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Phase II trial

Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer – A two stage phase II clinical trial ☆

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ABSTRACT

Background and purpose: The aim of this single-arm multicenter phase II clinical trial was to assess the feasibility and tolerability of preoperative radiotherapy and simultaneous capecitabine and bevacizumab. Secondary endpoints were downstaging-rate and induction of complete pathological response.

Material and methods: Patients with cT3 rectal cancer were eligible. Capecitabine (825 mg/sqm twice daily on radiotherapy-days weeks 1–4) and bevacizumab (5 mg/kg on days 1, 15 and 29) were administered concurrently to pelvic radiotherapy (1.8 Gy daily up to 45 Gy in 5 weeks). Surgery followed 6–8 weeks later. A two-stage trial was designed with early termination at eight patients if more than three patients had experienced a common toxicity criteria ⩾grade 3 according to the NCI CTC guidelines.

Results: In the first stage eight patients were enrolled. Median age was 70 years (range 55–76) and ECOG PS 0/1 (%) was 87.5/12.5. Major side effects were mostly intestinal bleeding (grade 3, 25%), diarrhea (grade 3, 25%), perianal and abdominal pain (grades 3 and 4, 25%) followed by anemia (grade 3, 12.5%). Tumor downstaging was observed in 37.5% of patients with complete pathological response in two patients (25%).

Conclusions: After interim analysis of feasibility and tolerability, accrual was terminated according to protocol due to ⩾grade 3 toxicities in 50% of patients. Complete pathological response was seen in 25% of patients but was accompanied by considerable toxicity. Further clinical trials are needed to clarify the role of bevacizumab in this setting.

Rectal cancer is a paradigm for multimodal management, as the combination of surgery, chemotherapy and radiotherapy (RT) is necessary to achieve the optimal outcome [1]. The incidence of rectal cancer in the European Union is approximately 35% of the total colorectal cancer incidence with 15–25/100.000 per year. The mortality is 4–10/100.000 per year with lower rates for females. [2].

Local recurrence and occurrence of metastases are serious problems in locally advanced, low rectal cancer (LARC). With conventional surgery alone the local recurrence rate was 20–45% and could be reduced to <10% by establishing the total mesorectal excision (TME) [3,4]. Preoperative treatment in LARC is designed to improve survival, reduce local recurrence and increase sphincter-saving surgery [5–8]. Efforts to improve such results have focused on preoperative combined radiochemotherapy (RCT) treatment regimens [9–11].

The addition of fluorouracil-based chemotherapy to preoperative RT demonstrated a significantly reduction in the rate of local recurrence in several trials versus RT alone but no trial showed any difference in OS [12–15]. The alternative use of capecitabine plus RT showed similar efficacy in pathologic downstaging rate and complete pathologic response (pCR) rate in two retrospective studies comparing neoadjuvant 5-FU-based versus capecitabine-based RT [16,17]. Sauer et al. [18] showed a significant reduction in local recurrence as well as a reduction in the acute and long-term toxicity by preoperative 5-FU based RCT versus postoperative RCT.

Targeted therapies have rapidly gained attraction in the treatment of advanced colorectal cancer and are under active investigation in adjuvant and neoadjuvant setting. Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor receptor (VEGF), demonstrated efficacy with significant improvement in progression free survival (PFS) and OS in patients with metastatic colorectal cancer [19–21].

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The aim of this single-arm multicenter phase II clinical trial was to assess the feasibility and tolerability of preoperative RT with concomitant combination of bevacizumab and capecitabine in a homogenous group of patients with LARC. Secondary endpoints were downstaging-rate and induction of pCR.

Patients and methods

Study design

This single-arm multicenter phase II clinical trial on behalf of the Austrian breast and colorectal cancer study group (ABCSG) evaluated the feasibility and safety of preoperative treatment with capecitabine, bevacizumab and RT in patients with LARC (Fig. 1). Secondary endpoints included downstaging and pathologic response. A two-stage trial was designed [22] with early termination at eight patients if more than three patients experienced a common toxicity criteria grade 3 or 4 according to the NCI CTC guidelines (version 3.0). Otherwise 25 patients were to be accrued. Clinical examination, computer tomography (CT) of the entire thorax and abdomen, pelvic magnetic resonance imaging (MRI) and standard laboratory work-up were undertaken within 28 days of study entry. A urine pregnancy test was required for all women with childbearing potential, and contraceptive use was required of patients of childbearing age. The trial was approved by the medical ethics committees of all participating centers. Written informed consent was obtained from all patients before randomization.

Eligibility and exclusion criteria

Patients with newly diagnosed clinical stage T3NxM0, locally advanced but potentially complete resectable (R0) adenocarcinoma of the rectum were eligible for this study. Other key eligibility criteria included: 18–80 years, adequate metabolic, hematological, renal and hepatic functions, WHO performance status grades 0–2. Excluded were patients with prior malignancies (except non-melanoma skin carcinoma or in situ cervix cancer), prior pelvic irradiation or chemotherapy, clinically significant cardiovascular disease, uncontrolled hypertension (systolic >150 mmHg, diastolic >100 mmHg) or arrhythmia, major surgery within 28 days before inclusion in this study, grade of common toxicity criteria more than 1 for peripheral neuropathy, active infection, history of significant neurological or psychiatric disorders. Pregnant or breastfeeding women were also excluded.

Radiotherapy

Radiotherapy was performed using a linear accelerator for >4 MeV photons. A computer plan was based on the CT scan in the same position. A three-field technique with lateral wedge filters was employed. Individualized blockings were used to protect lateral field corners, dorsal soft tissues (skin and rima ani), and, if necessary, cranial ventral parts of the small intestine. The upper field border was positioned at level L5–S1, depending on the location of the primary tumor. The ventral border depended on the location of the tumor and its degree of infiltration into the surrounding structures. Radiation therapy was delivered 5 days a week for 5 weeks with a fractionation of 1.8 Gy to the reference point (isocenter). Total dose in the reference point was 45 Gy. Radiation was discontinued if grade 4 toxicity according to the NCI CTC v3.0 guidelines occurred.

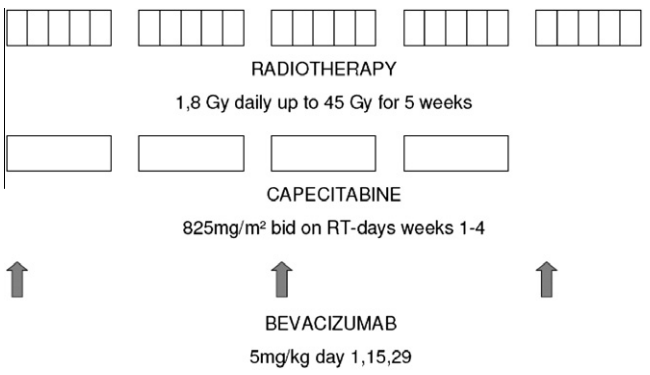

Fig. 1. Overview of the concomitant chemoradiation regimen.

Chemotherapy

Capecitabine was administered concurrently at 825 mg/m^2 bid on days of radiation during the first 4 weeks (days 1–5, 8–12, 15–19 and 22–26). Toxicities were assessed and recorded at every visit and graded (grades 1–4) according to NCIC CTC v3.0. The capecitabine dose-modification scheme was applied if patients experienced grades 2–4 toxicities. Dose modification was not required for toxicities that were considered unlikely to become serious or life-threatening (e.g. alopecia or altered taste).The monoclonal antibody bevacizumab was administered by a 90-min intravenous infusion at 5 mg/kg body weight on days 1, 15 and 29. If the first infusion was tolerated the second infusion was given in 60 min and all subsequent infusions over 30 min if 60 min infusion was tolerated. Dose reduction for toxicity was not recommended but dosing with bevacizumab was hold or discontinued for defined adverse events.

Surgery and postoperative chemotherapy

Surgery followed 6–8 weeks after completion of chemoradiotherapy. The goal of surgery was complete removal of the primary tumor according to the principles of total mesorectal excision (TME) either by low anterior resection (LAR) or abdomino-perineal excision (APE). Adjuvant chemotherapy was not subject of this study and was performed at the discretion of the treating physician.

Assessment of response

All patients were re-evaluated within 2 weeks before surgery by pelvic MRI, thoracic-abdomino CT, clinical examination and laboratory evaluations, consisting of hematology and serum biochemistry. Histopathologic examination of the resected tumor followed the guidelines of the TNM system [23].

Results

In the first stage of this two-stage phase II clinical trial eight patients with LARC enrolled in four Austrian institutions. All patients included in this trial had a histologically proven adenocarcinoma of the rectum with a clinical stage T3NxM0 detected by MRI without evidence of distant metastases. Median age at time of initiating treatment was 70 years (range 55–76). Of the patients, 4 (50%) were men and 4 (50%) were woman and ECOG performance status 0/1 (%) was 87.5/12.5. Four patients had hypertension as risk factor. One patient had additionally elevated liver enzyme grade 1. Baseline characteristics were listed in Table 1. RT with an amount of 45 Gy in 25 fractions was planned (1.8 Gy daily from Monday to Friday, days 1–33). Seven patients (87.5%) received the total dose of radiation. One patient missed 1 day of RT. Capecitabine was taken orally twice daily, concurrently on RT-days during the first 4 weeks (days 1–26, Monday to Friday). Seven patients (87.5%) received 100% of total planned dose of the oral prodrug capecitabine. Due to the occurrence of grade 3 diarrhea in week 3, one patient had a

Table 1
Baseline patients and tumor characteristics.

Characteristic	No. of patients (%)
N	8
Sex	
Male	4 (50%)
Female	4 (50%)
Age (years)	
Median	70
Range	55–76
ECOG performance status	
0	7 (87.5%)
1	1 (12.5%)
Clinical TN stage	
T3	8 (100%)
N0	1 (12.5%)
N1	4 (50%)
N2	1 (12.5%)
NX	2 (25%)

Table 2
Acute toxicities and perioperative complications grade 1–4 in patient 1–8; patient 3 and 6 had ypT0, patient 5 had ypT2.

Adverse event	Patient							
	1	2	3	4	5	6	7	8
Anemia	2		3					2
Thrombocytopenia	1		3			1		
Leukopenia	1	1	2			2		1
Neutropenia	1	1	1			1		1
Diarrhea			3	2		3		
Hand-food-syndrome	1	1						
Perianal bleeding	3		3					
Perianal pain	1		4					
Abdominal pain	3		3					
Nausea	1		1					
Dysuria		1	1					
Anastomotic dehiscence		2						
Postoperative ileus								3

drug-interruption for 5 days and capecitabine was restarted at 75% of the original dose according to the protocol. A further patient also experienced diarrhea grade 3 in week 3 which required an interruption for 2 days without dose adjustment in the following cycle. Bevacizumab was administered on day 1, 15 and 29. Six of eight patients received all three infusions. Two patients discontinued treatment due to bleeding grade 3 in week 5. Surgery was performed 6–8 weeks after completion of radiochemotherapy in seven patients. In one patient resection was not done due to peritoneal carcinomatosis at laparotomy. There were two perioperative complications, one postoperative ileus which required surgical intervention and one perineal wound dehiscence after abdominoperineal resection.

Severe side effects (grades 3 and 4) were mostly perianal bleeding (grade 3, 25%), diarrhea (grade 3, 25%), perianal and abdominal pain (grades 3 and 4, 25%) followed by hematological complications (anemia grade 3, 12.5%) and postoperative ileus (grade 3, 12.5%) (listed in Table 2). There were no deaths related to radiochemotherapy or surgery. After the preplanned safety interim analysis, accrual was terminated due to the fact that four patients had a toxicity grade 3 or 4 following radiochemotherapy.

Postoperative histology revealed a moderately differentiated tumor (grade 2) in 71.4% (5/7) and a poorly differentiated tumor (grade 3) in 28.6% (2/7). After radiochemotherapy for T3 rectal carcinomas, downstaging (defined as ypT0-2 lesions) occurred in 37.5% of patients (3/8). Two of them had ypT0 and one patient had ypT2. Three patients had N0 nodal status, 2 were N1 (1–3 lymph nodes) and 2 were N2 (>4 lymph nodes).

Discussion

5-FU based RCT and TME is considered a standard treatment for patients with stage II/III rectal cancer. Despite optimized local treatment with recurrence rates of 5–10%, distant metastases still occur in 25–30% [24,25]. In order to enhance the effect of RCT the role of radiation sensitizing agents are studied now in several trials. Capecitabine, oxaliplatin, irinotecan as well as targeted therapies improved results for colorectal cancer patients when treated in the metastatic and/or adjuvant setting. Combining these agents with standard therapy treatment in patients with LARC had received an increasing interest. In recent years our study group designed clinical trials to improve the efficacy in terms of local recurrence and prevention of metastases in rectal cancer. In the R02 study [26] the addition of capecitabine and oxaliplatin to RT in LARC was evaluated. Tumor downstaging was observed in 53% of patients (31/59) and the only clinically relevant toxicity was diarrhea in 8%. In the following R03 study [27] the therapy included capecitabine, cetuximab and external beam radiotherapy. The main toxicity was also diarrhea in 11% and tumor downstaging occurred in 50%. In this phase II study (R04), we evaluated the feasibility and efficacy of capecitabine, bevacizumab and RT in patients with LARC. To our knowledge there are only two other phase I/II clinical trials investigating the feasibility of bevacizumab in combination with RCT in LARC.

We initiated a two stage phase II trial. After eight patients an interim analysis was performed. Accrual was terminated according to protocol due to $\geqslant$grade 3 toxicities in half of patients. A tumor downstaging was achieved in 38% with pCR of 25%. Major side effects were mostly intestinal bleeding (grade 3, 25%), diarrhea (grade 3, 25%), perianal and abdominal pain (grades 3 and 4, 25%). However, both patients with pCR experienced grade 3 toxicities.

Study design and treatment schedule in our trial are comparable with the other two trials using bevacizumab and RCT in LARC. Willet et al. [28,29] investigated the safety and efficacy of neoadjuvant bevacizumab (5 or 10 mg/kg) on day one of each cycle, fluorouracil infusion (225 mg/m^2/24 h) during cycles 2–4 and RT (50.4 Gy in two fractions over 5.5 weeks) in a phase I/II study in 32 patients with LARC. In phase I six patients received 5 mg/kg of bevacizumab without dose-limiting toxicity (DLT) and five patients received 10 mg/kg bevacizumab, whereas in two of them gastrointestinal DLT occurred. Therefore 21 patients received the lower dose of bevacizumab in the following phase II study. T-downstaging was achieved in 50% of patients with pCR of 16% with acceptable toxicities [28,29]. Most adverse events were mild, only some patients experienced grade 3 toxicities: diarrhea in 22%, hypertension in 9%, radiation dermatitis in 6% and most of postoperative complications were wound infection (3/32), ileus (2/32), delayed healing of perineal incision (2/32) and pulmonary embolus, anastomotic leak, presacral abscess each in one patient. Crane et al. [30] evaluated the efficacy and safety of bevacizumab (5 mg/kg every 2 weeks), capecitabine (900 mg/m^2 twice daily on days of radiation) and RT (50.4 Gy in 28 fractions over 5.5 weeks) in 25 patients with cT3 rectal cancer. T-downstaging was achieved in 64% of patients with pCR of 32% without grade 3 hand-food syndrome, gastrointestinal toxicities or significant hematologic toxicities [30]. Perianal desquamation in 6/25 patients was the only grade 3 acute toxicity. Perioperative major complications included perianal wound dehiscence (2/25) and anastomotic dehiscence (1/25).

Response rates and toxicities including diarrhea are comparable to our study with the exception of hemorrhage. None of these studies reported bleeding complications whereas in our trial 2/8

patients had perianal bleeding complications requiring blood transfusions. The reason for the difference of this bleeding complication in our trial is not known. Phases I and II studies identified hypertension, hemorrhage, thrombembolism and proteinuria as possible bevacizumab-associated adverse reactions [31,32]. Overall the incidence of grade $\geqslant 3$ hemorrhagic events among patients receiving bevacizumab is indicated with 3.5% [33]. From the point of view our criteria for early termination might have been too restrictive because diarrhea is a common side effect of chemoradiotherapy and postoperative ileus is independent of RCT.

Concerning the efficacy of bevacizumab combined with RCT in early stage rectal cancer there are only results from three phase I/II clinical trials including 65 patients. Complete pathological response rates occurred in 16–32% of patients. Although these response rates are encouraging, increased toxicities seems to preclude the intensification of the standard RCT schedule. In the next protocol of our group we will incorporate bevacizumab into an induction chemotherapy followed by standard RCT and surgery to further improve the results.

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