TOPIC HIGHLIGHT

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Bevacizumab in the pre-operative treatment of locally advanced rectal cancer: A systematic review

Lorenzo Fornaro, Chiara Caparello, Caterina Vivaldi, Virginia Rotella, Gianna Musettini, Alfredo Falcone, Editta Baldini, Gianluca Masi

Lorenzo Fornaro, Virginia Rotella, Editta Baldini, Division of Medical Oncology, Azienda USL2 Lucca, 55100 Lucca, Italy
Chiara Caparello, Caterina Vivaldi, Gianna Musettini, Alfredo Falcone, Gianluca Masi, Division of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, 56126 Pisa, Italy
Author contributions: Fornaro L was responsible for manuscript design, review of the literature, data analysis and interpretation and manuscript writing; Caparello C, Vivaldi C, Rotella V and Musettini G performed research, analyzed the data and wrote the paper; Falcone A, Baldini E and Masi G contributed to data analysis and interpretation and manuscript writing.
Correspondence to: Dr. Lorenzo Fornaro, Division of Medical Oncology, Azienda USL2 Lucca, Via dell'Ospedale 1, 55100 Lucca, Italy. lorenzo.fornaro@gmail.com
Telephone: +39-583-970161 Fax: +39-583-449545

Abstract

Despite advances in the management of patients with locally advanced, non-metastatic rectal adenocarcinoma (LARC), prognosis remains largely unsatisfactory due to a high rate of distant relapse. In fact, currently available neoadjuvant protocols, represented by fluoropyrimidine-based chemo-radiotherapy (CT-RT) or short-course RT, together with improved surgical techniques, have largely reduced the risk of local relapse, with limited impact on distant recurrence. Available results of phase Ⅲ trials with additional cytotoxic agents combined with standard CT-RT are disappointing, as no significant reduction in the risk of recurrence has been demonstrated. In order to improve the control of micrometastatic disease, integrating targeted agents into neoadjuvant treatment protocols thus offers a rational approach. In particular, the antiangiogenic agent bevacizumab has demonstrated synergistic activity with both CT and RT in pre-clinical and clinical models, and thus may represent a suitable companion in the neoadjuvant treatment of LARC. Preliminary results of phase Ⅰ - Ⅱ clinical studies are promising and suggest potential clinical parameters and molecular predictive biomarkers useful for patient selection: treatment personalization is indeed the key in order to maximize the benefit while reducing the risk of more complex neoadjuvant treatment schedules.

Core tip: Pre-operative treatment of locally advanced rectal cancer is a challenging issue in gastrointestinal oncology. Integrating an antiangiogenic agent such as bevacizumab into neoadjuvant chemo-radiotherapy protocols is a promising approach. We review the different strategies currently under evaluation in order to complement bevacizumab within a multimodality approach for locally advanced rectal cancer patients.

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INTRODUCTION

Colorectal adenocarcinoma is the second cause of death due to cancer in developed countries, and rectal cancer accounts for about 35% of the total colorectal cancer

incidence in Europe[1]. Management of locally advanced rectal adenocarcinoma (LARC) has undergone significant changes in the last decade, thanks to the integration of multiple treatments such as surgery with total mesorectal excision, fluoropyrimidine chemotherapy (CT) and radiotherapy (RT) in the neoadjuvant setting.

Multimodality treatments have improved the prognosis of LARC, with local recurrences decreasing from 40% to less than 10%[2]. However, results in terms of eradication of distant micrometastases are less satisfactory, and randomized studies did not demonstrate a positive impact on overall survival (OS) of CT-RT compared with RT alone[2]. This is probably due to suboptimal medical treatment. In fact, fluoropyrimidine monotherapy during CT-RT mainly acts as a radiosensitizer (*i.e.*, it is administered at reduced dosing for a shorter period), thus its systemic cytotoxic activity may be ineffective. Moreover, single-agent fluoropyrimidine has only modest activity in colorectal cancer, and may be insufficient to reduce the risk of distant recurrence. Unfortunately, any attempt to improve the efficacy of conventional CT-RT by the addition of a second chemotherapeutic agent such as oxaliplatin has led to disappointing results[3-5]. There is therefore a great interest in the integration into RT and CT-RT protocols of the biologic agents with proven efficacy in the metastatic setting, such as anti-angiogenic and anti-epidermal growth factor receptor (EGFR) monoclonal antibodies[6].

Bevacizumab, a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), may represent a promising companion with standard RT and CT-RT. VEGF is a crucial regulator of normal and tumor angiogenesis, and elevated VEGF expression is correlated with lower OS in different malignancies[7]. Tumor invasion, growth and metastasis are strictly dependent on the angiogenic process: both hypoxia and growth factors (such as VEGF) can induce new vessel formation and are key promoters of radioresistance[7]. Several mechanisms have been proposed in order to explain the increased efficacy of CT-RT when combined with antiangiogenic agents[8]. First of all, the inhibition of the VEGF signaling axis can radiosensitize tumor-associated endothelial cells, thus inhibiting tumor neoangiogenesis and reducing vascular density, ultimately impairing blood supply to cancer cells. Anti-VEGF agents can also lead to vascular normalization, decreasing tumor hypoxia and improving radiosensitivity. Moreover, anti-VEGF agents can inhibit vessel growth by acting against circulating endothelial cells and progenitor cells. Pre-clinical and clinical data indicate that bevacizumab enhances tumor blood flow, reduces tumor interstitial pressure, and decreases mean vessel density when infused neoadjuvantly in rectal cancer patients: these physiologic changes may enhance the activity of RT and CT[9,10].

In the following sections, we will describe the currently presented or published phase I - II trials evaluating bevacizumab as pre-operative treatment in LARC

(defined as clinical stage T3 or more tumor, with or without nodal involvement at pre-operative imaging but with no evidence of distant metastases). In order to offer a comprehensive assessment of the currently available data, we have grouped the studies according to the general neoadjuvant treatment approach evaluated. We therefore identified four different strategies in which bevacizumab could be integrated in the multimodality management of LARC patients: (1) bevacizumab as a companion to conventional fluoropyrimidine-based CT-RT; (2) bevacizumab with intensified oxaliplatin-containing CT-RT; (3) bevacizumab plus CT as induction treatment before CT-RT; and (4) bevacizumab with CT without RT.

We will discuss the promises and pitfalls of these strategies and ultimately review the ongoing phase III trials in this setting.

PRELIMINARY RESULTS OF BEVACIZUMAB IN THE PRE-OPERATIVE TREATMENT OF LARC

Bevacizumab with conventional (fluoropyrimidine-based) CT-RT

Since pre-clinical and clinical data about the antivascular effects of bevacizumab became available[9], this anti-VEGF antibody has been tested with pre-operative RT or CT-RT in LARC in several phase I / II trials. The results achieved with bevacizumab plus fluoropyrimidine-based CT-RT are summarized in Table 1.

Willet *et al*[11] treated 32 patients with bevacizumab (at the dose of 5 or 10 mg/kg), in combination with standard CT-RT comprising 5-fluorouracil (5-FU, continuous infusion of 225 mg/m^2 per day) and external-beam RT (50.4 Gy in 28 fractions over 5.5 wk). Surgery was scheduled 7 to 10 wk after the completion of neoadjuvant treatment. The authors reported a pathologic complete response (pCR) rate of 16%, with a promising 5-year local control rate of 100% and 5-year disease-free survival (DFS) of 75%. These results were achieved at the price of acceptable toxicity: main post-operative complications (within 90 d of surgery) included anastomotic leak (one patient), pelvic hematoma and abscess requiring drainage (one patient), delayed healing of perineal incision (two patients), ileus (two patients), and wound infection (three patients).

These interesting results have been confirmed in a subsequent phase II trial with capecitabine-based CT-RT (50.4 Gy in 28 fractions over 5.5 wk plus capecitabine 900 mg/m^2 orally twice daily on the days of radiation), combined with bevacizumab administered every 2 wk for 3 cycles at the dose of 5 mg/kg (surgery has been performed after a median of 7.3 wk later): pCR has been reached in 8 out of 25 (32%) patients. Feasibility of the regimen and moderate toxicities were confirmed, with 3 cases of wound complications requiring surgical intervention[12].

Table 1 Bevacizumab with conventional chemo-radiotherapy: Overview of the discussed studies

Ref.	Phase	*n*	Treatment	Stage	Post-operative complications (*n*)	pCR
Willet *et al*[11], 2009	I - II	32	BV 5 or 10 mg/kg, 5-FU 225 mg/m² daily, RT 50.4 Gy in 28 fr.	II - III	Anastomotic leak with presacral abscess (1) Vaginal tear with presacral hematoma and abscess (1) Pelvic hematoma (1) Delayed healing of perineal incision (2) Ileus (2) Neurogenic bladder (1) Perforated ileostomy (1) Pulmonary embolus (1) Wound infection (3)	16%
Crane *et al*[12], 2010	II	25	BV 5 mg/kg, CAPE 900 mg/m² *bid*, RT 50.4 Gy in 28 fr.	II - III	Wound complications requiring surgical intervention (3) Minor complications (5)	32%
Velenik *et al*[13], 2011	II	61	BV 5 mg/kg, CAPE 825 mg/m² *bid*, RT 50.4 Gy in 28 fr.	II - III	Delayed wound healing (18) Infection/abscess (12) Anastomotic leakage (7) Pneumothorax (1)	13.3%
Villacampa *et al*[15], 2012	II b	90	Arm A: BV 5 mg/kg, CAPE 825 mg/m² *bid*, RT 45 Gy in 25 fr. Arm B: CAPE 825 mg/m² *bid*, RT 45 Gy in 25 fr.	II - III	19 *vs* 18 patients (not specified)	16% *vs* 11%
Gasparini *et al*[16], 2012	II	43	BV 5 mg/kg, CAPE 825 mg/m² *bid*, RT 50.4 Gy in 28 fr.	II - III	Bowel perforation (1) Anastomosis failure (1) Abscess (1)	14%
Marijnen *et al*[17], 2008	II	23	BV 5 mg /kg, CAPE 825 mg/m² *bid*, RT 50 Gy in 25 fr.	II - III	Perineal dehiscence (1) Rectovaginal fistula (1) Peri-operative bleeding (1) Pulmonary embolism (1)	9%

BV: Bevacizumab; RT: Radiotherapy; 5-FU: 5-fluorouracil; CAPE: Capecitabine; fr.: Fractions; pCR: Pathological complete response.

In a larger study, 61 patients with stage II/III LARC received single agent bevacizumab (at the dose of 5 mg/kg), followed after 2 wk by neoadjuvant CT-RT with bevacizumab (5 mg/kg every 2 wk for 3 cycles, starting the first day of RT) and conventional capecitabine-based CT-RT; surgery was scheduled 6-8 wk after the completion of neoadjuvant treatment[13]. The primary endpoint of the trial was pCR. A tumor regression grade (TRG) by Dworak *et al*[14] of 4 (equivalent to pCR) was achieved in 8 patients (13.3%), and TRG of 3 (*i.e.*, only a few tumor cells in the residual fibrotic tissue) was reported in 9 patients (15.0%). A radical resection was performed in 57 patients (95%), and 42 patients (70%) underwent sphincter-preserving surgery. Grade 3 adverse events included dermatitis (9.8%), proteinuria (6.5%) and leucocytopenia (4.9%). In contrast with the previously discussed trials, the authors reported potential safety concerns for the combination of bevacizumab with CT-RT; in fact, 38 (62.3%) patients developed peri-operative complications, such as delayed wound healing (30%), infection/abscess (20%) and anastomotic leakage (11.7%).

A recent randomized phase II study compared conventional CT-RT with CT-RT plus bevacizumab among 90 stage II/III LARC patients[15]. The primary endpoint was pCR. Overall grade 3-4 toxicity rates were somewhat (but non-significantly) higher in the CT-RT plus bevacizumab arm compared with the control arm (18% *vs* 13%; *P* = 0.50), while no grade 3-4 hematological toxicity was reported. Post-operative complications were slightly more frequent in the bevacizumab arm (43% *vs* 37%). As regards the primary endpoint, pCRs were numerically (but non-significantly) higher in the bevacizumab arm (16% *vs* 11%, *P* = 0.54).

Another Italian multicenter phase II study evaluated a similar strategy, *i.e.*, adding bevacizumab to standard CT-RT. Investigators enrolled 43 LARC patients: treatment comprised bevacizumab (5 mg/kg) every 2 wk for 4 cycles, plus capecitabine (825 mg/m² twice a day for 5.5 wk) and external-beam RT (50.4 Gy in 28 fractions over 5.5 wk), with surgery scheduled 6 to 8 wk after the completion of neoadjuvant therapy (and at least 6 wk after the last dose of bevacizumab)[16]. In line with previous data, 6 patients (14%) had no residual cancer cells at post-operative histopathologic examination, and radical tumor resection with negative circumferential margins was achieved in almost all patients (38 out of 40, 95%); a sphincter-sparing surgery was obtained in 31 (72.1%) patients. The regimen reported promising long-term results, as 3-year DFS was 75.4%. As regards safety, treatment was well tolerated: the most frequent toxicities were grade 1-2 diarrhea, hypertension, rectal bleeding and proctitis. Few patients experienced grade 3 toxicities, including diarrhea (3 patients), neutropenia (2 patients), asthenia and hypokalemia (1 patient each, respectively). Intriguingly, some molecular biomarkers were evaluated; however, despite a significant correlation between pretreatment CD-34 vessel density, post-treatment Ki-67 labeling index and VEGF receptor-2 (VEGFR-2) cancer cell expression with residual tumor area, no biomarker showed a statistically significant correlation with DFS.

Table 2 Bevacizumab with oxaliplatin-based chemo-radiotherapy: Overview of the discussed studies

Ref.	Phase	n	Treatment	Stage	Post-operative complications (n)	pCR
Czito *et al*[18], 2007	I	11	BV 15 mg/kg and 10 mg/kg, CAPE 625 mg/m² *bid*, oxaliplatin 50 mg/m² weekly, RT 50.4 Gy in 28 fr.	II-III	Abscess (1)	18%
Dellas *et al*[19], 2013	II	70	BV 5 mg/kg, CAPE 825 mg/m² *bid*, oxaliplatin 50 mg/m² weekly, RT 50.4 Gy in 28 fr.	II-III-IV	Anal fistula (1) Pelvic abscess (1) Delayed wound healing (1)	17.4%
Kennecke *et al*[20], 2012	II	42	BV 5 mg/kg, CAPE 825 mg/m² *bid*, oxaliplatin 50 mg/m² weekly, RT 50.4 Gy in 28 fr.	II-III-IV	Pelvic infection (11) Delayed healing (7) Anastomotic leak (6) Fistula (3)	18.4%
Landry *et al*[21], 2013	II	57	BV 5 mg/kg, CAPE 825 mg/m² *bid*, oxaliplatin 50 mg/m² weekly, RT 50.4 Gy in 28 fr. (+ post-operative FOLFOX + BV)	II-III	Early complications: Wound infection (8) Fascial dehiscence (5) Intra-abdominal abscess (1) Fistula (1) Bowel obstruction (1) Thromboembolism (1) Late complications: Wound infection (23) Wound/fascial dehiscence (12) Bowel obstruction/ileus (5) Intra-abdominal abscess (2) Anastomotic leak (1)	17%

CT-RT: Chemo-radiotherapy; BV: Bevacizumab; RT: Radiotherapy; CAPE: Capecitabine; fr.: Fractions; FOLFOX: 5-fluorouracil and oxaliplatin; pCR: Pathological complete response.

Regarding the feasibility of bevacizumab plus pre-operative CT-RT, additional information can be derived from the preliminary results of the Dutch Colorectal Cancer Group trial involving 23 patients with LARC treated with bevacizumab, capecitabine and RT. The authors reported a 30% rate of grade 3 adverse events (represented by cutaneous toxicity in 4 patients, diarrhea in 2 patients and tenesmus in 1 patient) and one case of grade 4 toxicity (anal mucositis) during CT-RT. Two small bowel and 1 rectal wall perforations occurred during treatment, and surgical complications were represented by perineal dehiscence, rectovaginal fistula and high-volume bleeding (1 patient each), suggesting the need for further investigation about the relationship between radiation-induced enteritis and the observed toxicity pattern[17].

As a whole, the majority of trials that tried to place bevacizumab concomitantly with fluoropyrimidine-based CT-RT have shown an acceptable safety profile, even though some concerns arise from the evidence of a slight (but not negligible) increase in peri-operative complications. In terms of pCR, only a mild benefit seems to be achieved with the combination, while the impact in terms of long-term outcome is difficult to estimate due to the phase I-II design of available trials.

Bevacizumab with oxaliplatin-based CT-RT

Moving from pre-clinical data and positive results in the advanced disease setting and as adjuvant treatment in colon cancer, several trials evaluated the integration of oxaliplatin into fluoropyrimidine-based pre-operative CT-RT protocols. This strategy aimed to improve both the

control of primary tumor (by increasing tumor shrinkage and pCR) and the eradication of distant micrometastases (by increasing the activity of the CT backbone in CT-RT protocols). However, as mentioned earlier, this strategy has so far achieved poor results in phase III trials[3-5]. Different groups thus evaluated the addition of bevacizumab to these intensified CT-RT regimens (Table 2).

Czito *et al*[18] conducted a phase I study among 11 LARC patients receiving 50.4 Gy of external beam RT plus capecitabine, oxaliplatin and bevacizumab, administered concurrently with RT. Primary endpoints included the evaluation of dose-limiting toxicity and the definition of a recommended phase II dose, non-dose-limiting toxicity and preliminary data on efficacy (radiographic and pathologic response rates). The recommended phase II dose in this study was bevacizumab 15 mg/kg on day 1 and 10 mg/kg on days 8 and 22, oxaliplatin 50 mg/m² weekly and capecitabine 625 mg/m² twice daily during radiation days. A pCR was reported in 2 patients and residual microscopic disease was evident in 3 patients. Most relevant toxicities were represented by post-operative abscess, a syncope episode and a subclinical myocardial infarction (1 patient each, both during adjuvant CT).

The results of a single-arm phase II study investigating the feasibility (in terms of surgical complications) and the activity (in terms of pCR rate, the primary endpoint) of the addition of bevacizumab to capecitabine, oxaliplatin and RT has been recently published[19]. Seventy patients with LARC received conventional RT (50.4 Gy in 1.8 Gy fractions) and concomitant CT with bevacizumab 5 mg/kg (on days 1, 15 and 29), capecitabine 825 mg/m² twice daily (on days 1 to 14 and 22 to 35)

Ref.	Phase	*n*	Treatment	Stage	Post-operative complications (*n*)	pCR
Dipetrillo *et al*[26], 2012	II	25	Induction FOLFOX + BV followed by BV 5 mg/kg, 5-FU 200 mg/ m^2 daily, oxaliplatin 50 mg/m^2 weekly, RT 50.4 Gy in 28 fr.	II - III	Infection (4) Delayed healing (3) Leak/abscess (2) Sterile fluid collection (2) Ischemic colonic reservoir (1) Fistula (1)	20%
Nogué *et al*[27], 2011	II	47	Induction XELOX + BV followed by BV 5 mg/kg, CAPE 825 mg/ m^2 *bid*, RT 50.4 Gy in 28 fr.	II - III	Wound infection (10) Intra-abdominal infections (7) Anastomotic leak (5) Stoma complications (2) Other (not specified) (10)	36%
Vivaldi *et al*[28], 2013	II	15	Induction FOLFOXIRI + BV followed by BV 5 mg/kg, CAPE 825 mg/m^2 *bid* or 5-FU 225 mg/m^2 daily, RT 50.4 Gy in 28 fr.	II - III	Dehiscence of anastomosis (1)	38%

Table 3 Bevacizumab with chemotherapy as induction therapy before chemo-radiotherapy: Overview of the discussed studies

CT: Chemotherapy; CT-RT: Chemo-radiotherapy; BV: Bevacizumab; RT: Radiotherapy; 5-FU: 5-fluorouracil; CAPE: Capecitabine; fr.: Fractions; FOLFOX: 5-FU and oxaliplatin; XELOX: Capecitabine and oxaliplatin; pCR: Pathological complete response.

and oxaliplatin 50 mg/m^2 (on days 1, 8, 22 and 29). A pCR was observed in 17.4% of cases, with R0 resection performed in 66 out of 69 patients (96%). As regards safety, the protocol was proved to be feasible and did not seem to result in increased peri-operative morbidity or mortality. Fifty-eight patients (83%) were able to complete the CT-RT protocol (*i.e.*, received full dose RT and full dose of all CT drugs). During pre-operative treatment, grade 3-4 toxicities were represented by gastrointestinal events (diarrhea, nausea and anal abscess). Thirty patients (46%) developed post-operative complications of any grade, which included one case of gastrointestinal perforation (2%), wound-healing delay in 7 patients (11%) and bleeding in 2 patients (3%).

Kennecke *et al*[20] evaluated a similar CT-RT protocol plus bevacizumab, consisting of capecitabine 825 mg/m^2 twice daily (on days 1 to 14 and 22 to 35), oxaliplatin 50 mg/m^2 (on days 1, 8, 22 and 29), bevacizumab 5 mg/kg (on days 1, 15 and 29), and RT (total dose 50.4 Gy). Again, pCR was the primary objective of this phase II study (surgery with total mesorectal excision was scheduled 7 to 9 wk after the end of CT-RT): complete disease eradication in the pelvis was achieved in 18.4% of the cases. Re-operation due to complications was required in 4 patients (11%), which is in line with historical data with CT-RT alone.

In a recent phase II study, 57 LARC patients were treated with neoadjuvant capecitabine (825 mg/m^2 twice daily, from Monday to Friday), oxaliplatin (50 mg/m^2 weekly), bevacizumab (5 mg/kg on days 1, 15 and 29) and RT (total dose 50.4 Gy); surgical resection was planned 6 wk after the end of therapy, then adjuvant FOLFOX plus bevacizumab for 12 cycles was administered 8 to 12 wk after surgery[21]. Notably, the pCR rate was in line with previous studies (17%). Even though the majority of patients (59%) achieved a pathologic downstaging of the tumor, the primary endpoint of the trial (30% of pCR) was not reached. Moreover, 47% of patients who underwent surgery experienced a surgical complication possibly related to the addition of bevaci-

zumab, oxaliplatin, or both.

Interestingly, a recent systematic review of the literature regarding 15 trials (enrolling 457 patients, with a range of 8-61) investigating the use of bevacizumab in association with CT-RT reported a pooled pCR rate of 20.8% (95%CI: 17.3-24.8), which is comparable with the available data for fluoropyrimidine-based CT-RT alone[22]. Among the studies included in the analysis, 5 used 5-FU and 10 used capecitabine as the CT backbone for CT-RT, while a second cytotoxic agent was administered in 7 trials. Even with the limitation of a pooled analysis of different studies with distinct bevacizumab and CT-RT schedules, this report confirms that simply adding bevacizumab to concurrent CT-RT is not the most suitable strategy to improve pCR rate in LARC; alternative options to include bevacizumab in the neoadjuvant treatment are therefore under investigation.

Bevacizumab with CT as induction therapy before CT-RT

As the administration of adjuvant CT after neoadjuvant CT-RT and surgery is not an established standard in LARC patients[23], an intriguing treatment option is based on induction CT before CT-RT[24,25]: in fact, this strategy allows an earlier exposure to systemic CT (with a putative higher control of distant micrometastases) and, as demonstrated by recent trials[24], a higher exposure to systemic CT (thanks to a more favorable safety profile compared to post-operative treatment). Pivotal trials are exploring the possibility of combining bevacizumab with induction CT and subsequent CT-RT in LARC patients (Table 3).

Dipetrillo *et al*[26] evaluated induction bevacizumab associated with modified infusional 5-FU, leucovorin and oxaliplatin followed by concurrent bevacizumab (5 mg/kg on days 1, 15 and 29), oxaliplatin (50 mg/m^2/wk for 6 wk), continuous infusion 5-FU (200 mg/m^2 per day) and RT (50.4 Gy). Five of 25 patients (20%) had a pCR, but the toxicity profile led to the early interruption of the study after the enrollment of 26 patients: grade 3-4 toxicities, such as diarrhea, neutropenia and pain, were

Table 4 Bevacizumab with chemotherapy without chemo-radiotherapy: Overview of the discussed studies

Ref.	Phase	*n*	Treatment	Stage	Post-operative complications (*n*)	pCR
Schrag *et al*[31], 2014	II	32	FOLFOX + BV for 4 cycles, then FOLFOX for 2 cycles, CT-RT in case of SD or PD (post-op. if R1-R2 resections, pT4 or pN2)	II-III (no T4)	Renal failure due to dehydration from high volume ileostomy output resulting in death (1)	25%
Hasegawa *et al*[32], 2013	II	25	XELOX + BV for 3 cycles, then XELOX for 1 cycle	II-III (T4 or N+)	Nine patients (not specified)	4%
Fernandez-Martos *et al*[33], 2012	II	46	XELOX + BV for 3 cycles, then XELOX for 1 cycle, CT-RT in case of PD	Intermediate-risk T3	Three patients (not specified)	15%

CT: Chemotherapy; CT-RT: Chemo-radiotherapy; BV: Bevacizumab; RT: Radiotherapy; post-op.: Post-operative; FOLFOX: 5-FU and oxaliplatin; XELOX: Capecitabine and oxaliplatin; SD: Stable disease; PD: Progressive disease; pCR: Pathological complete response.

experienced by 19 of 25 patients (76%), and 36% of patients developed post-surgical complications.

In the AVACROSS study reported by Nogué *et al*[27], bevacizumab was associated with four 21-d cycles of XELOX (capecitabine plus oxaliplatin) regimen and then patients underwent a concomitant treatment with RT (50.4 Gy) plus bevacizumab 5 mg/kg (every 2 wk) and capecitabine 825 mg/m^2 twice daily (on days 1 to 15). The primary endpoint of the study was pCR, achieved in 16 patients (36%), with an additional 38% of the cases reporting a Dworak TRG of 3. R0 resection was performed in 98% of the patients, and a surgical re-intervention was needed in 11 patients (24%). Most grade 3-4 adverse events (mainly CT-related diarrhea, fatigue and hematological adverse events) emerged during the induction phase.

On behalf of the GONO group, we are conducting a multicenter phase II neoadjuvant study (TRUST trial) in resectable LARC patients defined by the presence of positive lymph nodes or clinical T4 or high risk (by magnetic resonance imaging) T3 stage (*i.e.*, T3 with distal border of tumor > 5 cm from the anal verge and below the sacral promontory or tumor ≥ 2 mm from the mesorectal fascia)[28]. Patients are treated with 6 cycles of induction CT with biweekly FOLFOXIRI plus bevacizumab[29,30], followed by concomitant CT-RT (50.4 Gy in 28 fractions plus either 5-FU or capecitabine and bevacizumab). As the aim of the trial is to improve the control of distant disease, the primary endpoint is represented by 2-year DFS. Preliminary safety analyses in the first 15 patients enrolled show that induction FOLFOXIRI plus bevacizumab is feasible with manageable toxicities, as safety results are in line with the available data for this regimen[29,30]. During concomitant CT-RT and bevacizumab, no G4 toxicities were reported; we observed however an excessive incidence of G3 hand-foot syndrome (31%), proctalgia and proctitis (23%) and diarrhea (15%). We hypothesized that this excessive toxicity of capecitabine may be related to previous induction treatment with FOLFOXIRI plus bevacizumab (comprising high doses of IV folinic acid) that led to an excessive intra-cellular folate accumulation. The protocol was then amended by slightly modifying the schedule of capecitabine during concomitant CT-RT. One of the resected patients experienced an early post-surgical com-

plication (dehiscence of anastomosis). Preliminary activity results warrant further investigation of this strategy, as pCR was reported in 5 out of 13 resected patients (38%).

Bevacizumab with CT without CT-RT

The hypothesis of a comprehensive local and distant tumor control achieved by the early introduction of full dose CT without any RT in LARC has recently been under investigation. This strategy aims to spare RT toxicity for most patients (especially those with low-risk T3 tumors at imaging) who may achieve optimal disease control in the pelvis without the need for RT. In the attempt to enrich systemic treatment and reduce potential bevacizumab plus RT-related complications after surgery, the anti-VEGF antibody was also investigated in the neoadjuvant setting without the use of RT (Table 4).

Schrag *et al*[31] enrolled 32 patients with clinical stage II to III (excluding T4 tumors) rectal cancer who were candidates for sphincter-sparing surgical resection in a single-center phase II trial. Patients received 6 cycles of FOLFOX, with bevacizumab included in the first 4 cycles. Patients with stable/progressive disease were to have RT before total mesorectal excision, whereas responders were to have immediate surgery. Post-operative RT was planned if R0 resection was not achieved. The primary outcome was the R0 resection rate. All the 32 enrolled patients had R0 resection (100%). Two patients did not complete pre-operative CT due to cardiovascular toxicity; both safely received pre-operative CT-RT and then R0 resection. Of the 30 patients completing pre-operative CT, all had tumor regression and surgery without the need for pre-operative CT-RT. The pCR rate for CT alone was 25%, which compares well with historical data for CT-RT protocols. Of interest, the 4-year local recurrence rate was 0% and the 4-year DFS was 84%, suggesting that this strategy may be particularly effective in controlling both local and distant disease. The results of this provocative trial therefore indicate that, at least for a subgroup of selected patients with clinical stage II or III LARC, a modern strategy comprising neoadjuvant CT doublet plus bevacizumab and selective RT does not seem to compromise outcome.

A second trial evaluated the association of bevacizumab with the XELOX regimen in LARC (eligible

Table 5 Main ongoing trials with bevacizumab in locally-advanced rectal cancer

Study	Design	n	Pre-operative treatment	RT	Primary endpoint	Status	Comments
AXE BEAM trial (NCT00828672)	Randomized Phase II	80	Concomitant XELOX +/- BV + RT	CT-RT 45 Gy	pCR	Recruiting	
New Beat trial (NCT01554059)	Phase II	28	Concomitant FOLFOX + BV + RT	CT-RT 40 Gy/20 fractions	pCR	Recruiting	
NCT01818973	Phase II	45	XELOX + BV for 1 cycle followed by concomitant CT-RT with XELOX + BV for 2 cycles and RT	CT-RT 50 Gy/25 fractions	Tumor regression grade	Recruiting	Adjuvant CT with XELOX for 3 cycles followed by capecitabine for 2 cycles
BACCHUS trial (NCT01650428)	Randomized Phase II	60	FOLFOX + BV for 5 cycles followed by FOLFOX for 1 cycle vs FOLFOXIRI + BV for 5 cycles followed by FOLFOXIRI for 1 cycle	No	pCR	Recruiting	Magnetic resonance imaging-defined poor risk criteria
NCT01871571	Phase II	43	mFOLFOX7 + BV for 6 cycles	No	pCR	Recruiting	
NCT00865189	Randomized Phase II	91	FOLFOX + BV for 6 cycles followed by CT-RT with BV and 5-FU vs CT-RT alone	CT-RT	pCR	Ongoing, not recruiting	Not specified RT dose and fractioning
NCT00462501	Phase II	36	FOLFOX + BV for 4 cycles followed by FOLFOX for 2 cycles with selective use of CT-RT with 5-FU in patients not candidate for R0 resection	CT-RT	R0 resection rate	Ongoing, not recruiting	Not specified RT dose and fractioning
TRUST trial (EUDRACT 2011-003340-45)	Phase II	43	FOLFOXIRI + BV for 6 cycles followed by CTRT with BV and capecitabine or 5-FU	CT-RT 50.4 Gy/28 fractions	DFS rate at 2 yr	Recruiting	

LARC: Locally-advanced rectal cancer; BV: Bevacizumab; RT: Radiotherapy; CT: Chemotherapy; CT-RT: Chemo-radiotherapy; pCR: Pathological complete response; DFS: Disease-free survival; 5-FU: Fluorouracil; XELOX: Capecitabine and oxaliplatin; FOLFOX: 5-FU and oxaliplatin; FOLFOXIRI: 5-FU, oxaliplatin and irinotecan.

patients had T4 tumor or N-positive disease): 3 cycles of CT plus bevacizumab were administered and were then followed by one additional cycle without bevacizumab, with total mesorectal excision performed 3 to 8 wk after the last CT cycle[32]. The authors aimed to investigate the feasibility of the regimen, while secondary endpoints were R0 resection rate, down-staging rate and pCR rate. Twenty-five patients were enrolled: 92% of patients underwent surgery with a R0 resection in all cases, and pCR was reported in 4% (with a rate of pathological effect over grade TRG 2 of 61%). Again, even without RT, 39% of resected patients had post-operative complications. Even though reported in a limited number of patients and only in abstract form, these data suggest that high-risk T4 tumors (72% of the cases in the above-mentioned trial) are probably more prone to develop post-operative complications with bevacizumab-containing regimens. Moreover, RT seems to maintain a crucial role in T4 tumors, as suggested by the relative low rate of pCR in this trial compared with the results reported by Schrag and colleagues (4% *vs* 25%, respectively).

The association of the XELOX regimen with bevacizumab was also evaluated by Fernandez-Martos *et al*[33] in another multicenter phase II study. As in the report by Hasegawa *et al*[32], 3 cycles of XELOX plus bevacizumab were followed by one cycle of XELOX without the antibody. The authors enrolled patients with intermediate-risk LARC, defined as T3 middle-third rectal adenocarcinoma according to pelvic magnetic resonance imaging. Patients without progression after CT plus bevacizumab

(restaging was performed by magnetic resonance imaging) underwent total mesorectal excision 4 to 6 wk from the last CT cycle. In the case of progressive disease, patients were treated with conventional capecitabine-based CT-RT followed by total mesorectal excision. The primary endpoint of the trial was objective response by RECIST criteria. Among the 28 patients so far analyzed, the clinical overall response rate was 87.5% (21 patients) and 4 patients achieved a pCR (15%). Twenty-four (86%) patients completed the 4 cycles of treatment; grade 3-4 toxicity was reported in 50% of the patients, but severe surgical complications occurred at an acceptable rate (11%).

ONGOING TRIALS WITH BEVACIZUMAB IN LARC

Different trials are currently evaluating bevacizumab as a radiosensitizing agent alone or in combination with chemotherapy (Table 5). The Belgian AXE BEAM trial (NCT00828672) is a phase II study assessing neoadjuvant treatment with RT plus bevacizumab and capecitabine with or without oxaliplatin, followed by total mesorectal excision. Also, two phase II Chinese studies (NCT01554059 and NCT01818973) are examining the efficacy and safety of the combination of cytotoxic CT (oxaliplatin plus 5-FU and oxaliplatin plus capecitabine, respectively) with bevacizumab concomitantly with RT as neoadjuvant treatment for patients with resectable LARC.

As previously reported, omitting RT seems a reasonable strategy in selected cases. BACCHUS is a phase II randomized trial (NCT01650428) evaluating the efficacy, toxicity and feasibility of neoadjuvant therapy with either FOLFOX plus bevacizumab or FOLFOXIRI plus bevacizumab in poor prognosis LARC as defined by magnetic resonance imaging. In another phase II study (NCT01871571), patients with stage II-III rectal cancer are treated with neoadjuvant modified FOLFOX-7 plus bevacizumab and within 6 to 8 wk after induction treatment undergo surgery. In other studies, the prognostic value of modern imaging after induction treatment is exploited to offer RT only in unresponsive cases. For example, in a US trial (NCT00462501) including induction FOLFOX and bevacizumab for 4 cycles followed by 2 cycles of FOLFOX without bevacizumab, patients are reassessed after induction treatment, and surgery is offered to non-progressing patients only. If a patient is judged not to be a candidate for R0 resection after CT plus bevacizumab, standard pre-operative 5-FU-based CT-RT is performed.

Other trials are comparing the efficacy and safety of the conventional CT-RT schedules with the more modern induction treatment approach. In a French phase II trial (NCT00865189), patients are randomized to either induction bevacizumab plus FOLFOX-4, followed by CT-RT (comprising bevacizumab, 5-FU and RT), or CT-RT plus bevacizumab (at the same schedule).

DISCUSSION

The overview of the available data for bevacizumab in the neoadjuvant treatment of LARC offered in the previous sections clearly demonstrates that a lot of dark sides still persist. In particular, no definitive indications may be derived about the optimal timing of bevacizumab with respect to surgery and RT, the most suitable CT companion for bevacizumab and the best strategy to complement more effective CT regimens with conventional RT and CT-RT in such a heterogeneous patient population. Last but not least, reliable predictive biomarkers for bevacizumab activity are still lacking, so no molecular selection is on the horizon for antiangiogenic agents in colorectal cancer patients.

With respect to the timing of bevacizumab during neoadjuvant therapy, published and presented studies indicate potential safety concerns for increased rates of post-operative complications: a longer time interval between the last dose of bevacizumab and surgery may reduce the risks related to this agent (particularly for trials omitting pre-operative RT), but uncertainties still exist about the optimal schedule for total mesorectal excision after bevacizumab plus RT. Moving from the data on metastatic colorectal cancer (suggesting a pre-operative 5-wk bevacizumab-free interval as appropriate to reduce the risks of complications after hepatectomy[34]) and the above-mentioned data for bevacizumab in LARC, it is arguable that surgery may be safely performed 7 to 8 wk after the end of therapy. A recent meta-analysis suggested that a waiting interval longer than the classical 6-8 wk from the end of standard pre-operative CT-RT could increase the rate of pCR[35]: these data may be of interest not only for conventional CT-RT, but also when bevacizumab is integrated into the neoadjuvant treatment of LARC patients.

As reported, bevacizumab has been tested either alone or in combination with CT during RT. Moving on from the data in the metastatic setting (suggesting little if any activity of bevacizumab monotherapy)[6], it is unlikely that bevacizumab may simply substitute fluoropyrimidine CT during neoadjuvant RT. Bevacizumab may, however, improve the results of fluoropyrimidine-based CT-RT, even though the results of the discussed trials are not conclusive and do not definitively demonstrate a clear benefit from the addition of bevacizumab in terms of pCR. As several phase III trials failed to demonstrate a benefit from adding oxaliplatin to fluoropyrimidine in CT-RT protocols, even adding bevacizumab to combination CT during RT does not seem to represent the best way to improve patient outcome.

An interesting issue in the management of LARC is finally represented by the optimal integration of systemic CT with CT-RT and surgery. The role of adjuvant CT in LARC is still controversial[23]: in fact, different trials proved no benefit in terms of DFS and OS for fluoropyrimidine-based adjuvant CT after pre-operative CT-RT[36-38]. Possible explanations reside in the poor adherence to adjuvant CT, the use of suboptimal CT regimen and the delay of systemic treatment after surgery.

In this scenario, an alternative strategy is represented by induction CT: integrating bevacizumab with induction CT is therefore a reasonable and (on the basis of the limited data discussed previously in the text) promising approach to offer a potentially higher micrometastatic disease control. Moreover, induction CT may offer a more reliable evaluation of the chemosensitivity of the disease in single patients, as measured by the clinical response before CT-RT. Finally, it could pave the way to a more profound paradigm change in the pre-operative management of LARC: in fact, induction CT could select patients and provide the possibility of omitting RT (or limiting its use in unresponsive or high-risk, *e.g.*, T4, patients). This currently represents a provocative and intriguing treatment strategy in selected cases: modern imaging techniques (in particular, magnetic resonance imaging)[39] may define different risk categories and different patterns of response after CT and CT-RT, thus helping to select patients for an individualized treatment approach (CT or CT-RT before total mesorectal excision). The role of bevacizumab may therefore be valuable in improving the results of systemic CT administered before surgery, and not only during conventional CT-RT.

These issues reflect the consideration that alterna-

tive end points (other than pCR) in future trials may be more suitable in order to capture all the benefit of innovative treatment strategies: in fact, pCR is influenced by a variety of different factors (such as tumor stage at presentation, timing and quality of surgery and accuracy of pathological examination). Therefore, it could not effectively measure the impact of systemic treatment on tumor control, particularly on micrometastatic disease and finally on long-term outcome[40].

CONCLUSION

Preliminary results with bevacizumab in the pre-operative treatment of LARC hold promises and pitfalls. Among the different treatment strategies evaluated in LARC patients, induction CT followed by CT-RT seems to offer the most suitable and promising platform for the integration of bevacizumab into the multimodality approach to rectal cancer. In selected cases, a more intensive treatment with combination CT and bevacizumab may also allow us to spare RT in responsive patients, but a RT-free algorithm deserves further investigation. All members of the multidisciplinary team dealing with LARC patients should keep in mind the objective of treatment, which is not only to reduce the risk of local recurrence, but also to increase the chances of cure by eradicating micrometastases. In this regard, pCR should probably give way to DFS as a more useful study end point, even in early phase trials. To conclude, we believe that significant advances may be achieved only by extensive biologic insights into the mechanism of action of antiangiogenic agents and by evaluating innovative treatment approaches in selected patient populations on the basis of the risk of systemic and local recurrence.

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