)

Abbreviations: CAPOX, capecitabine and oxaliplatin; CAPOX-C, capecitabine, oxaliplatin, and cetuximab; CRM, circumferential resection margin; CRT, chemoradiotherapy; EMVI, extramural venous invasion; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOX-A, fluorouracil, leucovorin, oxaliplatin, and aflibercept; MRI, magnetic resonance imaging; NR, not reported; pCR, pathologic complete response.

[a] Intention-to-treat population.

[b] *KRAS*/*BRAF* wild type.

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